ADMET Predictor® 10.0 (APX) Release Webinar

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Outline

- Introduction to ADMET Predictor
- New Features in Version 10.0
- Software Demonstration

ADMET Predictor Overview

Property Prediction

Physicochemical
Metabolism
Transporters
Toxicity
ADMET Risk

PBPK Simulations

%Fa, %Fb
Cmax, Tmax, AUC, $T_{1/2}$, CL
Cp-time curves
Optimal dose

Model Building

Activity, properties
Molecular + atomic descriptors
Regression, classification
Uncertainty, confidence

Cheminformatics

Compound design
Scaffold clustering
R group analysis
Similarity / diversity

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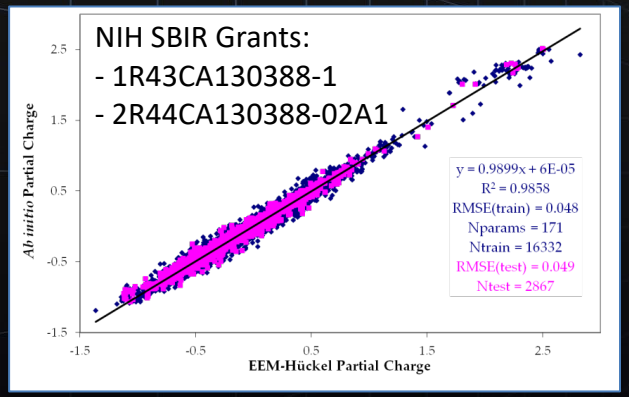
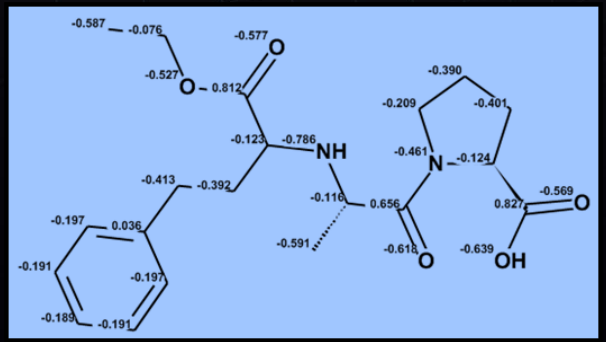
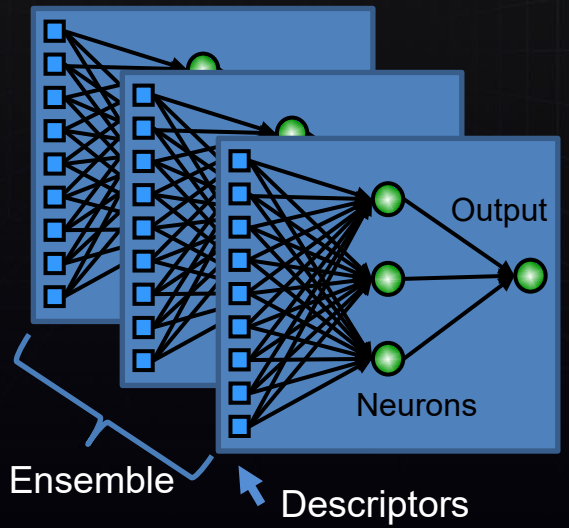
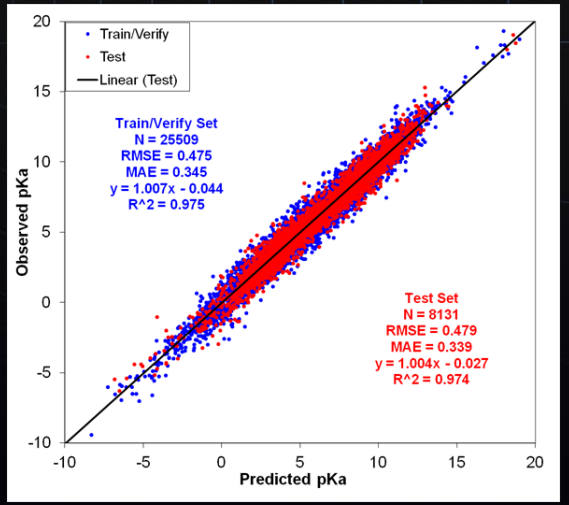
Property Prediction: Methodology







pKa model



Neurons

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AIDD Module

Artificial Intelligence-Driven Drug Design

New capabilities for evolutionary multi-objective compound optimization

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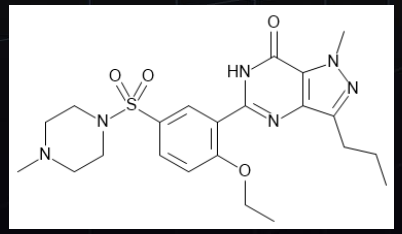
Analog Generation Using Rules

