SimulationsPlus

ADMET Predictor® X

New AI-driven drug design functionality offers scientists one-of-a-kind approach for lead optimization

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What is ADMET Predictor®?

ADMET Predictor is an advanced computer program that enables researchers to rapidly estimate a numberof ADMET properties of new chemical entities simply from molecular structure.

The eight (8) modules in ADMET Predictor are shown in the diagram above. The predictive models are grouped into Physicochemical and Biopharmaceutical (PCB), Transporters, Metabolism, and Toxicity modules. ADMET Predictor models have been consistently ranked as the most accurate in independent published comparisons.[1-4]

ADMET Predictor 10.0 (APX) introduces two new modules, Transporters and AIDD for AI-Driven Drug Design. The AIDD Module integrates ADMET Predictor's top-ranked ADMET property prediction models with multi-objective compound optimization capabilities. AIDD™ will take one or more starting structures and optimize them against a set of target properties. Activity models can be constructed in ADMET Modeler™ and used as part of the optimization to drive activity against one or multiple targets (e.g., selectivity). All numeric ADMET property prediction models as well as custom models can be used as part of the target profile. This includes mechanistic models from the HTPK Simulation module (%Fa and %Fb)!

1. DEARDEN JC. "*IN SILICO* PREDICTION OF AQUEOUS SOLUBILITY". EXPERT OPIN DRUG DISCOVERY 2006; 1 (1): 31-52.
2. TETKO IV AND PODA GI. IN "MOLECULAR DRUG PROPERTIES: MEASUREMENT AND PREDICTION." ED. MANNHOLD R., WEINHEIM, GERMANY, WILEY-VCH: 381-406. (2007).
3. MANNHOLD R, PODA GI. OSTERMANN C, TETKO IV. "CALCULATION OF MOLECULAR LIPOPHILICITY: STATE OF THE ART AND COMPARISON METHODS." J PHARM SCI. 2008; 98 (3): 84.
4. OYARZABAL J, PASTOR J, HOWE TJ. "OPTIMIZING THE PERFORMANCE OF *IN SILICO* ADMET GENERAL MODELS ACCORDING TO LOCAL REQUIREMENTS"; J. CHEM. MODEL 2009; 49 (11): 2572.

Regulatory agencies have issued guidance pertaining to transporters-related drug-drug interactions (DDIs) so it has become important to provide relevant models. The Transporters Module in ADMET Predictor contains a set of models specifically focused on transporters. In total, there are 24 models included with 18 of them being completely new in the ADMET Predictor 10.0 (APX) release.

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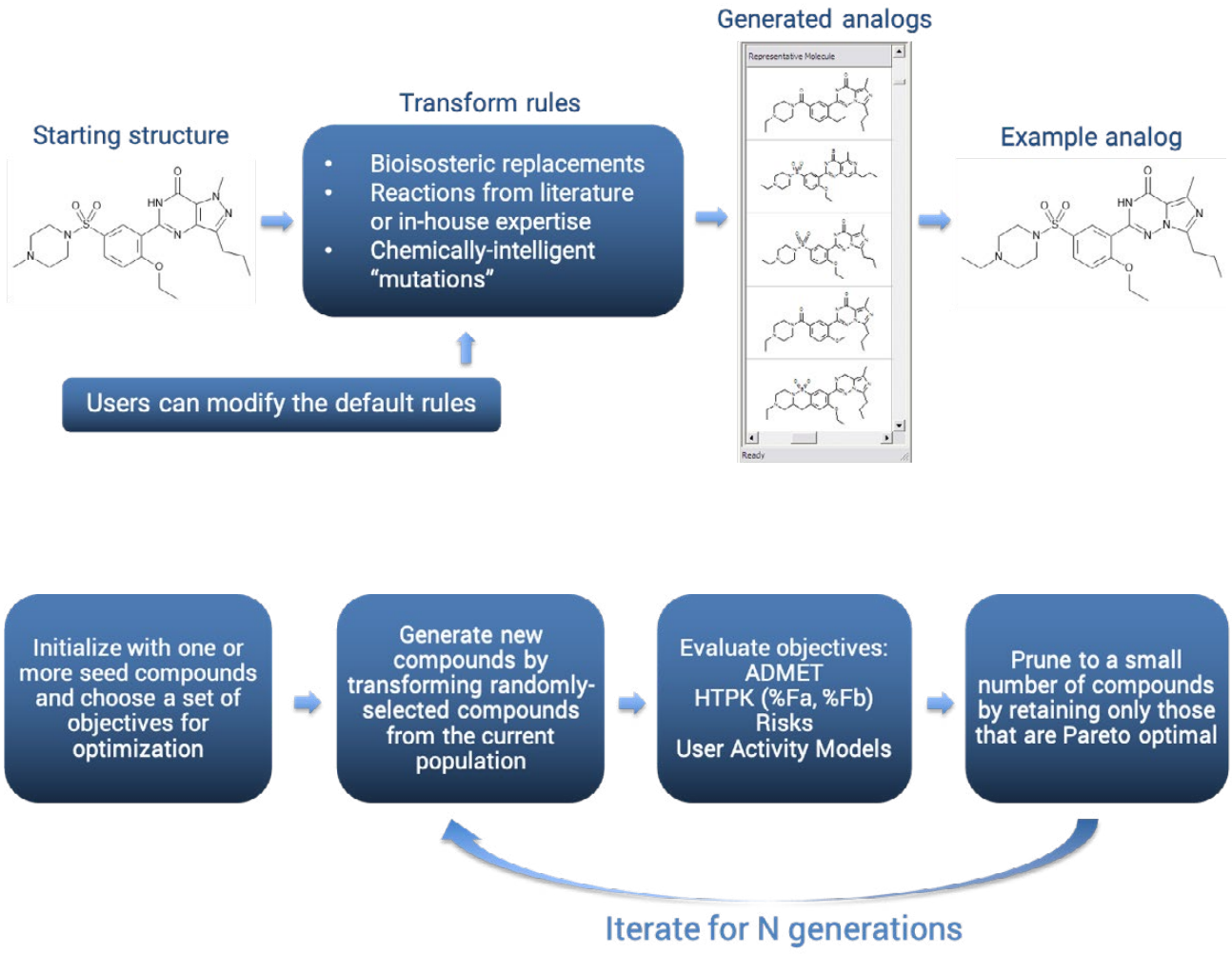
NEW Features in ADMET Predictor 10 (APX)

General

- New AIDD module for AI-driven compound optimization
- New Transporters module with models dedicated to molecular transporters
- Support for multi-core CPUs provides a 4-6x performance improvement over the previous version. No additional licenses are required.
- Significant industry-driven improvements to the HTPK simulation module
- Major improvements to important models such as hepatocyte clearance, BBB, Vd and hERG



New AI-Driven Drug Design (AIDD) module

- Enables users to generate candidate compounds optimized against multiple objectives
- Uses an iterative procedure starting from one or more seed compounds.
- Modifies compounds via transform rules which can be customized
- Evaluates compounds against the multi-objective targets
- Produces a library of compounds that are Pareto optimal against one or more of the objectives.

