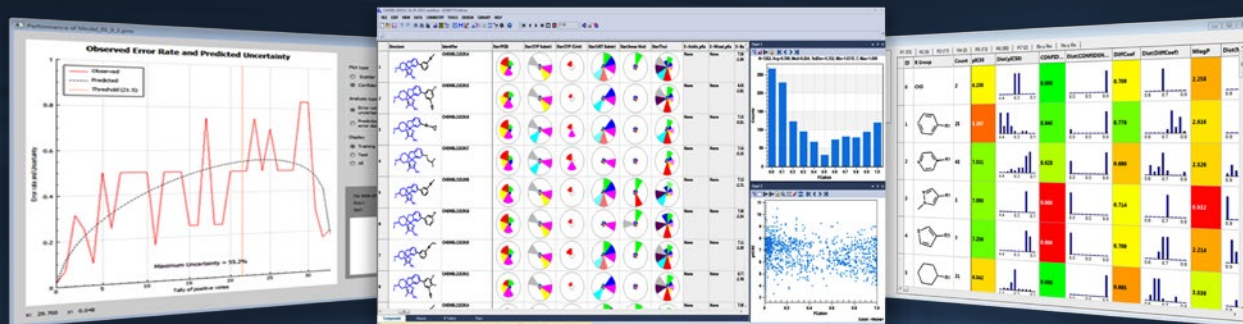


ADMET Predictor™

ADMET property estimation and
QSAR model building software



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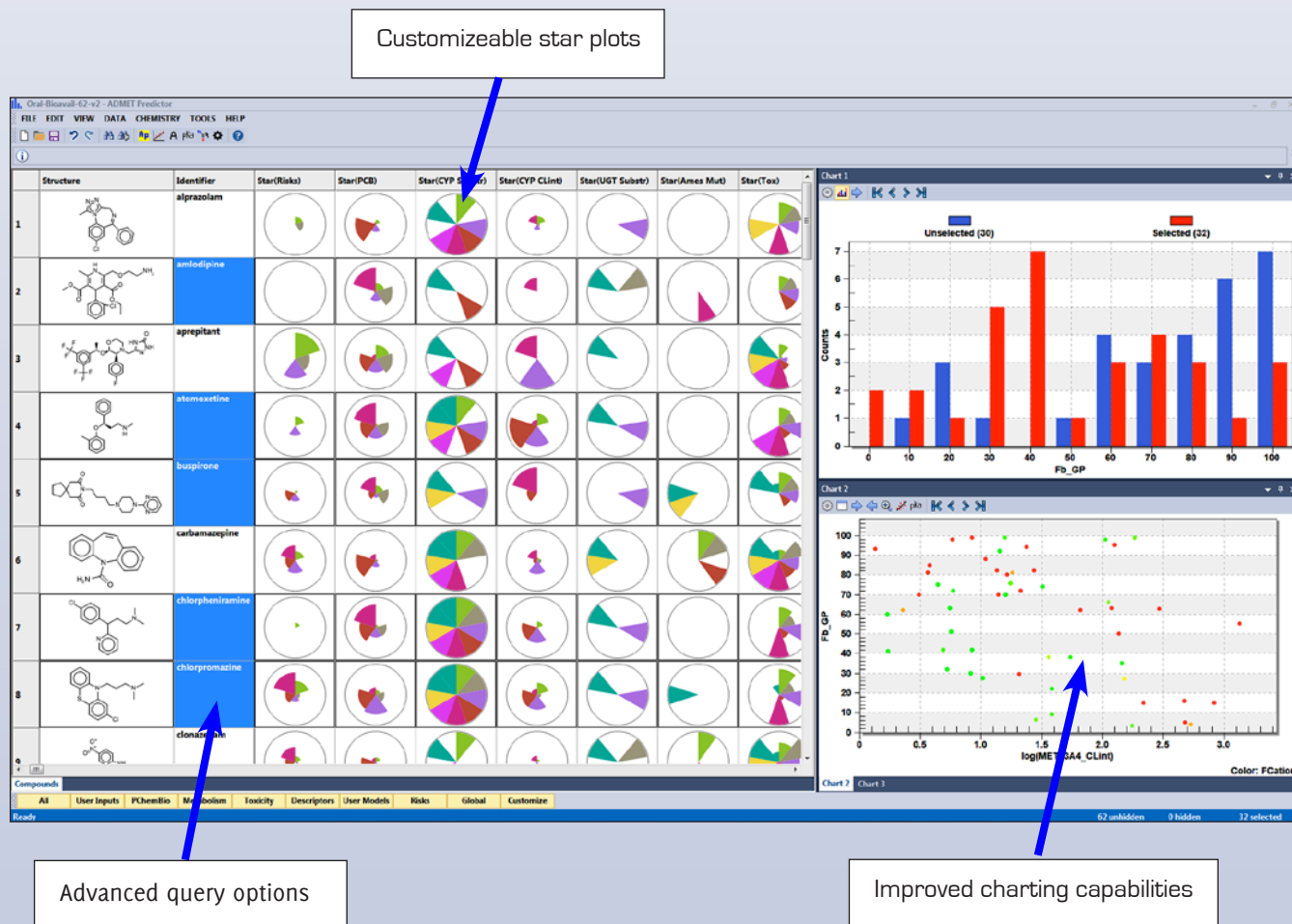
What is ADMET Predictor™?

ADMET Predictor™ is an advanced computer program that enables researchers to rapidly estimate a number of ADMET properties of new chemical entities (NCE's) from their molecular structure. Its predictive models are grouped into Physicochemical and Biopharmaceutical, Metabolism, and Toxicity modules. A compound's liabilities can be quickly assessed using our ADMET Risk™ scoring feature that

combines 24 predicted properties associated with absorption, metabolism, and toxicity. The ADMET Modeler™ module allows researchers to build high quality QSPR models using state of the art machine learning algorithms and atomic and molecular descriptors. Finally, ADMET Predictor models have been consistently ranked as the most accurate in independent published comparisons.^{1,4}

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.

