FORECASTER Suite 2018 Tutorial

IMPACTS, CONVERT, and SMART

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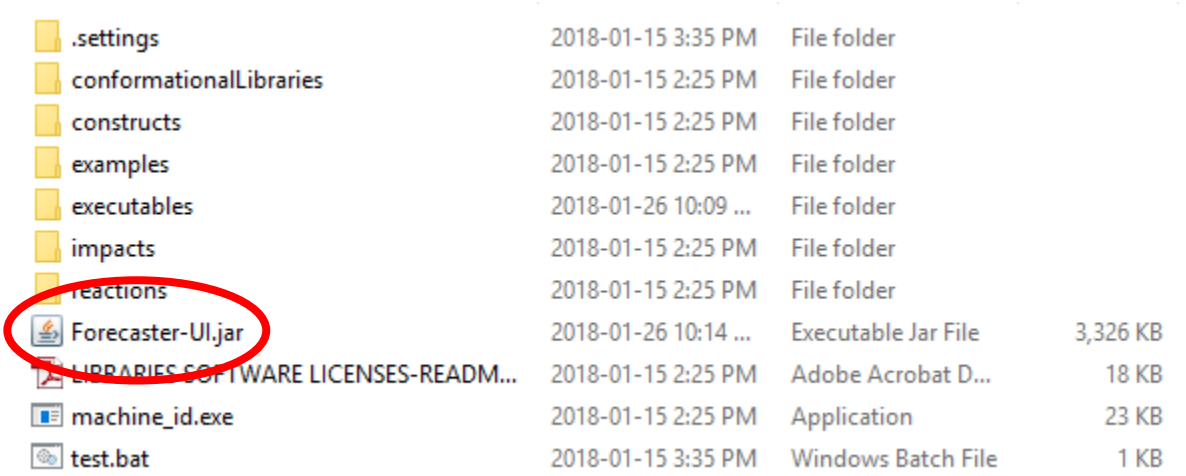
I. Running FORECASTER with the User Interface

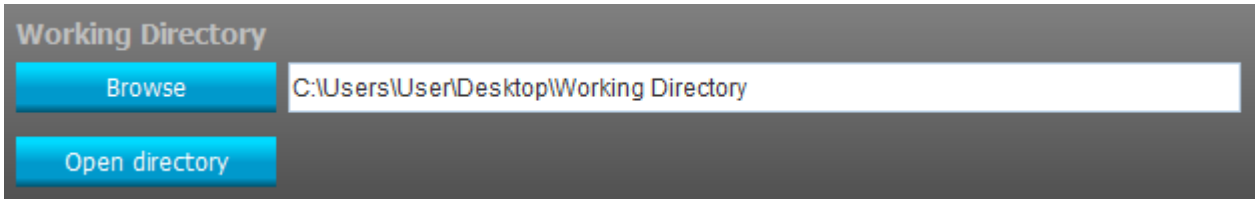
The user interface (UI) can be started by double clicking on the `Forecaster-UI.jar` file in the `Forecaster` folder. This will open the main window.

Under Linux and Mac OSX, it is recommended to launch it from a terminal window by typing the command below. Make sure that you are located in the folder where this jar file is.

Forecaster@Linux/Forecaster:~$ java -jar Forecaster-UI.jar



The first step is to set the working directory. Click **Browse**, under **Working Directory**. You will be prompted to navigate to the folder where you will save various files while working with FORECASTER. If this is the first time you use FORECASTER, you may need to create a new folder. This folder can have any name and can be located anywhere you want..

