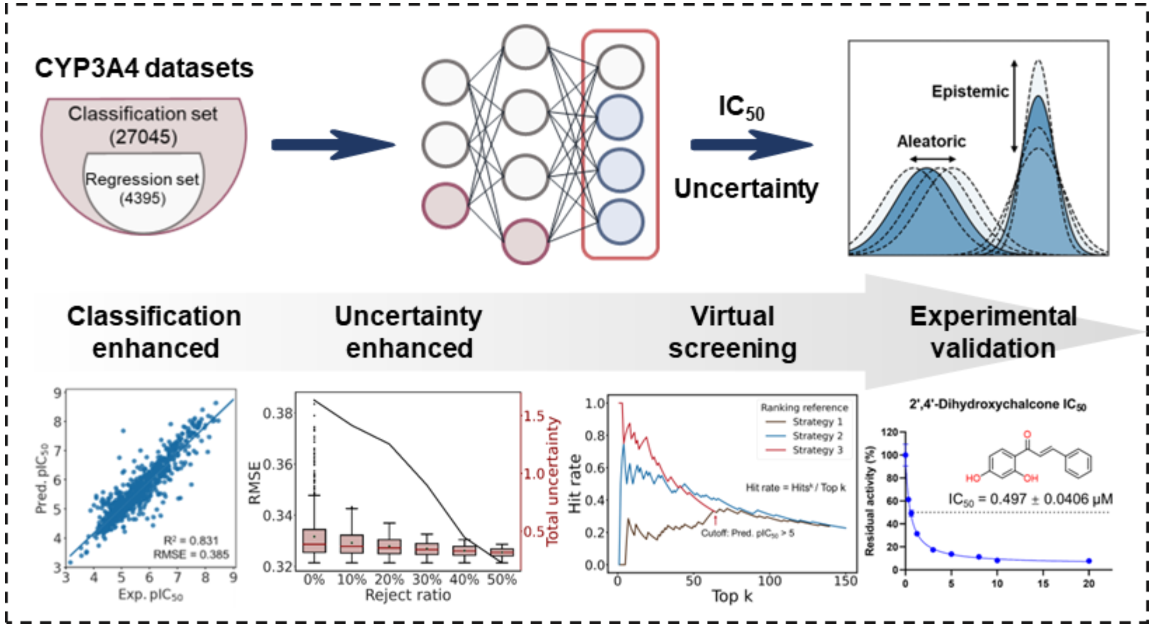
上海中醫藥大學
Shanghai University of Traditional Chinese Medicine

An uncertainty-guided deep learning method facilitates rapid screening of CYP3A4 inhibitors



王锐轩

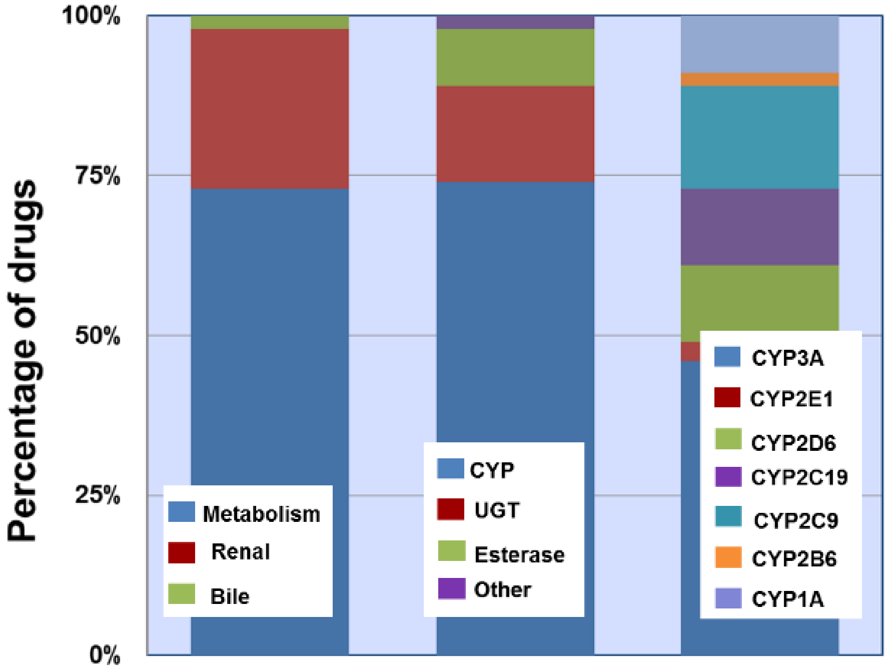
交叉科学研究院

2023.08.17

Contents

CYP3A4 & Drug Metabolism

CYP3A4 & Xenobiotic Metabolism

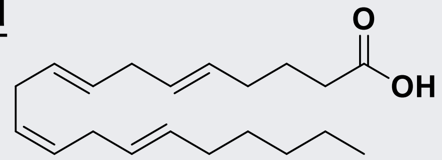


Routes of elimination of the top 200 most prescribed drugs in the United States (2002)

CYP3A4 & Endogenous Metabolism

- Cholesterol
- Cortisol
- Steroids
- vitamin D metabolites

Arachidonic acid



Inflammation ↑

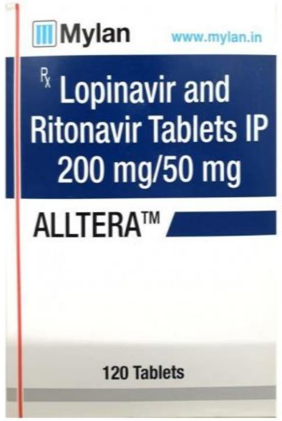
in vitro proliferation of cancer cells ↑

Drug Metab. Rev. 2010, 42: 202. & *Mol. Carcinog.* 2000, 29: 198-204.

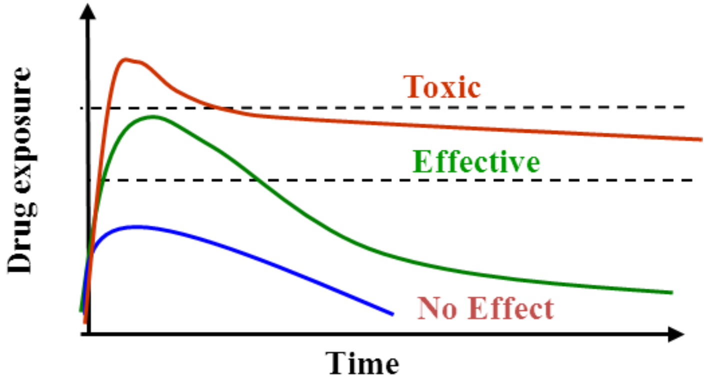
CYP3A4 & Drug-drug interactions

Inhibition of CYP3A4

+



→ **Efficacy ↑ Toxic ↓**



→ **Toxic, side effects ↑**

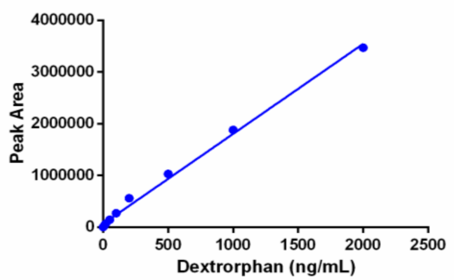
Drug Metab. Rev. 2010, 42: 202. & ***J. Biol. Chem.*** 2011, 20; 286:17543-59. & ***Cancer Res.*** 2015, 75:1470-81.

