



OpenTox Tutorials

Drug Discovery Predictive Toxicology Application I: Prioritizing Compounds

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Summary

This document represents the first part of a tutorial on the application of OpenTox facilities in a drug discovery workflow. The tutorial example of a predictive toxicology application in drug discovery is provided using the data on anti-malarial compounds made available at the ChEMBL Neglected Tropical Disease (NTD) archive (www.ebi.ac.uk/chemblntd/). The anti-malarial compounds are prioritized based on a strongly conservative model for predicting oral toxicity. Experimentally-determined cytotoxicities against human cells of the compounds predicted to be safe are further examined, and their mutagenicities predicted. Sites of cytochrome P450 metabolism are predicted for selected compounds with no mutagenicity alerts, low human cytotoxicity, but high anti-malarial activity.

All tutorials and their updates are made available online under www.opentox.org/tutorials.

This tutorial is available online under <http://opentox.org/tutorials/drug-discovery>

Drug Discovery Predictive Toxicology Application I: Prioritizing compounds

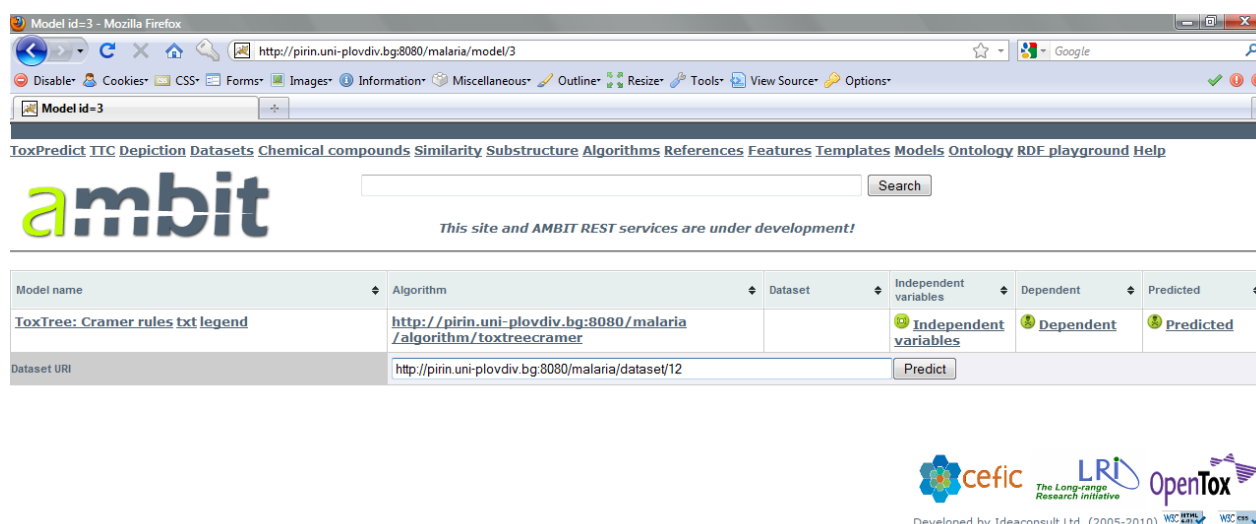
1 Introduction

An example of a predictive toxicology application in drug discovery is provided here using the data on antimalarial compounds made available at the ChEMBL Neglected Tropical Disease (NTD) archive (www.ebi.ac.uk/chemblntd/). In this tutorial example, the antimalarial compounds are prioritized based on a strongly conservative model for predicting oral toxicity. Experimentally-determined cytotoxicities against human cells of the compounds predicted to be safe are further examined, and their mutagenicities predicted. Sites of cytochrome P450 metabolism are predicted for selected compounds with no mutagenicity alerts, low human cytotoxicity, but high anti-malarial activity.

2 Step 1: Predicting Oral Toxicity

Go to the list of antimalarial datasets at <http://pirin.uni-plovdiv.bg:8080/malaria/dataset>. We'll first predict oral toxicity for the TCAMS dataset. Start by clicking on the TCAMS dataset link. The URL in the browser should read <http://pirin.uni-plovdiv.bg:8080/malaria/dataset/12>. You can browse the compounds.

In a new tab of your browser, go to the list of OpenTox models at <http://pirin.uni-plovdiv.bg:8080/malaria/model> (or follow the "Models" link at the top of the page listing the datasets). To predict oral toxicity we will use the "Toxtree Cramer rules" model. Clicking on the Cramer rules link will open its page (Figure 1). OpenTox models accept dataset URLs as input (instead of file names). Enter (or paste) the TCAMS URL ("<http://pirin.uni-plovdiv.bg:8080/malaria/dataset/12>") into the text box. Click "Predict".



