

FAQ

StarDrop: P450 Metabolism Models

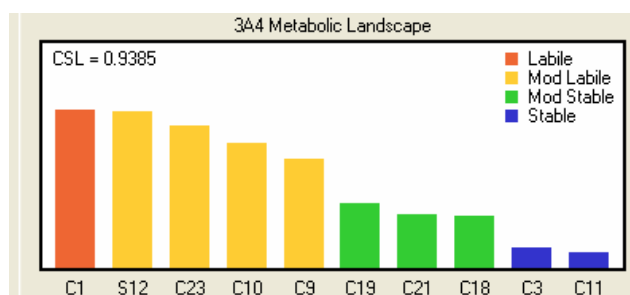
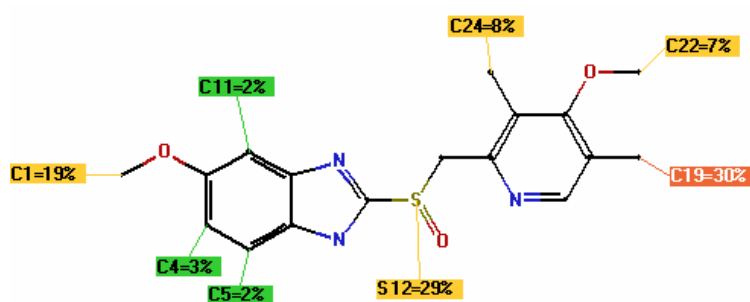
StarDrop's optional P450 module provides a set of proprietary P450 metabolism models which were originally developed by the Camitro Corporation. These models identify a molecule's most reactive sites towards metabolism for three human cytochrome P450 enzymes: CYP3A4, CYP2D6 and CYP2C9 (accounting for approximately 95% of human Phase 1 metabolism).

The StarDrop P450 models are based on quantum mechanical simulations of the chemical reactions that lead to the formation of metabolites. The reaction mechanisms leading to N- and O-dealkylation, aliphatic hydroxylation, aromatic- and S-oxidation are modelled. These represent approximately 90% of the observed reactions metabolised by P450 enzymes.

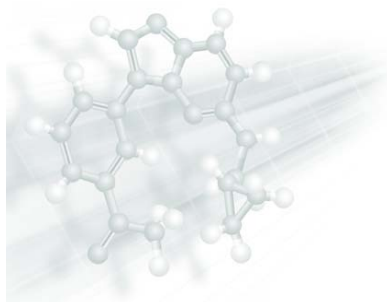
It is assumed in running the model that the molecule may be a substrate for one of the P450 isoforms modeled.

The output of the StarDrop P450 models consists of:

- A **Regioselectivity** map of the molecule for each isoform:
 - The relative proportion (%) of products formed by metabolism at each potential site, i.e. the most likely metabolites that will be formed if the molecule is a substrate for one of the isoforms modeled.
- A **Metabolic Landscape** for CYP3A4:
 - An estimate of the absolute vulnerability of each potential site of metabolism, which is a measure of the efficiency of metabolism at that position. The category assigned to each site is indicated by the colour of the bar, from red ('labile') to blue ('stable'). The vertical bars indicate the degree of lability of each site on the molecule.
 - Composite Site Lability (CSL): A number between 0-1 measuring the overall reactivity of the molecule towards CYP3A4. A value close to 1 indicates that the metabolism is likely to be extremely efficient. It is important to note that CSL is not a prediction of the rate of metabolism.



The metabolic landscape can be used to guide the redesign of compounds that have a high metabolic turnover by cytochrome P450 enzymes, particularly CYP3A4.



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Frequently Asked Questions

Are StarDrop's P450 models QSAR models?

No. The P450 models differ from the QSAR models, being based on simulation of the chemical reaction mechanisms which lead to the formation of metabolites. Although experimental data are used to tune the parameters of the model and validate the results, the form of the underlying model is not based on an empirical fit to a training data set and this gives greater transferability across a wide range of chemistry without loss of accuracy.