J. Biol. Chem. 2011, 20; 286:17543-59. & ***Cancer Res.*** 2015, 75:1470-81.

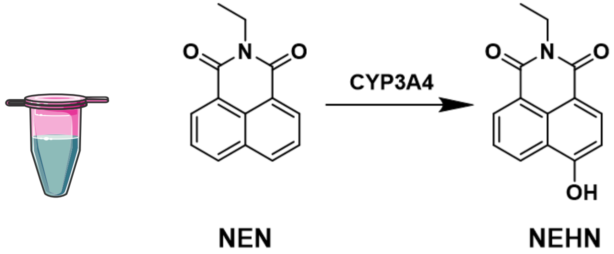
Screening methods of CYP3A4 inhibitors

1. Experimental methods

- LC-MS/MS methods

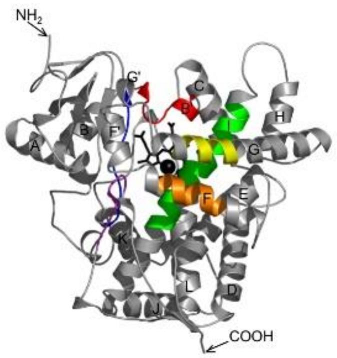


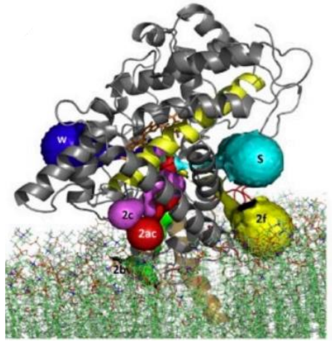
- Fluorescence enzyme-linked immunosorbent assay (ELISA) high-throughput screening



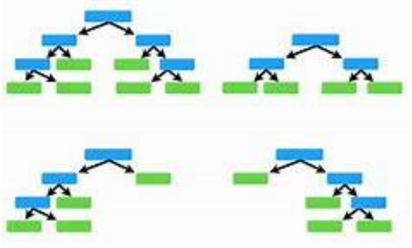
2. Virtual screening strategies

- Docking
- Molecular dynamics simulation



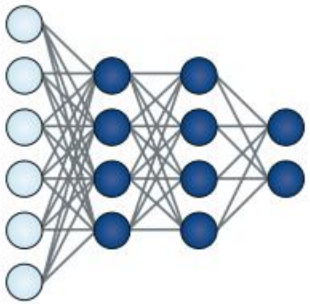


- Machine learning



Random Forest

- Deep learning

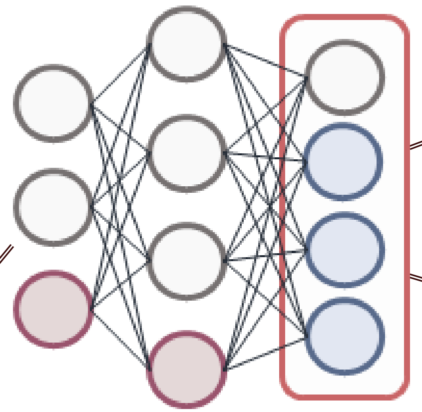


Overview of CYP3A4 inhibitor prediction model

Data source:
ChEMBL，PubChem...

Model input:

Molecular representation



Model

CypRules, SuperCYPsPred, iCYP-MFE,

Interpretable-ADMET, FP-ADMET, ADMET lab...

Downstream task type

Classification model (cutoff IC_{50}= 10 μM)

Evaluation metrics: AUC(0.7~0.9) 、ACC...

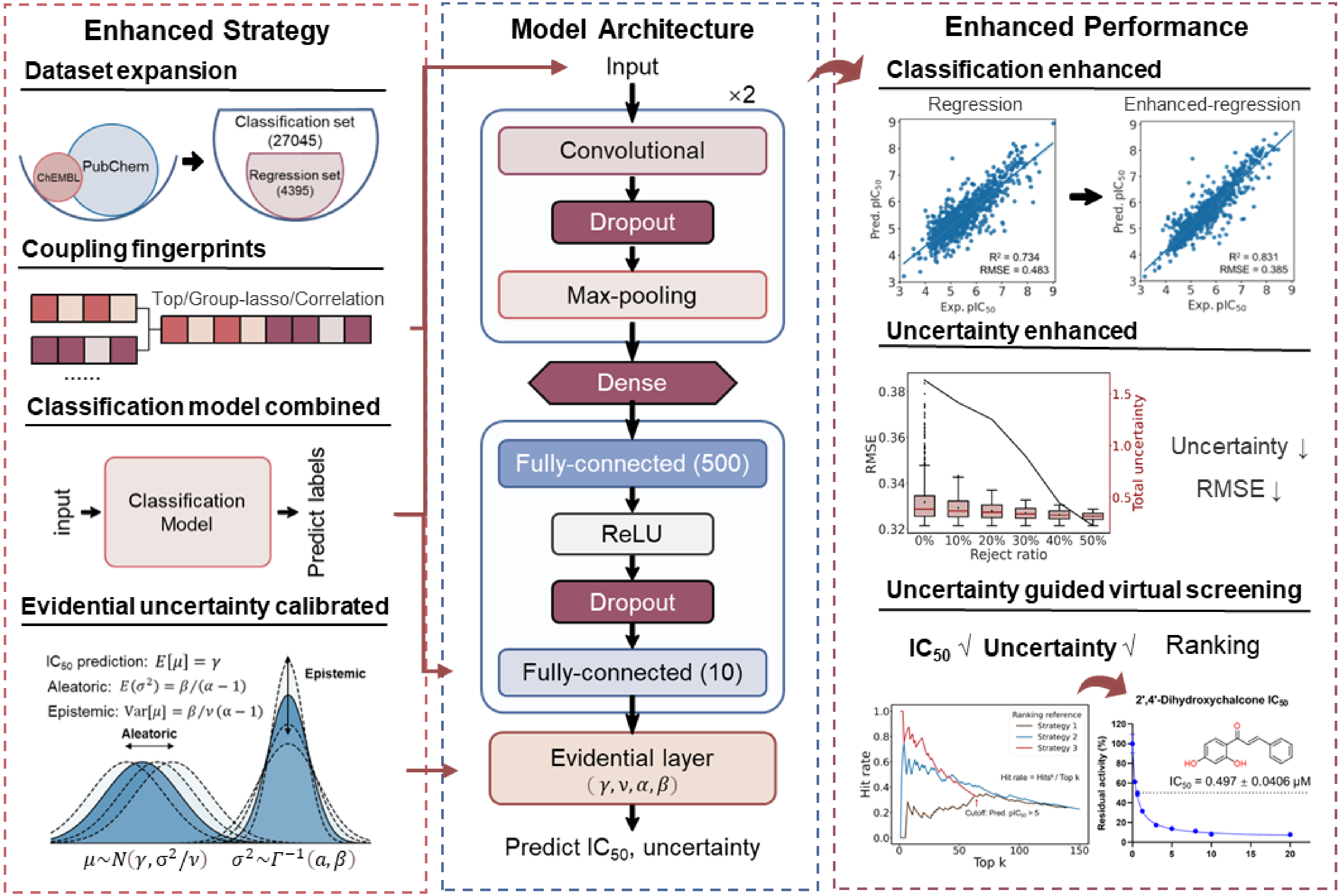
Our strategy:

1. **Build a regression model to predict specific inhibition values(IC_{50}).** The performance of regression model is significantly improved by incorporating classification results trained on larger datasets.