Apply transform rules to a lead compound

Starting structure

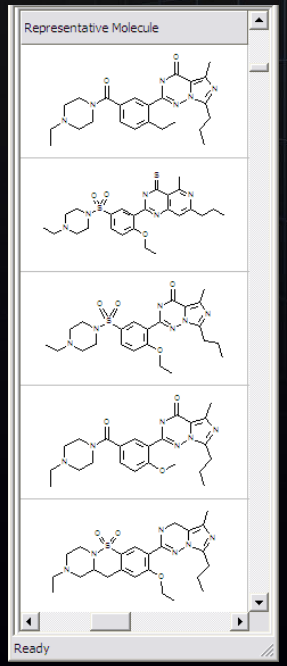


Transform rules

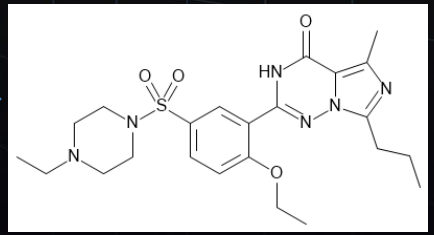
- Bioisosteric replacements
- Reactions from literature or in-house expertise
- Chemically-intelligent "mutations"

Users can modify the default rules

Generated analogs



Example analog



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AIDD Methodology

- Builds on the transform-based analog generation approach, with improved and expanded rules
- Incorporates property prediction:
  - ADMET, %Fa or %Fb, risks, user activity models
- Incorporates Synthetic Difficulty scores
- Uses iterative approach: in each generation the best analogs are retained using Pareto optimization

AIDD Methodology

Ertl's fragment-dictionary method reasonably predicts synthetic difficulties reported by chemists

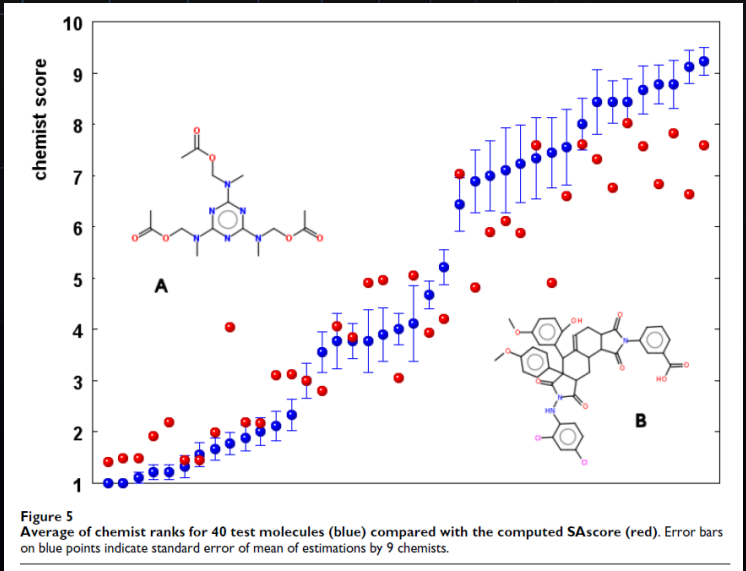
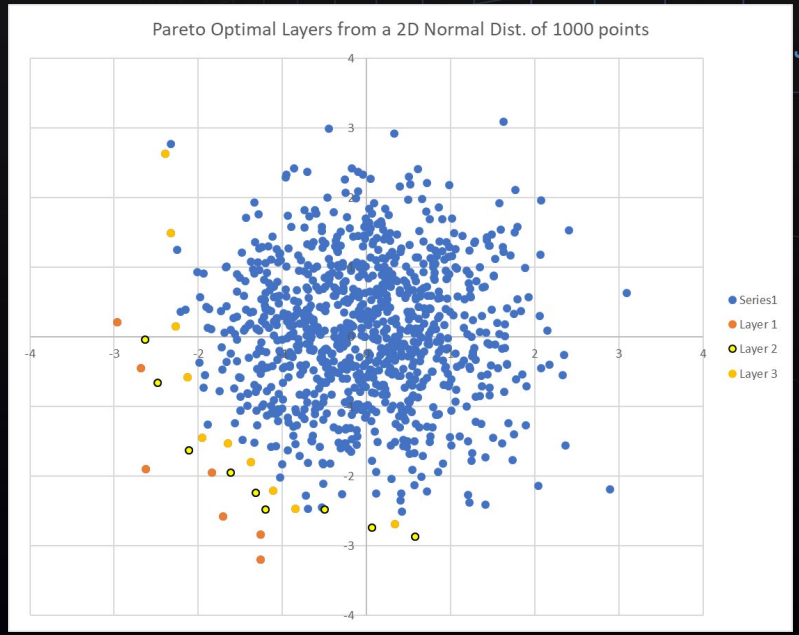


Figure 5
Average of chemist ranks for 40 test molecules (blue) compared with the computed SAscore (red). Error bars on blue points indicate standard error of mean of estimations by 9 chemists.

