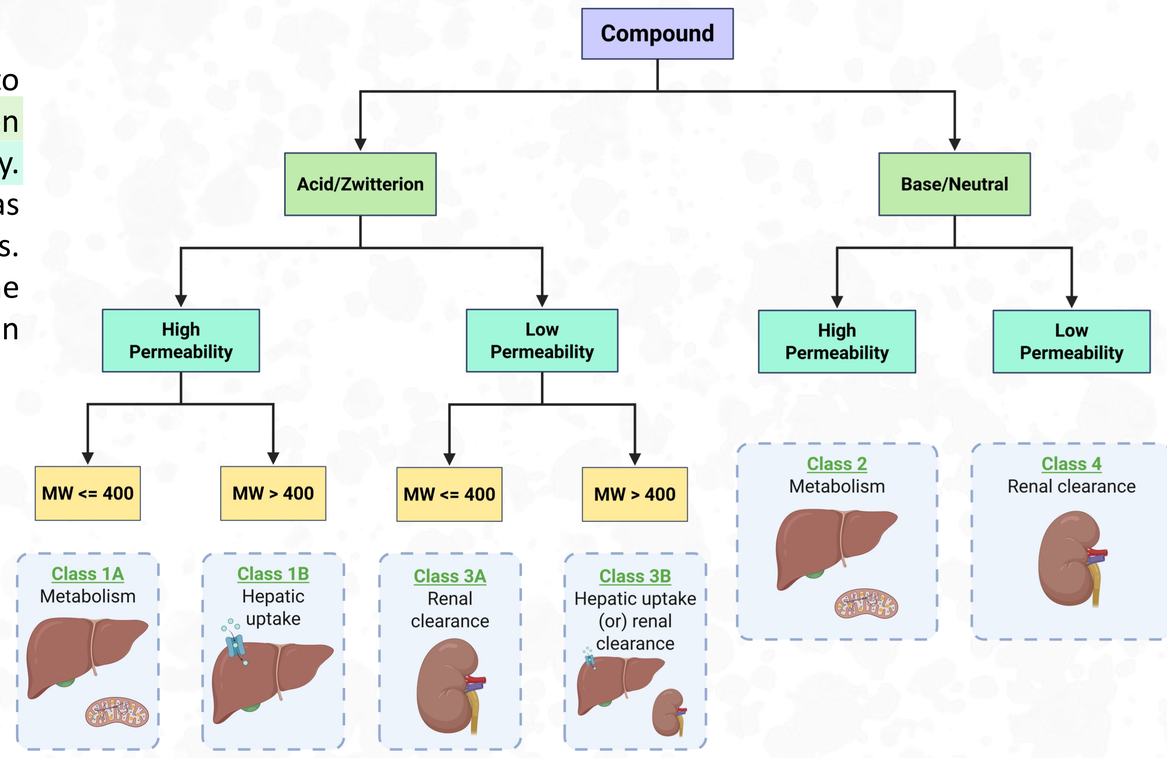
The Way Out: Implementation of an ECCS-based tool for predicting xenobiotic major elimination pathways

Enrique Llobet-Serra[a], Rita Ortega-Vallbona[a], Jessica Coto Palacio[a], Susana Proença[b], Domenico Gadaleta[c], Rafael Gozalbes[a,d], Eva Serrano-Candelas[a]*

[a]ProtoQSAR SL, Parque Tecnológico de Valencia, 46980 Valencia, Spain [b]ESQlabs GmbH, Saterland 26683, Germany [c]Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy [d]Moldrug AI Systems SL, Parque Tecnológico de Valencia, 46980 Valencia, Spain

INTRODUCTION

The Extended Clearance Classification System (ECCS) is a mechanistic framework used to predict the predominant elimination pathway of organic compounds based on ionization state, molecular weight, and passive membrane permeability. Despite its relevance for pharmacokinetics and toxicology, its practical application has been limited by the need for experimentally determined input parameters. Here, we present ECCS-DT, the first openly accessible web-based implementation of the ECCS decision tree, designed to support early mechanistic screening, even when experimental data are unavailable.