NEW! Interface features and spreadsheet functions in ADMET Predictor 8.0



NEW Heat maps in ADMET Predictor 8.0

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.

Structure	Identifier	Solubility (ug/ml)	SLogP	N_Atoms	N_AromR
	10037895	3.300	3.426	18	3
	10467247	17.700	1.757	18	1
	11838365	11.700	3.315	23	2
	12141299	18.800	3.057	22	3
	12238894	0.300	3.237	24	3
	15793062	1.700	1.874	20	1
	16187949	20.800	4.014	22	2
	16189514	51.100	4.981	24	3
	16192552	2.800	3.488	23	3
	16194440	0.400	3.416	27	3
	16194440	93.100	3.860	31	3

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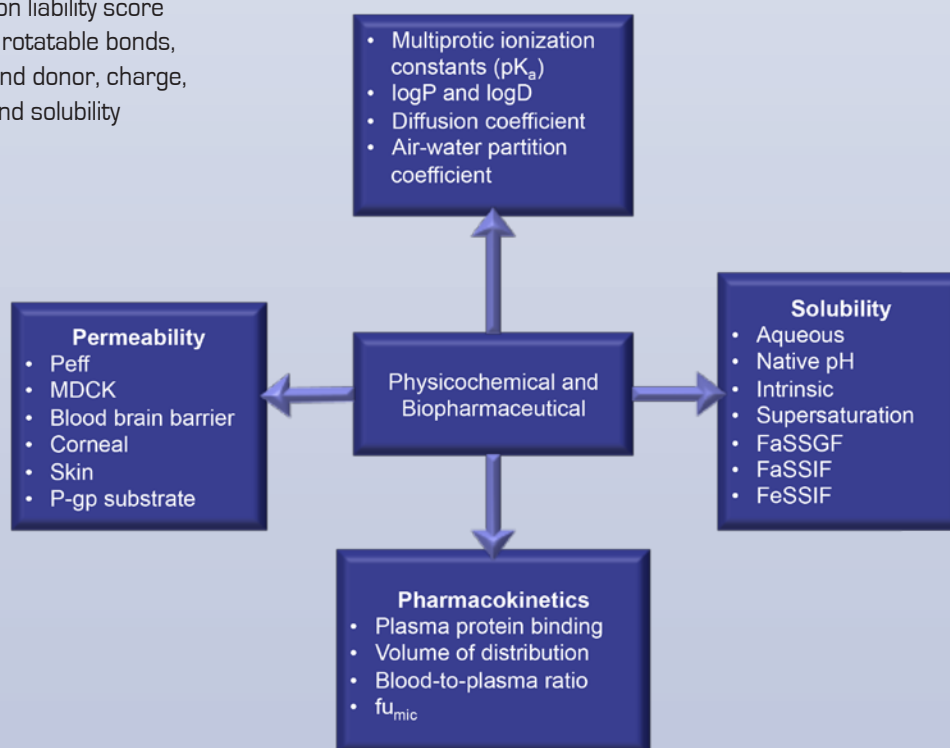
NEW Advanced query options

MedChem Designer™ can be used to specify simple substructure searches or more complicated Markush queries while the “Query Wizard” can be used for text and numeric searches.

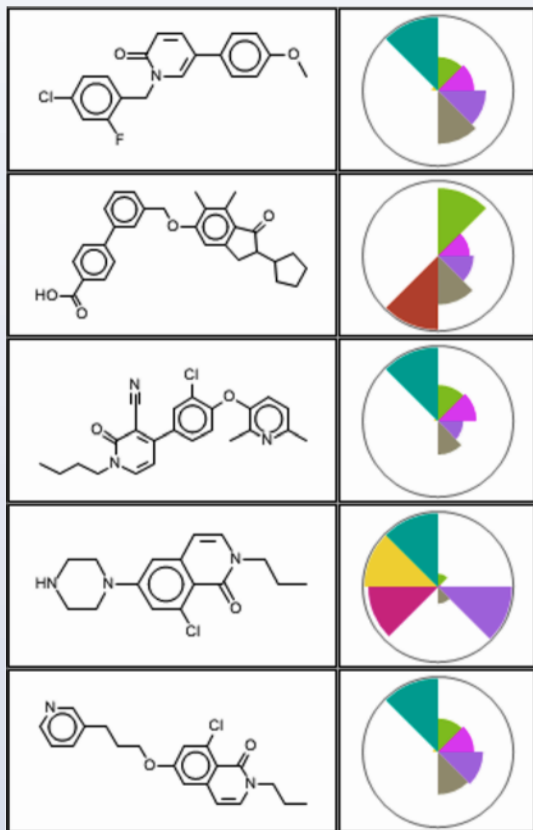
The screenshot displays the MedChem Designer software interface. The main window shows a chemical structure of a benzimidazole derivative. The 'Query Wizard' dialog box is open, showing a list of attributes including 'AP_Fragments', 'Atom count', 'Bond count', 'Duplicate Mols', 'Formal charge', 'H-bond acceptor', 'H-bond donor', 'Largest ring', 'Molecular weight', 'Name', 'Name', 'Negative charge', 'Positive charge', 'Pre-transform structure', 'PUBCHEM_ACTIVITY_OUTCOME', and 'PubChem_link'. The 'Query' field contains the text: 'TAU_PUBCHEM_ACTIVITY_OUTCOME = "Active" AND NPG_ArRing > 3'. The 'Current query' field is empty. The 'Logical operators' section shows 'AND' and 'OR' buttons. The 'Range operators' section shows '>', '<', and '=' buttons. The 'Query Wizard' dialog box also has buttons for 'Load From File', 'Add New Query', 'Save To File', 'Delete Query', 'Comment / Uncomment', and 'Undo Last'. The 'Search using a query' dialog box is also visible, with a 'Click here to enter SMARTS or other text' button and a 'Click a button on the right to input a query using a file or sketch tool' button. The 'Search using a query' dialog box has a 'Clear' button and 'OK' and 'Cancel' buttons. The 'Search using a query' dialog box also has checkboxes for 'Use exact matching', 'Search selected only', 'Do not deselect any items', and 'Do not alter structure highlighting'.