Ertl et al., J. Cheminformatics. 2009 1:8

Pareto-optimal compounds (3 layers)



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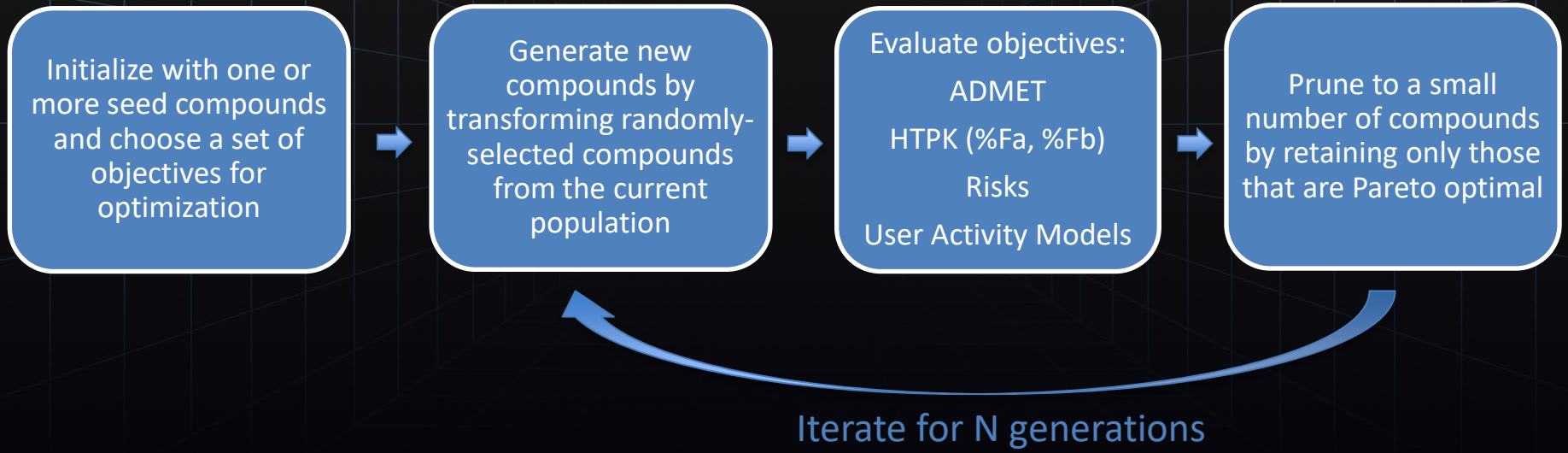
AIDD Workflow



Rapidly generates virtual compounds simultaneously optimized against multiple target objectives

Up to 10M analogs can be evaluated in a day using a computer with 4 physical cores

