Supplementary Information

Table S1 Molecular structures and inhibitory activity values of the 93 collected dual JAK2 and HDAC6 inhibitors.
https://www.scidb.cn/s/y63i22 1,436 JAK2 and 523 HDAC6 inhibitors for the regression model.
Table S2 The top ten features from all JAK2 regression models combined.
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Table S1 Molecular structures and inhibitory activity values of the 93 collected dual JAK2 and HDAC6 inhibitors

Name	SMILES	pIC_{50} value for JAK2 (nM)	pIC_{50} value for HDAC6 (nM)
Chem001	CCNC(=O)C1CC2C(-C3CC(OCCCCCCN4CC(-C5NC(NC6CCC(NC(=O)CCCCCCC(=O)O)CC6)NC6[NH]CCC56)CN4)C(CL)CC3CL)NC(N)NC2S1Z	3760	6300
Chem002	O=C(CCCCCCC(=O)NC1CCC(NC2NC(-C3CNN(CCCCOC4CCCCC4)C3)C3CC[NH]C3N2)CC1)NO	40	7
Chem003	COC(=O)CCCCCCOC1CCC(NC2NCCC(-C3CCC(NC(C)=O)CC3)N2)CC1	239	3150
Chem004	CC(=O)NC1CCC(-C2CCNC(NC3CCCC(OCCCCCC(=O)NO)C3)N2)CC1	3.4	2.4
Chem005	CC(=O)NC1CCC(-C2CCNC(NC3CCCC(OCCCCCCCC(=O)NO)C3)N2)CC1	3.6	1.8
Chem006	O=C(CCCCCCC(=O)NC1CCC(-C2CCNC(NC3CCCCC3)N2)CC1)NO	41.3	1.44
Chem007	O=C(CCCCCCC(=O)NC1CCC(-C2CCNC(NC3CCC(N4CCOCC4)CC3)N2)CC1)NO	3.1	1.2
Chem008	CC(=O)NC1CCC(-C2CCNC(NC3CCC(OCCCCCC(=O)NO)CC3)N2)CC1	33	1.3
Chem009	N#CC[C@H](C1CCCC1)N1CC(-C2NCNC3[NH]CCC23)CN1	26	15
Chem010	CC(=O)NC1CCC(-C2NC(NC3CCCC(OCCCCCCC(=O)NO)C3)NCC2C)CC1	3.9	6.1
Chem011	CC(=O)NC1CCC(-C2NC(NC3CCCC(OCCCCCCCC(=O)NO)C3)NCC2C)CC1	2.93	9.7
Chem012	O=C(CCCCCCC(=O)NC1CCC(-C2CCNC(NC3CCC(N4CCCCC4)CC3)N2)CC1)NO	18	23
Chem013	CN1CCN(CC(=O)NC2CCC(-C3CCNC(NC4CCC(OCCCCCCC(=O)NO)CC4)N3)CC2)CC1	95.5	6.1
Chem014	CC(NC1CCC(C2NC(NC3CC(OCCCCCCCC(NO)=O)CCC3)NCC2)CC1)=O	17	6.7
Chem015	CC(=O)NC1CCC(-C2CCNC(NC3CCC(OCCCCCCCC(=O)NO)CC3)N2)CC1	46	14
Chem016	O=C(CCCCCN1CC(NC2NCC(CL)C(NC3CCC(CL)CC3)N2)CN1)NO	4	14

