SUPPLEMENTARY MATERIAL

A Multitask GNN-based Interpretable Model for Discovery of Selective JAK Inhibitors

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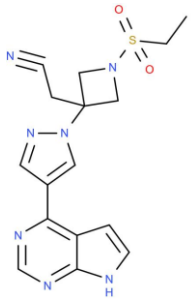
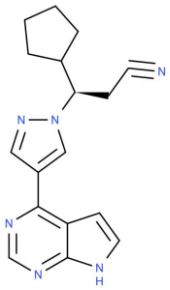
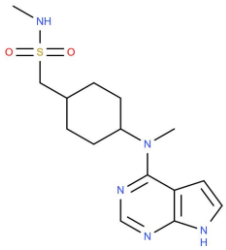
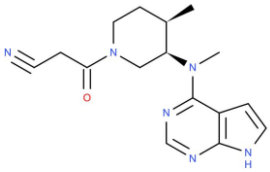
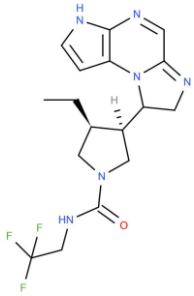
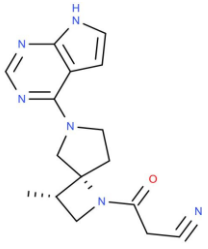
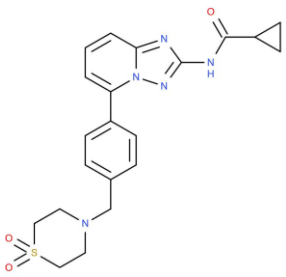
Table S1. Approved JAK inhibitors and their current indications

Drug	Target	Indication	Structures
Baricitinib	JAK1/JAK2	RA (EMA approved), COVID-19 (EUA)	
Ruxolitinib	JAK1/JAK2	MPN, acute GVHD RA (Japan approved)	
Oclacitinib	JAK1	Allergic dermatitis (FDA approved)	
Tofacitinib	JAK1/JAK2/JAK 3	RA (FDA approved, EMA approval recommended), PsA, UC	
Upadacitinib	JAK1	RA (FDA approved), PsA (approved in EMA), AS (approved in EMA)	
Delgocitinib	Pan-JAK	AD (approved in Japan)	

Filgotinib	JAK1	RA (approved in EU, Japan)	

AD, atopic dermatitis; EUA, Emergency Use Authorization; GVHD, graft-versus-host disease; MPN, myeloproliferative neoplasms; PsA, psoriatic arthritis; RA, rheumatoid arthritis; UC, ulcerative colitis.

Table S2. Some molecular graph features computed with RDKit[1, 2]

Atom Feature	**Size**	**Description**
atom symbol	16	[B, C, N, O, F, Si, P, S, Cl, As, Se, Br, Te, I, At, metal] (one-hot)
degree	6	number of covalent bonds [0,1,2,3,4,5] (one-hot)
formal charge	1	electrical charge (integer)
radical electrons	1	number of radical electrons (integer)
hybridization	6	[sp, sp2, sp3, sp3d, sp3d2, other] (one-hot)
aromaticity	1	whether the atom is part of an aromatic system [0/1] (one-hot)
hydrogens	5	umber of connected hydrogens [0,1,2,3,4] (one-hot)
chirality	1	whether the atom is chiral center [0/1] (one-hot)
chirality type	2	[R, S] (one-hot)
Bond Feature	**Size**	**Description**
bond type	4	[single, double, triple, aromatic] (one-hot)
conjugation	1	whether the bond is conjugated [0/1] (one-hot)
ring	1	whether the bond is in ring [0/1] (one-hot)
stereo	4	[StereoNone, StereoAny, StereoZ, StereoE] (one-hot)