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Transporters Module

In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies

Guidance for Industry

DRAFT GUIDANCE

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2017
Clinical Pharmacology

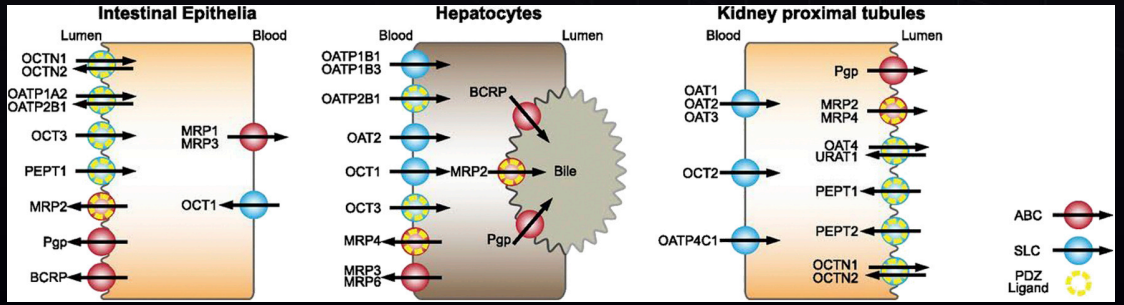
10/24/17

Examples of Transporter-Mediated Drug Interactions

Interacting Drug	Affected Drug	Consequence	Fold Changes in Substrate Plasma AUC
Quinidine	Digoxin	Digoxin Exposure 1.7-fold ↑	P-glycoprotein (P-gp, MDR1) Inhibition
Rifampin	Digoxin	Digoxin Exposure 30% ↓	P-gp Induction
Dronedarone	Digoxin	Digoxin Exposure 2.6-fold ↑	P-gp Inhibition
Probenecid	Cephradine	Cephradine Exposure 3.6-fold ↑	Organic Anion Transporter (OAT) Inhibition
Cimetidine	Metformin	Metformin Exposure 1.4-fold ↑	Organic Cation Transporter (OCT) Inhibition
Cyclosporine	Rosuvastatin	Rosuvastatin Exposure 7-fold ↑	Organic Anion Transporting Polypeptide (OATP) Inhibition & Breast Cancer Resistance Protein (BCRP) Inhibition
Lopinavir/ Ritonavir	Rosuvastatin	Rosuvastatin Exposure 2-fold ↑	OATP Inhibition

Adapted from **Transporter-Mediated Drug-Drug Interactions (DDIs)**

https://www.fda.gov/media/78640/download



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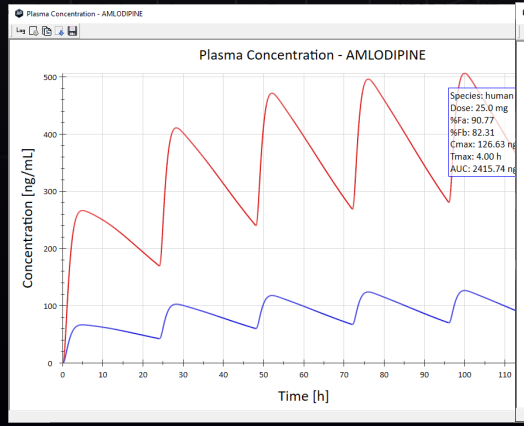
Advances in Chronic Kidney Disease, Vol 23, No 2 (March), 2016: pp 76-81.

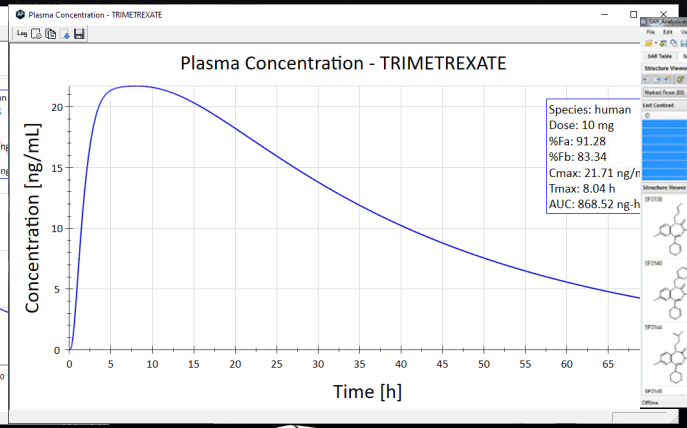
Transporter Models in APX

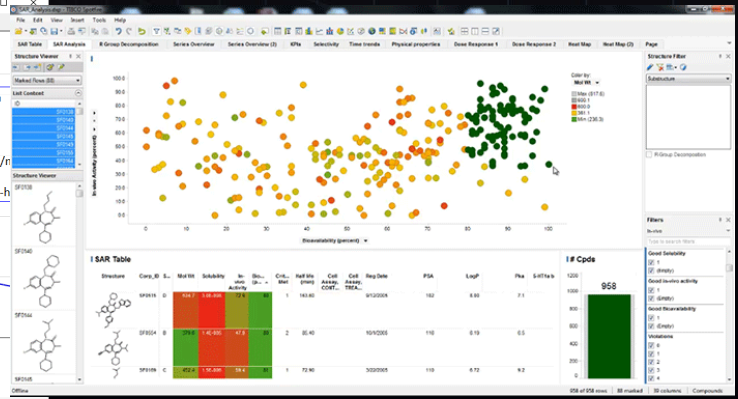
Transporter	P-gp	BCRP	OATP1B1	OATP1B3	OCT1	OCT2	OAT1	OAT3	BSEP
Substrate	Rebuilt	9.5	✓	✓	✓	✓	✓	✓	
Inhibitor	Rebuilt	✓	Rebuilt	✓	✓	9.5	✓	✓	9.5
Km			✓	✓	✓	✓	✓	✓	

HTPK Enhancements

- Driven by collaboration with large pharmaceutical company
- Support for longer/multiple dosing intervals
- Expanded command-line options
- Additional predicted PK parameters ($T_{1/2}$, CL, CL_{plasma})
- Further enhancements coming in 2021