Chem017	O=C(CCCCCCCN1CC(-C2NCNC3[NH]CCC23)CN1)NO	481	1.8
Chem018	O=C(CCCCCCN1CC(-C2NCNC3[NH]CCC23)CN1)NO	75	1.4
Chem019	O=C(CCCCCCC(=O)NC1CCC(NC(=O)CCCN2CC(-C3NCNC4[NH]CCC34)CN2)CC1)NO	1200	550
Chem020	CN1CCN(C2CCC(NC3NCCC(-C4CCC(NC(=O)CCCCCCC(=O)NO)CC4)N3)CC2)CC1	4.6	3.1
Chem021	O=C(CCCCCCC(=O)NC1CCC(NC2NC(-C3CNN(CCCCCCOC4CCCCC4)C3)C3CC[NH]C3N2)CC1)NO	19	15.8
Chem022	O=C(CCCCN1CC(-C2NCNC3[NH]CCC23)CN1)NO	219	6
Chem023	CS(=O)(=O)NC1CCC(-C2CCNC(NC3CCC(N4CCC(C(=O)NCCCCCCCC(=O)NO)CC4)CC3)N2)CC1	2	74
Chem024	O=C(NO)C1CCC(-C2CCNC(NC3CCC(N4CCOCC4)CC3)N2)CC1	85	419
Chem025	O=C(NO)C1CCC(CN2CC(NC3NCC(CL)C(NC4CCC(F)CC4)N3)CN2)CC1	21	13
Chem026	CC(=O)NC1CCC(-C2NC(NC3CCC(OCCCCCC(=O)NO)CC3)NCC2C)CC1	25.6	3.5
Chem027	COCCN1CC(-C2NC(NC3CCC(NC(=O)CCCCCCC(=O)NO)CC3)NC3[NH]CCC23)CN1	2.3	2.1
Chem028	CC(CCCCCC(=O)NO)N1CC(-C2NCNC3[NH]CCC23)CN1	65	1
Chem029	O=C(CCCN1CC(-C2NCNC3[NH]CCC23)CN1)NO	3560	604
Chem030	O=C(CCCCCCC(=O)NC1CCC(NC2NC(-C3CN[NH]C3)C3CC[NH]C3N2)CC1)NO	0.96	0.2
Chem031	C=CCCN1CC(-C2NC(NC3CCC(NC(=O)CCCCCCC(=O)NO)CC3)NC3[NH]CCC23)CN1	0.041	0.25
Chem032	N#CCCN1CC(-C2NC(NC3CCC(NC(=O)CCCCCCC(=O)NO)CC3)NC3[NH]CCC23)CN1	0.04	0.85
Chem033	CC1CNC(NC2CCC(N3CCN(C)CC3)CC2)NC1-C1CCC(NC(=O)CCCCCCC(=O)NO)CC1	4.3	2.1
Chem034	O=C(CCCCCN1CC(NC2NCC3CCN(CC4CCCC(F)C4)C3N2)CN1)NO	4.1	13.7
Chem035	CC(=O)NC1CCC(-C2CCNC(NC3CCCC(NC(=O)CCCCC(=O)NO)C3)N2)CC1	2.6	4.6
Chem036	O=C(NO)C1CCC(OCCOC2CCC3CC2COC/C=C/COCC2CCCC(C2)-C2CCNC(N2)N3)CC1	1.27	66
Chem037	O=C(CCCCCN1CC(-C2NCNC3[NH]CCC23)CN1)NO	200	2.9

