

Rapid optimization for drug-like properties to reduce downstream failures

Computational prediction based solely on chemical structures

ADMET Descriptors in Discovery Studio

One of the most daunting hurdles a drug candidate must pass is having favorable ADMET characteristics. ADMET refers to the absorption, distribution, metabolism, excretion, and toxicity properties of a molecule within an organism. Optimizing these properties during early drug discovery is crucial for reducing ADMET problems later in the development process¹. Such early identification helps to make your research process more efficient and cost-effective by allowing you to eliminate compounds with unfavorable ADMET characteristics early on, and evaluate proposed structural refinements that are designed to improve ADMET properties, prior to resource expenditure on synthesis.

ADMET Descriptors in Discovery Studio[®] include models for intestinal absorption, aqueous solubility, blood brain barrier penetration, plasma protein binding, cytochrome P450 2D6 inhibition, and hepatotoxicity. With these advanced predictive tools, you can optimize your drug discovery efforts and gain critical insight early on to avoid expensive reformulation later.

The Discovery Studio Research Environment

ADMET Descriptors are part of the Discovery Studio research environment, which is a comprehensive suite of modeling and simulation solutions for life science researchers. Because Discovery Studio is built on SciTegic Pipeline Pilot, Accelrys' scientific operating platform, these modules are extensively integrated with many other powerful software applications that will allow you to carry out such tasks as aligning sequences, creating protein homology models, building and analyzing pharmacophore models, and examining receptor ligand interactions.

ADMET Descriptors

ADMET Descriptors perform computational prediction based solely on the chemical structure of the molecule. Included are six models that provide a comprehensive analysis of ADMET characteristics:

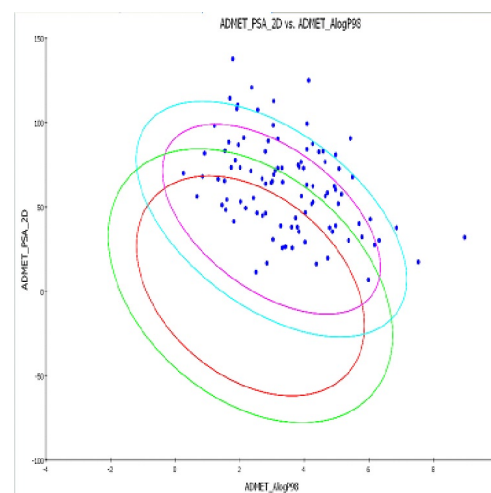
- **ADMET Absorption:** Predicts Human Intestinal Absorption (HIA) after oral administration and reports a classification of absorption level².

The pattern recognition model underlying the method is based on calculations of logP³ and polar surface area and is derived from a training set of 199 well-absorbed molecules with actively transported molecules removed.

- **ADMET Aqueous Solubility:** Predicts the solubility of each compound in water at 25°C and reports the predicted solubility and a ranking relative to the solubilities of a set of drug molecules. A genetic partial least squares method was used to derive the model based on a training set of 784 compounds with experimentally measured solubilities.
- **ADMET Blood Brain Barrier:** Predicts the blood brain barrier penetration of a molecule, defined as the ratio of the concentrations of solute (compound) on the both sides of the membrane after oral administration, and reports the predicted penetration as well as a classification of penetration level. The model combines a confidence ellipse derived from over 800 compounds classified as CNS therapeutics, and a robust regression model based on 120 compounds with measured penetration, to predict penetration values for those molecules falling within the confidence ellipse.
- **ADMET Plasma Protein Binding:** Predicts whether or not a compound is likely to be highly bound to carrier proteins in the blood. Predictions are based on the similarity between the candidate molecule and two sets of marker molecules; one used to flag binding at a level of 90 percent or greater and the other at 95 percent or greater. Binding

levels predicted by the marker similarities are modified according to conditions on calculated logP.

- ADMET CYP2D6 Binding:** Predicts cytochrome P450 2D6 enzyme inhibition and reports whether or not a compound is likely to be an inhibitor, as well as a probability estimate for the prediction. Predictions are based on an ensemble recursive partitioning model of a training set of 100 compounds with known CYP2D6 inhibitions.
- ADMET Hepatotoxicity:** Predicts the occurrence of dose-dependent human hepatotoxicity. Compounds are classified as either toxic or non-toxic, and a confidence level indicates the model's likely accuracy. Predictions are based on an ensemble recursive partitioning model of 382 training compounds known to exhibit liver toxicity or to trigger dose-related elevated aminotransferase levels in more than 10 percent of the human population.



Plot of Polar Surface Area (PSA) vs. LogP for a sample compounds from the the World Drug Index (WDI) database showing the 95% and 99% confidence limit ellipses corresponding to the Blood Brain Barrier and Intestinal Absorption models.

These ADMET Descriptors in Discovery Studio can allow you to gain critical insight to help you make well-informed, smart decisions during drug development. You'll be able to invest your time wisely, focusing on compounds with much higher probabilities for success in ADMET testing.

References:

1. Prentis, R.A., Lis, Y., and Walker, S.R., *Br. J. Clin. Pharmacol.*, **1988**, *25*, 387-396.
2. Egan, W.J., Merz, K.M., Jr., and Baldwin, J.J., *J. Med. Chem.*, **2000**, *43*, 3867-3877.
3. Ghose, A. K., Viswanadhan, V. N., Wendoloski, J. J., *J. Phys. Chem.*, **1998**, *102*, 3762-3772.

Required Software

DS Visualizer Pro Enterprise (or DS Visualizer Pro with Pipeline Pilot Server)