Alternate front end based on command line

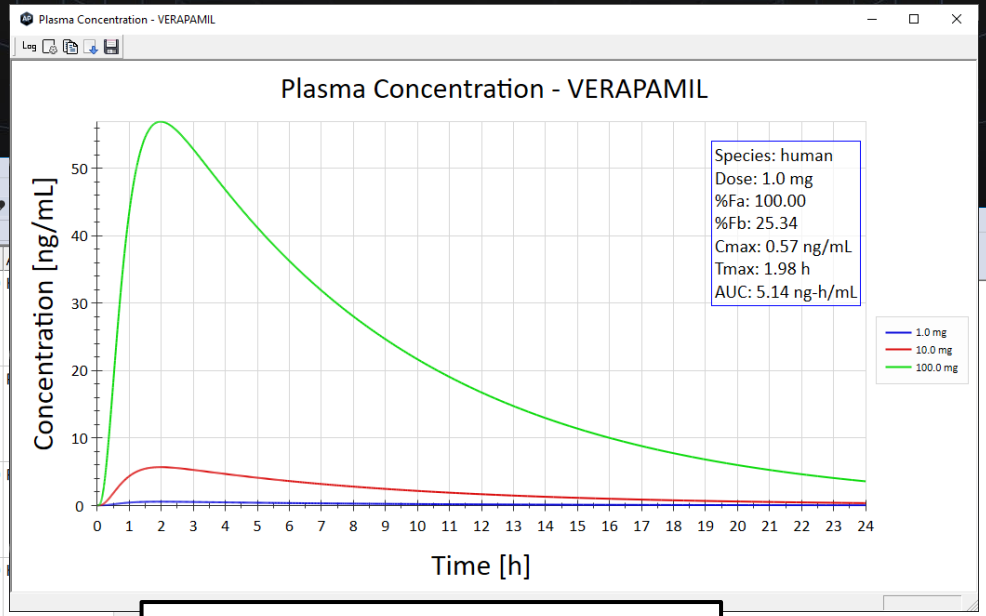
More New Features in APX

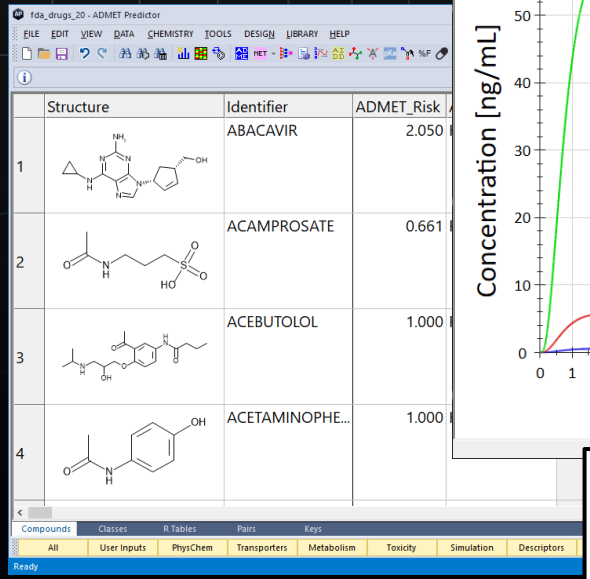
- New Models
  - Hepatocyte clearance (human and rat)
- Improved Models with New Data
  - Volume of distribution
  - Blood-brain barrier (BBB) classification
  - hERG blocker classification
  - hERG pIC50
  - OATP1B1 inhibitor classification
  - Pgp substrate classification
  - Pgp inhibitor classification