Chem038	O=C(CCCOC1CCC2CC1COC/C=C/COCC1CCCC(C1)-C1CCNC(N1)N2)NO	4.7	510
Chem039	CCCN1CC(-C2NC(NC3CCC(NC(=O)CCCCCCC(=O)NO)CC3)NC3[NH]CCC23)CN1	0.15	1.6
Chem040	O=C(CCCCCCC(=O)NC1CCC(NCCCN2CC(-C3NCNC4[NH]CCC34)CN2)CC1)NO	265	0.14
Chem041	O=C(NO)C1CCN(CCOC2CCC3CC2COC/C=C/COCC2CCCC(C2)-C2CCNC(N2)N3)CC1	0.97	899
Chem042	CS(=O)(=O)CCN1CC(-C2NC(NC3CCC(NC(=O)CCCCCCC(=O)NO)CC3)NC3[NH]CCC23)CN1	7.7	2.3
Chem043	O=C(CCCCOC1CCC2CC1COC/C=C/COCC1CCCC(C1)-C1CCNC(N1)N2)NO	2.45	107
Chem044	CNC1NC(NC2CNN(CCCCCCC(=O)NO)C2)NCC1CL	36	29
Chem045	O=C(CCCCCCN1CC(NC2NCC3CCN(CC4CCCC(CL)C4)C3N2)CN1)NO	39.8	36.8
Chem046	O=C(CCCCCCCN1CC(NC2NCC(CL)C(NC3CCC(F)CC3)N2)CN1)NO	61	300
Chem047	O=C(CCCCCCN1CC(NC2NCC3CCN(CC4CCCCC4F)C3N2)CN1)NO	32.9	8.4
Chem048	O=C(NO)C1CCC(NCCOC2CCC3CC2COC/C=C/COCC2CCCC(C2)-C2CCNC(N2)N3)CC1	1.71	395
Chem049	O=C(CCCCCCC(=O)NC1CCC(NCCOC2CCC3CC2COC/C=C/COCC2CCCC(C2)-C2CCNC(N2)N3)CC1)NO	30	2.3
Chem050	CC(=O)NC1CCC(-C2CCNC(NC3CCC(NC(=O)CCCCC(=O)NO)CC3)N2)CC1	58.3	117
Chem051	CN1CCN(CC(=O)NC2CCC(-C3CCNC(NC4CCCC(OCCCCCCC(=O)NO)C4)N3)CC2)CC1	109	6.8
Chem052	CC(=O)NC1CCC(-C2CCNC(NC3CCCC(NC(=O)CCCCCCC(=O)NO)C3)N2)CC1	9.2	0.81
Chem053	CC(=O)NC1CCC(-C2CCNC(NC3CCC(NC(=O)CCCCCCC(=O)NO)CC3)N2)CC1	0.9	0.1
Chem054	O=C(CCCCCCC(=O)NC1CCC(-C2CCNC(NC3CCCC(N4CCCCC4)C3)N2)CC1)NO	6.6	9
Chem055	CC1CNC(NC2CCC(N3CCOCC3)CC2)NC1-C1CCC(NC(=O)CCCCCCC(=O)NO)CC1	1.8	3.7
Chem056	O=C(/C=C/C1CCC(CN2CC(NC3NCC(CL)C(NC4CCC(F)CC4)N3)CN2)CC1)NO	43	63
Chem057	O=C(CCCCCCC(=O)NC1CCC(CCCN2CC(-C3NCNC4[NH]CCC34)CN2)CC1)NO	865	0.9
Chem058	O=C(CCCCCCCCCCN1CC(-C2NCNC3[NH]CCC23)CN1)NO	43	88

