



ADMET Predictor[®] 10.0 (APX)
Release Webinar

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

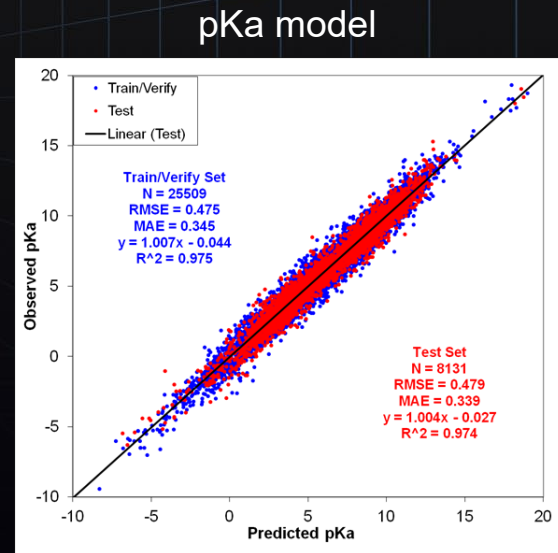
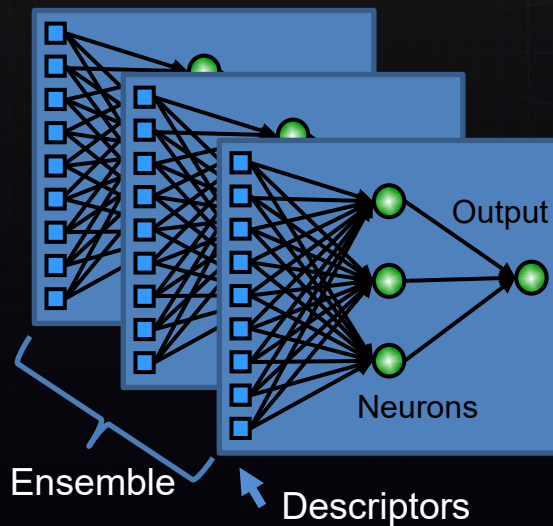
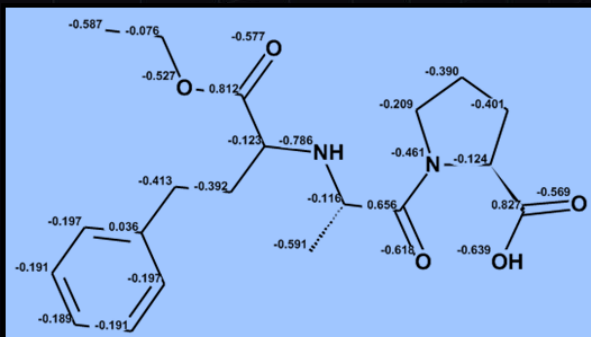
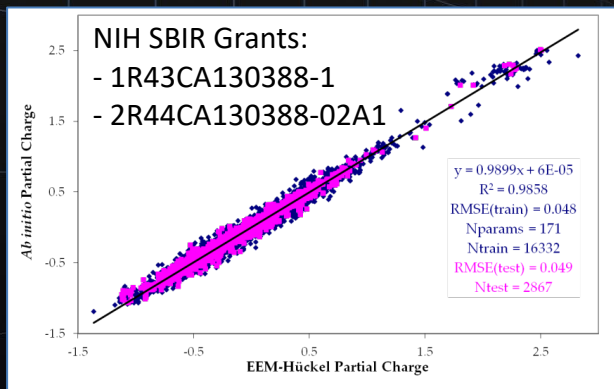
Model Building

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

Cheminformatics

Compound design
Scaffold clustering
R group analysis
Similarity / diversity

Property Prediction: Methodology



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AIDD Module

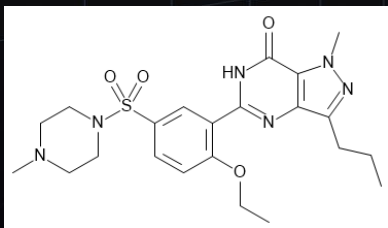
Artificial Intelligence-Driven Drug Design

