XXXII Symposium on Bioinformatics and Computer-Aided Drug Discovery (BCADD-2026)

Explainable Ai Guides Lead Optimization Of Human DHFR Inhibitors Using A PubChem Fingerprint-based QSAR Model

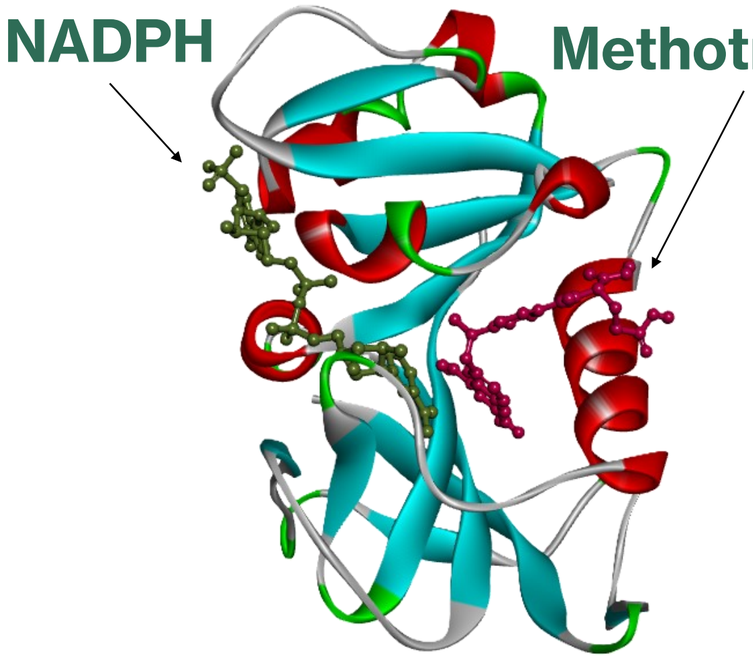
Ibrahim Maattallaoui[1] and Noureddine El Aouad[1]

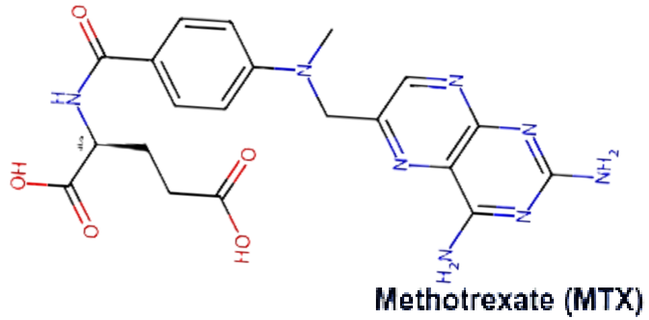
[1]Laboratory of Life and Health Sciences, Faculty of medicine and Pharmacy of tangier, road of rabat 15km Gzenaya BP 365 Tanger, Abdelmalek Essaadi University, Tetouan 92000, Morocco;