Table S3. Parameters' settings of LightGBM based model for four tasks

	Learning rate	**N estimators**	**Num leaves**	**Max depth**	**Min child samples**
JAK1_MD	0.2	173	19	7	5
JAK2_MD	0.4	295	15	4	8
JAK3_MD	0.3	101	16	5	14
TYK2_MD	0.2	92	19	6	8
JAK1_ECFP4	0.2	376	18	5	10
JAK2_ECFP4	0.2	405	18	5	9
JAK3_ECFP4	0.5	95	12	4	7
TYK2_ECFP4	0.2	165	15	4	6

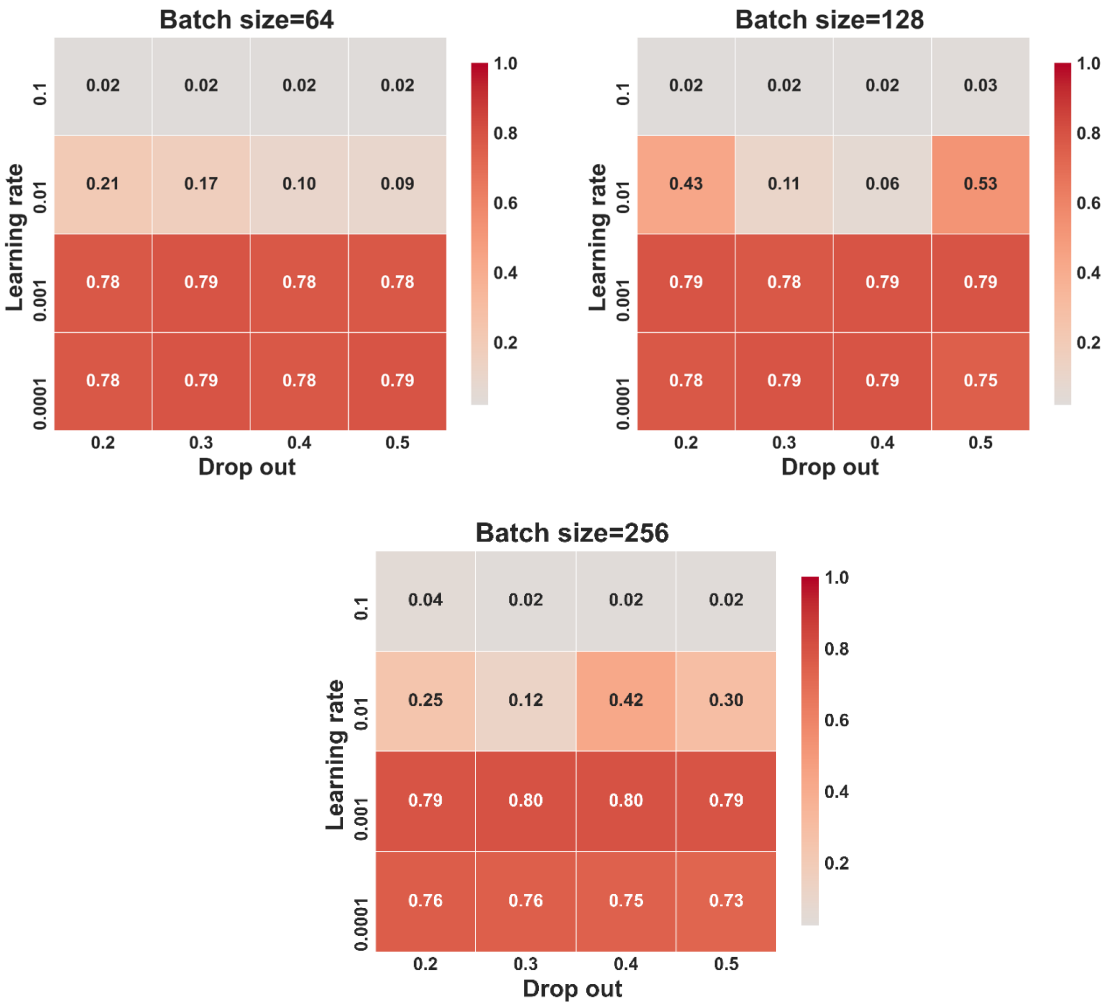


Figure S1. Heat map of optimal hyper-parameters search for a MTATFP model. Here, the default parameters were learning rate (0.1, 0.01, 0001 and 0.0001), drop out (0.2, 0.3, 0.4, 0.5), and search for parameters at different batch size (64, 128, 256) to determine the best ones. The darker the color is, the better the R^2 value of the validation set is.