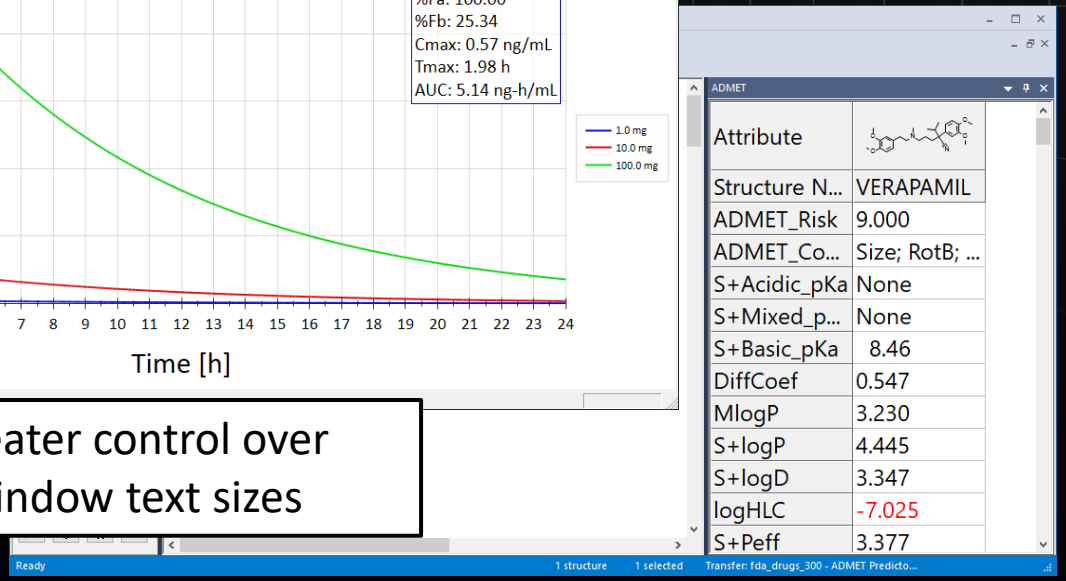
More New Features in APX

- Expanded Parallelization
  - ADMET property predictions and PK simulations can now take advantage of multi-core CPUs
  - A roughly 4- to 5-fold speed improvement can be expected on a typical computer with 4 physical cores
  - An even greater speed improvement can be expected for PK simulations due to enhancements to the equation solver
  - Enabled in both graphical interface and command line
  - No additional license required

More New Features in APX







Greater control over window text sizes

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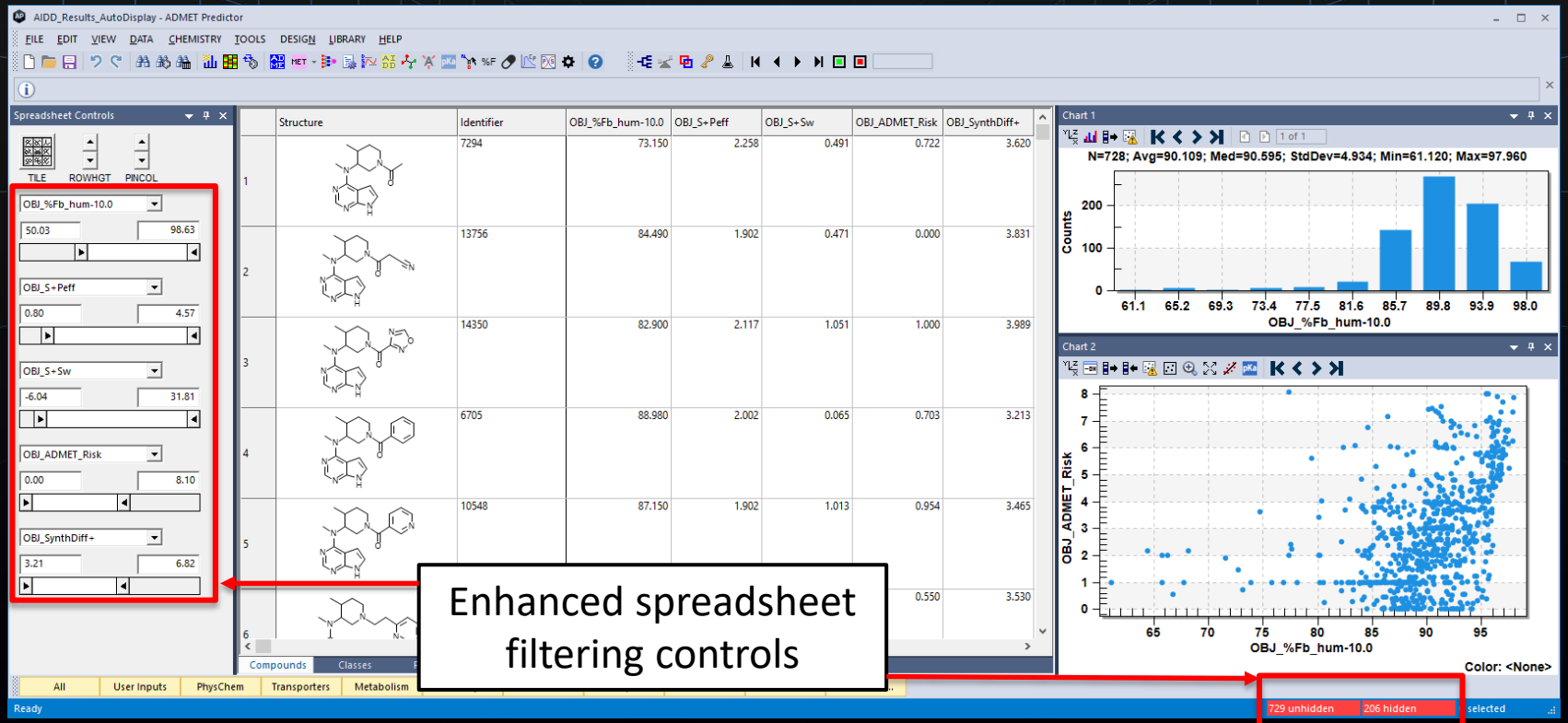
More New Features in APX