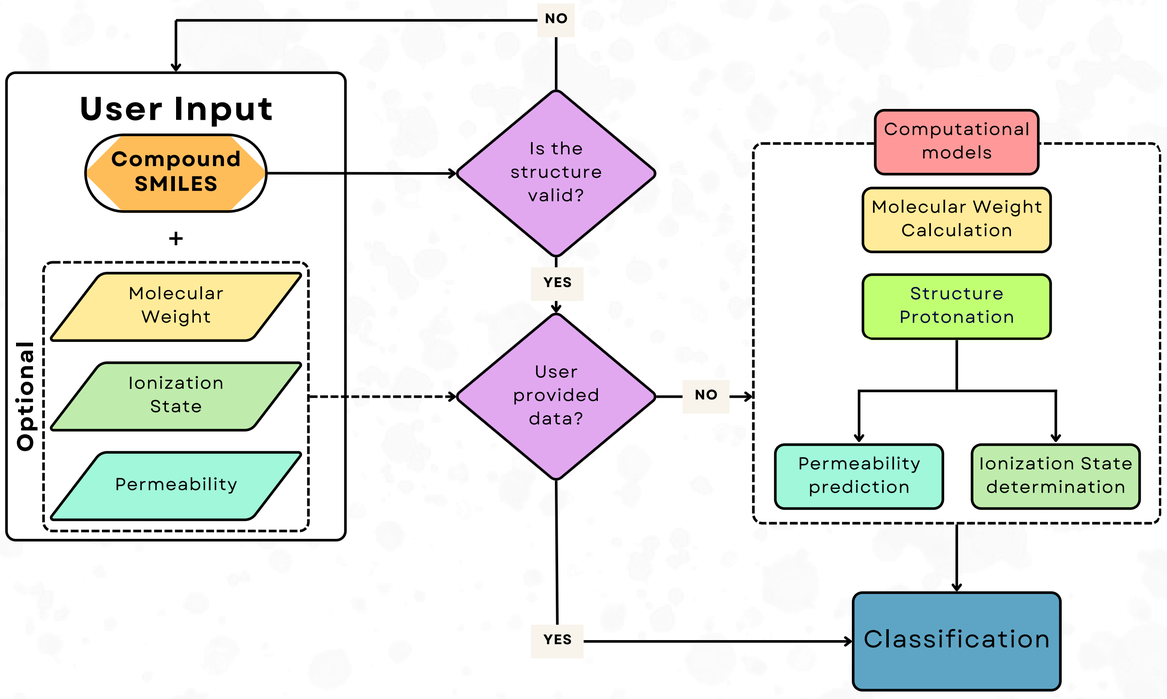
METHODOLOGY

ECCS-DT is implemented in the ChemoPredictionSuite platform.

Comming soon

The tool classifies organic molecules into one of the six ECCS classes using either user-provided experimental values or internally calculated parameters:

- Molecular weight calculated using RDKit [1].
- Ionization state at pH 7.4 predicted using Dimorphite-DL [2].
- Passive permeability in MDCKII-LE cells predicted using a dedicated QSAR model. Data from [3][4]



The full workflow was externally validated using two independent datasets:

- the pharmaceutical dataset published by Varma *et al*. in 2015 [5], where the ECCS framework was initially described;
- an ONTOX dataset including pharmaceuticals and other chemicals relevant to toxicological assessment.

CONCLUSION

ECCS-DT transforms the ECCS decision framework into a fully predictive and currently freely available web tool. By automatically estimating the parameters required for classification, ECCS-DT enables the application of ECCS to compounds lacking experimental permeability or ionization data. The tool supports early mechanistic interpretation of compound clearance and may be useful in pharmacokinetics, toxicology, and early-stage chemical prioritization.

RESULTS

The QSAR model for MDCKII-LE passive permeability showed external validation performance above 63 % for accuracy, sensitivity, and specificity.

	Train set	Validation set	Train set cross-validation	Validation set cross-validation	External validation
Accuracy	0.86	0.74	0.86 ± 0.01	0.77 ± 0.03	0.86
Sensitivity	0.85	0.71	0.86 ± 0.01	0.77 ± 0.05	0.63
Specificity	0.87	0.79	0.87 ± 0.01	0.77 ± 0.02	0.70

At the six-class ECCS level, the workflow achieved exact match rates of 60 % for the Varma dataset and 55.7 % for the ONTOX dataset.

When ECCS classes were grouped according to main clearance mechanisms, the agreement increased to 72.3 % and 60.3 %, respectively.

Including class 3B as a valid assignment for both hepatic uptake and renal clearance further increased agreement to 79.5 % for Varma and 69.2 % for ONTOX. Most errors were driven by permeability prediction rather than ionization state assignment.

REFERENCES

[1] RDKit: Open-source cheminformatics. https://www.rdkit.org
[2] Dimorphite-DL Ropp *et al.* J Cheminform. 2019;11:14. doi:10.1186/s13321-019-0336-9
[3] Varma *et al.* Mol Pharmaceutics. 2012;9:1199–1212. doi:10.1021/mp2004912
[4] Esaki *et al.* J Cheminform. 2024;16:30. doi:10.1186/s13321-024-00826-z
[5] Varma *et al.* Pharm Res. 2015;32:3785–3802. doi:10.1007/s11095-015-1749-4

This project received funding from the European Union's Horizon 2020 Research and Innovation programme under Grant Agreement No. 963845 (ONTOX)

The cluster receives funding from the EU's H2020 research and innovation programme under grant agreement: No. 963845, 965406, 964537.

aspis-cluster.eu