2. Introduce evidence-based uncertainty estimation. Our model could accurately characterize the correlation between uncertainty and prediction errors, and provide confidence in the accuracy of predictions.

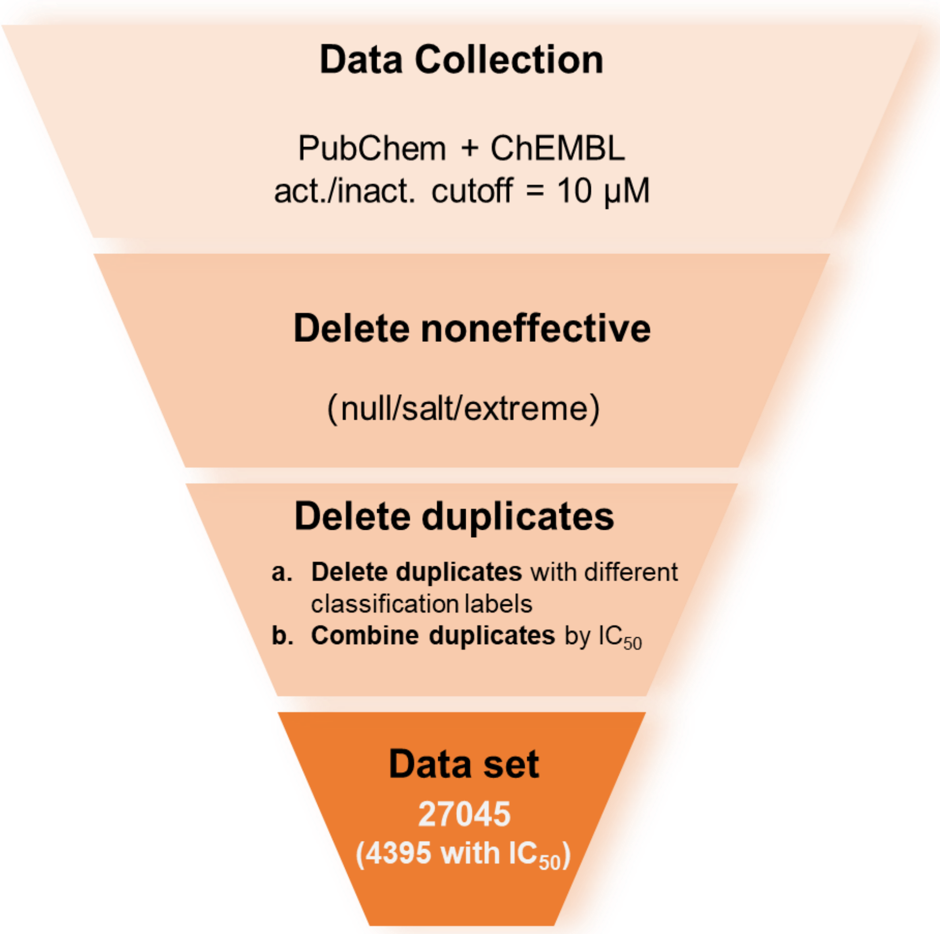
3. Apply our model in virtual screening and in vitro experiments.

Overall pipeline



Results Dataset collection & curation

Dataset curation pipeline:



Details of regression label (IC_{50}) combination :

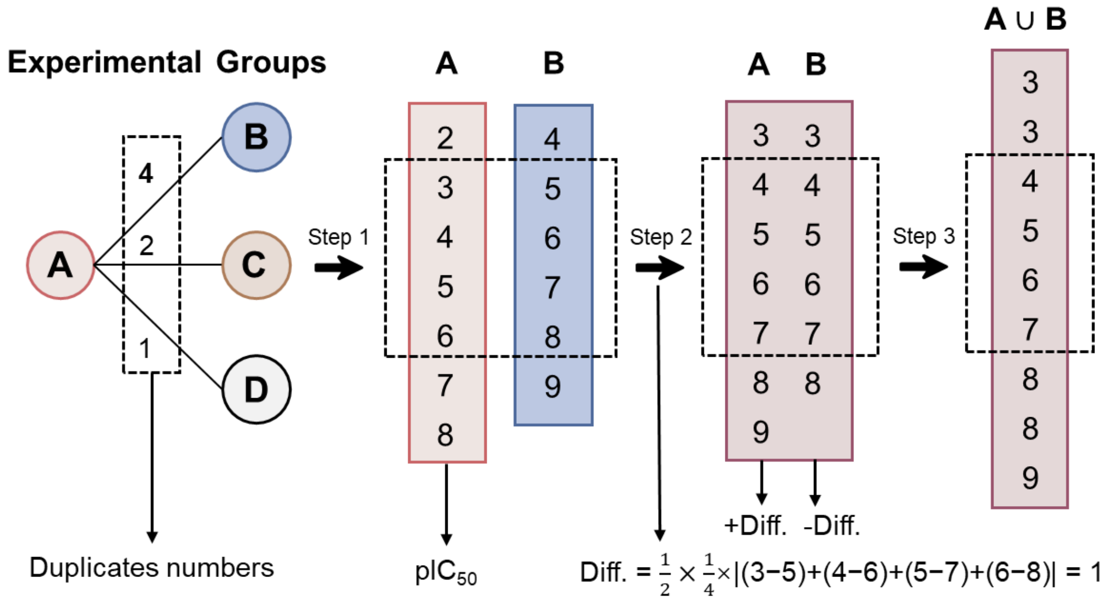


Table 1. Data splitting for model development and evaluation

Dataset	Data class	Training	Validation	Test	Total
Classification	noninhibitor	9196	3066	3065	15327
	inhibitor	7031	2344	2343	11718
	total	16227	5410	5408	27045
Regression	—	2812	703	880	4395