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

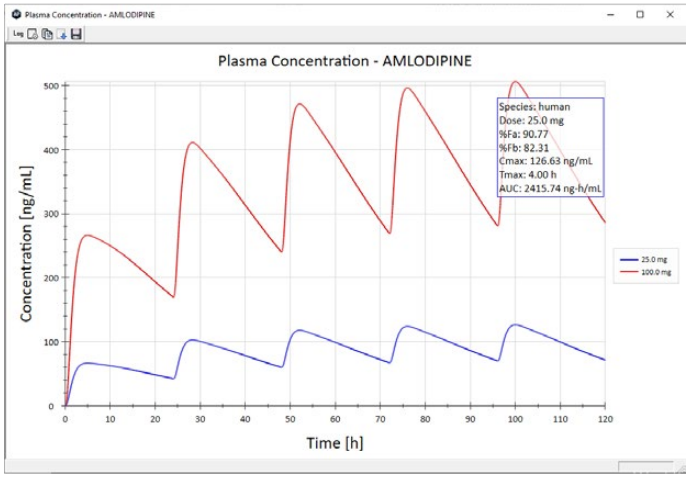
New Transporters module

- 18 brand new models for OATP, OCT and OAT transporters
- 6 improved models from previous version
- Substrate, inhibitor and Km models

Multi-threaded model calculations

- Multi-threaded mode available via Preference setting
- Supported for all models including custom models built in ADMET Modeler
- Supported for mechanistic models available through the HTPK simulation module
- Available in both GUI and command mode use
- No special licenses necessary to enable
- Only 1 license consumed in multi-threaded mode

Improvements to HTPK simulation module



- Estimation of fraction absorbed, fraction bioavailable and Cp-time curves
- Support for multiple dose intervals and intervals longer than 24 hours
- New PK parameters including half-life, pharmacokinetic clearance and plasma clearance
- New command-line options for specifying custom parameter files

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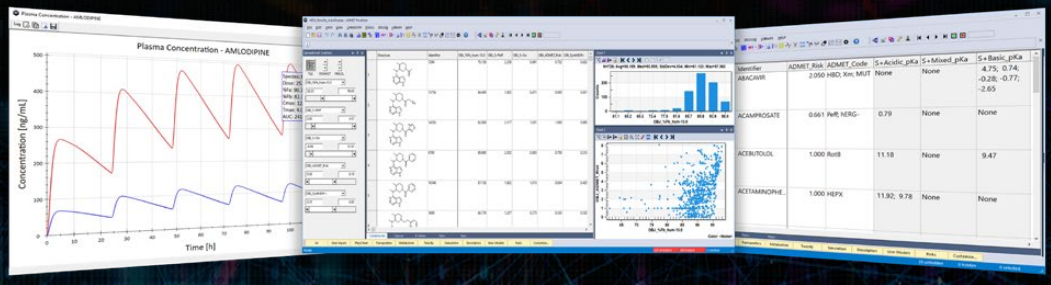
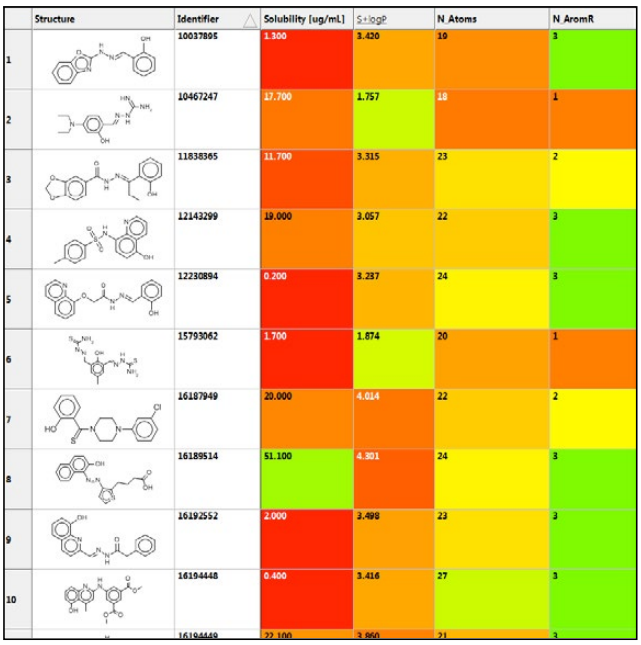
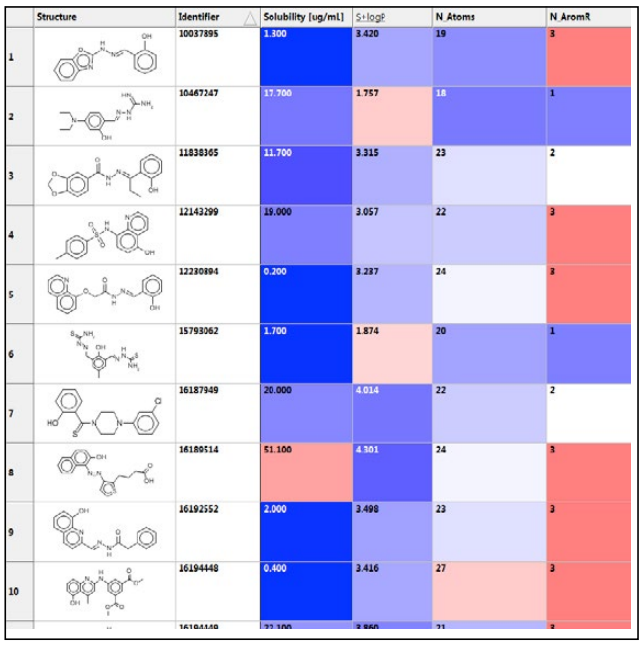


Interface features and spreadsheet functions

Heat maps

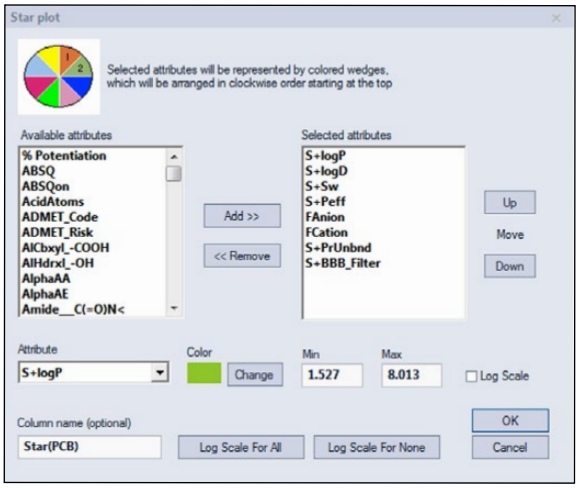
Heat maps can be created for any numeric attribute. The color progression can be red-yellow-green or blue-white-red. One can also specify the direction of the progression, e.g., the largest values are colored blue.

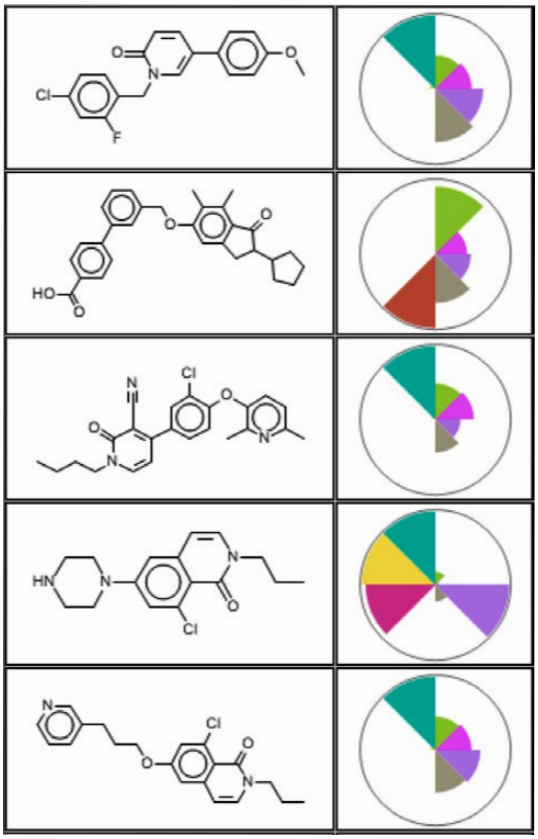




Automatic Star Plots

Star plots are automatically created after ADMET properties are computed. One can specify up to 16 properties per Star plot. The length of the wedge is proportional to the property range represented by the data. Optionally, one can specify the range minimum and maximum values for each wedge. Additionally, the wedge length can be proportional to the log of the property value.