New capabilities for evolutionary multi-objective compound optimization

Analog Generation Using Rules

Apply transform rules to a lead compound

Starting structure

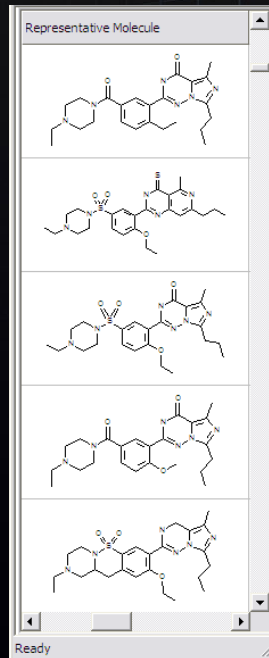


Transform rules

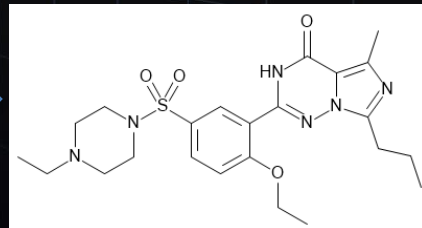
- Bioisosteric replacements
- Reactions from literature or in-house expertise
- Chemically-intelligent “mutations”

Users can modify the default rules

Generated analogs



Example analog



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

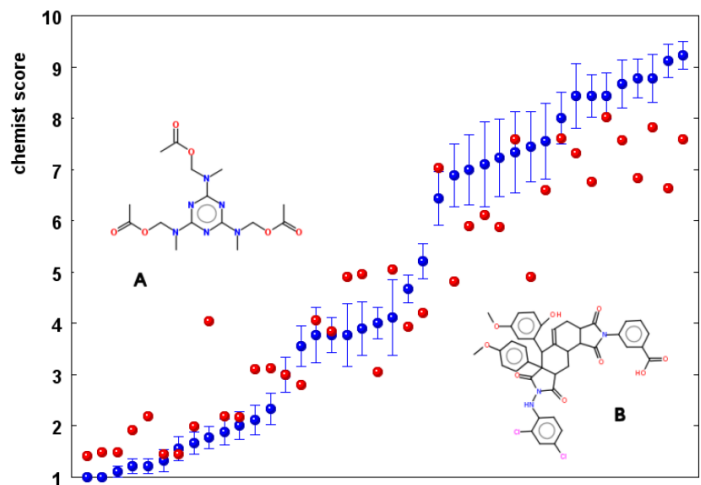
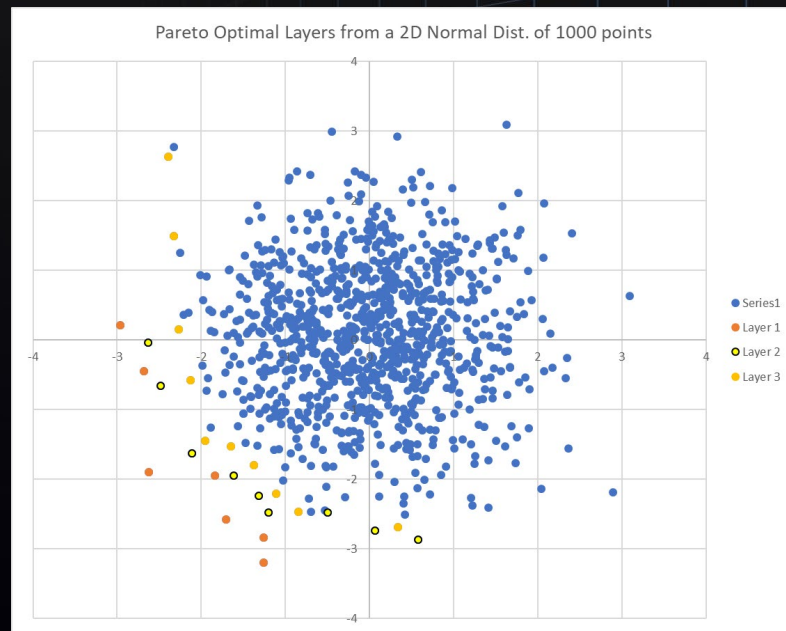


Figure 5
Average of chemist ranks for 40 test molecules (blue) compared with the computed SAscore (red). Error bars on blue points indicate standard error of mean of estimations by 9 chemists.

