

Predicting Chemical Liabilities with Bioclipse and OpenTox

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This tutorial features a hands-on session with Bioclipse and together with the OpenTox plugin. Users will run the Decision Support feature of Bioclipse and inspect the results of predictive models on chemical structures running on the desktop computer, and combine these with remote toxicity predictions via OpenTox. We will then investigate how predictions change when making structural modifications aiming at overcoming chemical liabilities.

Prerequisites

- Java 1.6+ installed
- Installing new features in Bioclipse or running OpenTox models requires an internet connection

Download and install Bioclipse

Alternative 1: Download and install Bioclipse with the pre-packaged OpenTox and Decision Support plugins from <http://www.bioclipse.net/opentox>.

Alternative 2: Download and install Bioclipse from www.bioclipse.net/download, and then use the menu **Help > Install DS Models...** to select both **OpenTox** and **Decision Support**. After installing the new features you will be prompted to restart.

Late notice: Due to a missing dependency, even if you select Alternative 1 above you might need to install the OpenTox Decision Support module as in Alternative 2.

Getting Started

On first startup, click the menu **Window > Open Perspective > Other...** then select **Decision Support** from the dialog. This opens up the Decision Support view of Bioclipse displaying several endpoints and models, both local (running on the local computer) and remote (available from OpenTox servers).

Authenticate with OpenTox

Some of the OpenTox models are only available to registered users of OpenTox. Therefore, enter your OpenTox credentials in Bioclipse (if you don't have an OpenTox account yet, get

one at http://opentox.org/join_form). To set up your OpenTox account in Bioclipse, go through the following steps:

1. Main menu **File > New**. A dialog will open, select **General > Account**.
2. Bioclipse requires a master password to store all your personal information encrypted. If this is your first account, you will need to create a new user by filling in the fields username + password + repeat password. Then click **Next** to open the following dialog:

The screenshot shows a window titled "Add an account to Bioclipse" with a "New Account" sub-dialog. The sub-dialog contains the following elements:

- Title: **New Account**
- Instructions: "Add a third-part account to Bioclipse. All fields denoted with an asterisk (*) are required."
- Account type: "Select account type:" dropdown menu with "OpenTox" selected.
- Account name: "Account name:" text field containing "OpenTox".
- Third-part account properties: A section containing:
 - "username: *" text field (empty)
 - "password: *" text field (empty)
 - "auth. service: *" text field containing "http://opensso.in-silico.ch/opensso/"
 - "Test log-in" button
- Navigation buttons at the bottom: "< Back", "Next >", "Cancel", and "Finish".

3. Here you need to enter your OpenTox username and password, as registered on http://opentox.org/join_form. You can use the **Test log-in** button to verify that the values you entered are valid. Then click **Finish**.

Import compounds

All files in Bioclipse must be contained within a Project; you can create one by using menu **File > New...** and in the opened dialog selecting **General > Project**. Now, drag and drop files (mol, cml, sdf) into the project. If you want to install sample data, select **Data > Sample data** from the previous dialog.

Run predictions

Double-click on a chemical structure to open it for editing in the 2D-editor. Note how the models become active in the Decision Support View.