Model name	Algorithm	Dataset	Independent variables	Dependent	Predicted
ToxTree: Cramer rules txt legend	http://pirin.uni-plovdiv.bg:8080/malaria/algorithm/toxtreecramer		Independent variables	Dependent	Predicted
Dataset URI	http://pirin.uni-plovdiv.bg:8080/malaria/dataset/12		Predict		

Figure 1 Launching a predictive model on a chosen dataset URL from within the AMBIT data service

which will launch calculations. You might click on the links to find out if the calculations are completed. When completed, clicking on the link will lead to a dataset with the results (Figure 2).

Tasks: [Running](#) [Cancelled](#) [Completed](#) [Error](#)

Start time	Elapsed time,ms	Task	Name	Status
Mon Sep 13 22:35:59 EEST 2010		11c84b75-90ce-4ba4-a035-56e2ab8d78bb	Apply_Model_ToxTree: Cramer rules to http://pirin.uni-plovdiv.bg:8080/malaria/dataset/12	Running

Figure 2 The results of the predictive model are delivered as a URL

The Cramer rules model is an implementation of Cramer et al., *Estimation of Toxic Hazard – A Decision Tree Approach*, J Cosmet Toxicol, Vol. 16, pp. 255–276, Pergamon Press, 1978. It comprises 33 structural rules and places evaluated compounds into one of three classes:

- Class I substances are simple chemical structures with efficient modes of metabolism suggesting a low order of oral toxicity;
- Class III substances are those that permit no strong initial presumption of safety, or may even suggest significant toxicity or have reactive functional groups; and finally,
- Class II are intermediate. This model is very conservative and places most of the compounds in Class III.

During this exercise, we'll look for compounds of low toxicity (Class I) and high antimalarial activity. There are a small number of Class I compounds, the distribution can be seen via the OpenTox chart generation service

[http://pirin.uni-plovdiv.bg:8080/malaria/chart/pie?dataset_uri=http://pirin.uni-plovdiv.bg:8080/malaria/dataset/12&feature_uris\[\]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/212](http://pirin.uni-plovdiv.bg:8080/malaria/chart/pie?dataset_uri=http://pirin.uni-plovdiv.bg:8080/malaria/dataset/12&feature_uris[]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/212)

toxTree.tree.cramer.CramerRules

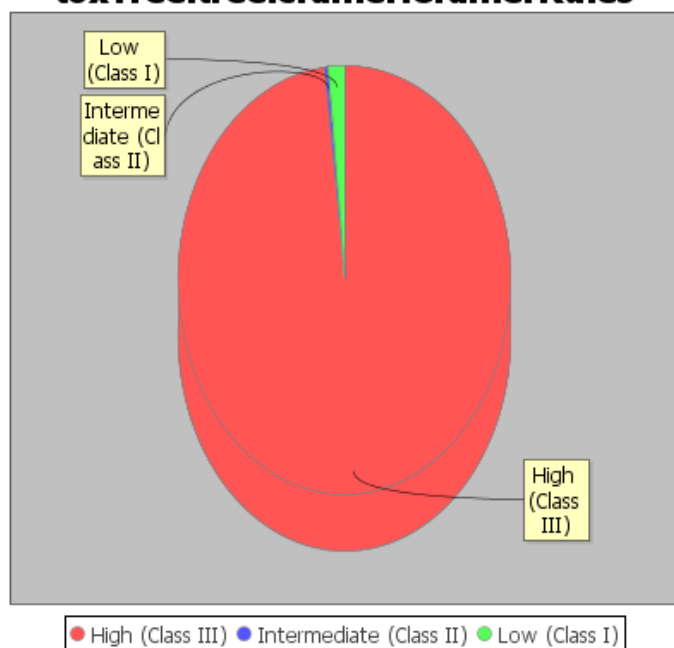
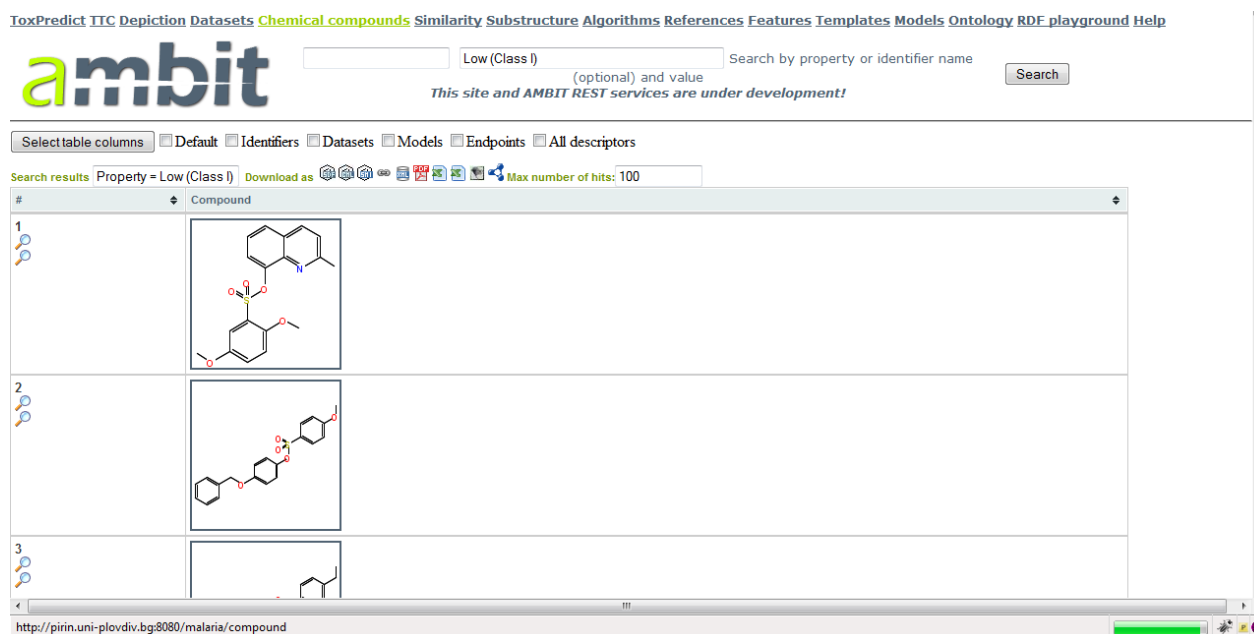