The Physicochemical and Biopharmaceutical Module in ADMET Predictor allows researchers to access several industry leading predictive models:

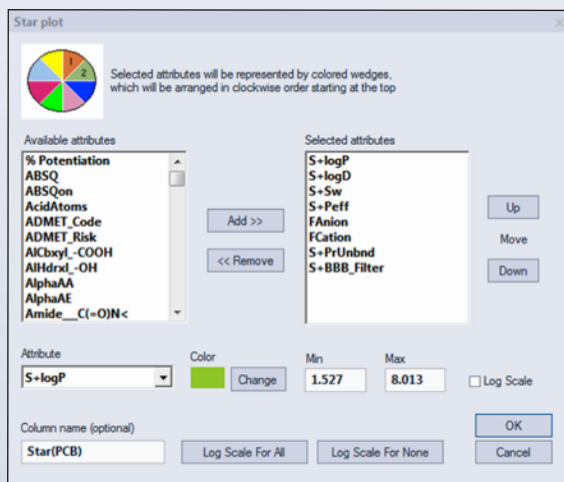
- Enhanced pKa (ionization constants; a multiprotic model)
- Diffusion coefficient in water (Hayduk-Laudie formula)
- logP (two models: artificial neural network ensemble and Moriguchi)
- logD (estimation of octanol-water distribution coefficient at user-defined pH)
- Air-water partition coefficient (Henry's Law Constant)
- Human effective permeability in jejunum (P_{eff})
- MDCK apparent permeability (P_{app})
- Permeability through rabbit cornea
- Human skin permeability
- Solubility
 - Native solubility (solubility in pure water @ 25°C)
 - Native pH at saturation in pure water @ 25°C
 - Intrinsic solubility in pure water @ 25°C
 - Salt solubility factor @ 25°C
 - Water solubility at user-specified pH
 - Biorelevant solubility in FaSSIF, FeSSIF & FaSGF
- Tendency to supersaturate (SupSat) in water.
- Two blood-brain barrier (BBB) models (a qualitative permeability model and a blood-brain partition coefficient model)
- Human plasma protein binding as percent unbound
- Human volume of distribution
- Blood-to-plasma concentration ratio
- Likelihood of P-glycoprotein efflux
- Likelihood of P-glycoprotein inhibition
- Likelihood of the hepatic OATP1B1 transporter inhibition
- Fraction unbound in liver microsomes
- S+Absn_Risk™ - absorption liability score composed of 8 rules; size, rotatable bonds, hydrogen bond acceptor and donor, charge, lipophilicity, permeability, and solubility



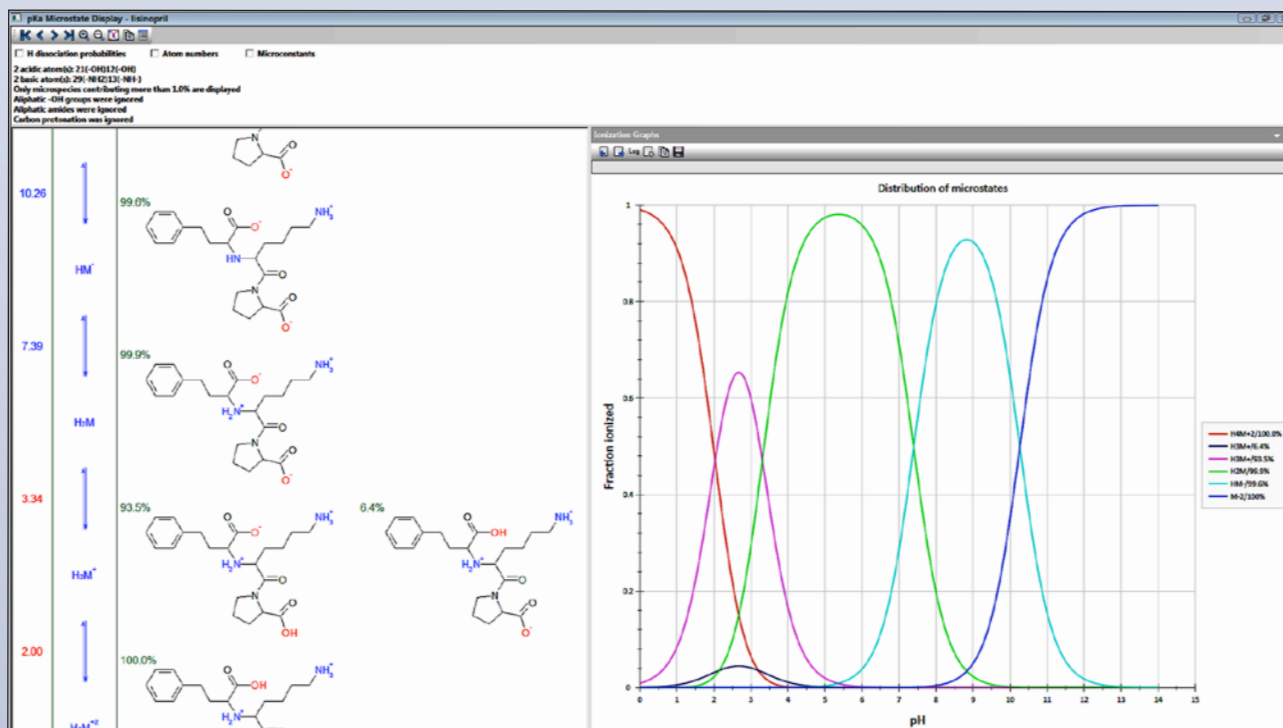
NEW! Automatic Star Plots



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.