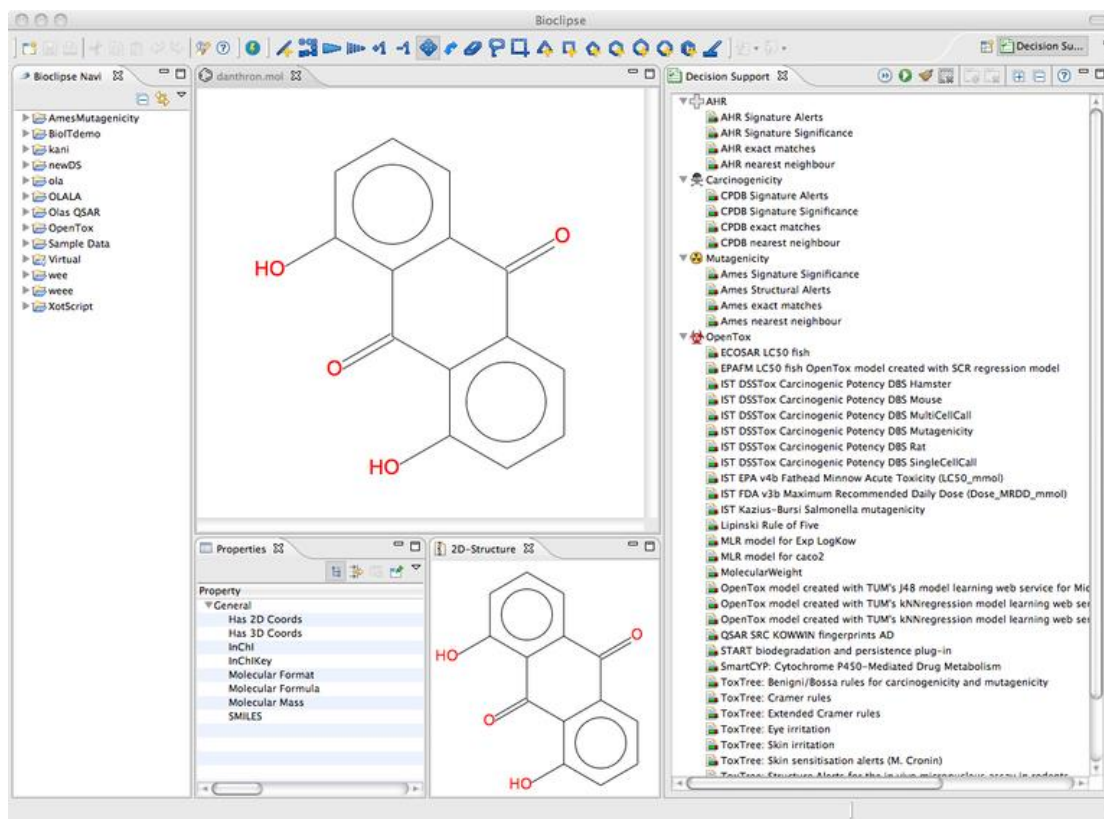
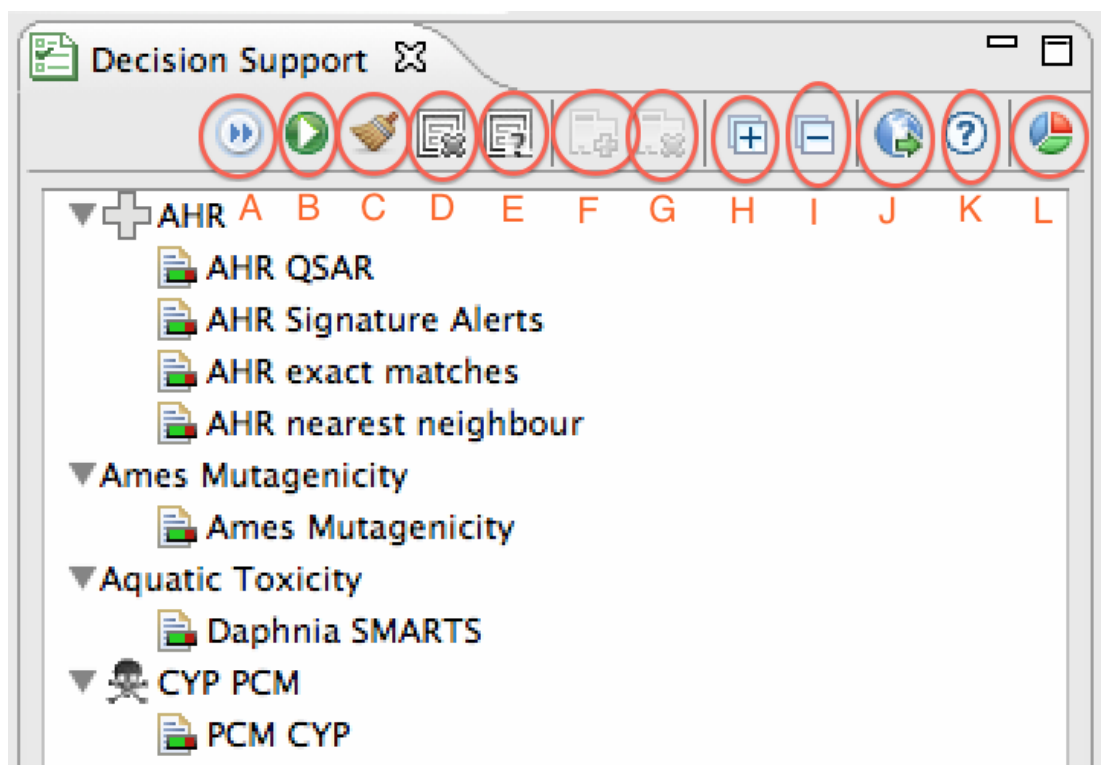


Figure: Showing the withdrawn drug Danthron and the active models in the Decision Support View (right).