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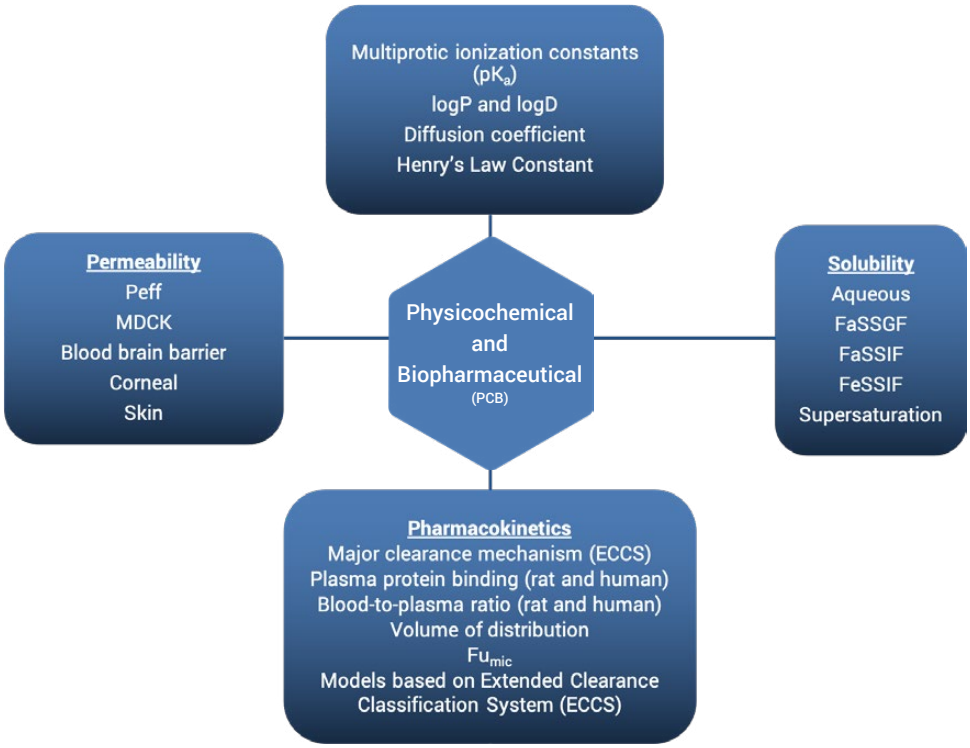
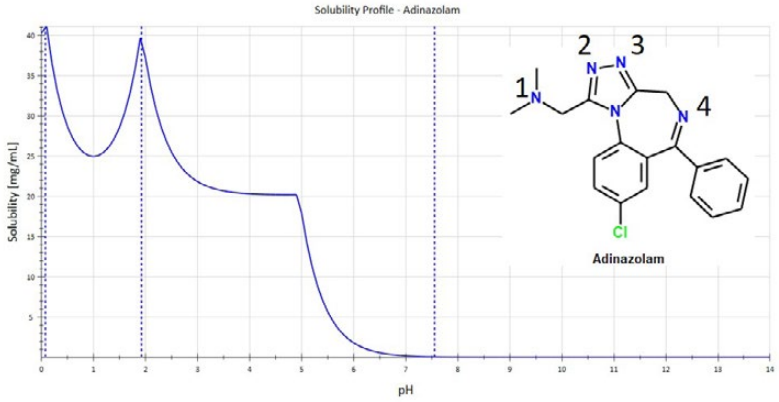
Physicochemical and Biopharmaceutical (PCB) Module

The models in the PCB module are shown in the figure below.

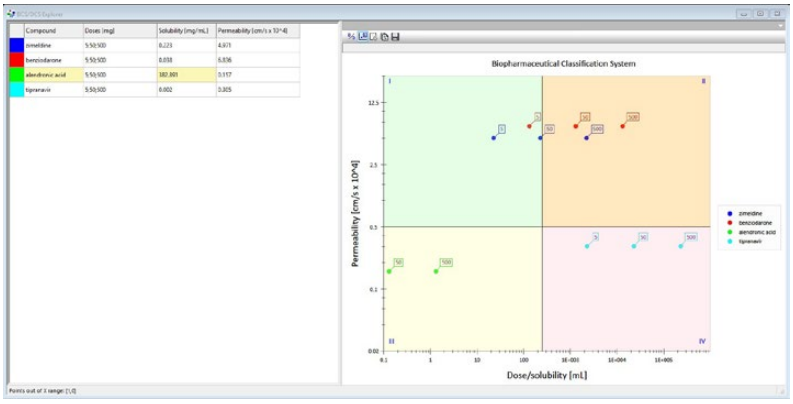


Graphics in ADMET Predictor include sol. v. pH & BCS shown in the images below.



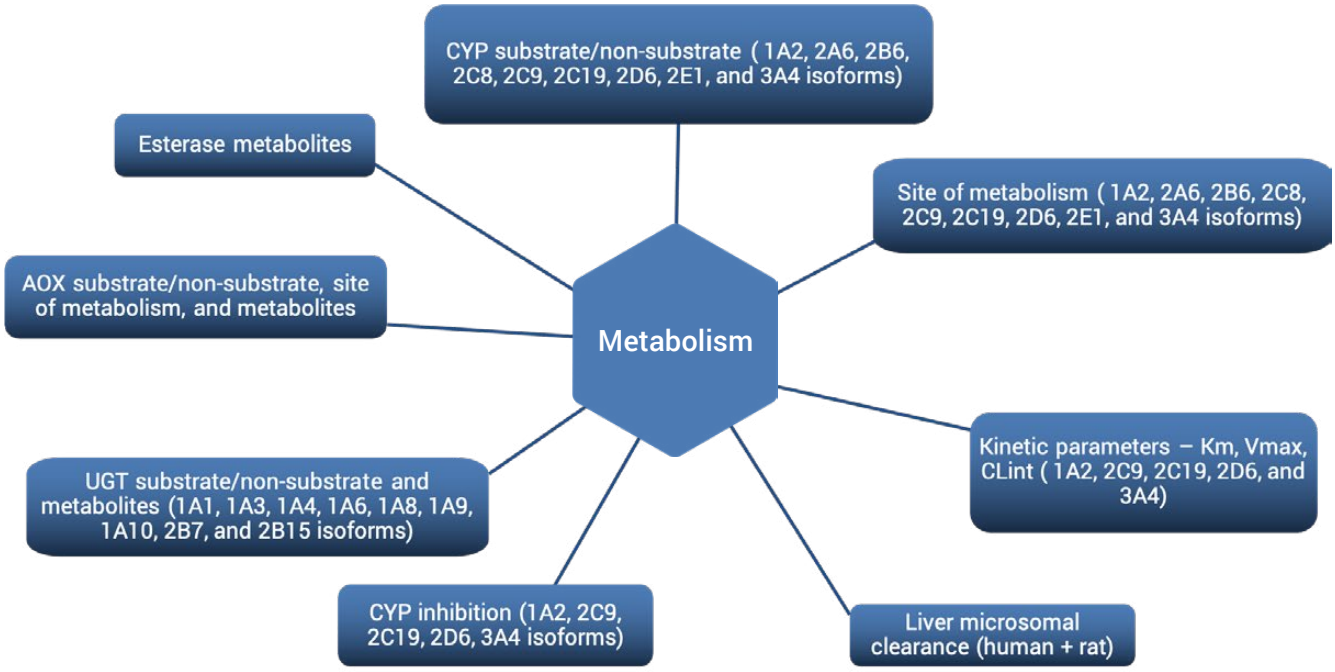
The predicted solubility versus pH profile for adinazolam. There are 4 basic amines, labeled 1 – 4. The vertical dashed lines represent pKa of the macrostates. The highest pKa is 7.56, where the solubility starts to increase with decreasing pH. Macrostates that include protonation of either nitrogens 3 or 4, in addition to nitrogen 1, begin to affect the solubility starting at just below pH 5.