Pareto-optimal compounds (3 layers)

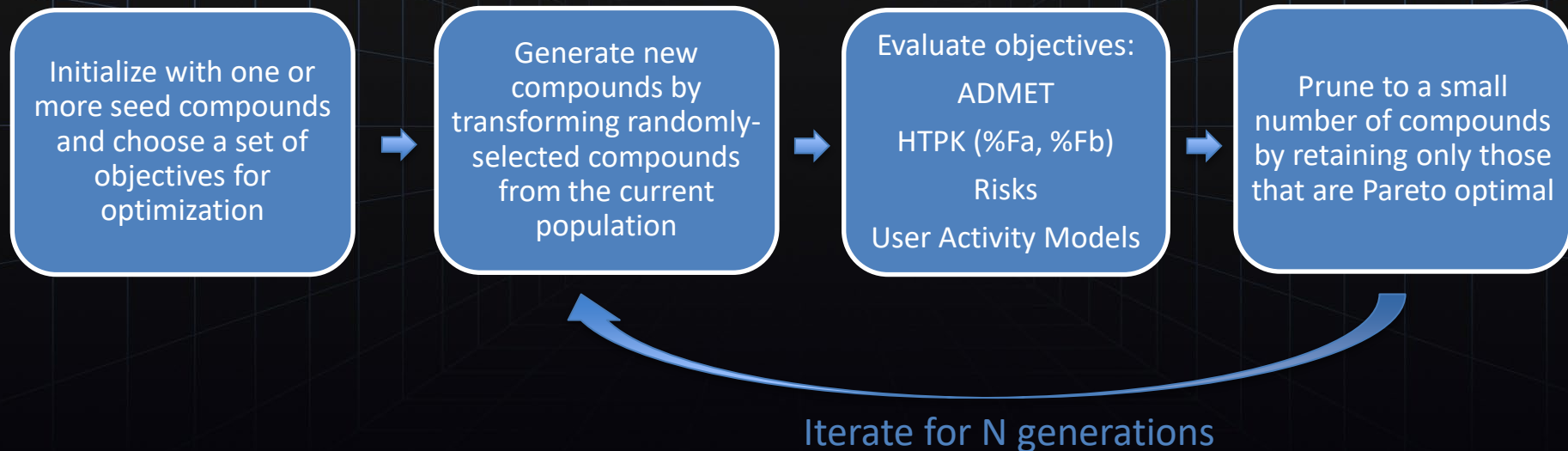


Objective 2

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

Objective 1

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

Transporters Module

In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies Guidance for Industry

DRAFT GUIDANCE

IV. EVALUATING TRANSPORTER-MEDIATED DRUG INTERACTIONS 9

- A. Determining if the Investigational Drug is a **Substrate of the Transporters P-gp and BCRP**..... 10
- B. Determining if the Investigational Drug is a Substrate of the Hepatic Transporters **OATP1B1 and OATP1B3**..... 11
- C. Determining if the Investigational Drug is a Substrate of the Renal Transporters **OAT, OCT, and MATE**..... 12
- D. Determining if the Investigational Drug is an **Inhibitor of a Transporter**..... 13
- E. Determining if the Investigational Drug is an **Inducer of a Transporter**..... 16