The toolbar in the Decision support view to the right has a Run button. Click it to run all predictive models for the compound.



Decision Support toolbar options:

- A) Toggle automatic model re-running on changes to 2D-structure.
- B) Run predictive models on the active 2D-structure
- C) Clear model results
- D) Toggle if models with errors should be hidden
- E) Toggle if models with inconsistent results should be hidden
- F) Include selected model
- G) Exclude selected model
- H) Expand all results under selection
- I) Collapse all results under selection
- J) Open dialog to install more models from update site
- K) Open Decision Support Help topic
- L) Create report from predicitions

The screenshot shows the 'Decision Support' window with the following structure:

- AHR**
 - AHR Signature Alerts [no hits]
 - AHR Signature Significance [1 neg]
 - [C]
 - AHR exact matches [no hits]
 - AHR nearest neighbour [no hits]
- Carcinogenicity**
 - CPDB Signature Alerts [3 pos]
 - [C]([C](p[C]p[C])[C](p[C]p[C])=[O])
 - [C](p[C](p[C](p[C,0]))p[C](p[C]([C]p[C,0])[C]([C]=[O])))
 - [O](=[C]([C](p[C]p[C])[C](p[C]p[C])))
 - CPDB Signature Significance [1 pos]
 - [C](p[C](p[C])p[C]([C]p[C]))
 - CPDB exact matches [1 pos]
 - Index 185
 - CPDB nearest neighbour [2 pos, 1 neg]
 - Index 425 [tanimoto=0.98]
 - Index 752 [tanimoto=0.87]
 - Index 328 [tanimoto=0.76]
- Mutagenicity**
 - Ames Signature Significance [1 pos]
 - [O]([C])
 - Ames Structural Alerts [no hits]
 - Ames exact matches [1 pos]
 - 117-10-2
 - Ames nearest neighbour [16 pos, 1 neg]
 - 129-43-1 [tanimoto=0.98]
 - 81-64-1 [tanimoto=0.97]
 - 117-12-4 [tanimoto=0.97]
 - 72-48-0 [tanimoto=0.9]

Figure: Results from prediction on Danthron.

Click on one of the lines with a bulls-eye icon (in the figure above e.g. "[O]([C])" under "Ames Signature Significance [1 pos]" within the Mutagenicity model. This will highlight the atoms in your molecule responsible for this prediction.

You can make changes to the compound and try again. Scroll down in the Decision Support View to see the OpenTox predictions.