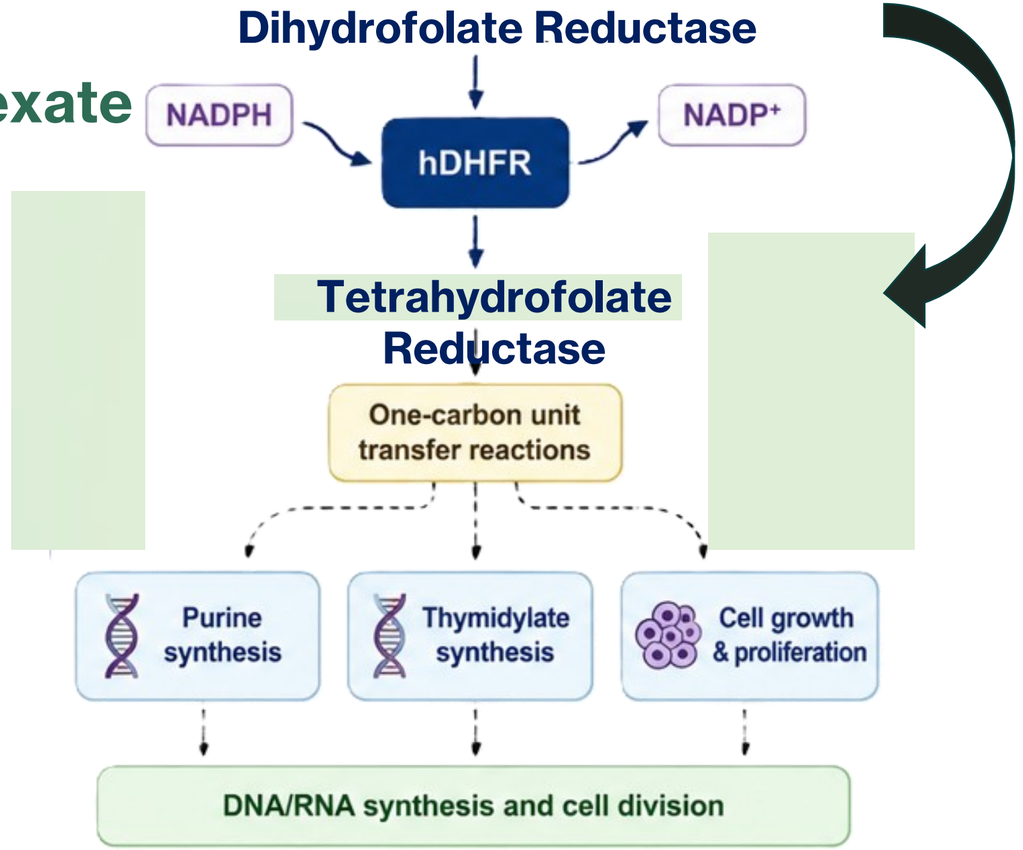
Presented by
Ibrahim Maattallaoui

Why hDHFR?

Human Dihydrofolate Reductase (hDHFR)