S+pKa data set

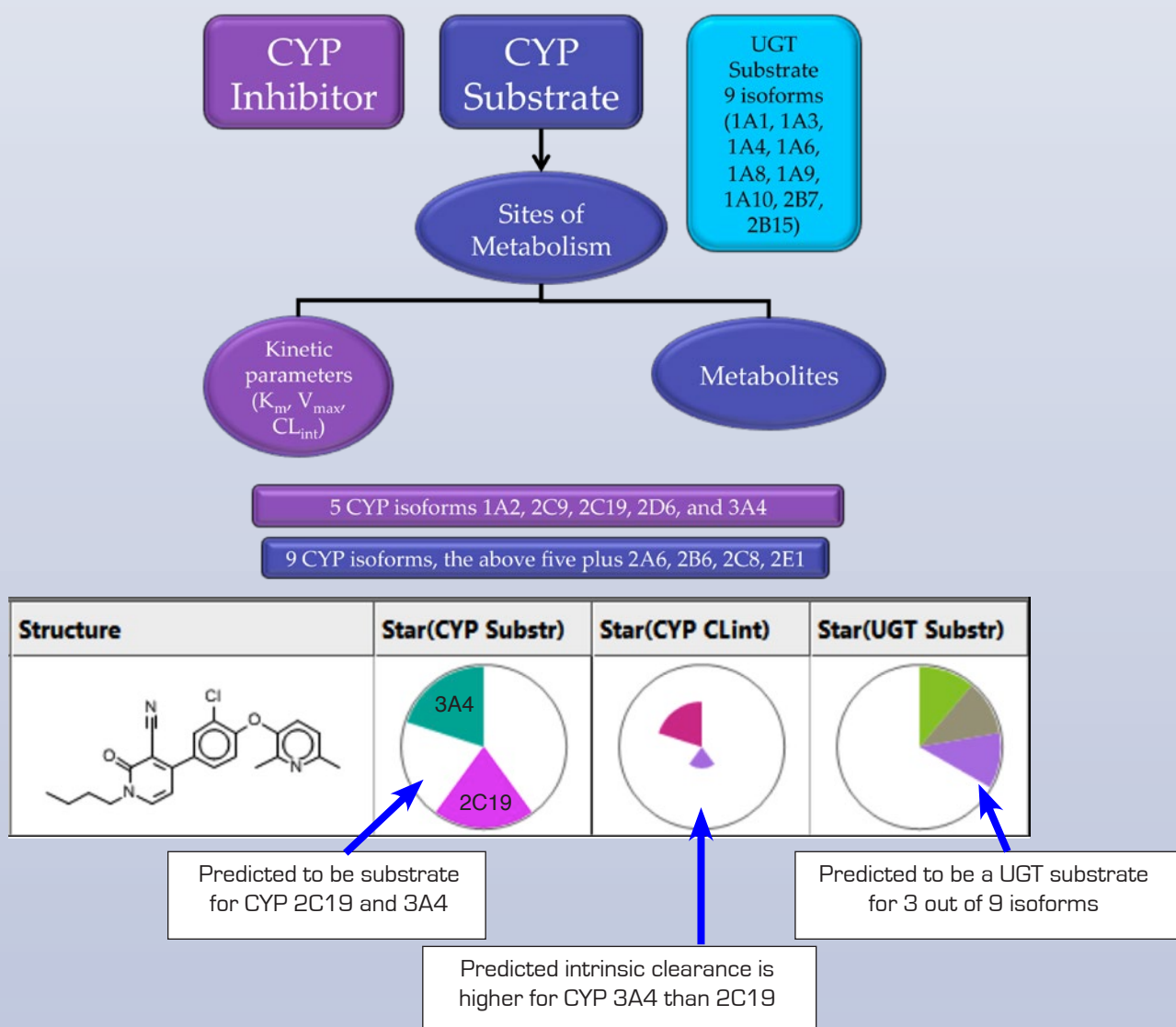


Microstate display for lisinopril. The graph shows the predicted fraction of each microstate at various pH values.

The ADMET Predictor Metabolism Module contains:

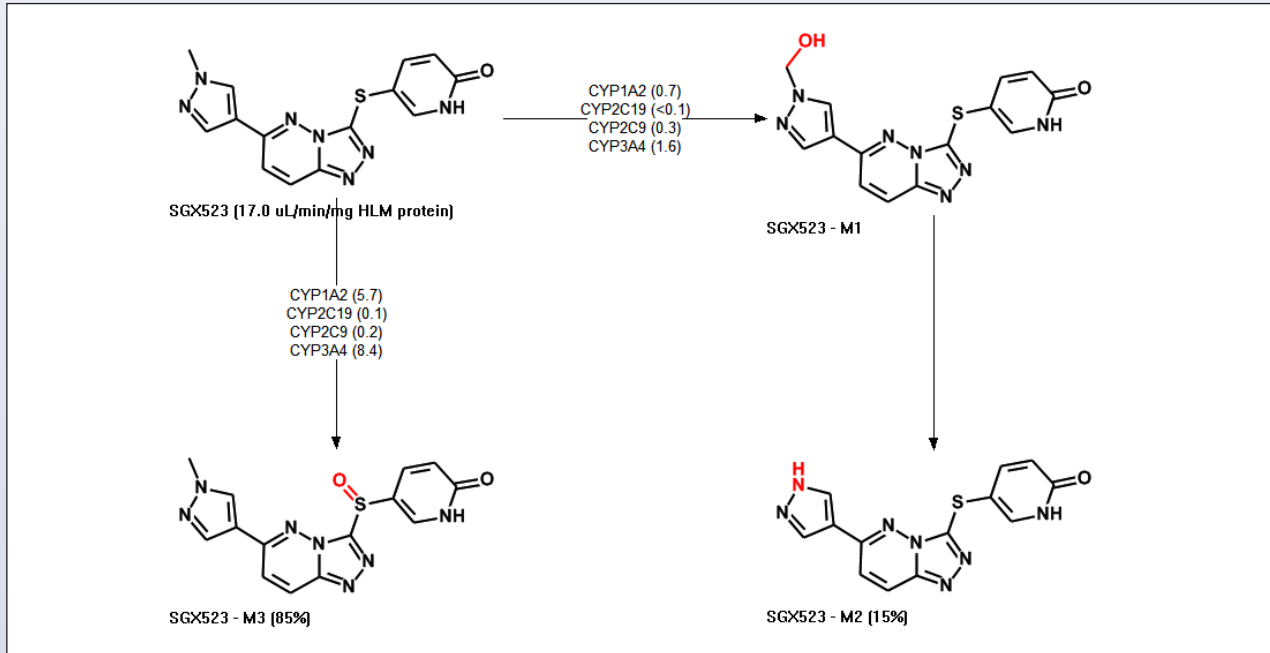
- Models to classify compounds as general inhibitors of 5 major CYP isoforms
- Qualitative and quantitative inhibition models for CYP3A4 with either midazolam or testosterone as the substrate
- Models to classify compounds as human uridine 5'-diphosphate-glucuronosyltransferase (UGT) substrates for 9 UGT isoforms
- Human liver microsome (HLM) intrinsic clearance (CL_{int}) scaled to fraction unbound in liver microsomes
- Models to classify compounds as substrate/nonsubstrate for 9 CYP isoforms
- Sites of metabolism models – if a compound is predicted to be a substrate of a particular CYP then the sites of metabolism will be predicted
 - Metabolites can be visualized in MedChem Designer™
 - Structures can be modified in MedChem Designer in order to quickly determine how the change affects metabolic sites and kinetic parameters
- Kinetic parameter models
 - K_m, V_{max}, and CL_{int} are predicted for each atom that is predicted to be a site of metabolism
 - Atomic and molecular kinetic parameters are reconciled via:

$$CL_{int} = V_{max} / K_m$$
- CYP_Risk™ - cytochrome P450 liability score composed of 8 rules: high predicted clearance for the five major CYP isoforms, high predicted HLM clearance, and inhibition of CYP 3A4 with midazolam or testosterone as the substrate

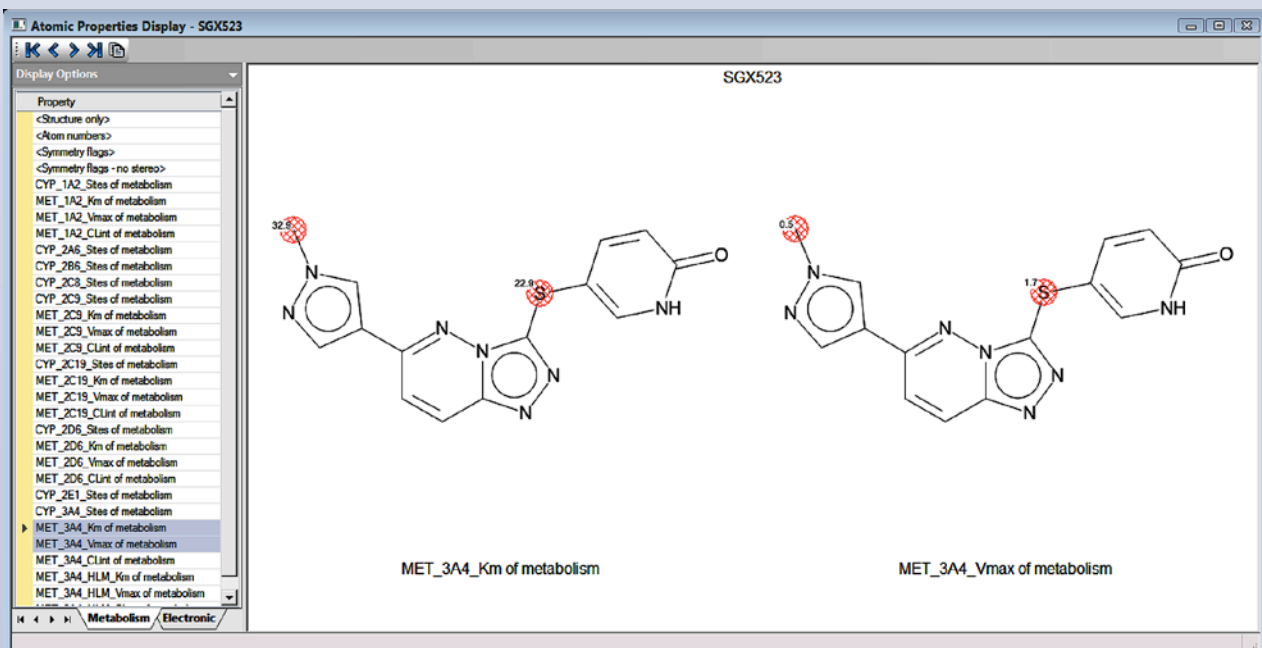


Metabolism Module continued

Metabolite prediction: the CL_{int} of the parent molecule is displaced 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.