Figure 3 Distribution of the Cramer classes in the TCAMS dataset, depicted using the OpenTox chart generation service

To filter for Class I compounds, click the “Chemical compounds” links on the top, and enter “Low (Class I)” in the search box. This results in the following web address:

<http://pirin.uni-plovdiv.bg:8080/malaria/compound?type=smiles&property=&search=Low+%28Class+I%29>

(which could be also used directly, instead of typing the search query in the text box). The results can be browsed as below (Figure 4).



The screenshot shows the AMBIT web interface. At the top, there is a navigation menu with links: ToxPredict, TTC Depiction, Datasets, Chemical compounds, Similarity, Substructure, Algorithms, References, Features, Templates, Models, Ontology, RDF playground, and Help. Below the menu is the 'ambit' logo and a search bar containing 'Low (Class I)'. A message below the search bar states: 'This site and AMBIT REST services are under development!'. Underneath, there are checkboxes for 'Select table columns' with options: Default, Identifiers, Datasets, Models, Endpoints, and All descriptors. The search results section shows 'Property = Low (Class I)' and 'Max number of hits: 100'. A table with three rows is visible, each containing a chemical structure. The first structure is a complex heterocyclic molecule with a quinoline ring system and a sulfonamide group. The second structure is a long-chain molecule with multiple ether linkages and a terminal hydroxyl group. The third structure is a simpler molecule with a central carbon atom bonded to several other atoms.

Figure 4 Browsing the results

3 Step 2: Analyse Cytotoxicities of the Cramer Class I compounds

From the previous step we ended up with a list of compounds considered safe according to Cramer rules. However, we would like to have some more information other than just the chemical structures. For example, we would like to know the antimalarial activity of these compounds.

To add such a column, we need to edit the URL by adding an entry denoting the antimalarial activity given in the TCAMS Dataset. All data columns in OpenTox have their unique URL, and in this example, the URL of the data indicating the percentage inhibition of the growth of the *P. falciparum* strain 3D7 (column "Percentage_Inhibition_3D7" in the TCAMS dataset) is

<http://pirin.uni-plovdiv.bg:8080/malaria/feature/190>

Commercial Supplier Reference	Chemical cluster Nr	EXT_CMPD_NUMBERXC50 MOD 3D7	P. falciparum locus	Percentage inhibition 3D7	Percentage inhibition 3D7 PFLDI
	1185.0	TCMDC-131240		100.0	-8.0
	544.0	TCMDC-131241		99.0	0.0
	544.0	TCMDC-131242		94.0	-2.0