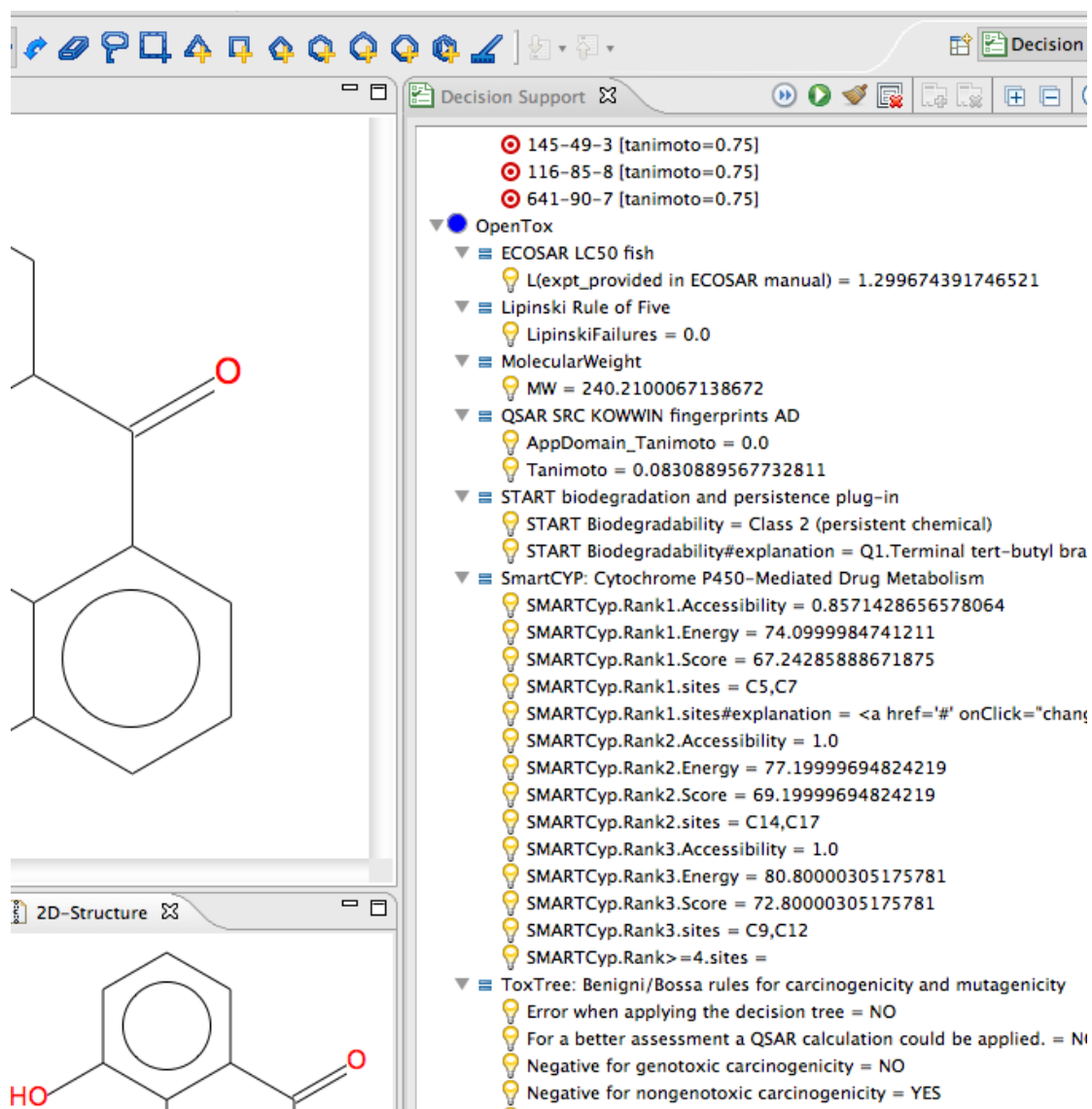


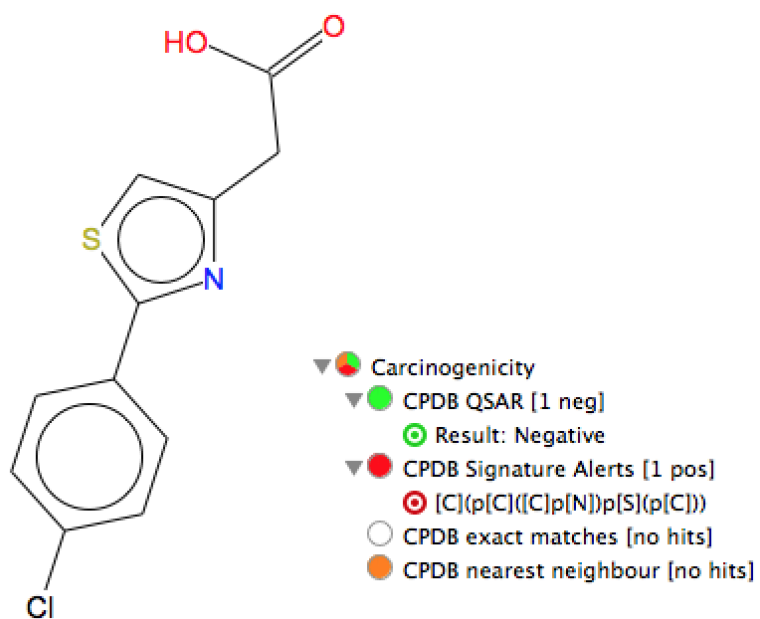
Figure: OpenTox results for Danthron.