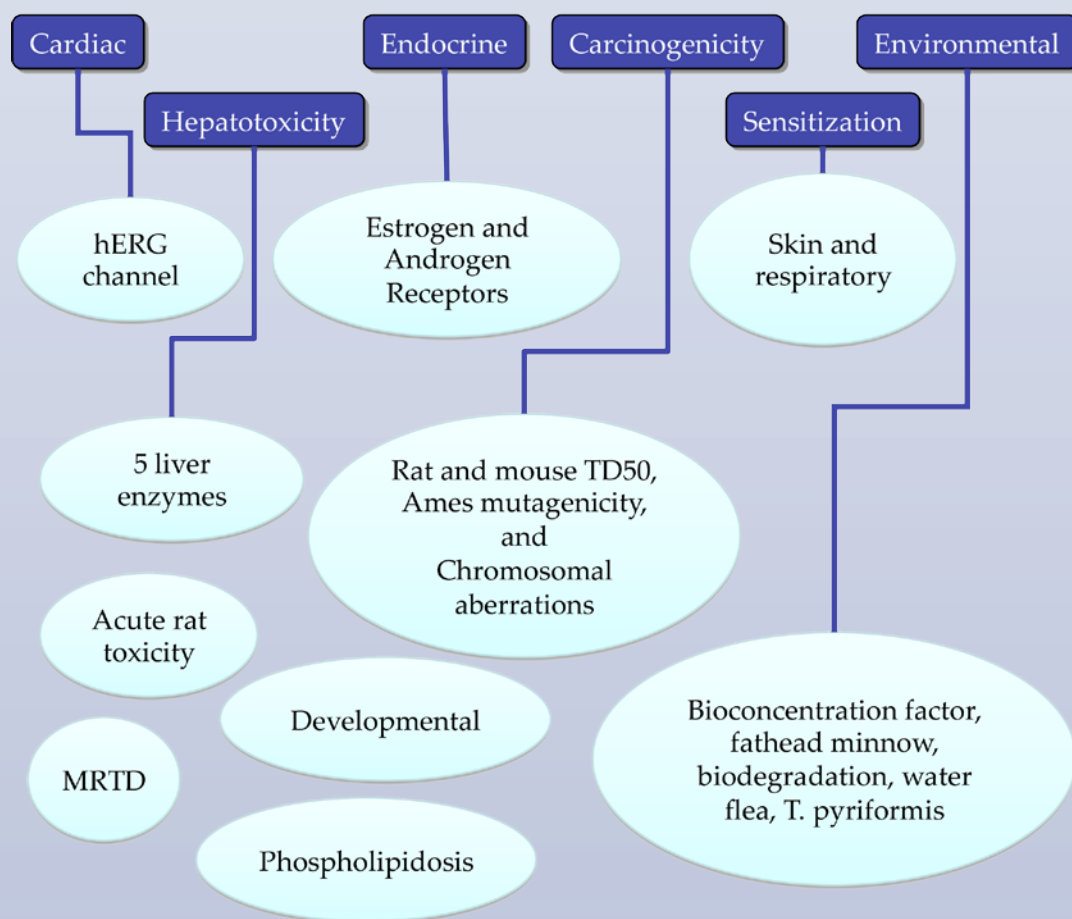
ADMET Predictor predicts K_m and V_{max} for each site of metabolism.



Toxicity Module

The ADMET Predictor Toxicity Module contains models that predict toxicity relative to food products, pharmaceuticals, and environmental chemicals:

- hERG-encoded K⁺ channel affinity as pIC50
- Estrogen receptor toxicity
- Androgen receptor toxicity
- Maximum recommended therapeutic dose (MRTD)
- Chromosomal aberrations
- Phospholipidosis
- Qualitative filter of mutagenicity in 5 strains of Salmonella bacteria with and without microsomal activation
- Carcinogenicity in rats as TD50
- Carcinogenicity in mice as TD50
- Human liver adverse effects
- Likelihood of biodegradation
- Fathead minnow lethality as LC50
- Acute toxicity in Daphnia magna (water fleas) as pLC50
- Acute lethal toxicity in rat as LD50
- Allergic skin sensitization
- Environmental bioconcentration factor
- Allergic respiratory sensitization
- Reproductive/developmental toxicity
- Acute toxicity in Tetrahymena pyriformis as IGC50
- TOX_Risk™ - toxicity liability score composed of 7 rules: hERG, acute rat toxicity, rat and mouse carcinogenicity, hepatotoxicity, liver enzyme elevation, and Ames mutagenicity



Simulation Module

The Simulation Module uses selected ADMET estimations, doses, and predefined 9-compartment human gut physiology model (ACAT™) to predict fraction absorbed (Fa). A deterministic, region-dependent system of differential equations is solved assuming that the drug undergoes instant dissolution to maintain saturation if sufficient dose is available to saturate in the compartment.

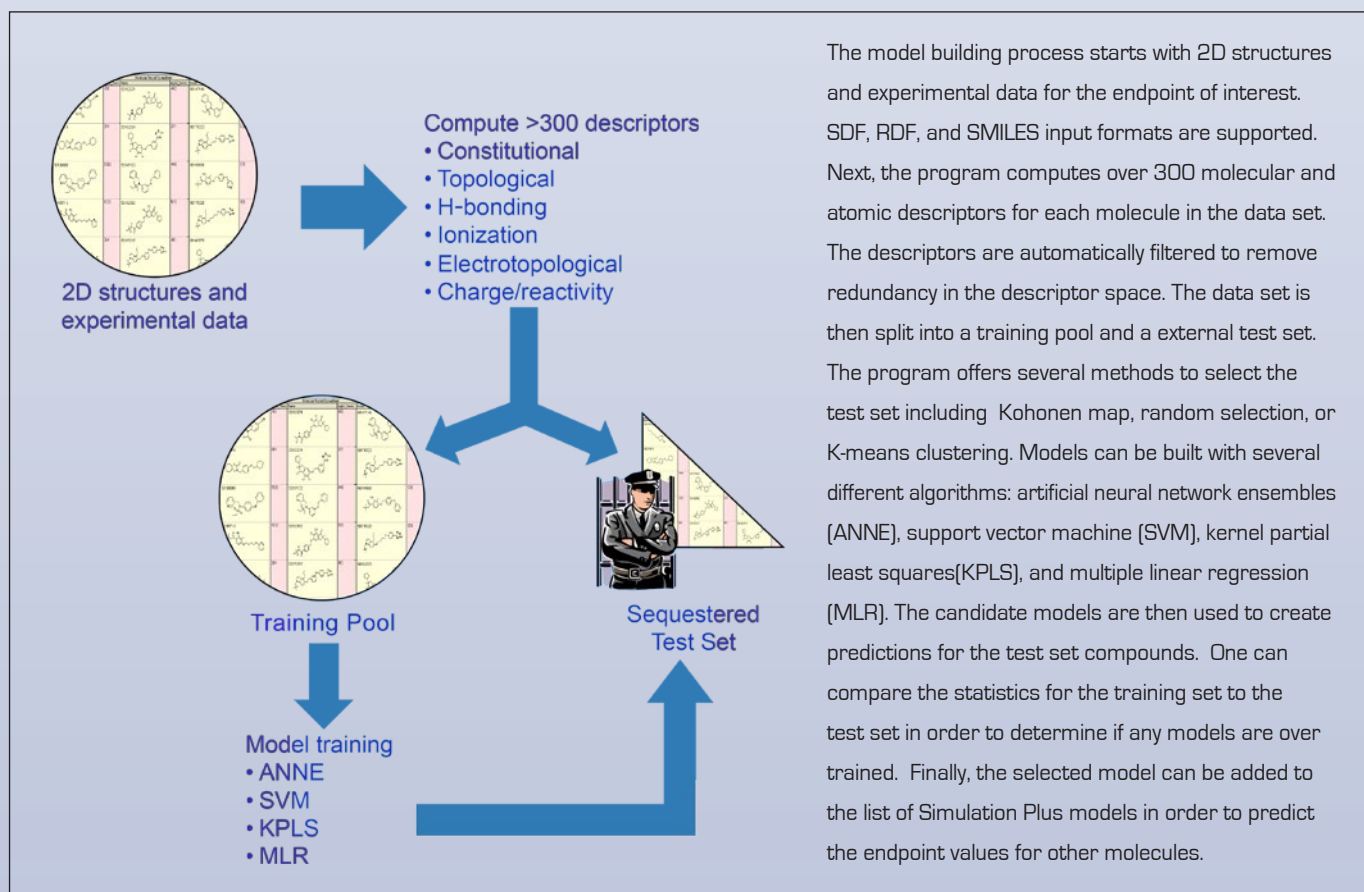
- Human fraction absorbed (by simulation at 1 mg, 10 mg, 100 mg, and 1000 mg dose levels)
- SimDOSE - assess the likely dose needed to achieve a therapeutic concentration at steady-state