The Biopharmaceutical Classification System (BCS) viewer allows one to plot the BCS class of up to sixteen (16) compounds at user specified doses.

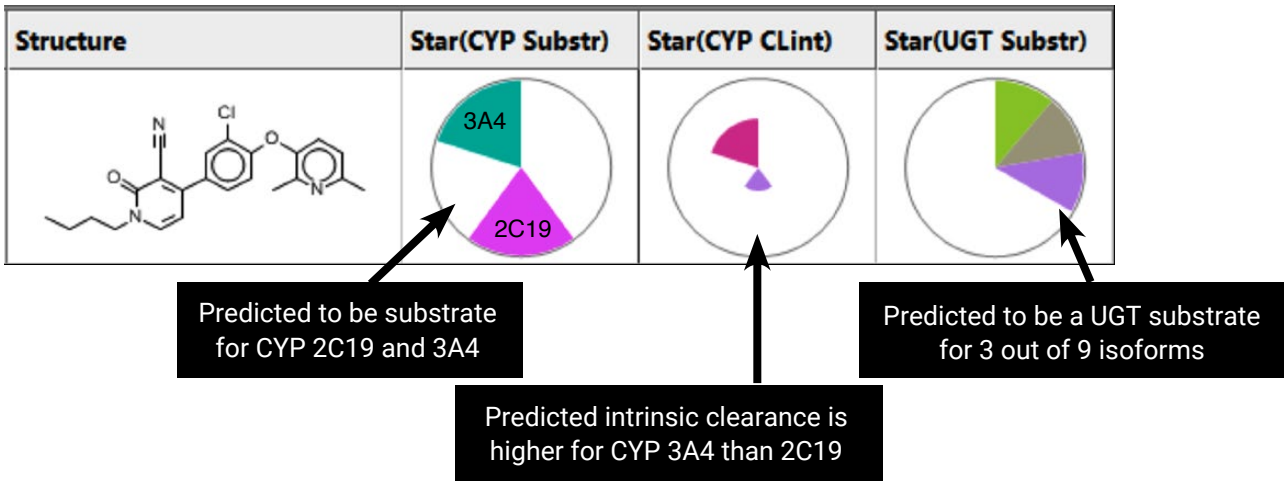


Metabolism Module

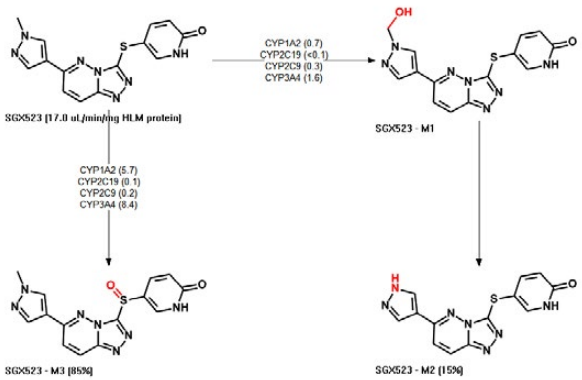
The models in the Metabolism module are shown in the image below.



"Star" plots allow one to quickly assess model results.



Metabolite prediction: the CLint of the parent molecule is displayed along with the percentage of each metabolite produced. Hydroxylation of the methyl group results in an unstable intermediate that decomposes to the desmethyl product and formaldehyde (not shown).



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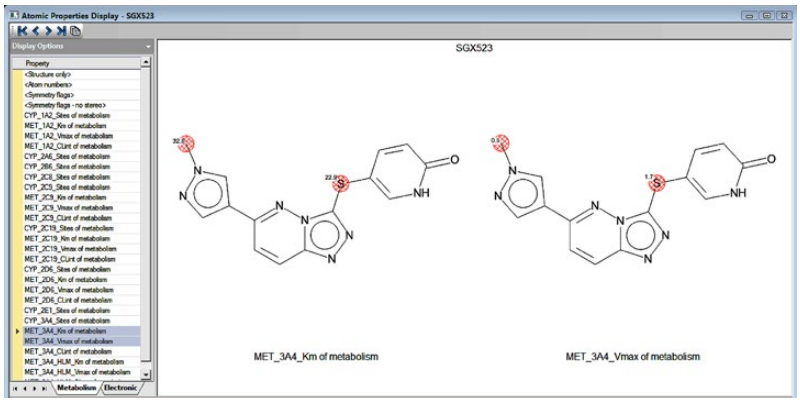
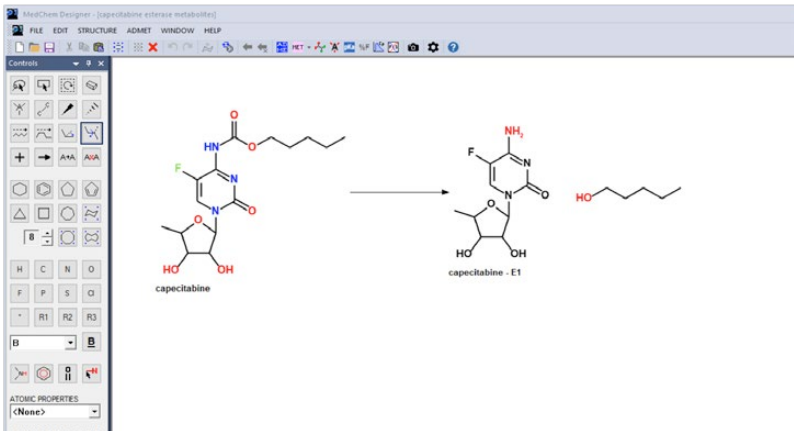
ADMET Predictor predicts Km and Vmax for each site of metabolism.

