Integrated QSAR-ML and QST Modeling for Early Mechanistic Prediction of Clinical Hepatotoxicity Across Multiple Drug Classes

Hana Mohd[1], Christina Battista[2], Kyunghee Yang[2], Lisl K.M. Shoda[2], Michael S. Lawless[2], James J. Beaudoin[2,*]

[1]Rutgers, The State University of New Jersey, Piscataway, NJ, USA; [2]Simulations Plus, Inc., Research Triangle Park, NC, USA

***CONTACT INFORMATION:** james.beaudoin@simulations-plus.com

SimulationsPlus

BACKGROUND

Drug-induced liver injury (DILI) is a major cause of drug attrition, often undetected until late-stage clinical trials. Early hepatotoxicity prediction reduces cost and risk in development. To address this, we developed quantitative structure-activity relationship (QSAR)-machine learning (ML) models to provide mechanistic hepatotoxicity inputs for DILIsym, a quantitative systems toxicology (QST) model of DILI. This integrated QSAR-ML+QST workflow enables prospective hepatotoxicity screening in early development.

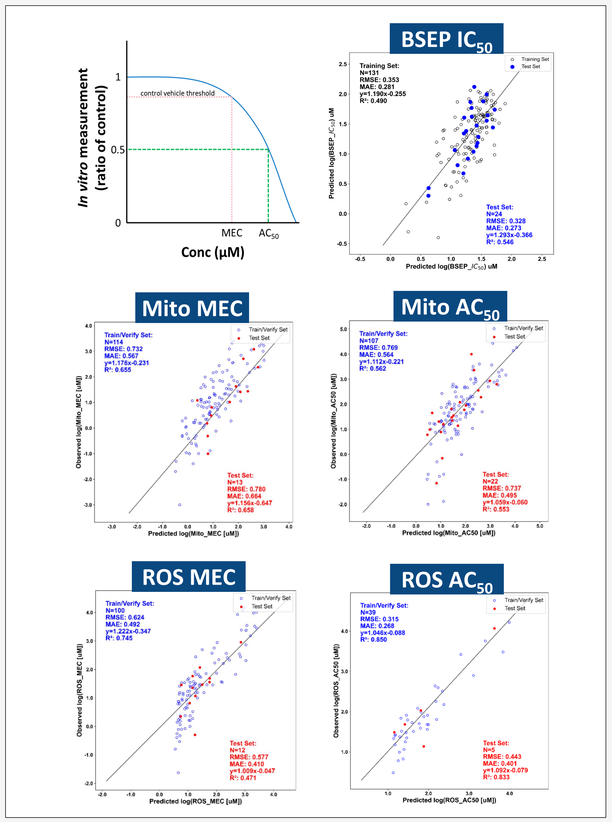
METHODS

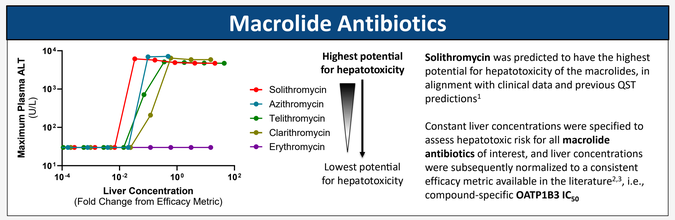
QSAR-ML models were built using ADMET Predictor 12 to predict compound activity on key DILI mechanisms: mitochondrial dysfunction, oxidative stress, and bile salt export pump (BSEP) inhibition. Mitochondrial dysfunction and oxidative stress models predicted classification outcomes and quantitative metrics [minimal effective concentration (MEC), half-maximal activity concentration (AC_{50})]; the BSEP model predicted half-maximal inhibitory concentration (IC_{50}). MEC and AC_{50} values were converted to estimated hepatocellular concentrations for use in DILIsym via the liver partition coefficient, estimated using the ADMET Predictor high-throughput pharmacokinetics (HTPK) module. Only parent compounds were assessed. The workflow was applied to several compound classes: macrolide antibiotics, calcitonin gene-related peptide (CGRP) receptor antagonists, endothelin receptor antagonists, catechol-*O*-methyltransferase (COMT) inhibitors, and thiazolidinediones.