Accurate modeling of the chemical reactions requires quantum mechanical simulations, which are much more computationally expensive than the descriptor calculations employed by QSAR models. Consequently, the P450 metabolism models are significantly slower, taking several minutes per compound. However, identifying the most likely cause of metabolic instability for a compound can help to guide chemical modifications aimed at reducing the vulnerability.

How does StarDrop calculate quantum mechanical reaction energies for the P450 models?

We use an adapted version of MOPAC97 employing the AM1 method. As a semi-empirical method, AM1 is known to exhibit some systematic errors. Therefore, *post hoc* corrections are applied which have been derived from extensive *ab initio* calculations.

How are 3D geometries generated within the P450 models?

Initial 3D geometries are generated using Corina (developed by Molecular Networks) and these are then optimised further within MOPAC97. Unconstrained geometries are used, as experimental analysis has shown that the results are relatively insensitive to the geometry provided a good local minimum is used.

Can we use the CSL values in the scoring profile?

Yes, the CSL values are reported with an uncertainty in prediction and can be used in the scoring profile.

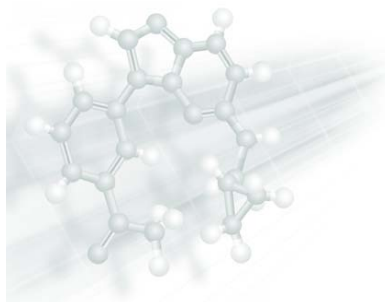
Can you predict the metabolic rate?

In addition to the vulnerability of individual sites on a molecule, whether a compound is metabolised, and the overall rate of metabolism, will depend upon many factors in the P450 catalytic cycle in addition to site lability, including the affinity of the molecule for the enzyme, the rates of reduction and rates of decoupling via peroxide formation. These are currently unknowns and hence metabolic rate, as opposed to lability, cannot be predicted in general.

However, for individual chemical series typically only a small number of these factors dictate the rate of product formation. In this case it is possible to build local models, using the CSL as a descriptor.

Can these P450 models tell us which isoform is responsible for metabolism of a compound?

No, these models do not predict the most likely isoform responsible for metabolism.



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How accurate are the P450 models?

The accuracies of the models for each isoform when tested on independent test sets are shown below:

Results of the P450 Regioselectivity Models on independent test sets.

Isoform	N ^a	All metabolites correctly predicted ^b	At least one metabolite correctly predicted ^b	Incorrect
CYP3A4	168	68%	17%	15%
CYP2D6	188	75%	12%	13%
CYP2C9	139	72%	12%	16%

^{a)} N = number of compounds in **independent test set**.

^{b)} Observed metabolites in the top 3 predicted sites or >10% predicted metabolism

Only 14 of the 22 molecules that form the top 20 drugs in this study are metabolised by Cytochrome P450 enzymes. These 14 drugs produce a total of 22 major metabolites of which 19 are correctly identified (86%), and a total of 6 minor metabolites of which 5 are correctly identified (83%). The results of the study are summarised below.

Summary of Results for Top20 Drugs Using Regioselectivity Models*

Rank	Active	Indication	Major Metabolising Enzymes				Metabolites Correctly Identified
			3A4	2D6	2C9	Other	
1	Atorvastatin	Elevated cholesterol	√			3A5	2/2
2	Simvastatin	Elevated cholesterol	√			3A5, 2C8	2/3
3	Salmeterol xinafoate	Asthma	√				1/1
3	Fluticasone propionate	Asthma	√				1/1
5	Olanzapine	Psychosis/schizophrenia		√		1A2, MAO	2/2
6	Esomeprazole	Gastrointestinal disorders	√			2C19	4/4
8	Sertraline	Depression	√				1/1
9	Venlafaxine	Depression	√	√			3/3
11	Celecoxib	Arthritis			√		1/1
13	Valsartan	Hypertension			√		1/1
14	Risperidone	Psychosis/schizophrenia		√			0/2
15	Losartan	Hypertension	√		√		1/1
18	Montelukast	Asthma	√		√		3/4
20	Lansoprazole	Gastrointestinal disorders	√		√	2C19	2/2

*By sales for 2004. Source: Med. Ad. News May 2005.