<http://pirin.uni-plovdiv.bg:8080/malaria/feature/190>

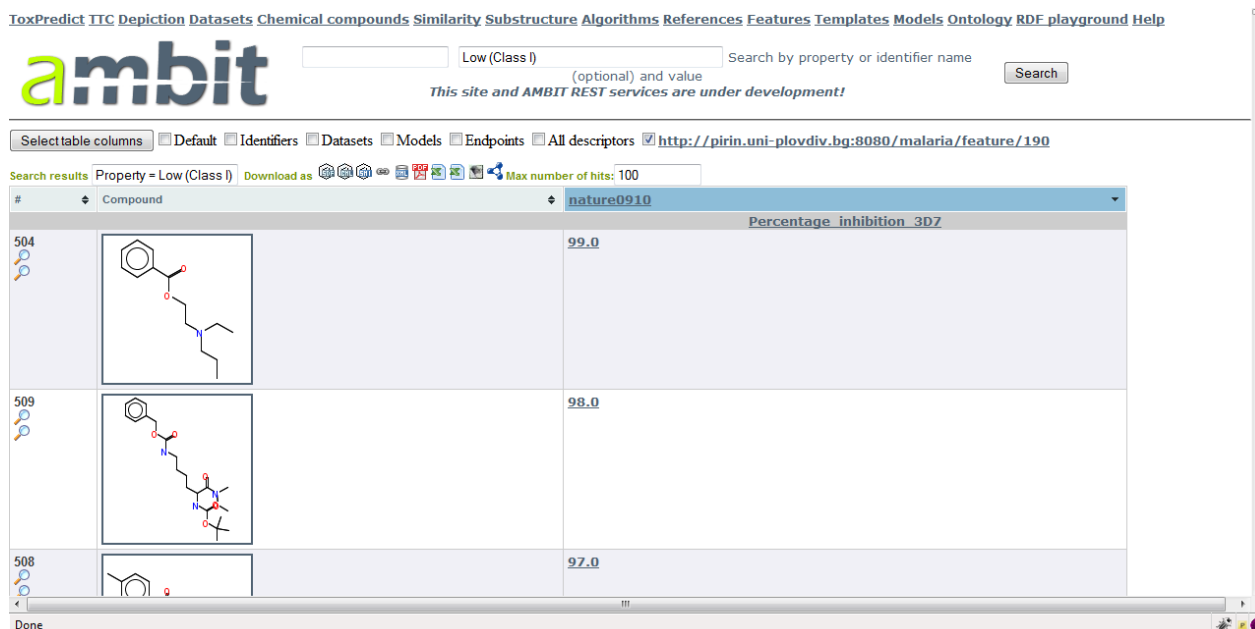
Figure 5 Retrieving the feature URL

To add this column to our filtered list of compounds considered safe according to Cramer rules (Cramer class I), we simply add a `feature_uris[]` parameter to the URL of our filtered list:

[http://pirin.uni-plovdiv.bg:8080/malaria/compound?type=smiles&property=&search=Low+%28Class+I%29&feature_uris\[\]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/190](http://pirin.uni-plovdiv.bg:8080/malaria/compound?type=smiles&property=&search=Low+%28Class+I%29&feature_uris[]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/190)

Copy this address into the web browser. There will be a small number of nonempty entries in the second column (see Figure 6).

ToxPredict TIC Depiction Datasets Chemical compounds Similarity Substructure Algorithms References Features Templates Models Ontology RDF playground Help



Low (Class I) Search by property or identifier name (optional) and value

Selectable columns Default Identifiers Datasets Models Endpoints All descriptors <http://pirin.uni-plovdiv.bg:8080/malaria/feature/190>

Search results Property = Low (Class I) Download as Max number of hits: 100

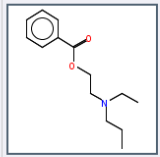
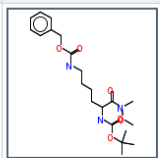
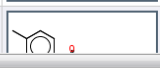
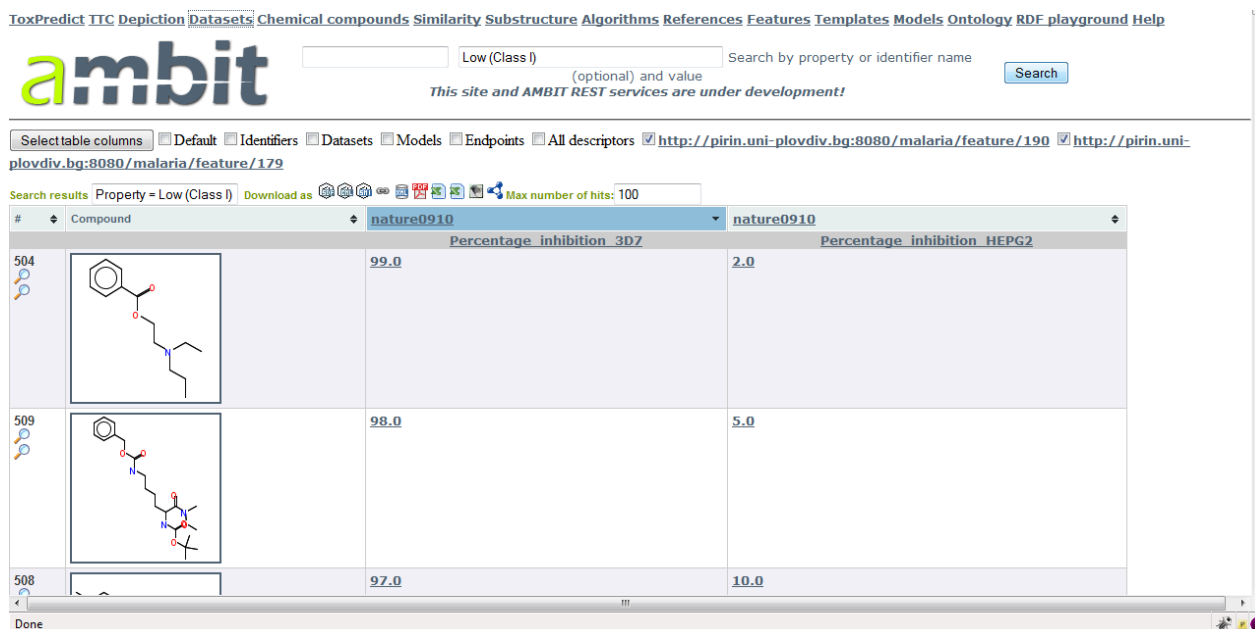
#	Compound	nature0910	Percentage inhibition 3D7
504		99.0	
509		98.0	
508		97.0	