Chem059	COC1CCCC(CN2CCC3CNC(NC4CNN(CCCCCC(=O)NO)C4)NC32)C1	123.9	37.6
Chem060	O=C(O)CCCCCCOC1CCC2CC1COC/C=C/COCC1CCCC(C1)-C1CCNC(N1)N2	2.57	2800
Chem061	O=C(CCCCCCCOC1CCC2CC1COC/C=C/COCC1CCCC(C1)-C1CCNC(N1)N2)NO	5	15.8
Chem062	CS(=O)(=O)NC1CCC(-C2CCNC(NC3CCC(N4CCC(C(=O)NC5CCC(/C=C/C(=O)NO)CC5)CC4)CC3)N2)CC1	8	46
Chem063	O=C(CCCCCCC(=O)NC1CCC(NC2NC(-C3CNN(CC4CCCC4)C3)C3CC[NH]C3N2)CC1)NO	3	9.6
Chem064	O=C(CCCCCCN1CC(NC2NCC3CCN(-C4CCC(CL)CC4)C3N2)CN1)NO	48.2	33.4
Chem065	O=C(CCCCCCN1CC(NC2NCC3CCN(CC4CCCCC4)C3N2)CN1)NO	51	12.5
Chem066	CS(=O)(=O)C1CCC(-N2CCC3CNC(NC4CNN(CCCCCCC(=O)NO)C4)NC32)CC1	15.7	5.9
Chem067	O=C(CCCCCN1CC(NC2NCC3CCN(-C4CCC(BR)CC4)C3N2)CN1)NO	17.5	11.3
Chem068	O=C(CCCCCCC(=O)NC1CCC(NC2NC(-C3CNN(CCCCCOC4CCCCC4)C3)C3CC[NH]C3N2)CC1)NO	21	5.2
Chem069	O=C(CCCCCC(=O)NC1CCC(NCCOC2CCC3CC2COC/C=C/COCC2CCCC(C2)-C2CCNC(N2)N3)CC1)NO	6.9	2.5
Chem070	O=C(CCCCCCN1CC(NC2NCC(CL)C(NC3CCCC(CL)C3)N2)CN1)NO	10	41
Chem071	O=C(NO)C1CCCC(NCCOC2CCC3CC2COC/C=C/COCC2CCCC(C2)-C2CCNC(N2)N3)C1	9	2900
Chem072	O=C(CCCCCOC1CCC2CC1COC/C=C/COCC1CCCC(C1)-C1CCNC(N1)N2)NO	4.3	28
Chem073	O=C(/C=C/C1CCC(NCCCN2CC(-C3NCNC4[NH]CCC34)CN2)CC1)NO	502	148
Chem074	CC(=O)NC1CCC(-C2CCNC(NC3CCC(OCCCCCCCC(=O)NO)CC3)N2)CC1	23	3
Chem075	O=C(O)CCCCCCCC(=O)NC1CCC(NCCOC2CCC3CC2COC/C=C/COCC2CCCC(C2)-C2CCNC(N2)N3)CC1	2.31	2600
Chem076	O=C(CCCCCCCOC1CCC2CC1COC/C=C/COCC1CCCC(C1)-C1CCNC(N1)N2)NO	1.4	2.1
Chem077	CS(=O)(=O)C1CCC(-N2CCC3CNC(NC4CNN(CCCCCC(=O)NO)C4)NC32)CC1	9.8	10.8
Chem078	O=C(CCCCCCN1CC(NC2NCC3CCN(CC4CCCC(F)C4)C3N2)CN1)NO	15.7	14.7
Chem079	O=C(CCCCCCN1CC(NC2NCC3CCN(-	16.8	13.1

	C4CCCCC4)C3N2)CN1)NO		
Chem080	O=C(CCCCN1CC(NC2NCC(CL)C(NC3CCC(F)CC3)N2)CN1)NO	46	310
Chem081	O=C(CCCCCN1CC(NC2NCC3CCN(CC4CCCCC4)C3N2)CN1)NO	33	13.8
Chem082	O=C(CCCCCCN1CC(NC2NCC3CCN(CC4CCCCC4)C3N2)CN1)NO	69	88
Chem083	O=C(CCCCCCN1CC(NC2NCC3CCN(-C4CCC(F)CC4)C3N2)CN1)NO	32.9	21.6
Chem084	O=C(CCCCCN1CC(NC2NCC3CCN(CC4CCCCC4F)C3N2)CN1)NO	10	15.3
Chem085	O=C(CCCCCN1CC(NC2NCC3CCN(CC4CCCCC4CL)C3N2)CN1)NO	24.8	45
Chem086	O=C(CCCCCCN1CC(NC2NCC3CCN(CC4CCCCC4CL)C3N2)CN1)NO	30.8	41.5
Chem087	O=C(CCCCCCN1CC(NC2NCC3CCN(-C4CCC(BR)CC4)C3N2)CN1)NO	54.8	20.2
Chem088	COC1CCCC(CN2CCC3CNC(NC4CNN(CCCCCCC(=O)NO)C4)NC32)C1	209.2	28.8
Chem089	O=C(CCCCCN1CC(NC2NCC3CCN(CC4CCCC(CL)C4)C3N2)CN1)NO	17.7	34.4
Chem090	OC(CCCCCCOC1=CC=C2C=C1COC/C=C/COCC3=CC=CC(C4=CC=NC(N2)=N4)=C3)=O	2.57	3800
Chem091	O=C(O)CCCCCCCOC1=CC=C2C=C1COC/C=C/COCC3=CC=CC(C4=CC=NC(N2)=N4)=C3	39	10000
Chem092	O=C(C1CCN(C2=CC=C(NC3=NC=CC(C4=CC=C(NS(=O)(C)=O)C=C4)=N3)C=C2)CC1)NC5=CC=C(/C=C/C(NO)=O)C=C5	8.4	46
Chem093	O=C(C1CCN(C2=CC=C(NC3=NC=CC(C4=CC=C(NS(=O)(C)=O)C=C4)=N3)C=C2)CC1)NCCCCCCCC(NO)=O	2.2	74