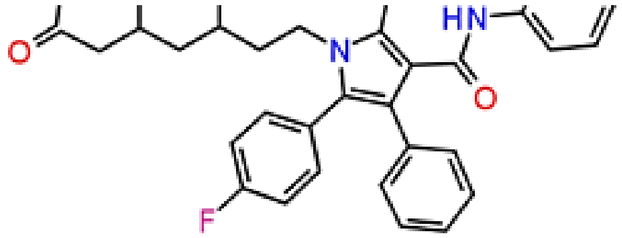


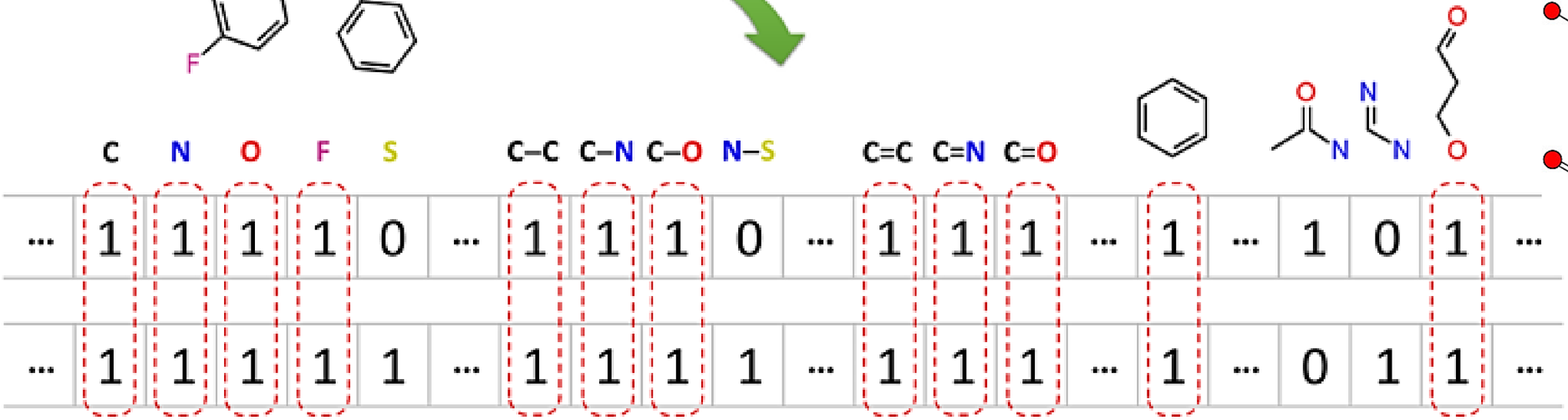


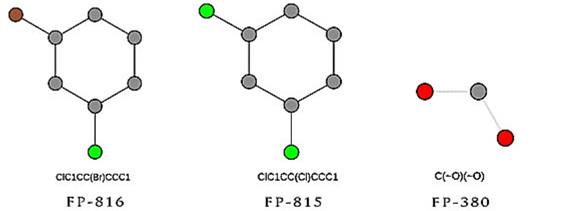


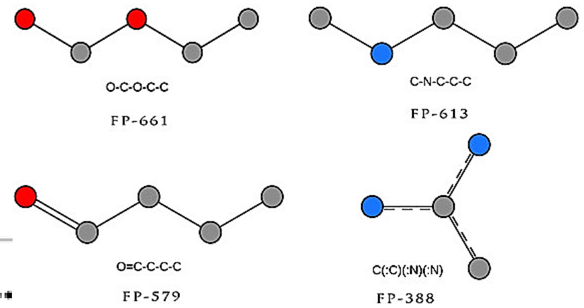
1. **Toxicity**
2. **Emergence of resistance**
3. **Suboptimal pharmacokinetics**

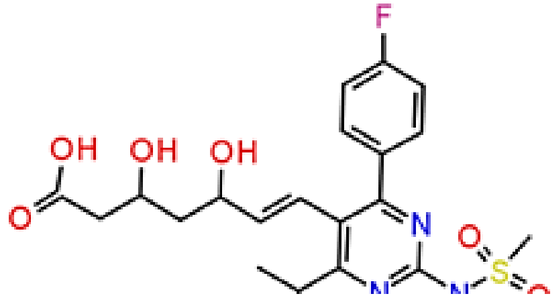
PubChem Fingerprints









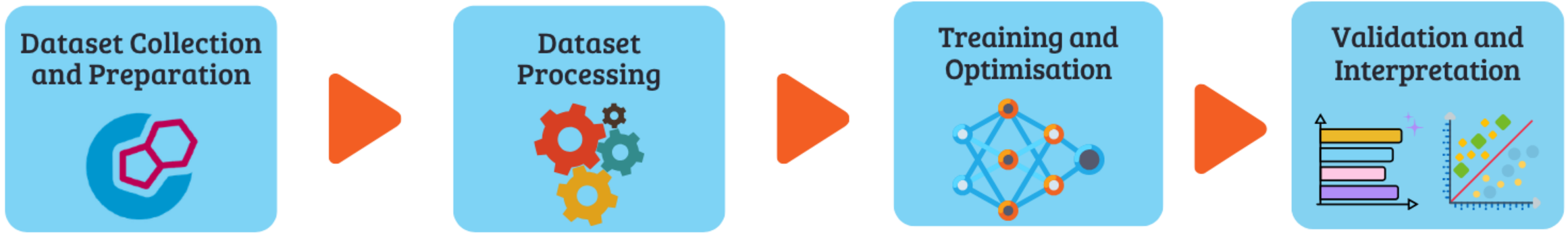


Our previous work

Open Access Article

Development of QSAR Models and Web Applications for Predicting hDHFR Inhibitor Bioactivity Using Machine Learning

by Ibrahim Maattallaoui [1], Mahamadou Sakho [1], Abdellah Maatallaoui [2], Enrique Barrajón-Catalán [3,*] and Noureddine El Aouad [1,*]