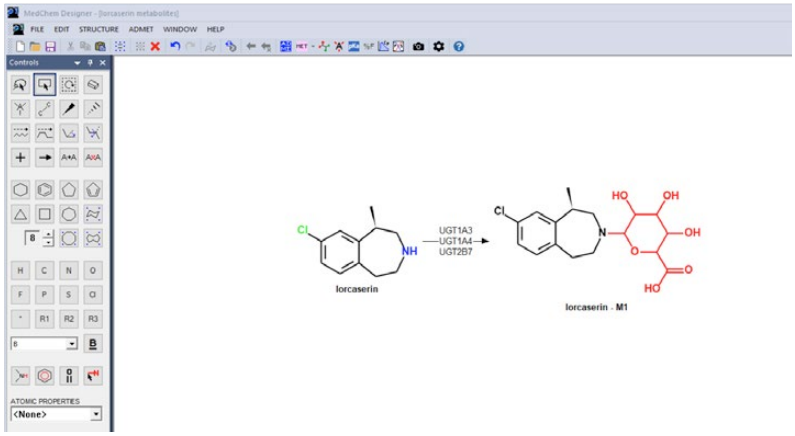


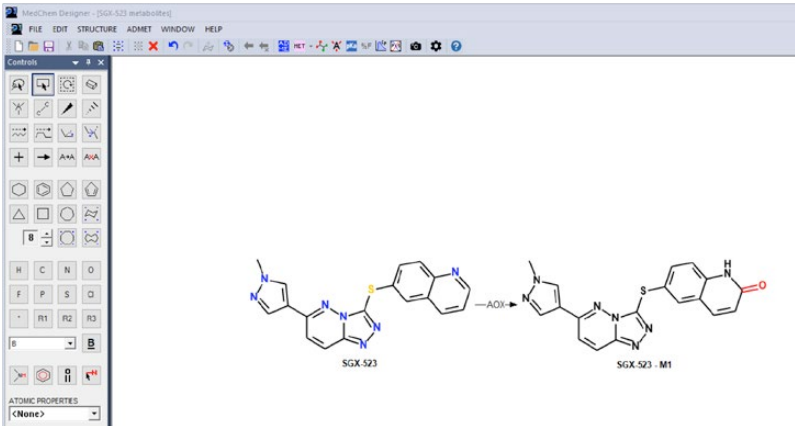


Cleavage of the carbamate group by an esterase is the first step in activation of the prodrug capecitabine.

- Expert rules help ensure that only legitimate substrates produce metabolites
- Users can easily customize rules
- Generate esterase metabolites

MedChem Designer will now display **glucuronidated metabolites**.

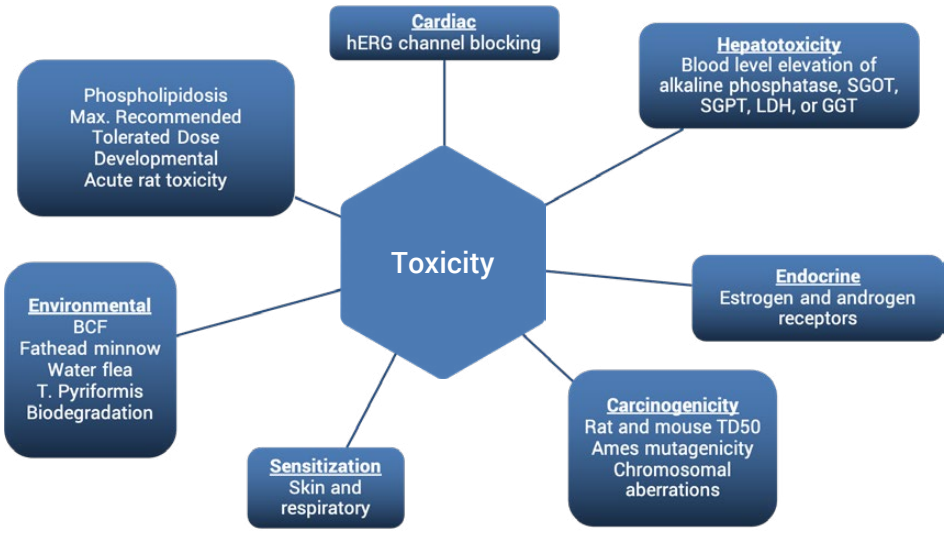




AOX_Substr and AOX_Sites models are applied to a molecule and **AOX metabolites** are displayed in MedChem Designer.

Toxicity Module

No early compound candidate screening tool should neglect toxicity aspects. Living up to its name, ADMET Predictor features a rapidly growing array of toxicity prediction models. The module features models covering a large range of toxicities included cardiac, hepatotoxicity, endocrine, carcinogenicity, sensitivity and environmental.



ADMET Modeler™ Module

ADMET Modeler automates the difficult and tedious process of developing high quality predictive structure-property models from experimental data. It works seamlessly with ADMET Predictor structural descriptors as inputs and appends the selected final models back to ADMET Predictor as an additional predicted property. Below are three keys to developing good predictive models:

1. Clean and consistent data
2. Appropriate and accurate descriptors
3. Good training algorithms

ADMET Predictor provides many tools for assessing the quality of the data. For example, it is easy to find duplicate structures within a spreadsheet. If duplicates exist, do they have the same experimental value. Matched molecular pair analysis can be used to find pairs of molecules that have high molecular similarity and very different experiment end points. It is important to verify the experimental results in these cases. ADMET Predictor computes over 300 descriptors from the 2D structure of a molecule.

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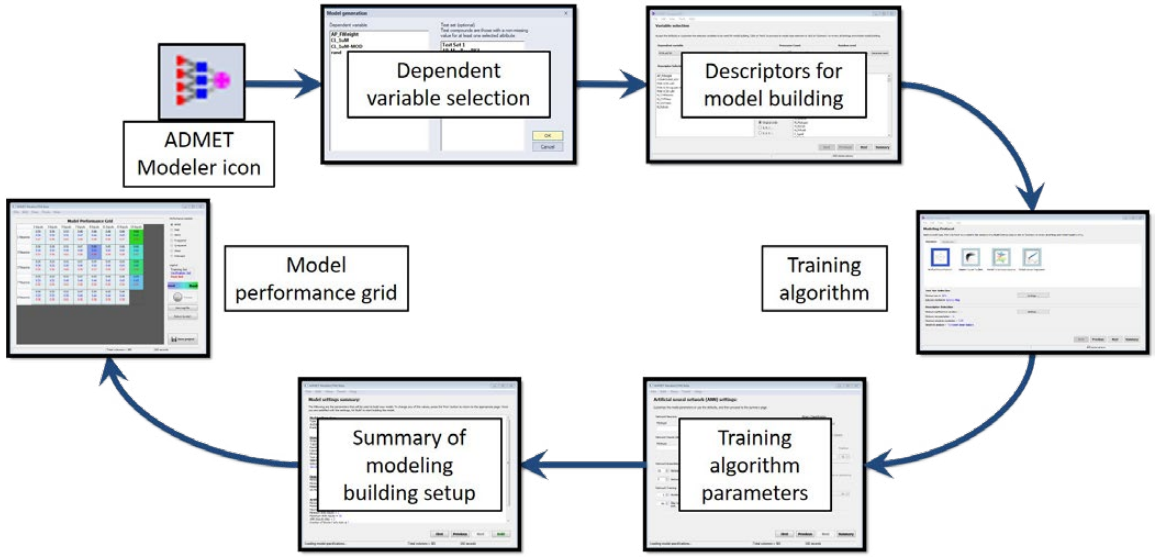
This includes atomic and reactivity descriptors produced by our EEM (Electronegativity Equalization Method) Hückel model that is parameterized to reproduce high level ab initio calculations. Training algorithms include artificial neural network (ANN), support vector machine (SVM), kernel partial least squares (KPLS), and multiple linear regression (MLR).

The diagram below illustrates the intuitive model building workflow in ADMET Modeler. The first step is to select the dependent variable, i.e., the property you'd like to model. Next, one can select the descriptors to use during the model building process. Users can select models, e.g., S+logP as descriptors in the new model. Additionally, one can select their own descriptors, provided that they are present in the spreadsheet. The next step is to select the training algorithm and parameters for model building. A summary of the setup is presented and if it is acceptable then models are built using the specified algorithm.