Table S2 The top ten features from all JAK2 regression models combined

Descriptor Name	Mean Score	Appearance	Explanation	Type
ECFP_227	0.191	3	aminopropionitrile group	ECFP4 fingerprint
MAXDP	0.091	3	Maximal electrotopological positive variation	Topological descriptors
VSA_EState4	0.071	4	VSA EState Descriptor 4 (5.41 <= x < 5.74)	VSA descriptors
ZMIC2	0.067	1	2-ordered Z-modified information content	Topological descriptors
Mor12m	0.057	2	3D-MoRSE-signal 12/weighted by atomic masses	3D-MoRSE descriptors
ATSC8c	0.056	3	centered moreau-broto autocorrelation of lag 8 weighted by gasteiger charge	2D autocorrelations
ATSC4i	0.050	1	centered moreau-broto autocorrelation of lag 4 weighted by ionization potential	2D autocorrelations
AATS4i	0.049	1	averaged moreau-broto autocorrelation of lag 4 weighted by ionization potential	2D autocorrelations
AATS7i	0.048	4	averaged moreau-broto autocorrelation of lag 7 weighted by ionization potential	2D autocorrelations
Mor31u	0.047	1	3D-MoRSE-signal 31/unweighted	3D-MoRSE descriptors

Table S3 The top ten features from all HDAC6 regression models combined

Descriptor Name	Mean Score	Appearance	Explanation	Type
SMR_VSA9	0.190	3	MOE MR VSA Descriptor 9 (3.80 <= x < 4.00)	VSA descriptors
SaasC	0.084	4	sum of aasC	Topological descriptors
MinEStateIndex	0.067	3	Minimum E-State index	Constitutional descriptors
ATSC3i	0.061	3	centered moreau-broto autocorrelation of lag 3 weighted by ionization potentia	2D autocorrelations
PEOE_VSA3	0.058	2	MOE Charge VSA Descriptor 3 (-0.25 <= x < -0.20)	VSA descriptors
MLOGP	0.056	2	Moriguchi octanol–water partition coeff. (log P)	Molecular properties
ALOGP	0.055	4	Ghose–Crippen octanol–water partition coeff. (log P).	Molecular properties
GATS8m.1	0.053	2	geary coefficient of lag 8 weighted by mass	Topological descriptors
RDF035m	0.050	3	Radial distribution function – 3.5/weighted by atomic masses	RDF descriptors
RDF030u	0.049	1	Radial distribution function – 3.0/unweighted	RDF descriptors