Enhanced spreadsheet filtering controls

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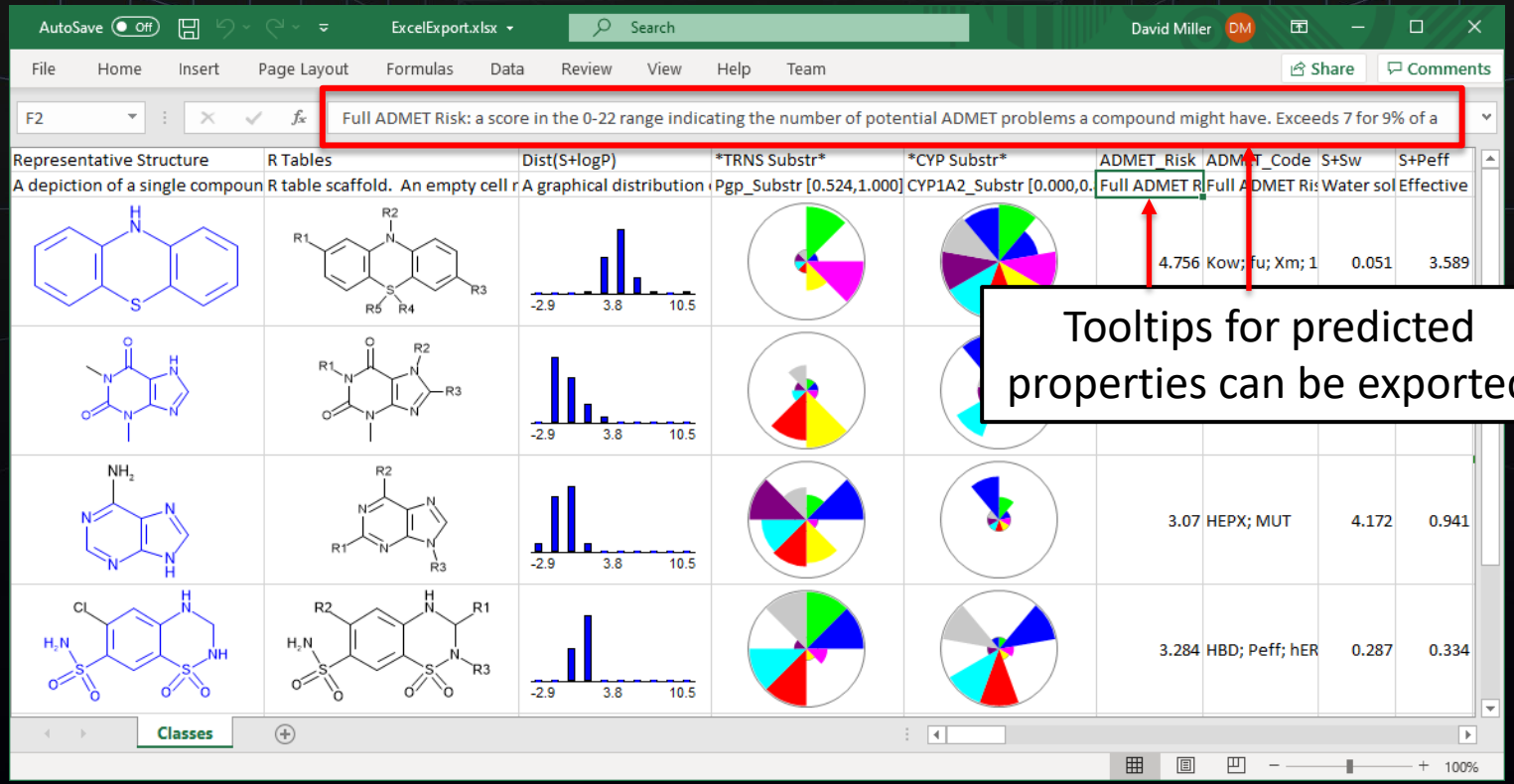
More New Features in APX



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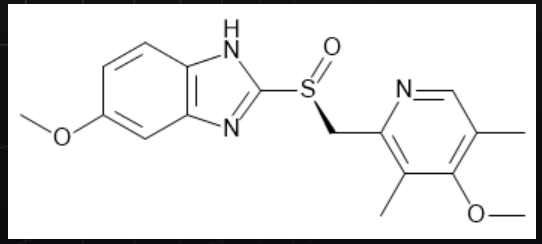
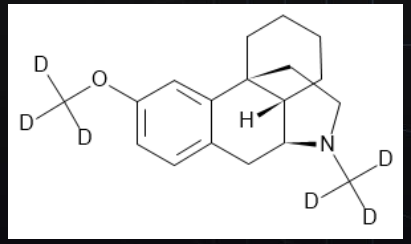
More New Features in APX