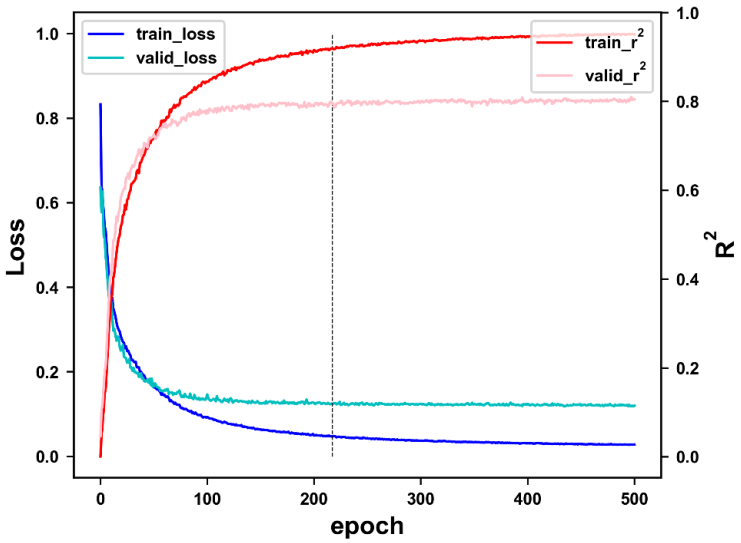


Figure S2. A curve graphs of Loss and R^2 during training process on multitask models. Early stopping criterion for training is that the R^2 on validation set is no longer improving in 20 epochs and get the best epoch 217 eventually.

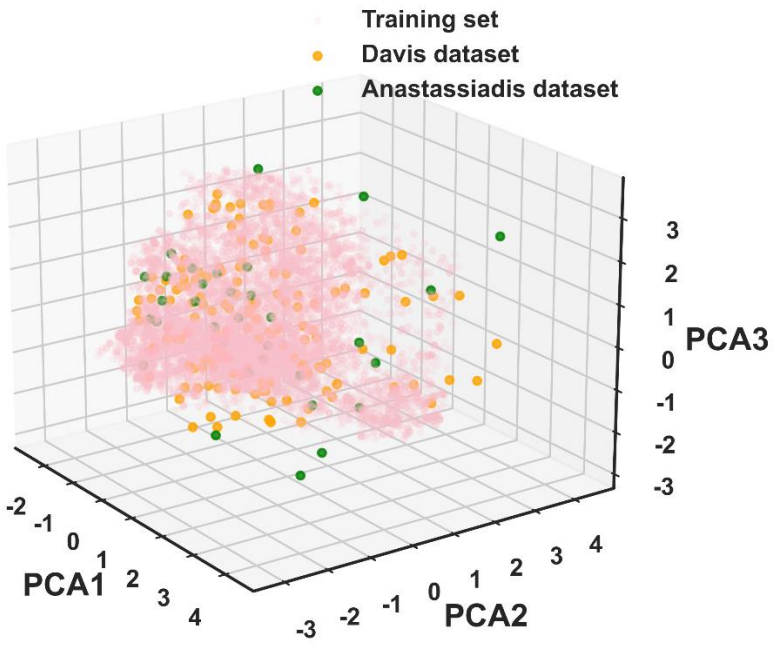


Figure S3. The chemical spatial distributions of the training, Davis and Anastassiadis dataset. It represented as the first three principal components of the PCA of the JAK small molecular inhibitors.

References

1. Landrum G, Tosco P, Kelley B (2020) rdkit/rdkit: 2020_03_1 (Q1 2020) Release 10

2. Xiong Z, Wang D, Liu X et al (2020) Pushing the boundaries of molecular representation for drug discovery with the graph attention mechanism. J Med Chem 63(16):8749-8760