Table S4 Eleven compounds for external validation in regression

Name	SMILES	pIC_{50} value for JAK2 (nM)	pIC_{50} value for HDAC6 (nM)
Chem023	CS(=O)(=O)NC1CCC(-C2CCNC(NC3CCC(N4CCC(C(=O)NCCCCCCCC(=O)NO)CC4)CC3)N2)CC1	8.699	7.131
Chem036	O=C(NO)C1CCC(OCCOC2CCC3CC2COC/C=C/COCC2CCCC(C2)-C2CCNC(N2)N3)CC1	8.896	7.180
Chem041	O=C(NO)C1CCN(CCOC2CCC3CC2COC/C=C/COCC2CCCC(C2)-C2CCNC(N2)N3)CC1	9.013	6.046
Chem043	O=C(CCCCOC1CCC2CC1COC/C=C/COCC1CCCC(C1)-C1CCNC(N1)N2)NO	8.611	6.971
Chem048	O=C(NO)C1CCC(NCCOC2CCC3CC2COC/C=C/COCC2CCCC(C2)-C2CCNC(N2)N3)CC1	8.767	6.403
Chem062	CS(=O)(=O)NC1CCC(-C2CCNC(NC3CCC(N4CCC(C(=O)NC5CCC(/C=C/C(=O)NO)CC5)CC4)CC3)N2)CC1	8.097	7.337
Chem072	O=C(CCCCCOC1CCC2CC1COC/C=C/COCC1CCCC(C1)-C1CCNC(N1)N2)NO	8.367	7.553
Chem075	O=C(O)CCCCCCC(=O)NC1CCC(NCCOC2CCC3CC2COC/C=C/COCC2CCCC(C2)-C2CCNC(N2)N3)CC1	8.636	5.585
Chem090	OC(CCCCCCOC1=CC=C2C=C1COC/C=C/COCC3=CC=CC(C4=CC=NC(N2)=N4)=C3)=O	8.590	5.420
Chem92	O=C(C1CCN(C2=CC=C(NC3=NC=CC(C4=CC=C(NS(=O)(C)=O)C=C4)=N3)C=C2)CC1)NC5=CC=C(/C=C/C(NO)=O)C=C5	8.076	7.337
Chem093	O=C(C1CCN(C2=CC=C(NC3=NC=CC(C4=CC=C(NS(=O)(C)=O)C=C4)=N3)C=C2)CC1)NCCCCCCCCC(NO)=O	8.658	7.131

Table S5 The binding energy of the thirteen compounds to the JAK2 and HDAC6 protein receptors

Name	SMILES	Binding energy for JAK2 (kcal/mol)	Binding energy for HDAC6 (kcal/mol)
Chem023	CS(=O)(=O)NC1CCC(-C2CCNC(NC3CCC(N4CCC(C(=O)NCCCCCCCC(=O)NO)CC4)CC3)N2)CC1	-10.3	-8.51
Chem036	O=C(NO)C1CCC(OCCOC2CCC3CC2COC/C=C/COCC2CCCC(C2)-C2CCNC(N2)N3)CC1	-11.4	-10.05
Chem041	O=C(NO)C1CCN(CCOC2CCC3CC2COC/C=C/COCC2CCCC(C2)-C2CCNC(N2)N3)CC1	-10.9	-10.51
Chem043	O=C(CCCCOC1CCC2CC1COC/C=C/COCC1CCCC(C1)-C1CCNC(N1)N2)NO	-10.4	-8.59
Chem048	O=C(NO)C1CCC(NCCOC2CCC3CC2COC/C=C/COCC2CCCC(C2)-C2CCNC(N2)N3)CC1	-11.1	-11.43
Chem062	CS(=O)(=O)NC1CCC(-C2CCNC(NC3CCC(N4CCC(C(=O)NC5CCC(/C=C/C(=O)NO)CC5)CC4)CC3)N2)CC1	-11.2	-10.43
Chem072	O=C(CCCCCOC1CCC2CC1COC/C=C/COCC1CCCC(C1)-C1CCNC(N1)N2)NO	-10.5	-9.58
Chem075	O=C(O)CCCCCCC(=O)NC1CCC(NCCOC2CCC3CC2COC/C=C/COCC2CCCC(C2)-C2CCNC(N2)N3)CC1	-11.3	-4.49
Chem090	OC(CCCCCCOC1=CC=C2C=C1COC/C=C/COCC3=CC=CC(C4=CC=NC(N2)=N4)=C3)=O	-9.6	-7.84
Chem092	O=C(C1CCN(C2=CC=C(NC3=NC=CC(C4=CC=C(NS(=O)(C)=O)C=C4)=N3)C=C2)CC1)NC5=CC=C(/C=C/C(NO)=O)C=C5	-10.4	-11.7
Chem093	O=C(C1CCN(C2=CC=C(NC3=NC=CC(C4=CC=C(NS(=O)(C)=O)C=C4)=N3)C=C2)CC1)NCCCCCCCCC(NO)=O	-10.2	-8.84