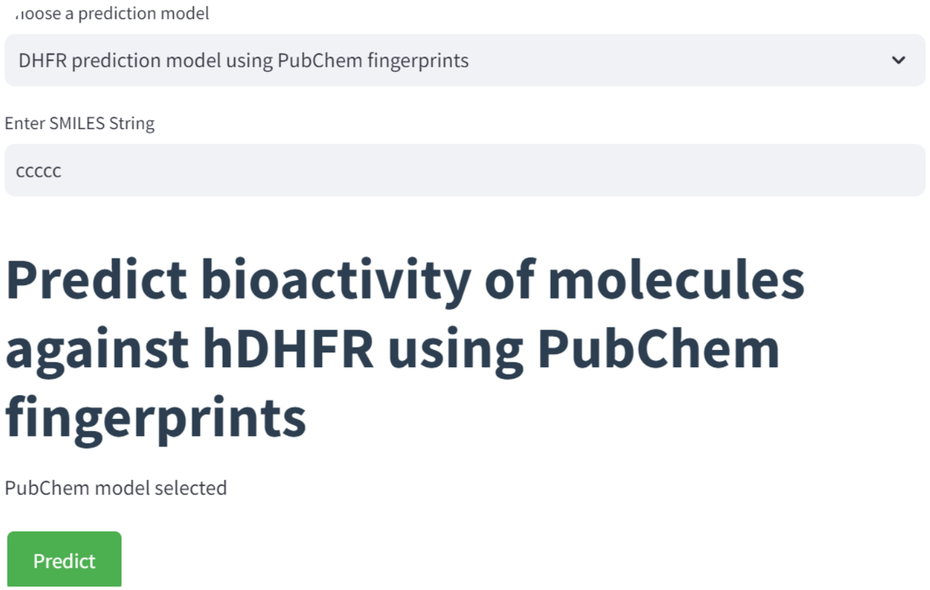


Prediction

Which molecular features are responsible for this prediction?

From Prediction to Explanation

Random Forest Predicted pIC_{50}



Explainable AI

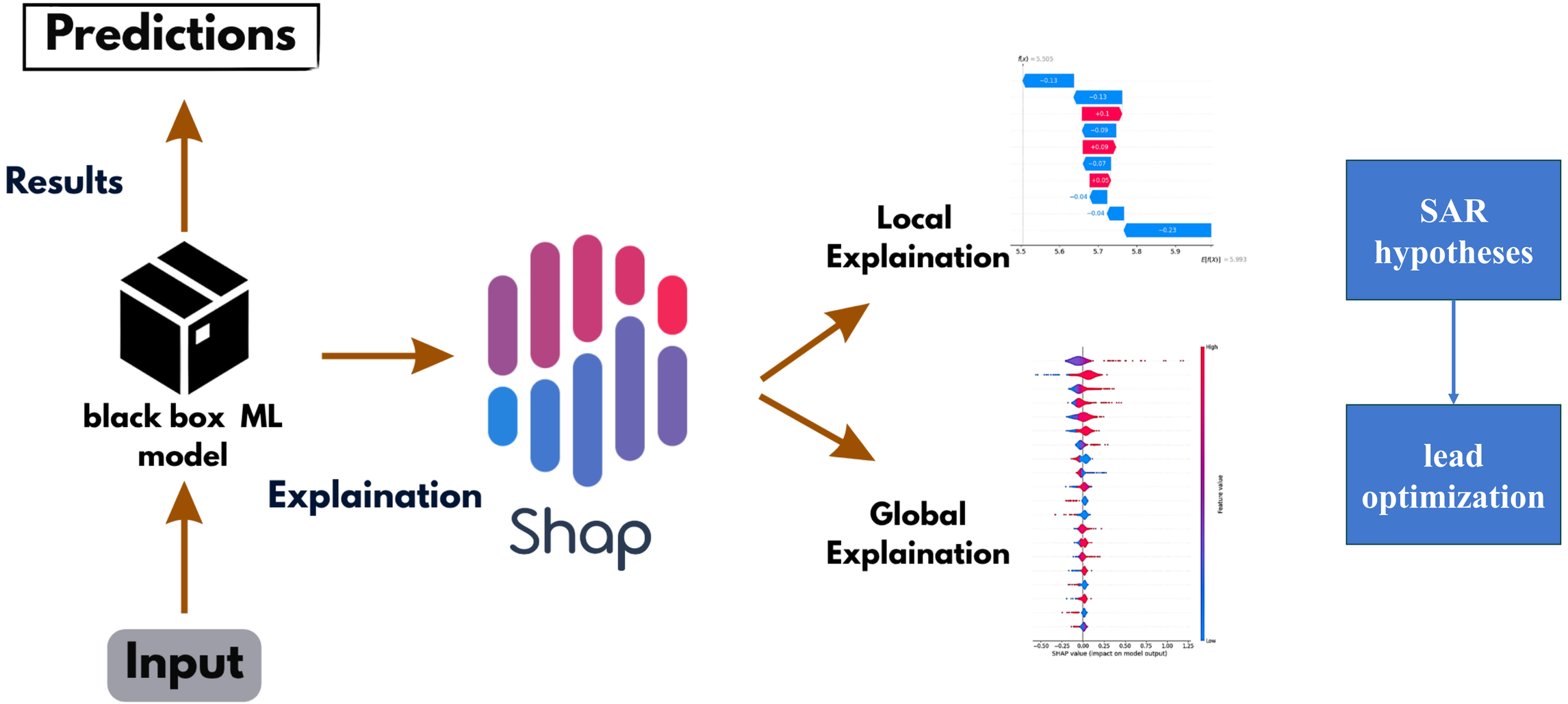
Which features?