Results Regression model construction

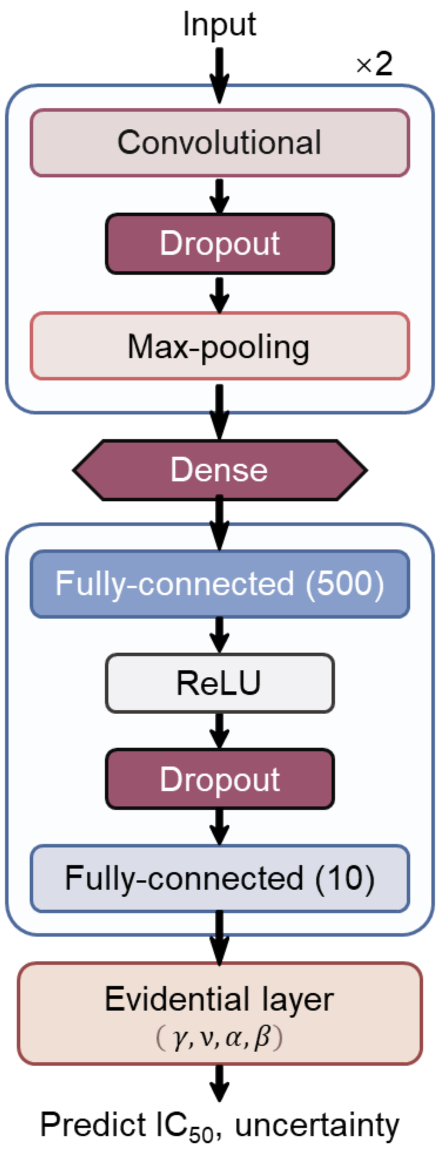


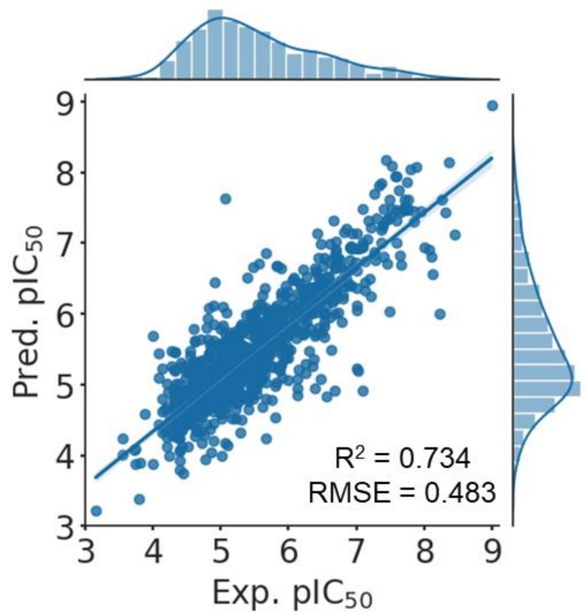
Table 3. Performance of regression models trained on **Coupling fingerprints**

Splicing Mode*	RMSE	R	R^2	Epistemic	Aleatoric	Total
TOP	**0.483**	**0.858**	**0.734**	**0.337**	**0.279**	**0.616**
GL	0.711	0.655	0.428	0.526	0.486	1.012
PCC	0.712	0.657	0.427	0.677	0.569	1.246

Table 2. Performance of regression models trained on **15 individual fingerprints**

Fingerprints	RMSE	R	R^2
FCFP4[a]	**0.607**	**0.762**	**0.567**
Morgan[a]	**0.618**	**0.756**	**0.554**
ECFP6[b]	0.627	0.747	0.534
PubChem	0.650	0.740	0.510
ExtFP[c]	0.654	0.727	0.493
Avalon	0.667	0.753	0.473
FP[b,c]	0.673	0.695	0.475
RDKit	0.674	0.719	0.472
GraphFP	0.678	0.724	0.467
MACCS	0.685	0.715	0.444
SubFPC	0.709	0.653	0.406
AP2D	0.720	0.674	0.392
SubFP	0.720	0.669	0.393
APC	0.732	0.645	0.378
EStateFP	0.781	0.592	0.291

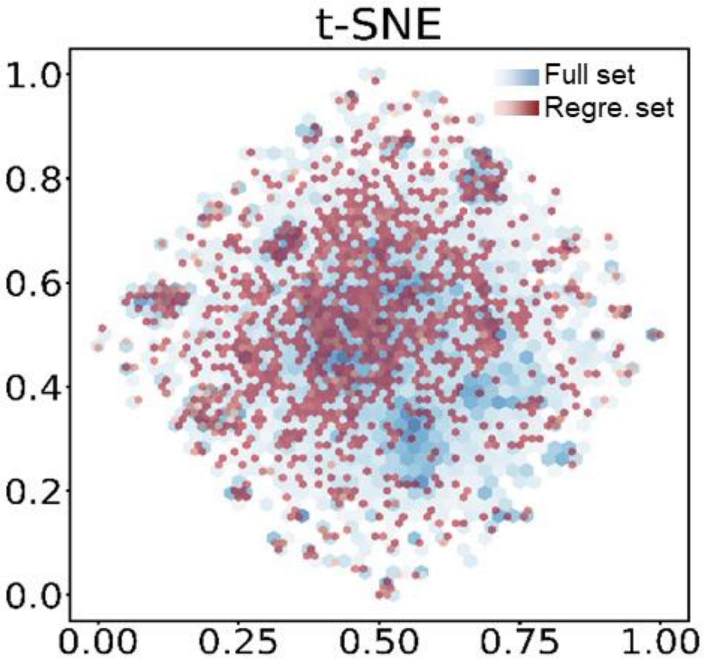
Performance of **TOP**

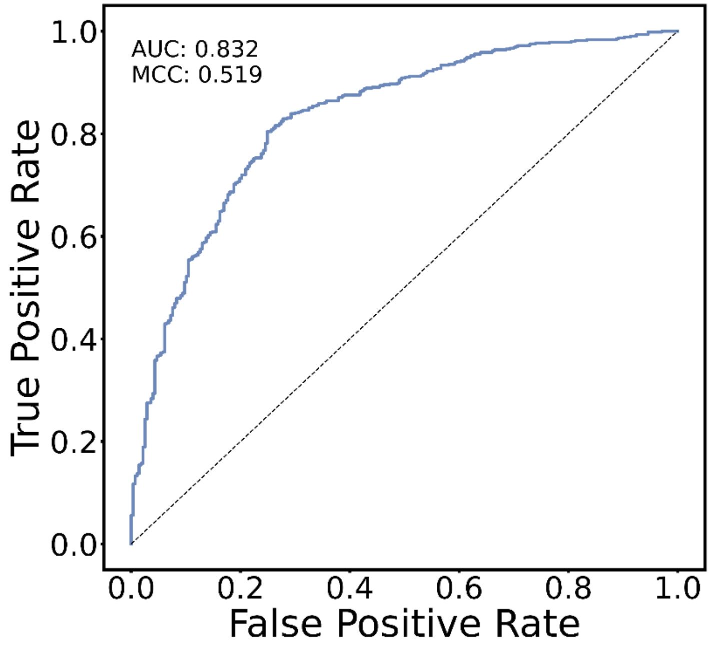


Results Classification-enhanced regression model

Table 4. Performance of the classification and the regression model on the regression independent test set of 880 samples

Model	AUC	ACC	PR	RE	SP	MCC	F1	BACC
Classification	0.832	0.794	0.845	0.857	0.657	0.519	0.851	0.757
Regression[a]	—	0.547	0.664	0.685	0.245	-0.071	0.674	0.465