ADMET Modeler™ Module

Automated and seamless QSPR model building module

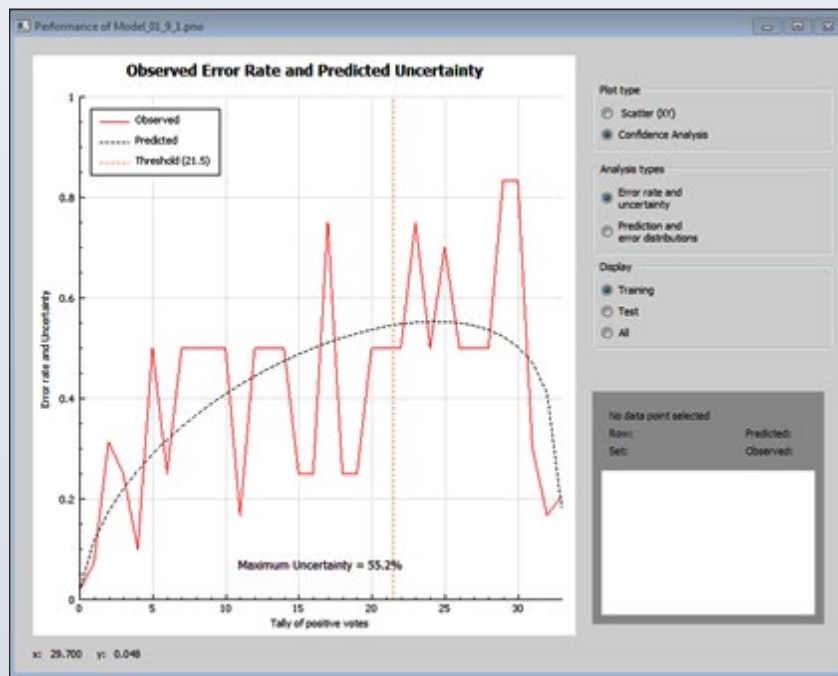
ADMET Modeler is an integrated module of ADMET Predictor™ that automates the difficult and tedious process of making high quality, predictive structure-property models from sets of experimental data. It works seamlessly with ADMET Predictor structural descriptors as its inputs, and appends the selected final model back to ADMET Predictor as an additional predicted property. The following modeling methods are offered by ADMET Modeler:

- Kohonen Self-Organizing Maps
- Artificial Neural Network Ensembles for regression and binary classification
- Support Vector Machine Ensembles for regression and classification
- Kernel Partial Least Squares and Ordinary PLS for regression
- Multiple Linear Regression
- SALI analysis



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 observed and predicted error rate and uncertainty distribution across the tally of positive votes is shown below. The red line shows the observed error rate for the training set. The black dashed line represents the probability distribution function from the beta binomial.