Positive or negative?

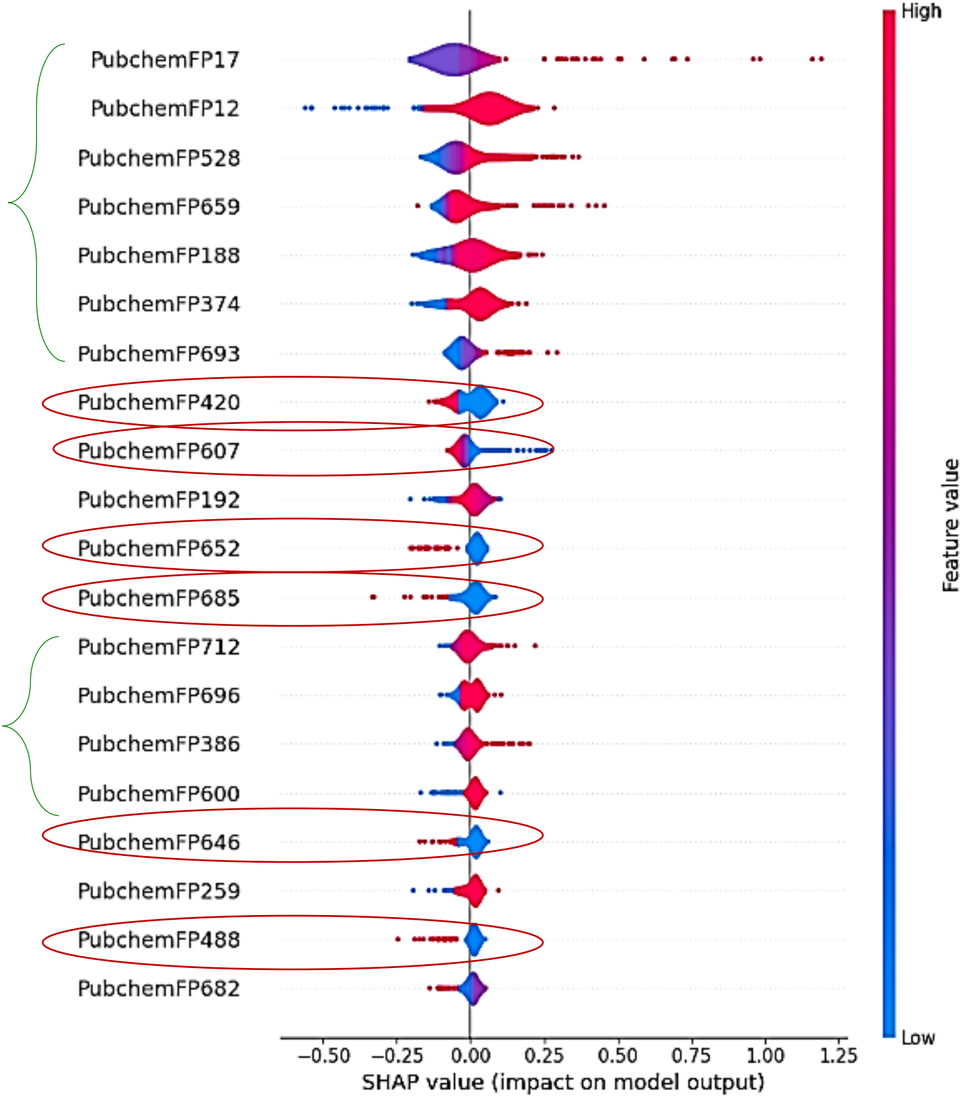
SAR hypothesis

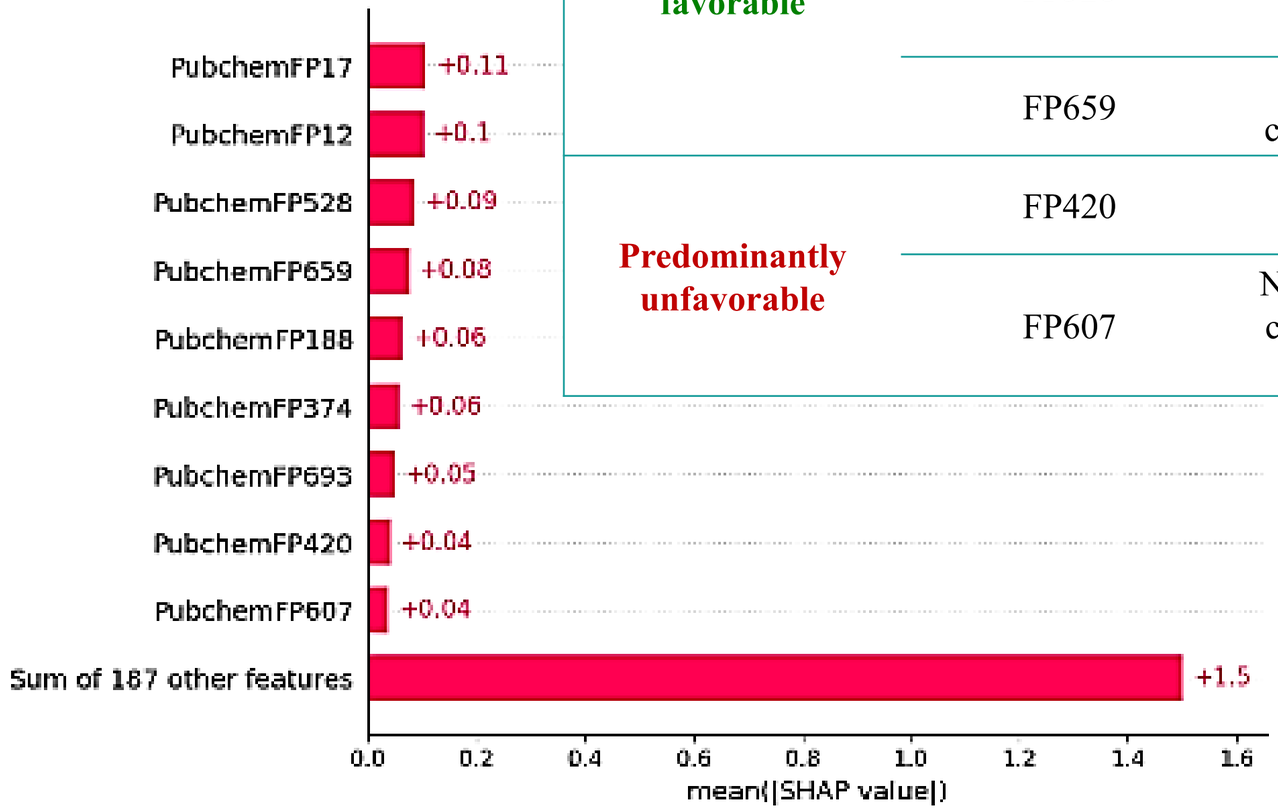
Objective: Identify and interpret the molecular features driving hDHFR activity predictions using SHAP.