Results　Classification-enhanced regression model

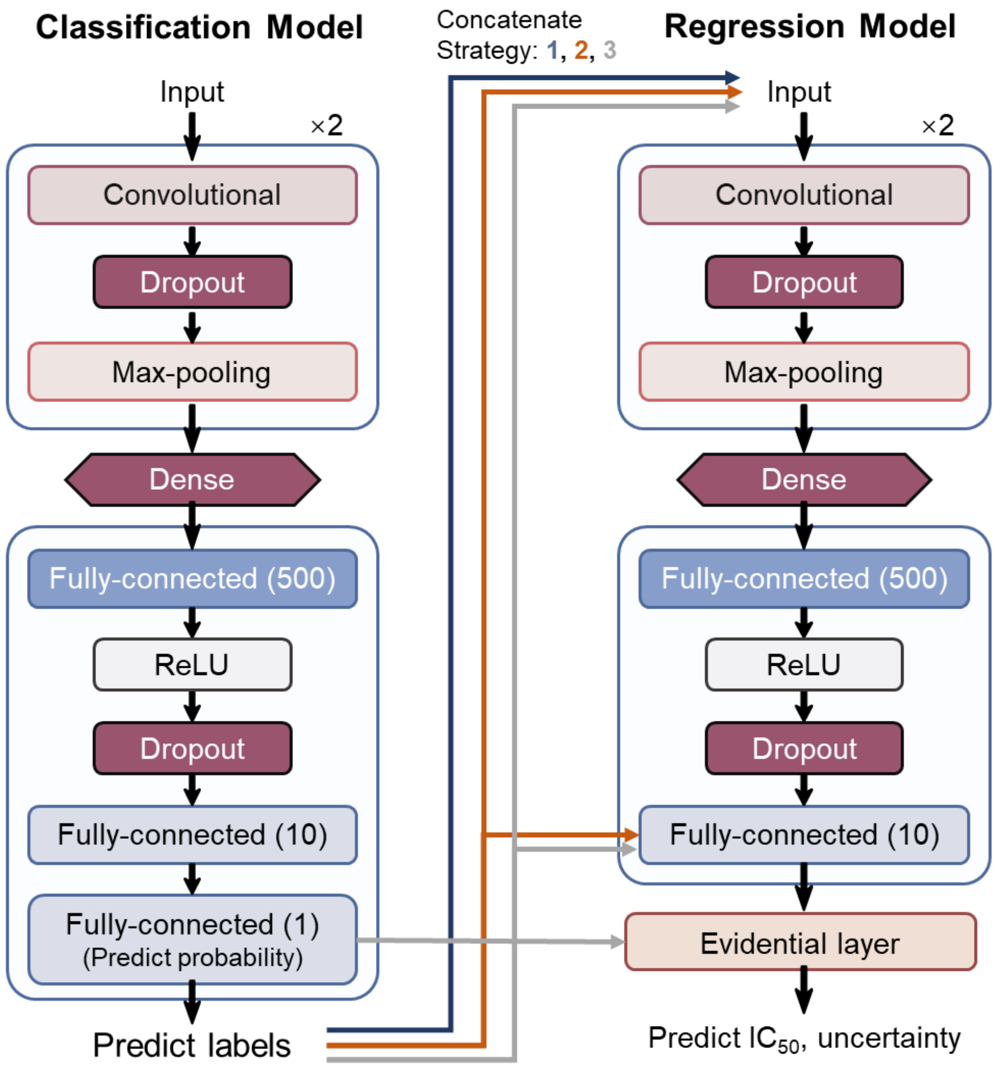
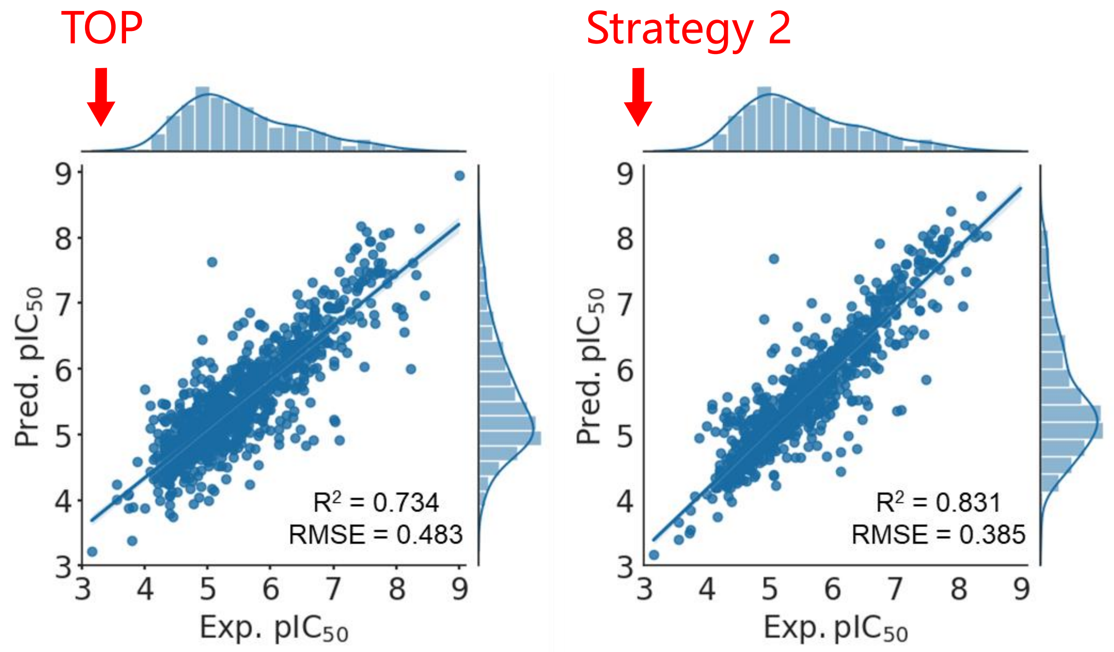


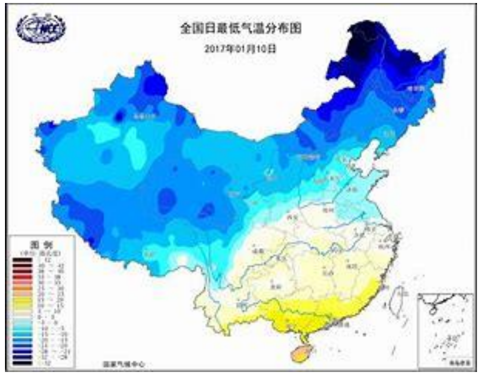
Table 5. The corresponding results of the three concatenating strategies of the classification model and regression model

Concatenate Strategy	RMSE	R	R^2	Epistemic	Aleatoric	Total
TOP	0.483	0.858	0.734	0.337	0.279	0.616
Strategy 1	0.459	0.877	0.759	0.347	0.294	0.641
Strategy 2	**0.385**	**0.916**	**0.831**	**0.234**	**0.219**	**0.453**
Strategy 3	0.476	0.872	0.742	0.368	0.303	0.670

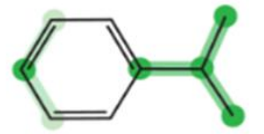


Introduction of uncertainty

UQ methods	Representative methods
Bayesian approximation	Monte Carlo dropout
	Markov Chain Monte Carlo
	Variational inference
	Bayes By Backprop
	Gaussian Approximation
Ensemble	Deep Ensembles
	Gradient Boosting
	Bagging
Conformal prediction	Inductive Conformal Prediction
	Transductive Conformal Prediction
Evidence-based	Deep Evidential Regression