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

October 2017
Clinical Pharmacology

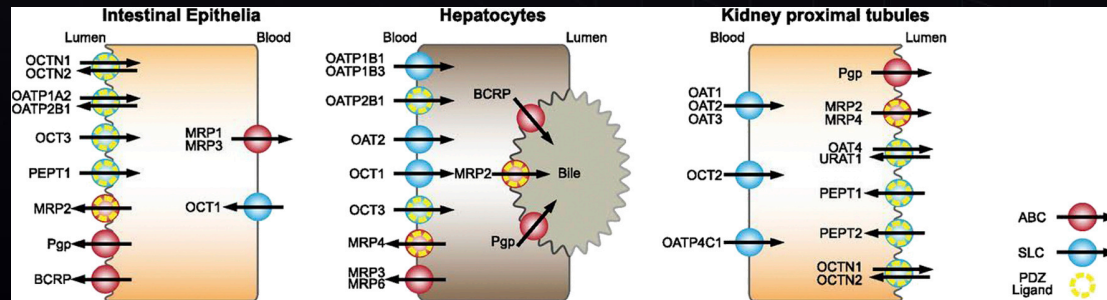
10/24/17

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	Cephadrine	Cephadrine 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>

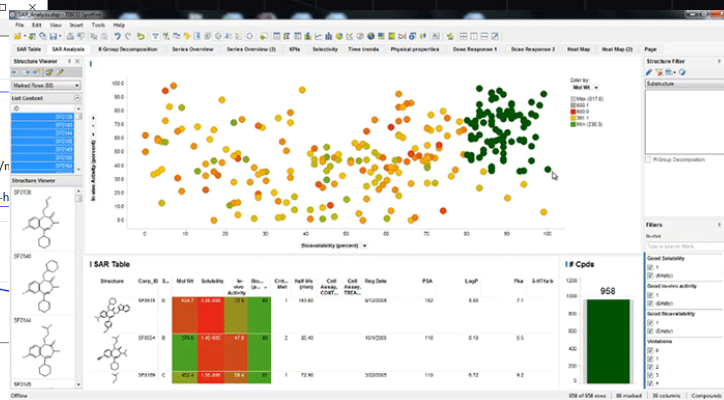
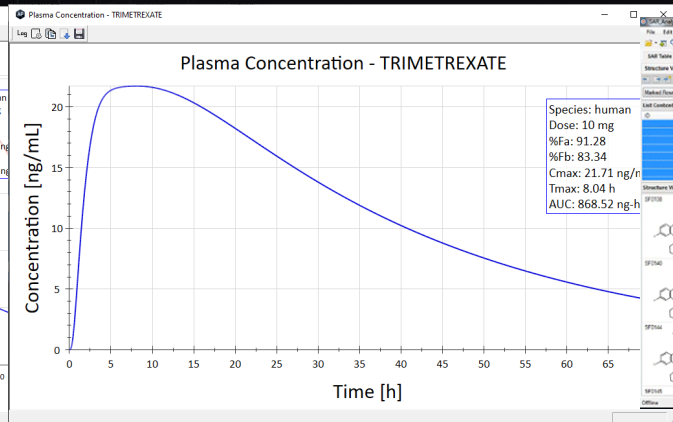
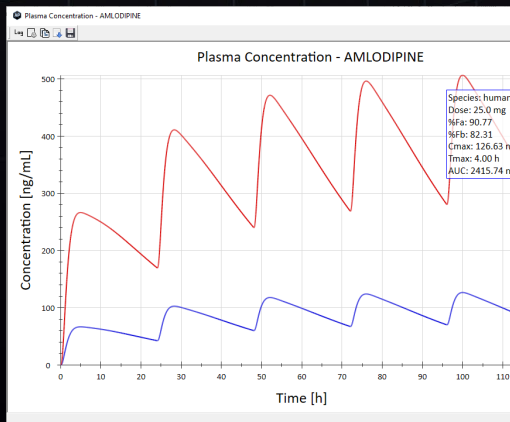