Additional features:

- Multi-class (greater than 2) classification models can now be built using Artificial Neural Network Ensembles (ANNEs)
- Performance plots for binary classification models can be now be colored coded by confidence value
- DELTA model approach allows users to incorporate in-house data into our global models



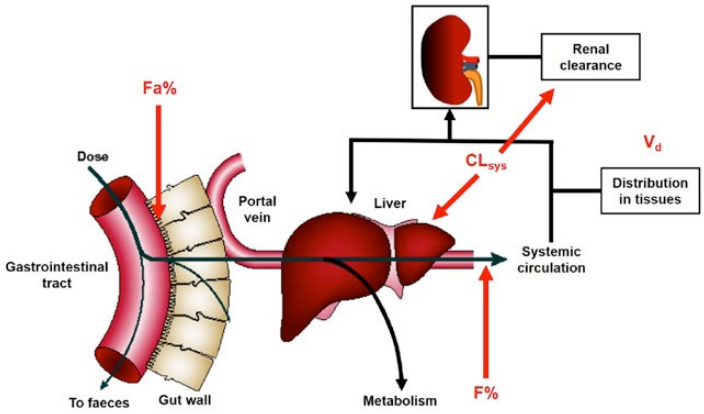
Clark R.D., Daga P.R. (2019) Building a Quantitative Structure-Property Relationship (QSPR) Model. In: Larson R., Oprea T. (eds) Bioinformatics and Drug Discovery. Methods in Molecular Biology, vol 1939. Humana Press, New York, NY. **https://doi.org/10.1007/978-1-4939-9089-4_8**

HTPK Simulation Module

The HTPK Simulation Module combines the **#1-ranked mechanistic absorption/PBPK models** with the **#1-ranked ADME property predictions** in order to predict the following *in vivo* properties in **rats** and **humans**:

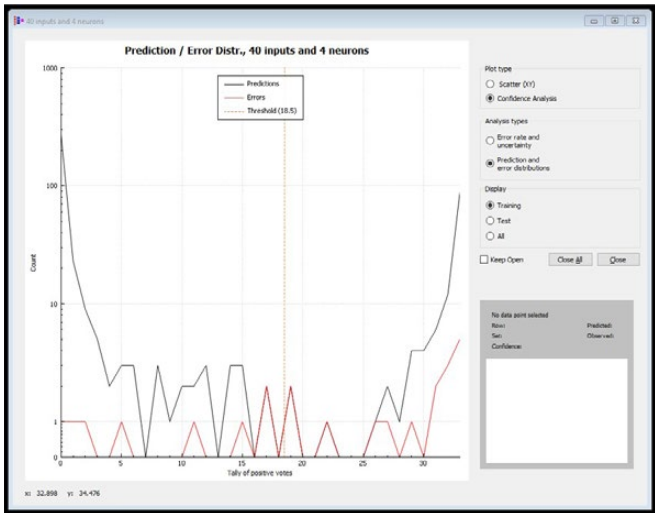
- Fraction absorbed (Fa%)
- Oral bioavailability (F%)
- Mechanistic Volume of distribution (Vd)
- Dose (D) needed to reach a user-specified plasma concentration (Ceff)
- Cmax
- Tmax
- AUC

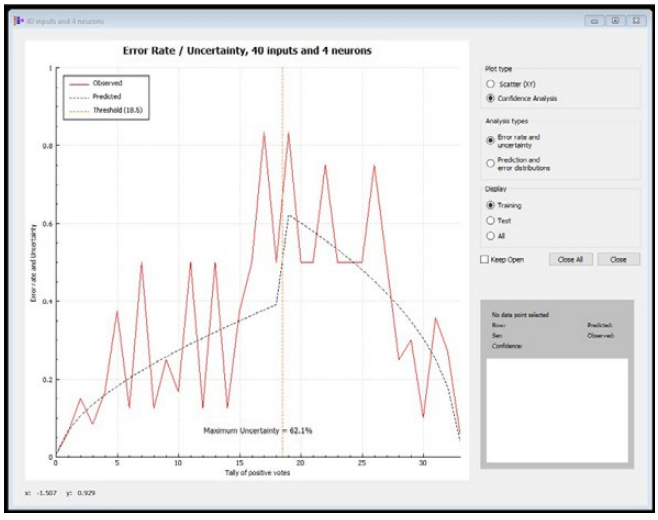
The image on the left illustrates processes that occur *in vivo*. The gastrointestinal tract is represented by our ACAT™ (Advanced Compartmental Absorption and Transit) model that consists of nine compartments. The drug molecule is represented in the unreleased, undissolved, and dissolved states. Molecules can be absorbed into the enterocyte via trans and para cellular diffusion. First pass liver clearance is computed using our rat or human intrinsic clearance models. Users can also supply *in vitro* liver microsomal or hepatocyte intrinsic clearance values. Sixteen compartments, e.g., adipose, brain, heart, are used in the PBPK model to compute volume of distribution (Vd). Systemic clearance is computed from liver and kidney clearance or it can be provided by the user. These values are incorporated in the prediction of the dose required to reach a user specified plasma concentration.



Confidence Analysis

Confidence analysis is based on the degree of concordance among the individual neural networks in an artificial neural network ensemble (ANNE) model. An example of the analysis is shown below. The image on the left is a plot of the count of total predictions (black line) and number of incorrect predictions (red line) at each "count of positive votes" (x-axis). There are over 100 predictions that have zero (0) positive votes, i.e., all of the 33 artificial neural networks predicted a negative. The red line shows that only one (1) of these predictions was incorrect. This data is converted to an error rate in the plot on the right. The dashed line represents two beta binomials, one for the negatives and one for the positives. Confidence estimates for arbitrary compounds are based on the number of positive votes and then derived from this type of plot.