Figure 6 A column is added to the compounds with the `feature_uris[]` directive

We're not only interested in the antimalarial activity, but would also like to take into account the experimentally determined human cytotoxicity. To do so, we add a second data column to our filtered list, now with human cytotoxicity data from the TCAMS dataset ([Percentage_inhibition_HEPG2](#)).

<http://pirin.uni-plovdiv.bg:8080/malaria/feature/179>). The combination of the two features – antimalarial activity and human cytotoxicity – will result in the following URL (see Figure 7):

[http://pirin.uni-plovdiv.bg:8080/malaria/compound?type=smiles&property=&search=Low+%28Class+I%29&feature_uris\[\]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/190&feature_uris\[\]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/179](http://pirin.uni-plovdiv.bg:8080/malaria/compound?type=smiles&property=&search=Low+%28Class+I%29&feature_uris[]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/190&feature_uris[]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/179)



The screenshot shows the AMBIT web interface. At the top, there is a search bar with the text 'Low (Class I)' and a 'Search' button. Below the search bar, there are several tabs: 'ToxPredict', 'TIC Depiction', 'Datasets', 'Chemical compounds', 'Similarity', 'Substructure', 'Algorithms', 'References', 'Features', 'Templates', 'Models', 'Ontology', 'RDF playground', and 'Help'. The 'Features' tab is selected. Below the tabs, there is a table of search results. The table has columns for '#', 'Compound', 'nature0910', and 'nature0910'. The 'nature0910' columns are further divided into 'Percentage inhibition 3D7' and 'Percentage inhibition HEPG2'. The table shows three rows of results:

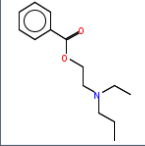
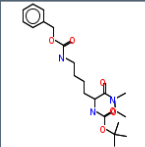

#	Compound	nature0910	nature0910
		Percentage inhibition 3D7	Percentage inhibition HEPG2
504		99.0	2.0
509		98.0	5.0
508		97.0	10.0

Figure 7 Another column is added to the compounds with the feature_uris[] directive

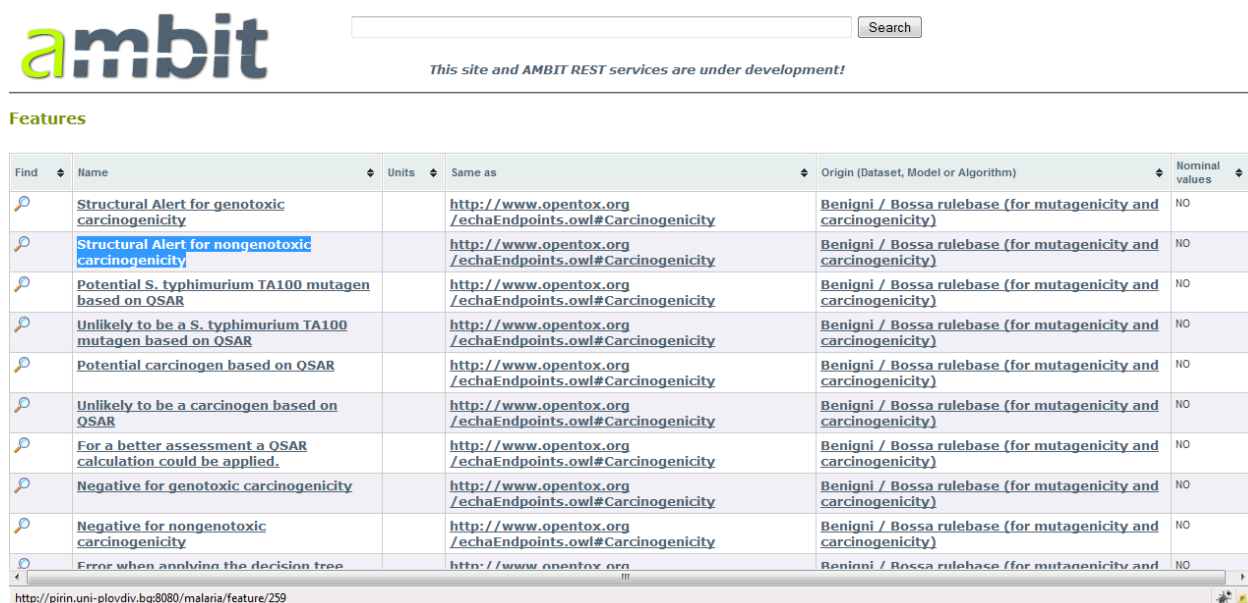
4 Step 3: Predicting the Mutagenicity of the Selected Compounds

To add a further criterion to be used when selecting our drug candidate, we predict the compounds' mutagenicities. To do so, we'll use the Toxtree Benigni/Bossa rules for mutagenicity and carcinogenicity (Benigni et al., *Mechanistic QSAR of aromatic amines: new models for discriminating between mutagens and nonmutagens, and validation of models for carcinogens*, Environ Mol. Mutag. **48**:754–771 (2007).). The URL of this model is <http://pirin.uni-plovdiv.bg:8080/malaria/model/12>.