SHAP Analysis



Global SHAP results



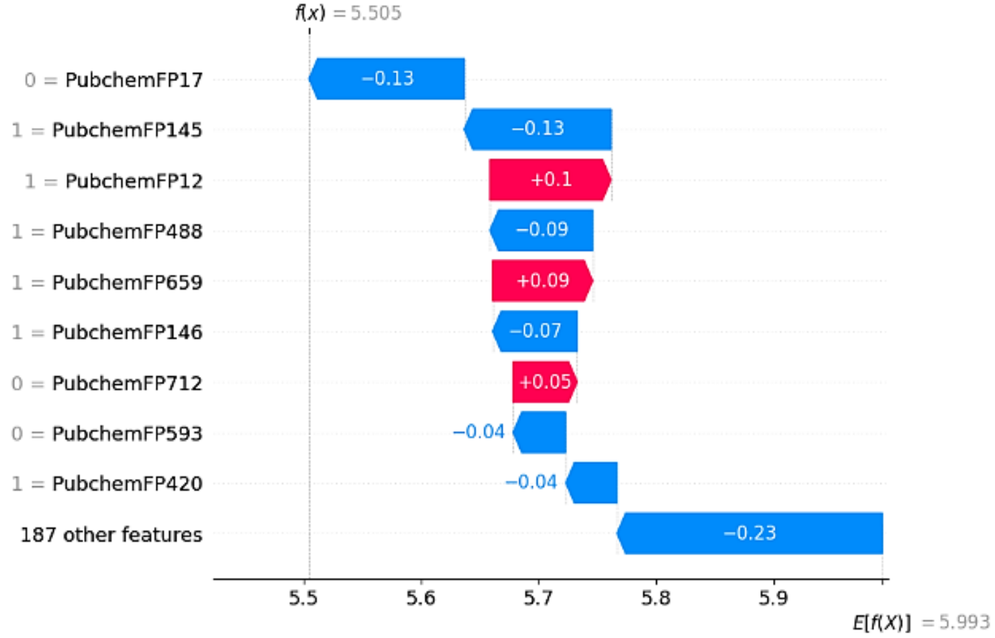


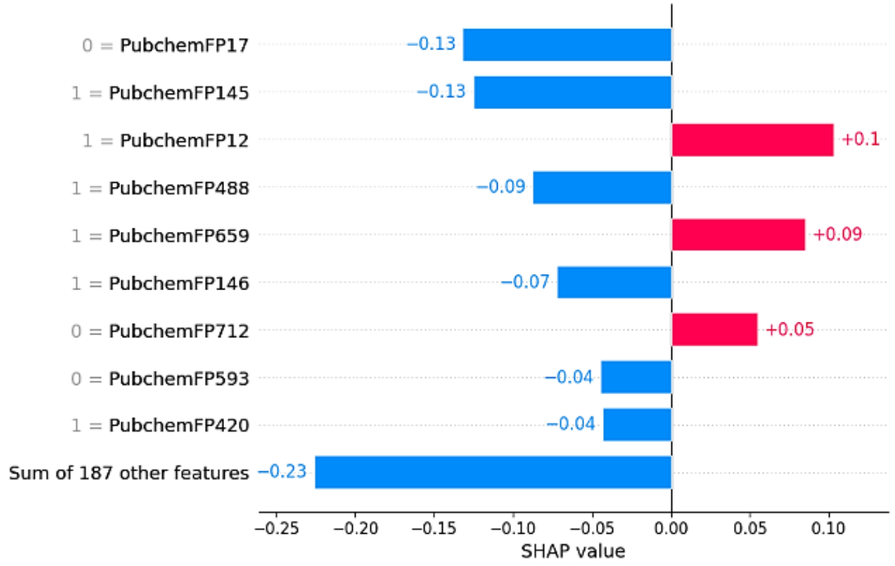
Contribution	PubChem Fingerprint	Interpretation
Predominantly favorable	FP17	≥8 nitrogen atoms
	FP12	≥16 carbon atoms
	FP528	[#1]-N-C-[#1] — N–C–H_2 environment
	FP659	O–C–C–N–C connectivity pattern
Predominantly unfavorable	FP420	Carbonyl-related descriptor (C=O)
	FP607	N–C–C–C–aromatic carbon connectivity pattern