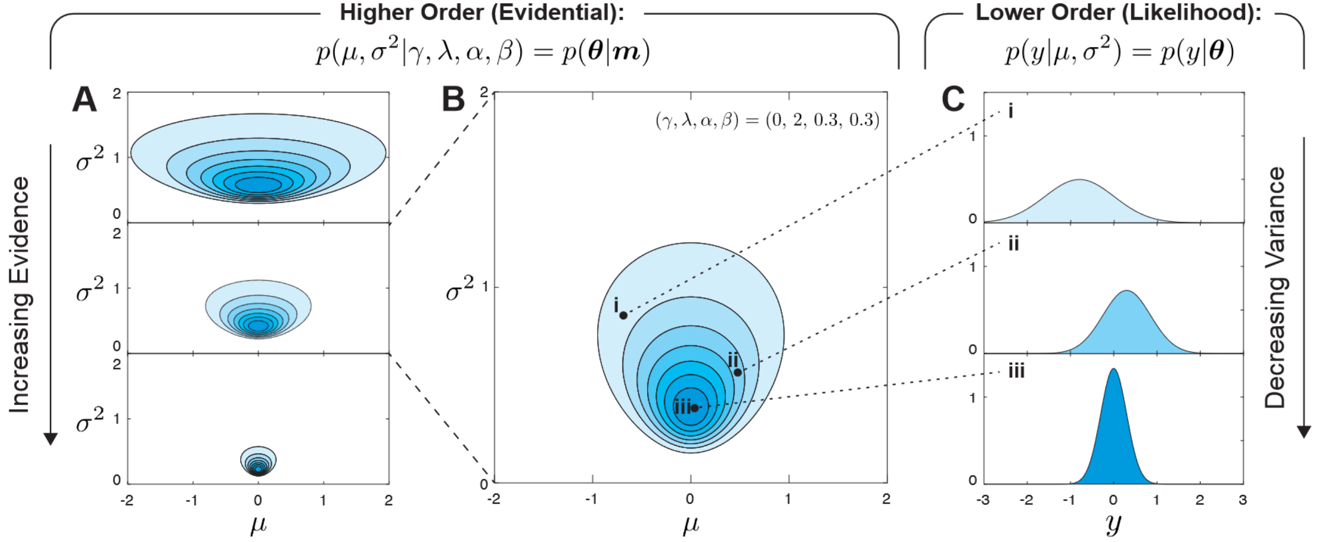
Property prediction

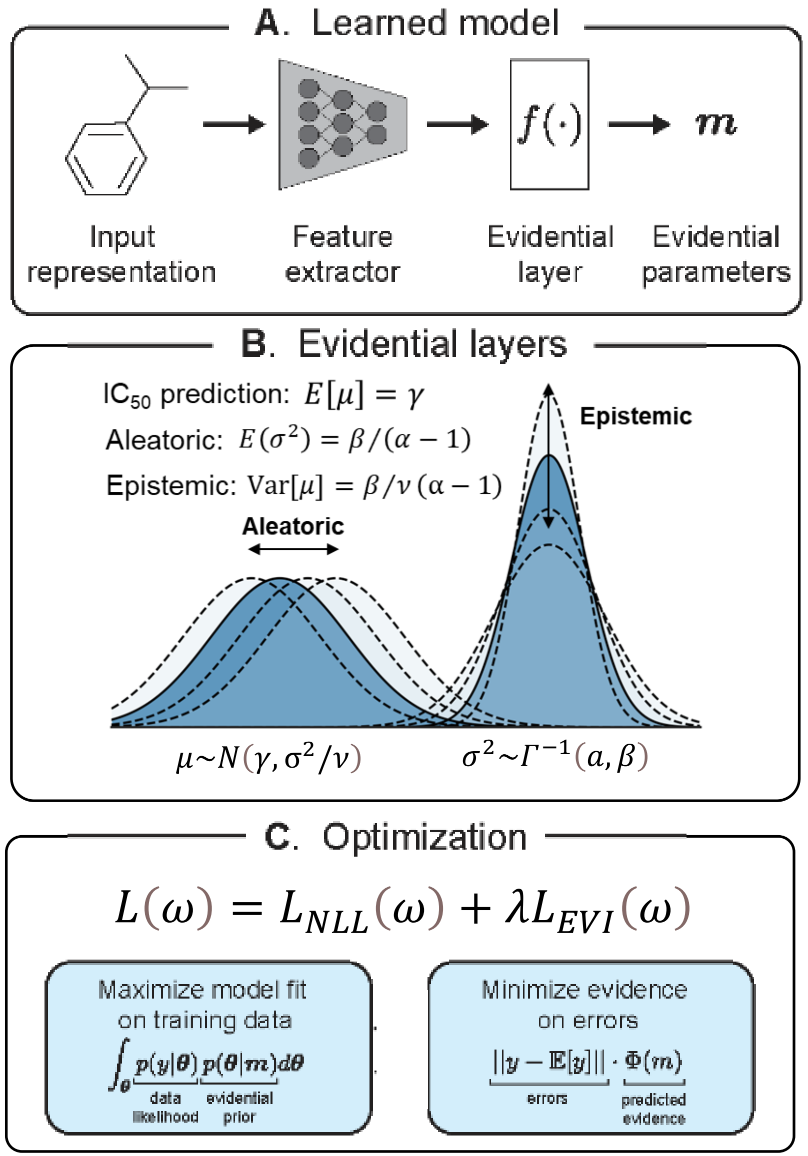


to be explored...

Evidence-based uncertainty estimation

“non-Bayesian model”， “without sampling”