Analogously as you have done for the Cramer rules, follow the URL of the Benigni/Bossa model (<http://pirin.uni-plovdiv.bg:8080/malaria/model/12>), type or paste the URL or the TCAMS dataset (<http://pirin.uni-plovdiv.bg:8080/malaria/dataset/12>) in the text box and click "Predict". Alternatively, the URL of the filtered list could be entered here, as well.

OpenTox models store the prediction results again under data columns with unique URL. These are available via <http://host/model/{id}/predicted> , which in our example corresponds to

<http://pirin.uni-plovdiv.bg:8080/malaria/model/12/predicted>



Find	Name	Units	Same as	Origin (Dataset, Model or Algorithm)	Nominal values
	Structural Alert for genotoxic carcinogenicity		http://www.opentox.org/echaEndpoints.owl#Carcinogenicity	Benigni / Bossa rulebase (for mutagenicity and carcinogenicity)	NO
	Structural Alert for nongenotoxic carcinogenicity		http://www.opentox.org/echaEndpoints.owl#Carcinogenicity	Benigni / Bossa rulebase (for mutagenicity and carcinogenicity)	NO
	Potential <i>S. typhimurium</i> TA100 mutagen based on QSAR		http://www.opentox.org/echaEndpoints.owl#Carcinogenicity	Benigni / Bossa rulebase (for mutagenicity and carcinogenicity)	NO
	Unlikely to be a <i>S. typhimurium</i> TA100 mutagen based on QSAR		http://www.opentox.org/echaEndpoints.owl#Carcinogenicity	Benigni / Bossa rulebase (for mutagenicity and carcinogenicity)	NO
	Potential carcinogen based on QSAR		http://www.opentox.org/echaEndpoints.owl#Carcinogenicity	Benigni / Bossa rulebase (for mutagenicity and carcinogenicity)	NO
	Unlikely to be a carcinogen based on QSAR		http://www.opentox.org/echaEndpoints.owl#Carcinogenicity	Benigni / Bossa rulebase (for mutagenicity and carcinogenicity)	NO
	For a better assessment a QSAR calculation could be applied.		http://www.opentox.org/echaEndpoints.owl#Carcinogenicity	Benigni / Bossa rulebase (for mutagenicity and carcinogenicity)	NO
	Negative for genotoxic carcinogenicity		http://www.opentox.org/echaEndpoints.owl#Carcinogenicity	Benigni / Bossa rulebase (for mutagenicity and carcinogenicity)	NO
	Negative for nongenotoxic carcinogenicity		http://www.opentox.org/echaEndpoints.owl#Carcinogenicity	Benigni / Bossa rulebase (for mutagenicity and carcinogenicity)	NO
	Error when applying the decision tree		http://www.opentox.org	Benigni / Bossa rulebase (for mutagenicity and	NO

Figure 8 Selecting the Benigni/Bossa rulebase for mutagenicity and carcinogenicity


The Toxtree mutagenicity and carcinogenicity model predicts whether there are structural alerts for genotoxic or nongenotoxic carcinogenicity, and also uses a linear discriminant model for specific classes of compounds.

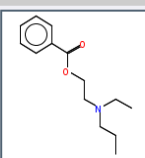
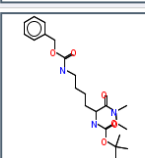
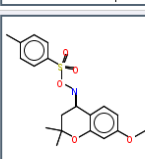
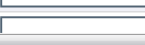
For our purpose, we select the columns “[Structural Alert for genotoxic carcinogenicity](http://pirin.uni-plovdiv.bg:8080/malaria/feature/258)“ (<http://pirin.uni-plovdiv.bg:8080/malaria/feature/258>) and “[Structural Alert for nongenotoxic carcinogenicity](http://pirin.uni-plovdiv.bg:8080/malaria/feature/259)“ (<http://pirin.uni-plovdiv.bg:8080/malaria/feature/259>). As before, we add data columns for these structural alerts to our Cramer-class filtered list of compounds, again using the `feature_uris[]` method. The resulting URL is:

[http://pirin.uni-plovdiv.bg:8080/malaria/compound?type=smiles&property=&search=Low+\(Class+I\)&feature_uris\[\]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/190&feature_uris\[\]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/179&feature_uris\[\]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/258&feature_uris\[\]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/259](http://pirin.uni-plovdiv.bg:8080/malaria/compound?type=smiles&property=&search=Low+(Class+I)&feature_uris[]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/190&feature_uris[]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/179&feature_uris[]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/258&feature_uris[]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/259)

The resulting table (as well as any other) can be sorted according to the values in any column by clicking on the column header.