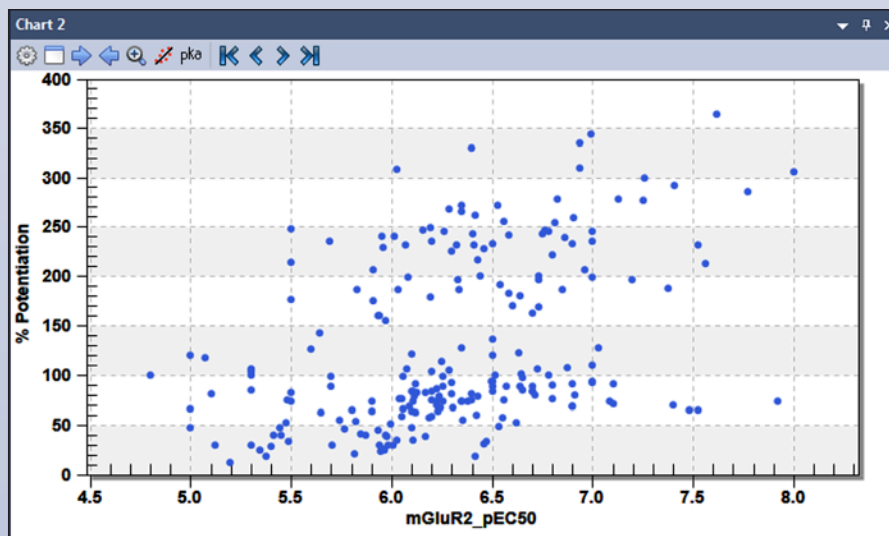
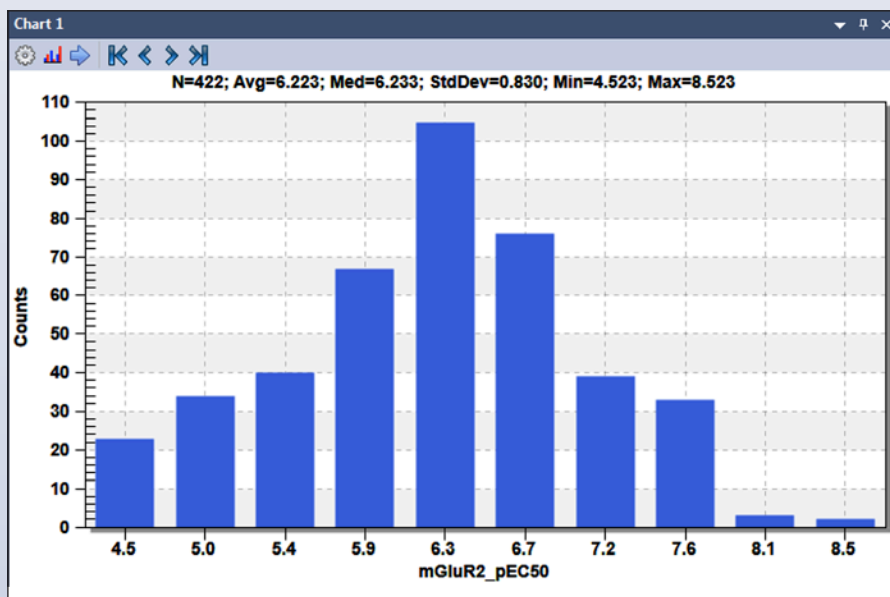
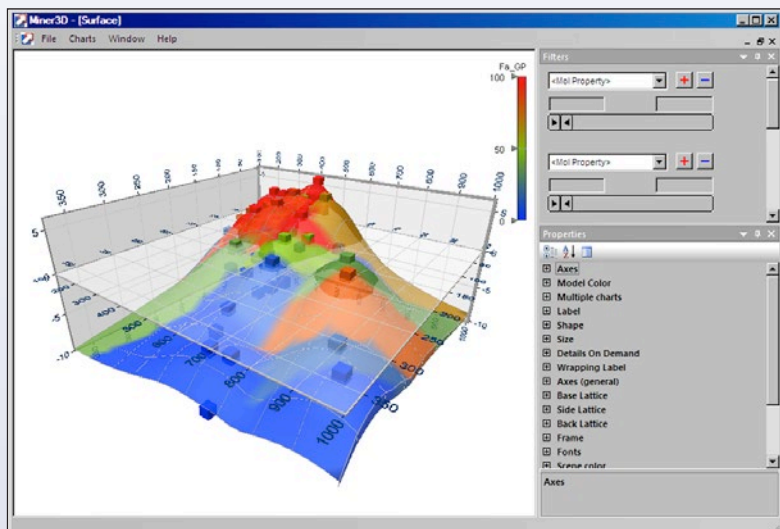


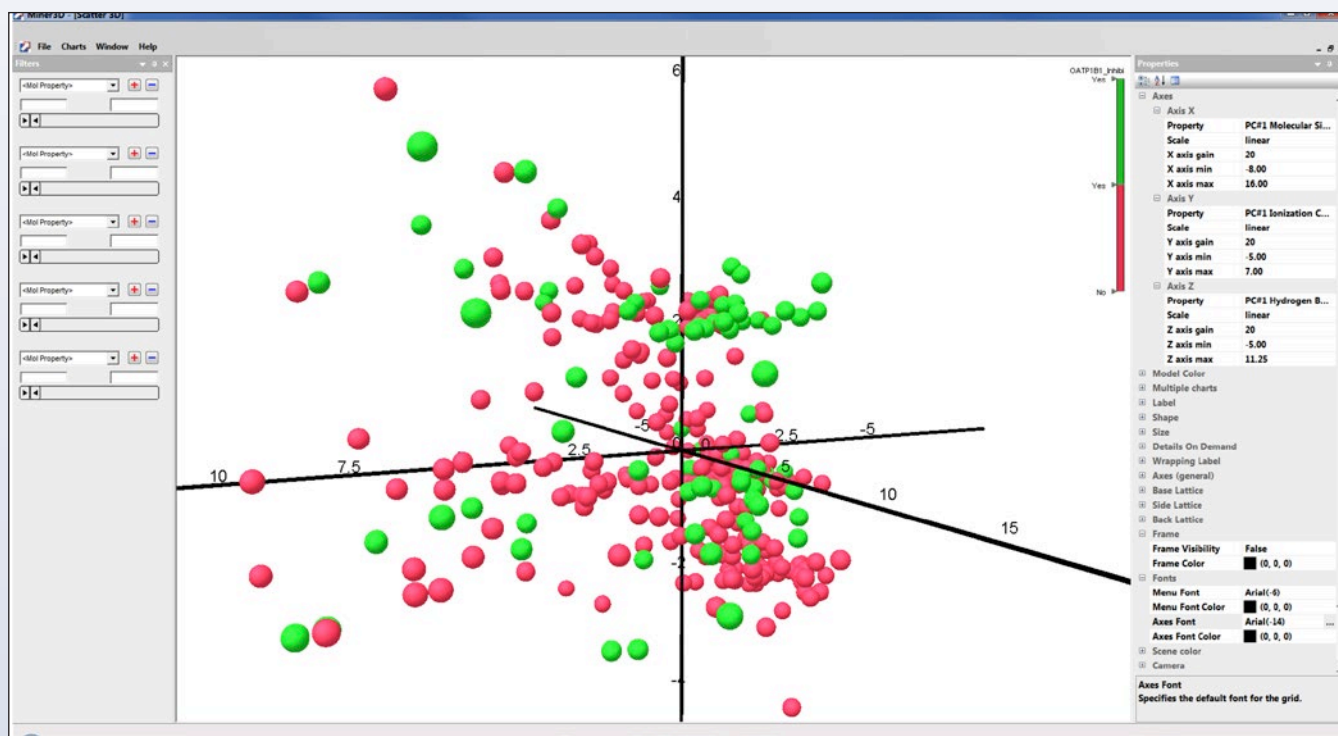
Customizable ADMET Risk™ Filters

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

Plotting Capabilities





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

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