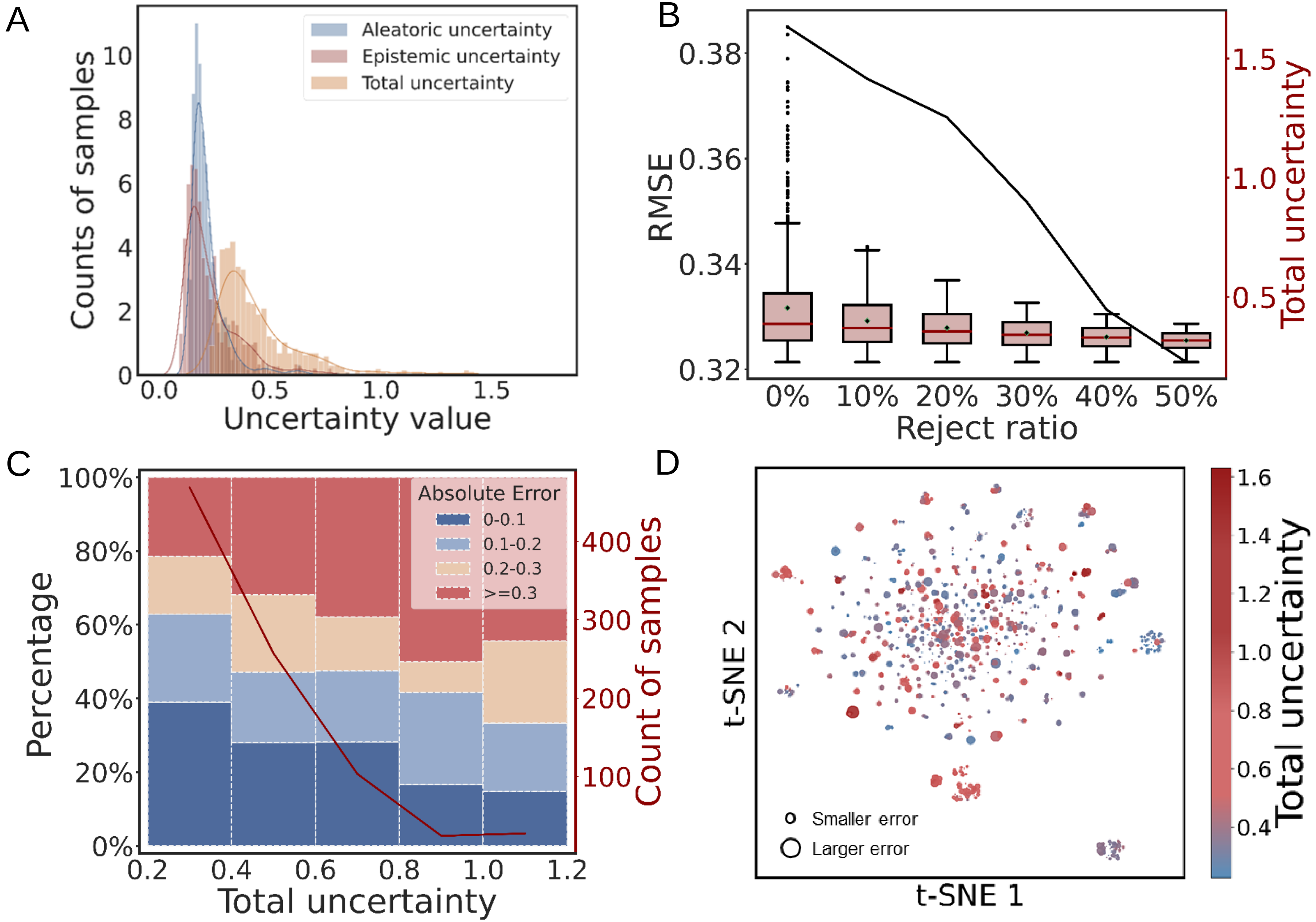


Normal Inverse-Gamma (NIG) distribution:

$$p(\underbrace{\mu,\sigma^2}_{\boldsymbol{\theta}} \,|\, \underbrace{\gamma,\upsilon,\alpha,\beta}_{\boldsymbol{m}}) = \frac{\beta^\alpha\sqrt{\upsilon}}{\Gamma(\alpha)\sqrt{2\pi\sigma^2}}\left(\frac{1}{\sigma^2}\right)^{\alpha+1}\exp\left\{-\frac{2\beta+\upsilon(\gamma-\mu)^2}{2\sigma^2}\right\}.$$

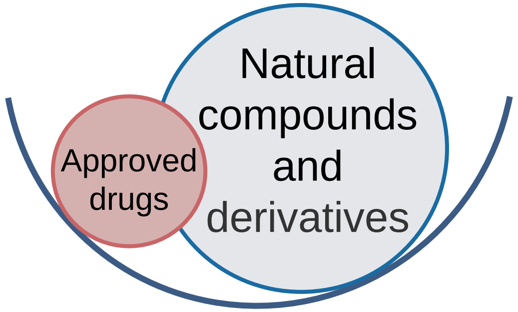
ACS Cent. Sci. 2021, 7, 1356−1367;
34th Conference on Neural Information Processing Systems (NeurIPS 2020), Vancouver, Canada.

Results Uncertainty-enhanced regression model

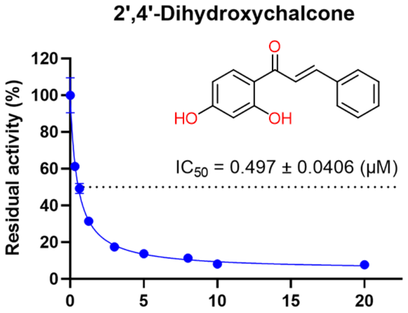


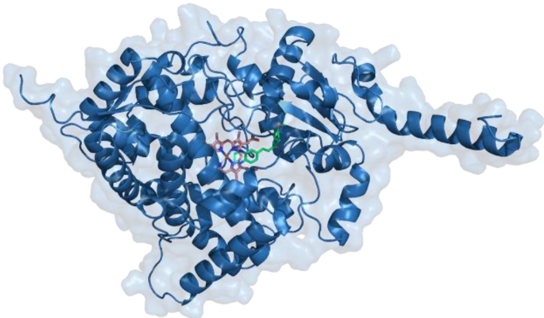
Results Uncertainty-guided virtual screening

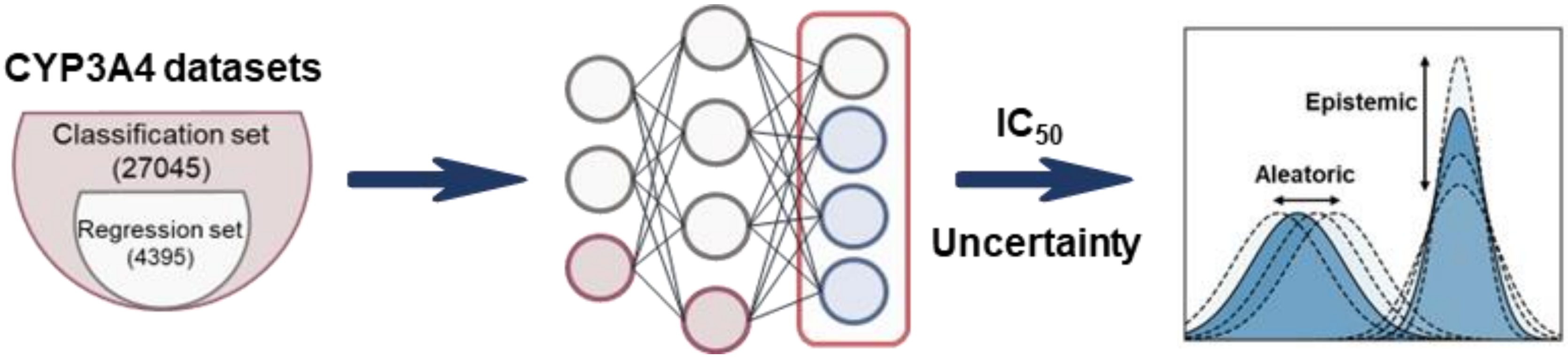
Uncertainty-guided virtual screening pipeline



150 compounds







Results Uncertainty-guided virtual screening

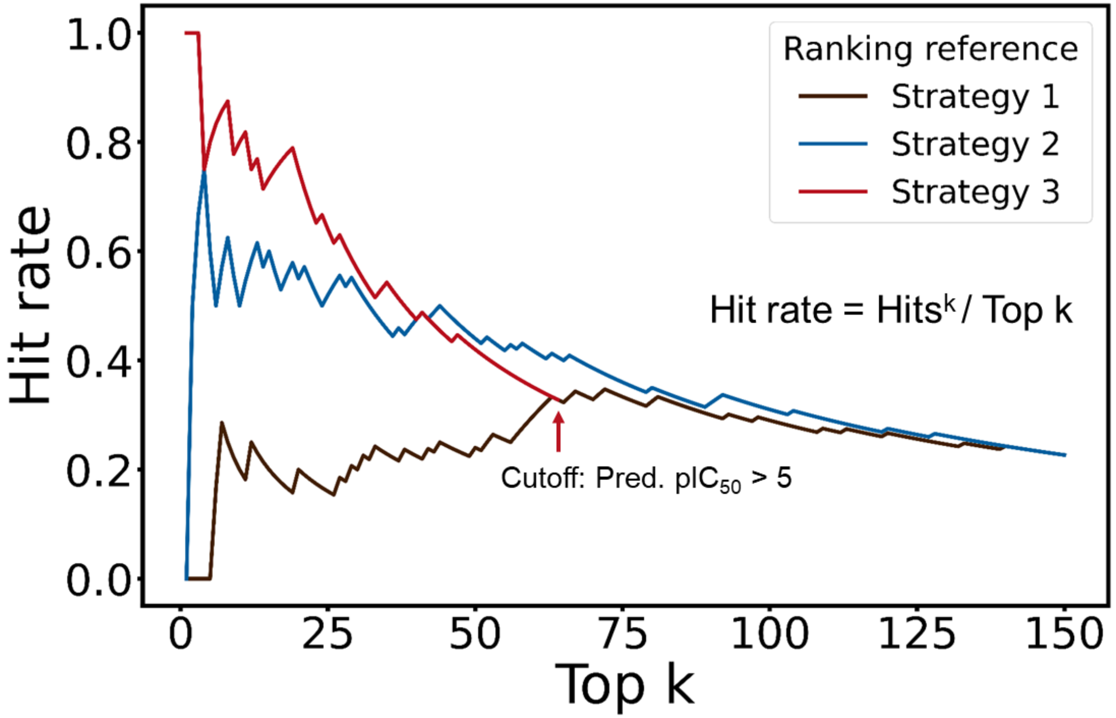


Table 6. Hit rates and RMSEs of the top-ranking predictions by Strategy 3

Top k	Hit number	Hit rate	RMSE
top 10	**8**	**0.800**	**0.538**
top 20	15	0.750	0.667
top 30	17	0.567	0.733