Transporter Models in APX

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



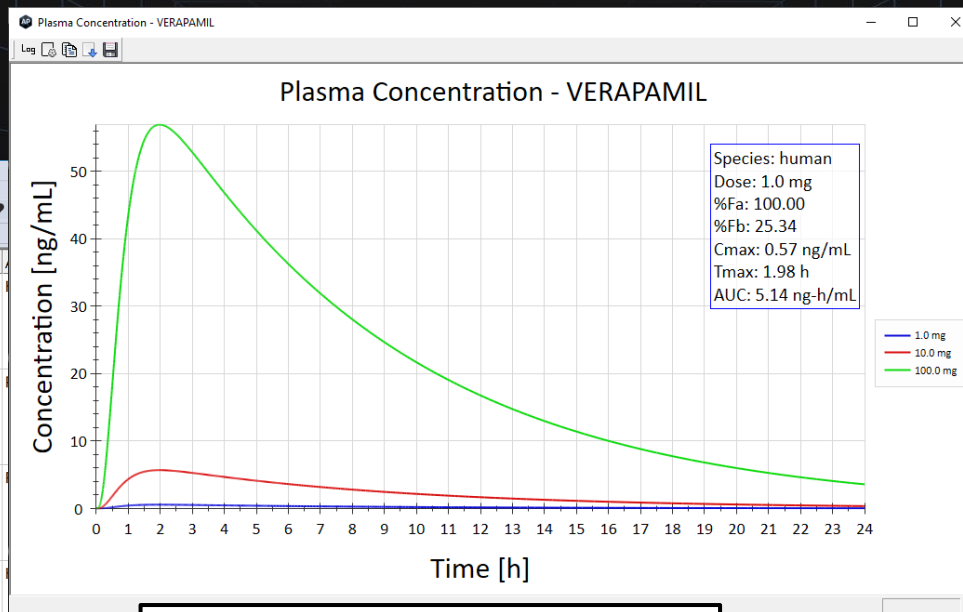
More New Features in APX

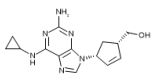
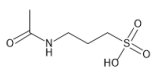
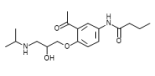
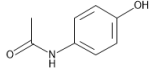
- New Models
 - Hepatocyte clearance (human and rat)
- Improved Models with New Data
 - Volume of distribution
 - Blood-brain barrier (BBB) classification
 - hERG blocker classification
 - hERG pIC50
 - OATP1B1 inhibitor classification
 - Pgp substrate classification
 - Pgp inhibitor classification

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



Structure	Identifier	ADMET_Risk
	ABACAVIR	2.050
	ACAMPROSATE	0.661
	ACEBUTOLOL	1.000
	ACETAMINOPHE...	1.000

Attribute	
Structure N...	VERAPAMIL
ADMET_Risk	9.000
ADMET_Co...	Size; RotB; ...
S+Acidic_pKa	None
S+Mixed_p...	None
S+Basic_pKa	8.46
DiffCoef	0.547
MlogP	3.230
S+logP	4.445
S+logD	3.347
logHLC	-7.025
S+Peff	3.377

Greater control over window text sizes

More New Features in APX

AIDD_Results_AutoDisplay - ADMET Predictor

FILE EDIT VIEW DATA CHEMISTRY TOOLS DESIGN LIBRARY HELP

Spreadsheet Controls

OBJ_%Fb_hum-10.0
50.03 98.63

OBJ_S+Peff
0.80 4.57

OBJ_S+Sw
-6.04 31.81

OBJ_ADMET_Risk
0.00 8.10

OBJ_SynthDiff+
3.21 6.82

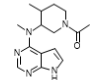
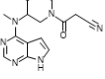
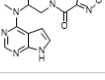
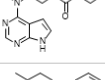
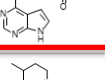
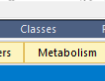
Structure	Identifier	OBJ_%Fb_hum-10.0	OBJ_S+Peff	OBJ_S+Sw	OBJ_ADMET_Risk	OBJ_SynthDiff+
	7294	73.150	2.258	0.491	0.722	3.620
	13756	84.490	1.902	0.471	0.000	3.831
	14350	82.900	2.117	1.051	1.000	3.989
	6705	88.980	2.002	0.065	0.703	3.213
	10548	87.150	1.902	1.013	0.954	3.465
				0.550		3.530