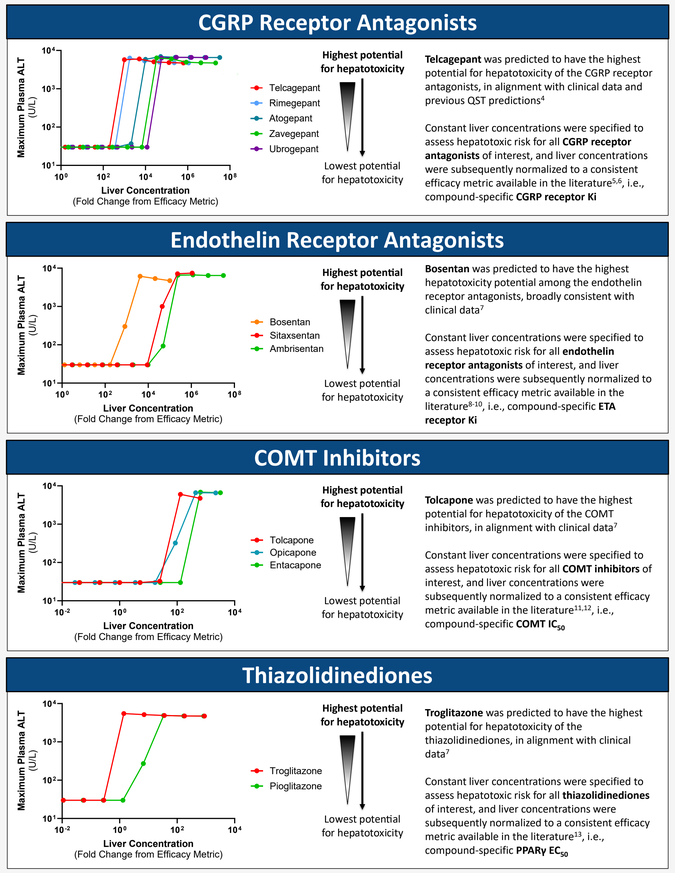
RESULTS

QSAR-ML models showed strong performance (classification model sensitivity/specificity ≥75%; mean absolute error <0.67 for quantitative models). Integrated QSAR-ML+QST predictions identified solithromycin as the most hepatotoxic among macrolide antibiotics, telcagepant among CGRP receptor antagonists, bosentan among endothelin receptor antagonists, tolcapone among COMT inhibitors, and troglitazone among thiazolidinediones. These results generally aligned with clinical data, despite requiring minimal input compared to traditional QST workflows.

Classification Model	Set	Negatives	Positives	Total	Sensitivity	Specificity
Mito Tox	Training	25	154	179	85.7%	92.0%
	Test	4	21	25	81.0%	75.0%
ROS Tox	Training	70	148	218	80.4%	75.7%
	Test	6	19	25	81.4%	76.3%
BSEP Tox	Training	415	108	523	89.8%	90.4%
	Test	73	19	92	89.5%	86.3%







CONCLUSION

The QSAR-ML+QST approach enables early, mechanism-informed hepatotoxicity risk prediction using limited experimental data.

Mechanistic integration: QSAR-ML-predicted mitochondrial dysfunction, oxidative stress, and BSEP inhibition provide biologically interpretable inputs for QST simulations.

Translational relevance: Predictions generally aligned with known clinical hepatotoxicity across multiple drug classes.

Outlook: This framework supports early compound prioritization and the reduction of DILI-related failures.

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CONFLICT OF INTEREST

Christina Battista, Lisl K.M. Shoda, Michael S. Lawless and James J. Beaudoin are employees of Simulations Plus, Inc. Kyunghee Yang was an employee of Simulations Plus, Inc. at the time the work was conducted. Hana Mohd has no conflicts of interest to disclose.

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