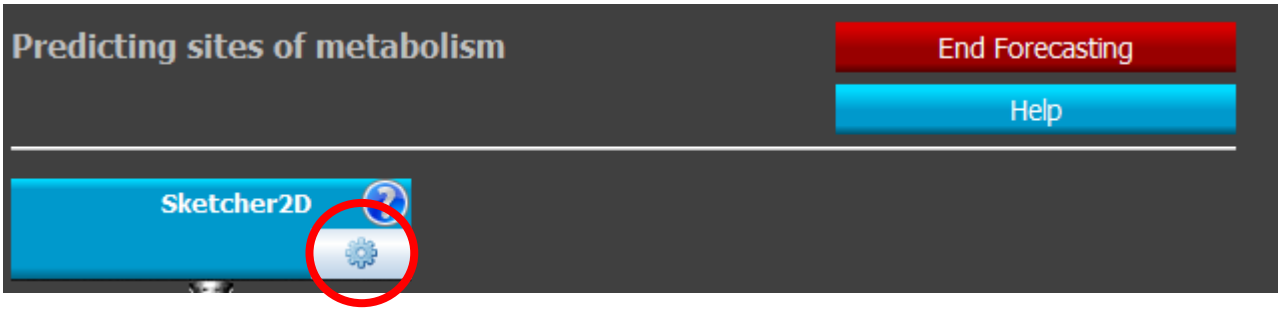


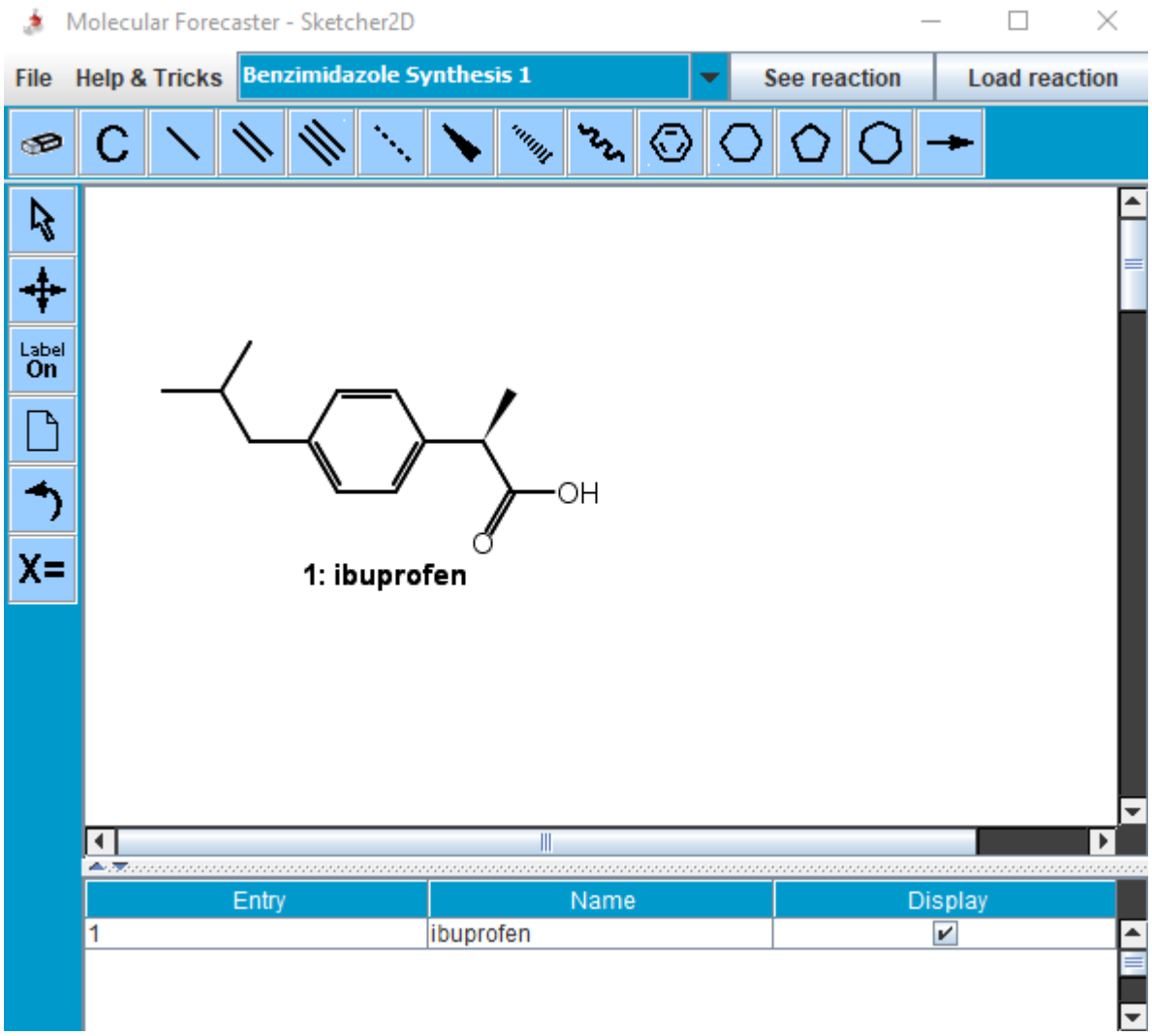
You may then click **Start Forecasting** to expand the "*Predicting Sites of Metabolism*" workflow.