Chart 1
N=728; Avg=90.109; Med=90.595; StdDev=4.934; Min=61.120; Max=97.960

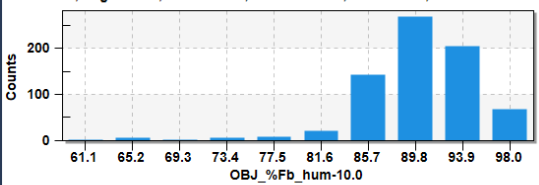
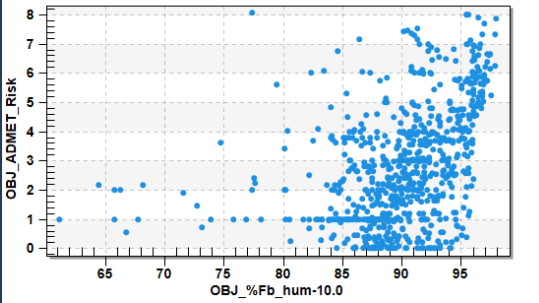


Chart 2



729 unhidden 206 hidden selected

Enhanced spreadsheet filtering controls

More New Features in APX

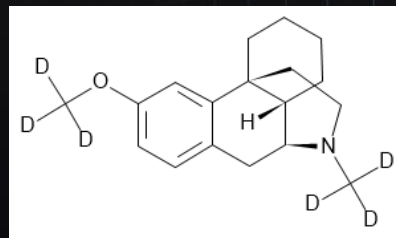
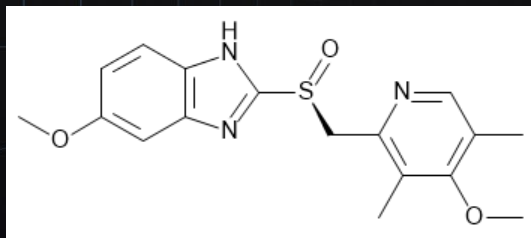
The screenshot displays the APX software interface with a table of predicted properties. A tooltip is visible over the 'Full ADMET Risk' column, and a callout box states 'Tooltips for predicted properties can be exported'.

Full ADMET Risk: a score in the 0-22 range indicating the number of potential ADMET problems a compound might have. Exceeds 7 for 9% of a

Representative Structure	R Tables	Dist(S+logP)	*TRNS Substr*	*CYP Substr*	ADMET Risk	ADMET Code	S+Sw	S+Peff
					4.756	Kow; fu; Xm; 1	0.051	3.589
					3.07	HEPX; MUT	4.172	0.941
					3.284	HBD; Peff; hER	0.287	0.334

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**

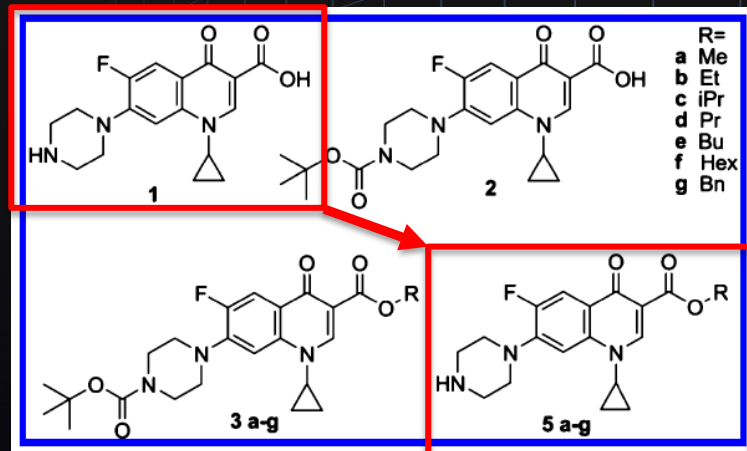
Brief Article

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!



ADMET Predictor®

Delivering on the promise of AI-driven drug discovery with ADMET Predictor® 10.0 (APX). Background and applications examples.

Webinar: Wednesday, September 30

5 PM CET (Paris) / 8 AM PDT (Los Angeles) / 11AM EDT (New York)

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