In the following examples, we’ll consider the first compound in the image below as our antimalarial drug candidate. It is a Cramer class I compound that inhibits growth of *P. falciparum* 3D7 by 99% at the concentration tested (2µM), has a very low human cytotoxicity and no structural alerts for carcinogenicity. (You may choose a different compound).

Search results Property = Low (Class I) Download as  Max number of hits: 100

#	Compound	nature0910	nature0910	Benigni /	Benigni /
		Percentage inhibition 3D7	Percentage inhibition HEPG2	Structural Alert for genotoxic carcinogenicity	Structural Alert for nongenotoxic carcinogenicity
504		99.0	2.0	NO	NO
509		98.0	5.0	YES	NO
508		97.0	10.0	NO	NO
512		96.0	30.0	NO	NO

Done

Figure 9 Search results enhanced with columns for carcinogenicity predictions

Similarly to datasets and models, each compound in OpenTox services also has its unique URL. You can find the URL of a compound by clicking on its 2D structure, and stripping off the “?media=text/html” part at the end of the URL this brings you to.

The URL of the compound selected above is

<http://pirin.uni-plovdiv.bg:8080/malaria/compound/458166/conformer/773441>.


5 Step 4: Predicting Sites of Cytochrome P450 Metabolism

The URL of our drug candidate will be used to submit this compound to two models predicting cytochrome P450 sites of metabolism, namely SmartCYP¹ (<http://pirin.uni-plovdiv.bg:8080/malaria/model/10>) and SOME² (<http://pirin.uni-plovdiv.bg:8080/malaria/model/21>).

Model prediction is done analogously to the two models used in this exercise. Go to

<http://pirin.uni-plovdiv.bg:8080/malaria/model/10> and copy the compound URL into the text box.

ToxPredict TIC Depiction Datasets Chemical compounds Similarity Substructure Algorithms References Features Templates Models Ontology RDF playground Help



This site and AMBIT REST services are under development!




Model name	Algorithm	Dataset	Independent variables	Dependent	Predicted
SmartCYP: Cytochrome P450-Mediated Drug Metabolism txt legend	http://pirin.uni-plovdiv.bg:8080/malaria/algorithm/toxtreesmartcyp		 Independent variables	 Dependent	 Predicted
Dataset URI	http://pirin.uni-plovdiv.bg:8080/malaria/compound/458166/conformer/773441		<input type="button" value="Predict"/>		

Figure 10 Running SmartCYP on the malaria box

¹ Rydberg P. et al. SMARTCyp: A 2D Method for Prediction of Cytochrome P450-Mediated Drug Metabolism. ACS Medicinal Chemistry Letters, 1(3), 96–100 (2010)

² Zheng M. et al. Site of metabolism prediction for six biotransformations mediated by cytochromes P450. Bioinformatics 25(10): 1251–1258 (2010)

When completed, the results will be available at

[http://pirin.uni-plovdiv.bg:8080/malaria/compound/458166/conformer/773441?feature_uris\[\]=http%3A%2F%2Fpirin.uni-plovdiv.bg%3A8080%2Fmalaria%2Fmodel%2F10%2Fpredicted](http://pirin.uni-plovdiv.bg:8080/malaria/compound/458166/conformer/773441?feature_uris[]=http%3A%2F%2Fpirin.uni-plovdiv.bg%3A8080%2Fmalaria%2Fmodel%2F10%2Fpredicted)

and will consist of information on which atoms are of rank 1, 2, 3 or lower. Higher rank means a more labile site. This information will be best viewed graphically, which could be achieved by the following URL

http://pirin.uni-plovdiv.bg:8080/malaria/compound/458166/conformer/773441?model_uri=http://pirin.uni-plovdiv.bg:8080/malaria/model/10 (see Figure 11).