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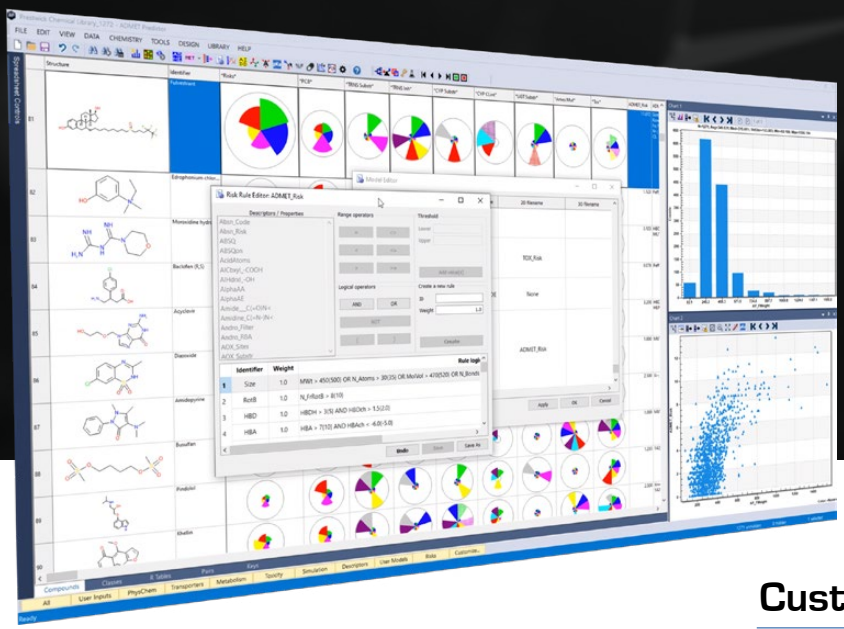
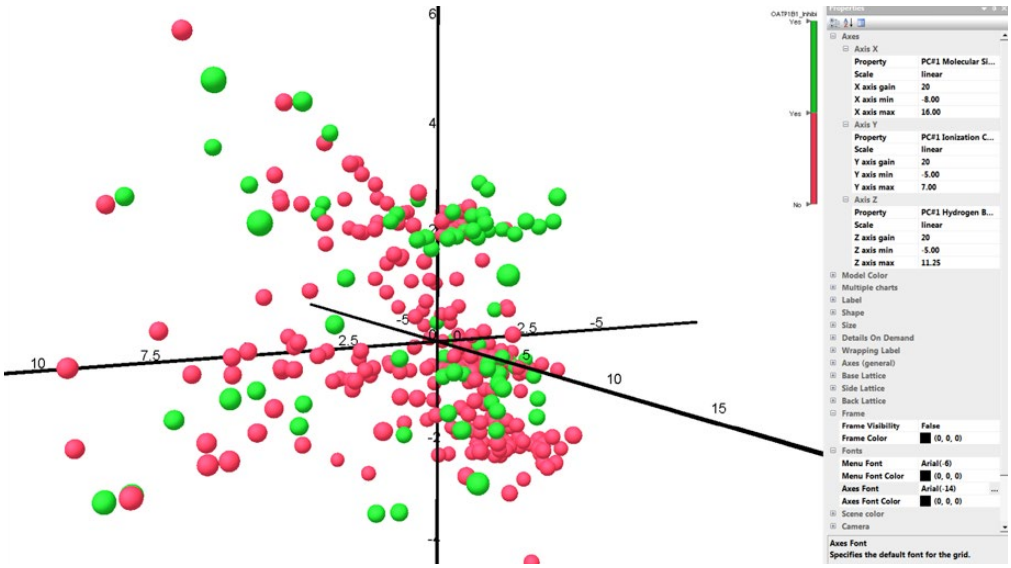


Customizable ADMET Risk™ Filters

A drug molecule's potential liability can be quickly assessed using our ADMET Risk scoring function. Property predictions were calculated for a subset of greater than 2,000 compounds from the World Drug Index (WDI). Cutoff values for each property were determined by considering the overall distribution of the property and setting the threshold so that 10% of the WDI compounds would be removed. The score is increased by one for each prediction that falls outside of the acceptable boundaries.

- **Absorption Risk** - Risk of low absorption from an oral dose
  - Incorporates size, charge, number of rotatable bonds, h-bond acceptors and donors, lipophilicity, solubility and permeability
- **CYP Risk** - Risk of high clearance or possible CYP inhibition
- **TOX Risk** - Risk of overall toxicity
  - hERG inhibition, acute rat or mouse toxicity, hepatotoxicity, and mutagenicity
- Global **ADMET Risk** summarizing all of the above in one
- Scoring functions can be customized to incorporate user's preferred cutoffs or properties

Chemical Space Visualization



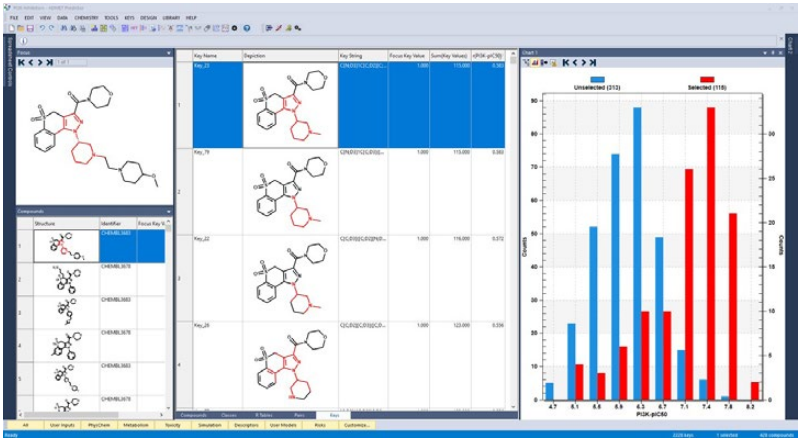
Molecular descriptors calculated by ADMET Predictor can be used to visualize chemical space. The graph above shows the principal components of molecular sizeand shape, ionization characteristics, and hydrogen bonding for a set of compounds that were tested for OATP1B1 inhibition. The green colored points are OATP1B1 inhibitors.

MedChem Studio™ Module - Intuitive Class Generation

ADMET Predictor 10.0, can compute various types of fingerprints including Extended-Connectivity Fingerprints (ECFPs), internal (MACCS) fingerprints, unbranched fragments, and ring systems. Each fingerprint is represented by a row in the "Keys" tab. The portion of the molecule corresponding to the key is highlighted in red and the key in SMARTS format is displayed in the "Key String" column. The Pearson correlation coefficient between the fingerprint and a property, e.g. IC50, can be added as a column. The image below shows some of the fingerprints for a dataset of 428 PI3K inhibitors. The highlighted fragment (Key_23) is present in 115 out of the 428 compounds in the data set. The red bars in the PI3K-pIC50 chart represent the pIC50 values for these compounds. Compounds that contain this fragment have higher PI3K IC50 values, e.g., they are more active.

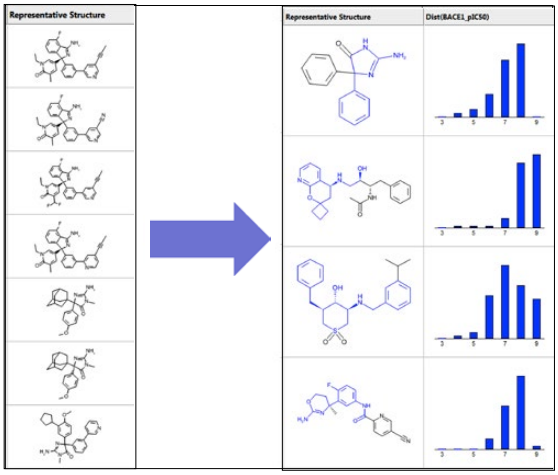
Additional features:

- Functionality to compute fingerprints, including Extended-Connectivity Fingerprints (EFCPs)
- Visualize fingerprints using new interface that highlights atoms on the molecule that correspond to the fingerprint
- Add column containing Pearson correlation coefficient between fingerprint and molecular property, e.g., IC_{50} value



MedChem Studio's class generation technology reproduces a chemist's reasoning by automatically organizing molecules into chemotypes based on shared scaffolds:

- Uses maximum common substructures (MCSs) rather than fingerprints, so results are chemically intuitive
- Generates scaffolds from the data rather than reading them from a pre-defined list, so novel structural motifs can be discovered
- Provides an ideal starting point for local QSAR generation, molecule design, and other analysis tasks
- User-defined scaffolds can also be used to generate classes
- "Frameworks" class generation option similar to the Murcko assemblies method



Example: The MedChem Studio Module was used to group 718 BACE1 inhibitors into 27 families containing common scaffolds. The largest class contains 243 compounds.

Each row corresponds to a unique class. A representative molecule in the class is displayed with the scaffold highlighted in blue. A distribution chart of the pIC50 values for the compounds in the class is also shown. Property values for the class can be shown as the average, minimum, maximum, or a variety of other statistical functions.