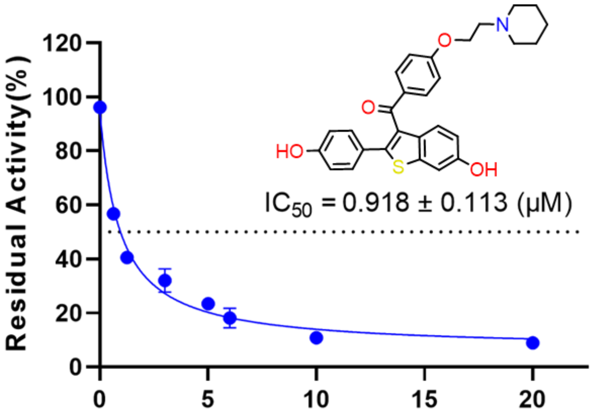
Strategy 1: ranking by predictive pIC50 values;

Strategy 2: ranking by total uncertainty values;

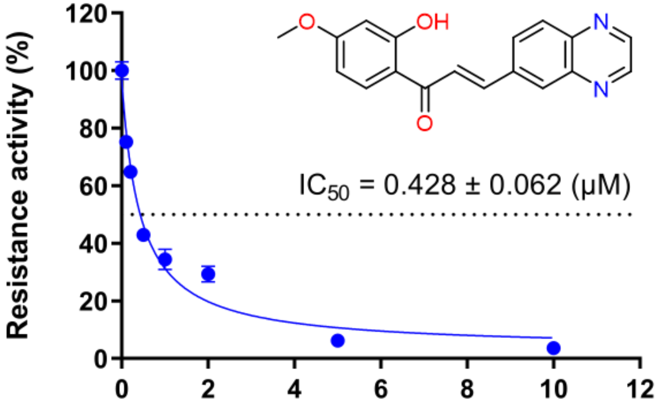
Strategy 3: ranking data with predictive pIC_{50} > 5 by total uncertainty values.

Results Experimental validation

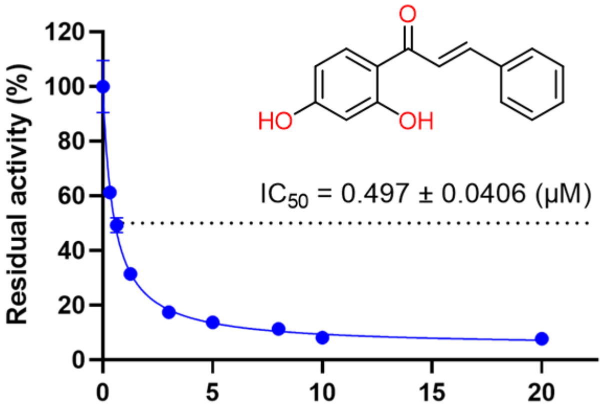
Raloxifene



4'-Methoxy-2'-hydroxy quinoxaline-chalcone



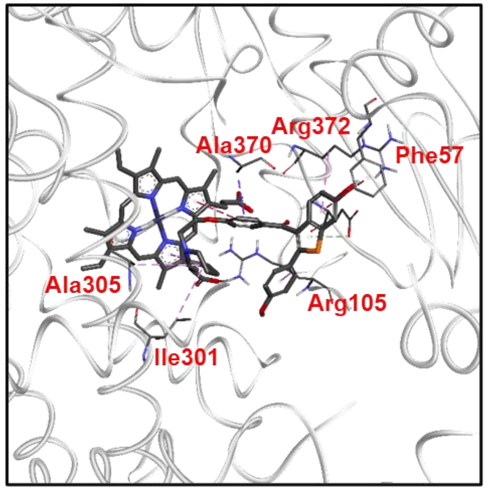
2',4'-Dihydroxychalcone

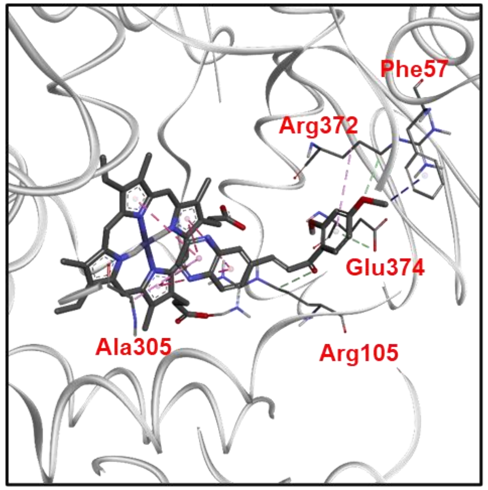


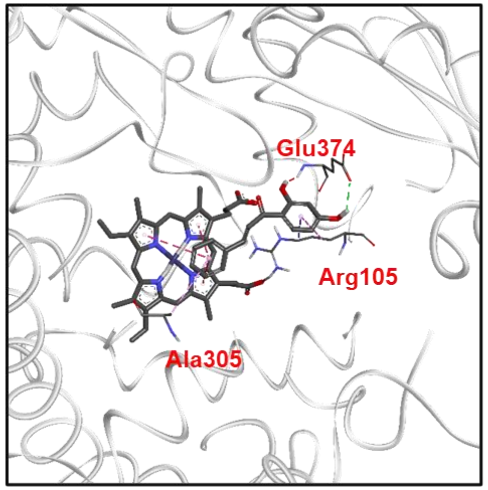
Ranking：1 (uq = 0.266)

Ranking：7 (uq = 0.311)

Ranking：17 (uq = 0.346)







Docking score：-9.608 kcal/mol

Docking score：-8.369 kcal/mol

Docking score：-7.715 kcal/mol

Conclusion

1. We demonstrate that the performance of our **regression model** based on relatively small datasets can be significantly improved **by incorporating classification results** trained on larger datasets.

2. By introducing **evidence-based uncertainty estimation**, our model could accurately characterize the correlation between uncertainty and prediction errors, and provide confidence in the accuracy of predictions.

3. Applying our model in **virtual screening** of an in-house compound set and ***in vitro* experiments**, we showcased how evidential uncertainties significantly enhanced hit ratio and reduced false positives among the top-ranked compounds.

Perspective

- Using more advanced models, such as graph neural networks or language learning neural networks.
- Evaluating the effectiveness of other uncertainty estimation methods in virtual screening .
- Performing virtual screening and experimental validation on a larger and more diverse dataset.

Q&A

汇报人：王锐轩

2023.8.17