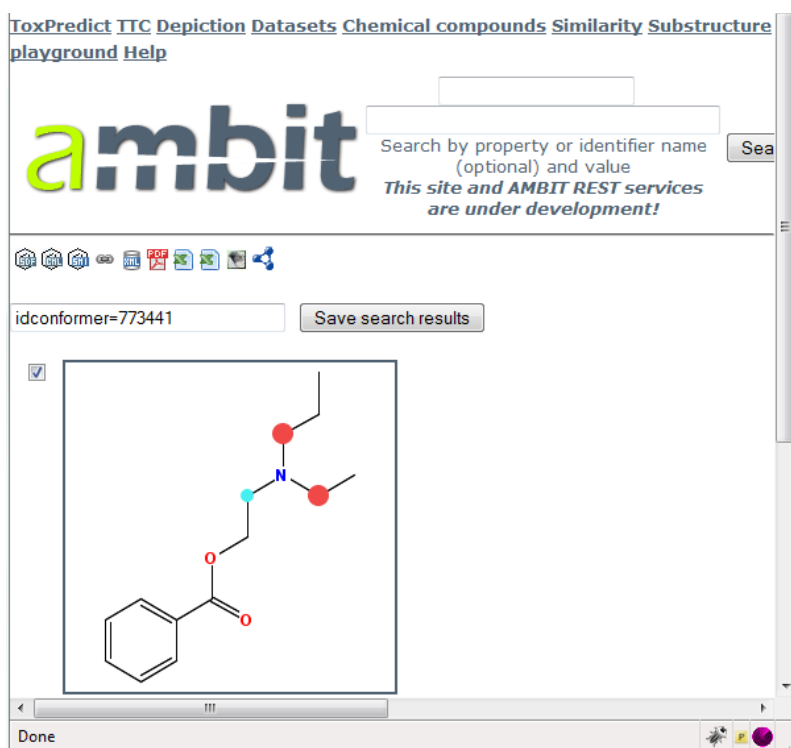


Figure 11 Example SmartCYP output

The colour code for the result can be found by clicking on the “legend” link on the model page.



Figure 12 SmartCYP color code

Similarly, the SOME model predictions are visualized via

http://pirin.uni-plovdiv.bg:8080/malaria/compound/458166/conformer/773441?model_uri=http://pirin.uni-plovdiv.bg:8080/malaria/model/21

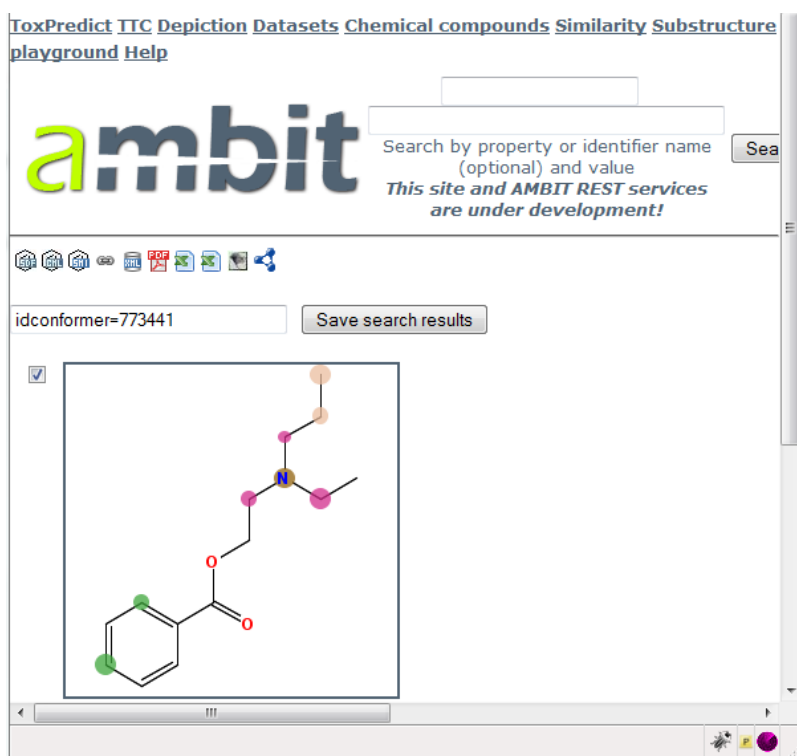


Figure 13 Example SOME output

And the color code is

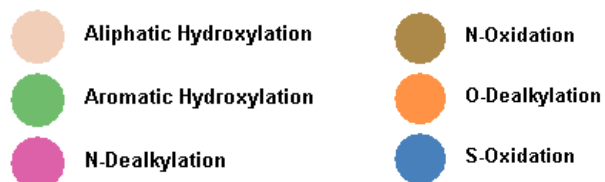


Figure 14 SOME color code

The color-coding of the metabolic sites according to the type of metabolic reaction taking place allows the user – with a little knowledge in organic chemistry – to work out the metabolites of the compound.

To obtain the predictions of the sites of metabolism for the entire dataset, one can use the following URL:
[http://pirin.uni-plovdiv.bg:8080/malaria/compound?type=smiles&property=&search=Low+%28Class+l%29&feature_uris\[\]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/190&feature_uris\[\]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/179&feature_uris\[\]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/258&feature_uris\[\]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/259&model_uri=http://pirin.uni-plovdiv.bg:8080/malaria/model/21&w=250&h=250](http://pirin.uni-plovdiv.bg:8080/malaria/compound?type=smiles&property=&search=Low+%28Class+l%29&feature_uris[]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/190&feature_uris[]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/179&feature_uris[]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/258&feature_uris[]=http://pirin.uni-plovdiv.bg:8080/malaria/feature/259&model_uri=http://pirin.uni-plovdiv.bg:8080/malaria/model/21&w=250&h=250)