Local SHAP results

Negative contributions

- absence of FP17
- FP145
- FP488
- FP146
- FP593





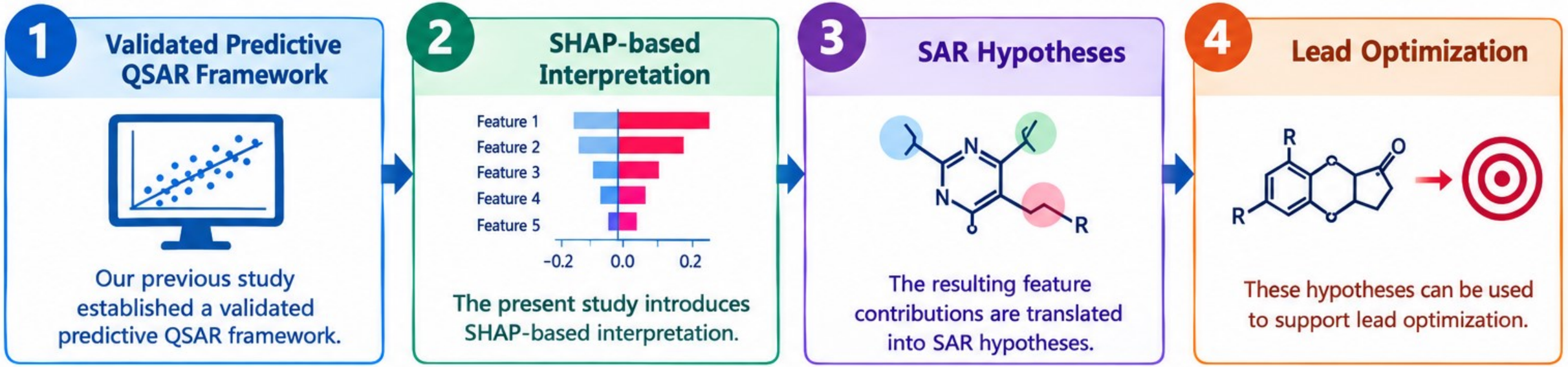
Positive contributions

- FP12
- FP659
- FP712

From SHAP to SAR

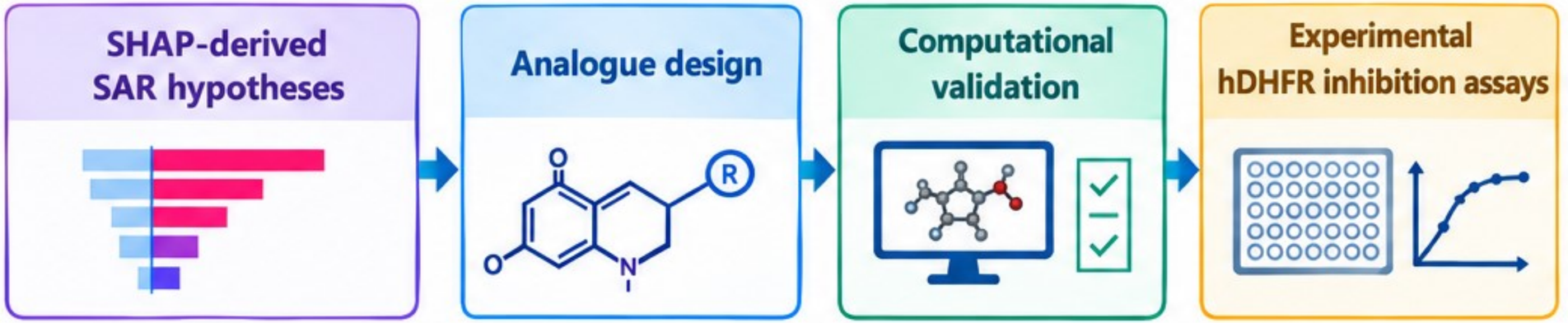
SHAP finding	Structural interpretation	SAR implication	Lead optimization
FP17 ↑	≥8 N atoms	Favorable association with predicted activity	Preserve / explore
FP12 ↑	≥16 C atoms	Favorable association with predicted activity	Preserve / explore
FP659 ↑	O–C–C–N–C connectivity	Favorable association	Retain / optimize
FP420 ↓	Carbonyl-related descriptor	Unfavorable model contribution	Modify / replace
FP607 ↓	N–C–C–C–aromatic connectivity	Unfavorable model contribution	Modify / replace

Overall workflow

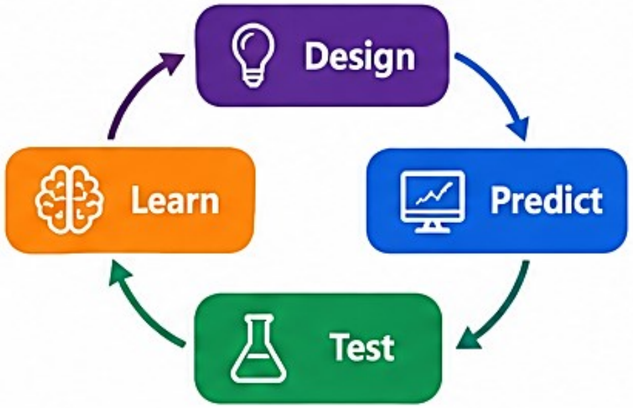


Future Direction

Our next step is to move from interpretation toward **validation.**
The future workflow will involve:



The experimental results can then be incorporated into an iterative:



Conclusion

SHAP successfully interprets the previously validated PubChem-RF QSAR model.

Global analysis identifies the most influential fingerprint descriptors and their contribution directions.

Local analysis explains individual compound predictions through feature-level attribution.

XAI transforms predictive QSAR into an interpretable framework for SAR analysis and lead optimization.

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Université Abdelmalek Essaadi

Drug Sciences Department,
Laboratory of Health and Life Sciences
FMP- Tangier

Faculté de Médecine et de pharmacie Tanger
كلية الطب والصيدلة طنجة

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Thank You!