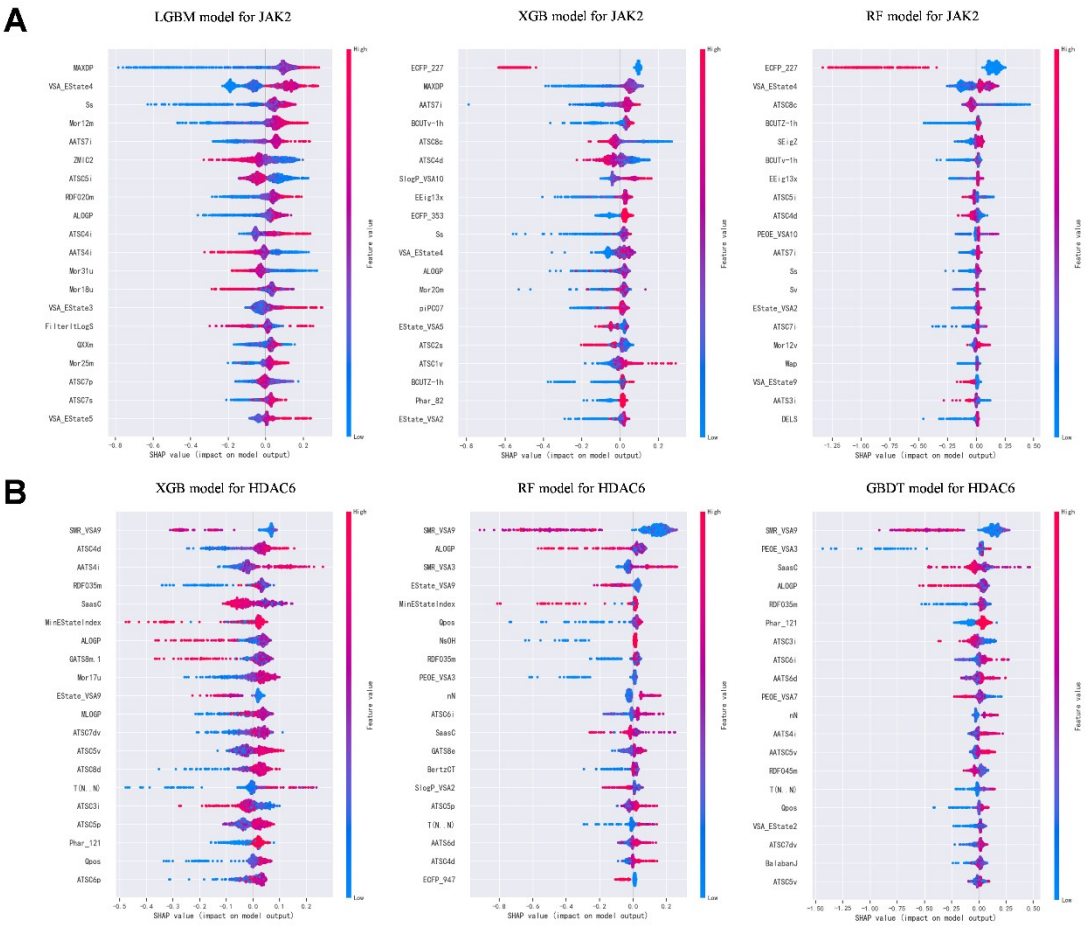

Fig.S1 Global interpretation of SHAP plots for the regression models. (A) LGBM, XGB, RF models for JAK2. (B) XGB, RF, GBDT models for JAK2. The y-axis is sorted by the average absolute SHAP values for each feature, the x-axis represents the SHAP values. The color indicates the feature value, with red corresponding to high values and blue corresponding to low values.