Structural modifications

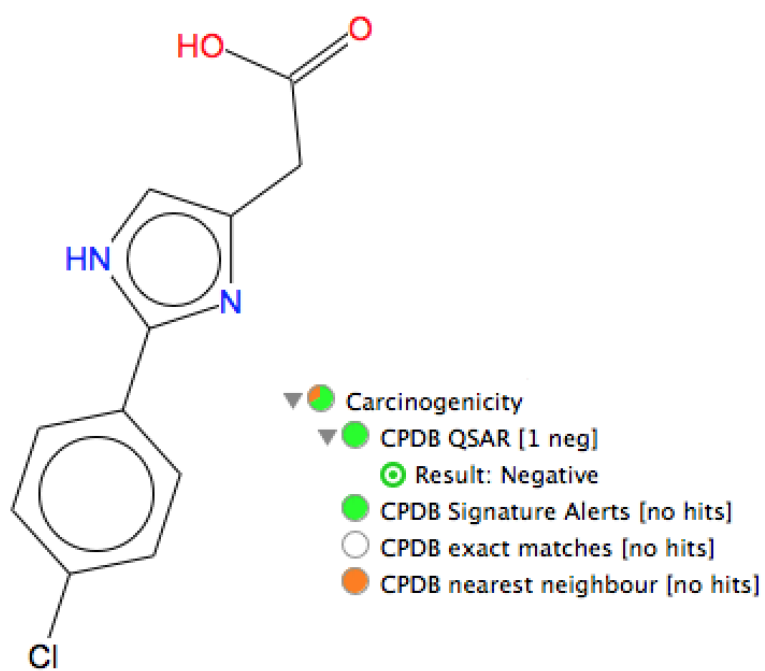
Explore Bioclipse Decision Support and OpenTox results for the compounds below. To instantiate a molecule from SMILES, select menu: **File > New...** and in dialog **Cheminformatics > Molecule from SMILES**.

Example 1

Draw or instantiate the chemical structure of Fenclozic acid (Myalex); SMILES: O=C(O)Cc2nc(c1ccc(cc1)C1)sc2. This is an NSAID found to be hepatotoxic in 1970.

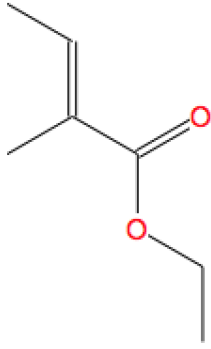


Change of central thiazole to imidazole removes the structural alert for carcinogenicity.

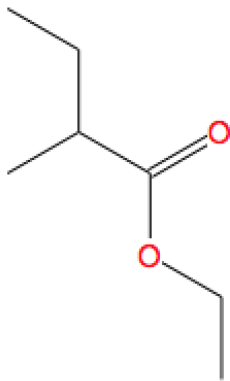


Example 2:

SMILES: O=C(OCC)C(=CC)C

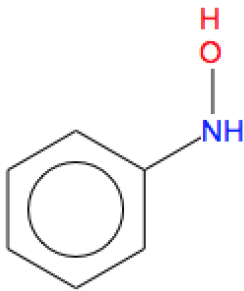


Reduction of alkene lowers the chances for toxicity:

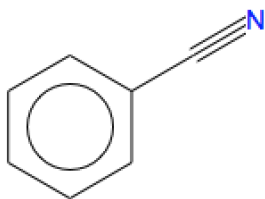


Example 3

Simplified example of a metabolite of an aromatic nitro compound (specifically, hydroxylamine). SMILES: ONc1ccccc1



Changing to a common substitution for nitro (namely, cyano) eliminates most of the problems.



View it in Action

Screencast 1: Illustrates the Decision Support and OpenTox functionality in action.

<http://opentox.org/data/documents/development/tutorialfiles/downloads/CalculateAsYouDraw-OT.mov/view>

Screencast 2: Online tutorial session from May 2011.

http://opentox.org/data/documents/development/tutorialfiles/downloads/2011-05-25_Bioclipse-OpenTox-Integration.wmv

Bioclipse youtube channel: <http://www.youtube.com/user/Bioclipse>

Scripting OpenTox from Bioclipse

If you are interested in learning how to use and develop scripts in Bioclipse to access OpenTox services, visit the following page:

<http://chem-bla-ics.blogspot.com/2011/05/my-slides-for-this-afternoons-bioclipse.html>