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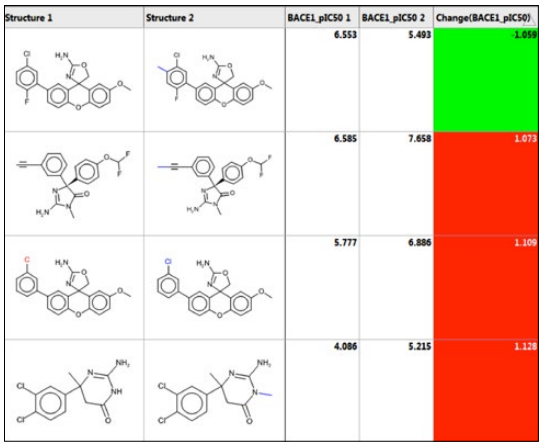
MedChem Studio™ Module - Matched Molecular Pairs

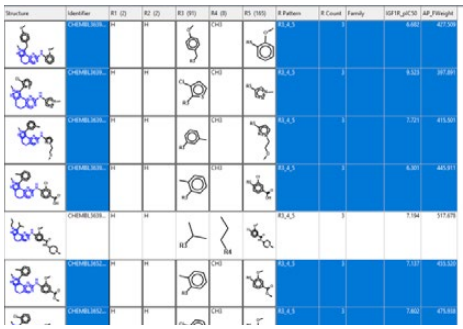


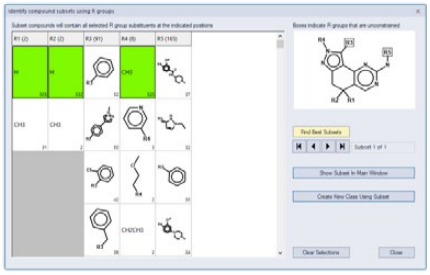
The pairs above result in less dramatic activity differences but they illustrate interesting SAR.

Matched molecular pairs (MMP) can be used to identify activity cliffs in a data set or to perform an analysis to identify and possibly exploit structural trends in property values:

- A MMP is a pair of molecules with a small, specific structural transformation
- MMP analysis (MMPA) is the automated identification of matched molecule pairs and analysis of the change in property values between the pairs
- The average change in property value is the expected size of the property value when the transformation is applied to another molecule
- MedChem Studio automatically creates a SMIRKS string that encodes each transformation rule
- These rules can be added to our "Combinatorial Transform feature in order to generate novel molecules potentially containing the desired change in property value

"Find Subsets using R-groups" finds the largest subset(s) of molecules with only two R-groups. In the example below, R1=R2=H and R4=CH3 represents 489 of the 534 compounds. This simplifies the data set and allows one to "drill down" into the data to understand SAR associated with R3 and R5.





License management with FlexNet Manager™ from Flexera Software LLC

ADMET Predictor uses the FlexNet Manager software for license management. This offers several advantages over our previous method:

- Program files are not split between server and client machines

- Improved license administration and handling between applications
  - Centralizes license structure: multiple vendor license files can be hosted by the same server
  - Monitor license status and usage details
  - Control access to the Flexera license server by configuring the communications port
  - Efficiently perform license server administration (start, stop, restart license servers, etc.) in real time

- Ease of implementation for companies already using Flexera based applications

- Ease of obtaining a license
  - No need to call in order to exchange licensing codes
  - Licenses will be made available through download

- Reduces license denials by allowing server redundancies

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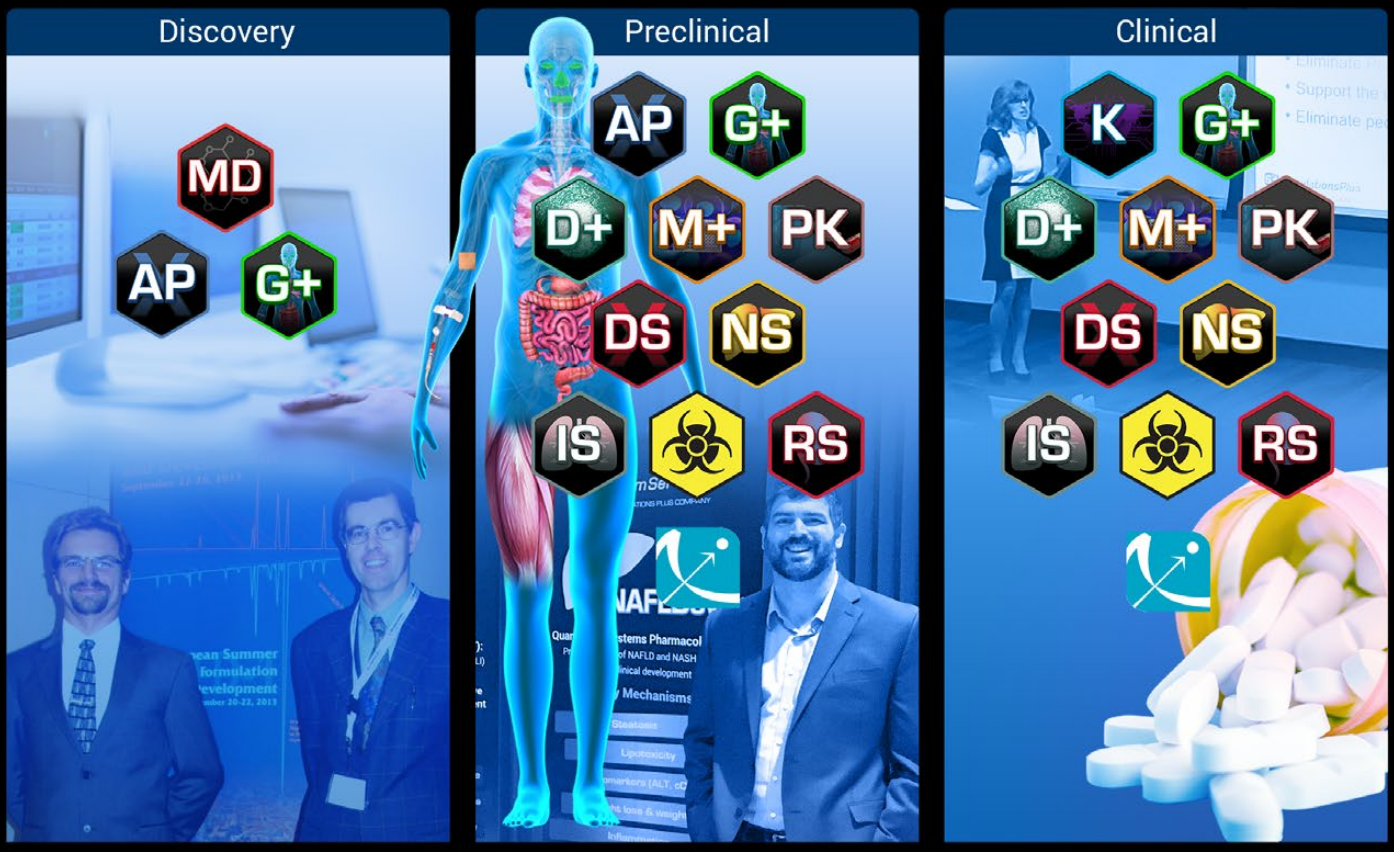
Model-Based Drug Development To Make Better Data-Driven Decisions

Our reputation as thought leaders in the areas of ADMET property prediction, PBPK PBBM modeling, pharmacometrics, and quantitative systems pharmacology/toxicology is earned through the success our clients have found through their relationship with us. We have the talent and 20+ years experience to translate science into **user-friendly software** and provide **expert consulting** supporting drug discovery, clinical development research, and regulatory submissions.



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