- Support for heteroatom stereocenters and hydrogen isotopes





- Support for exporting version 3000 SD files
- Improved license handling
- Many more user-requested enhancements

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AIDD Example

Journal of Medicinal Chemistry

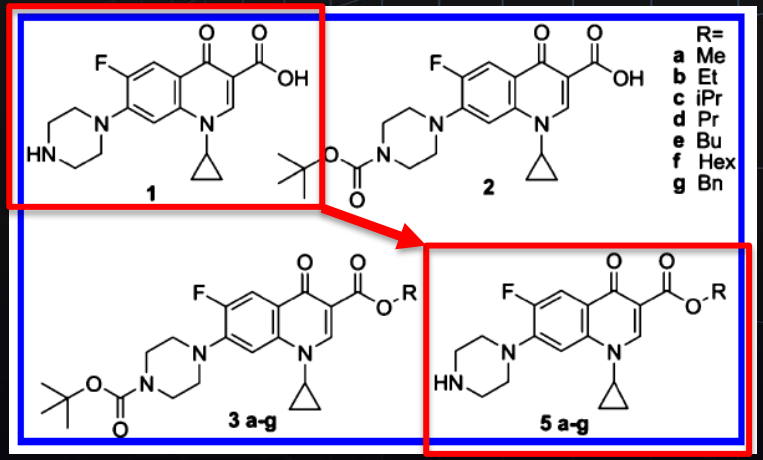
Brief Article

pubs.acs.org/jmc

Optimizing Solubility and Permeability of a Biopharmaceutics Classification System (BCS) Class 4 Antibiotic Drug Using Lipophilic Fragments Disturbing the Crystal Lattice

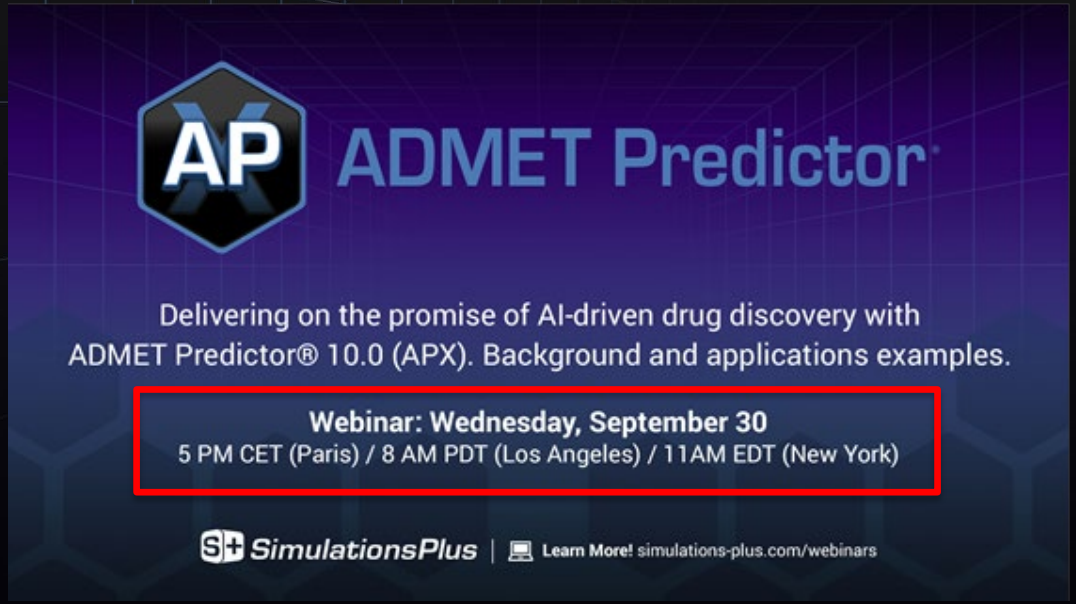
Ulrika Tehler,[†,§] Jonas H. Fagerberg,[†] Richard Svensson,[†] Mats Larhed,[‡] Per Artursson,[†] and Christel A. S. Bergström*[,†]

dx.doi.org/10.1021/jm301721e | J. Med. Chem. 2013, 56, 2690−2694



ABSTRACT: Esterification was used to simultaneously increase solubility and permeability of ciprofloxacin, a biopharmaceutics classification system (BCS) class 4 drug (low solubility/low permeability) with solid-state limited solubility. Molecular flexibility was increased to disturb the crystal lattice, lower the melting point, and thereby improve the solubility, whereas lipophilicity was increased to enhance the intestinal permeability. These structural changes resulted in BCS class 1 analogues (high solubility/high permeability) emphasizing that simple medicinal chemistry may improve both these properties.

Thank You!



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