II. Sites of metabolism prediction

SKETCHER2D and CONVERT: The conversion of the ligand from 2D to 3D

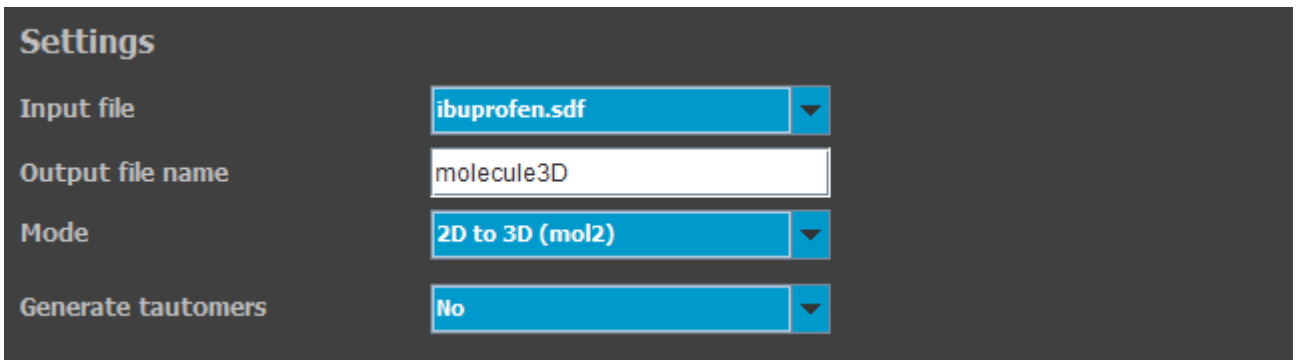
CONVERT will convert a 2D molecule into an energy-minimized 3D structure. The 2D molecule can either be imported as a file (supported input formats are mol and sdf) or drawn directly using the integrated sketcher. In this example, we will draw the molecule with the sketcher. Click the gear icon in the Sketcher2D box to open the sketcher window.





Once the Ibuprofen molecule is drawn, the file is saved by clicking on **File** and **Save structure (sdf)**. After saving, the sketcher can be closed.

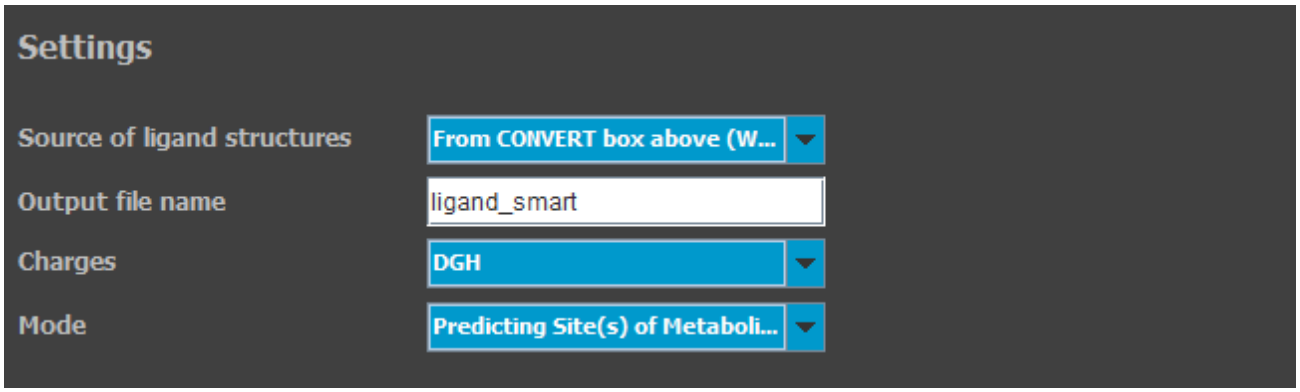
Clicking on the gear icon in the CONVERT box will open the parameters section. The newly created ligand file (`.sdf`) should automatically be selected as the **Input file**. The **Ouput file** can be set to any desired name and the **Mode** to "2D to 3D (mol2)".



Once all the parameters are set, the keyword file needs to be written by clicking the **Write keyword file** button. Clicking the **Exit** button will close the CONVERT parameters section and return to the main workflow. A green check should now appear in the CONVERT box.

SMART: The setup of the ligand for sites of metabolism prediction

SMART will setup the ligand (3D molecules only) for the SOM prediction with IMPACTS. Once again, click on the gear icon to open the parameters. The **Source of ligand structures** should be set to "From CONVERT box above". The file that will be created by CONVERT will automatically be selected as the **Input file**. The **Output file name** can be filled with any desired name. The atomic partial charges method can be selected under **Charges**. The methods available are DGH (recommended), none (no charge), and Input (will keep input file charges). The **Mode** should be set to "Predicting Site(s) of Metabolism".

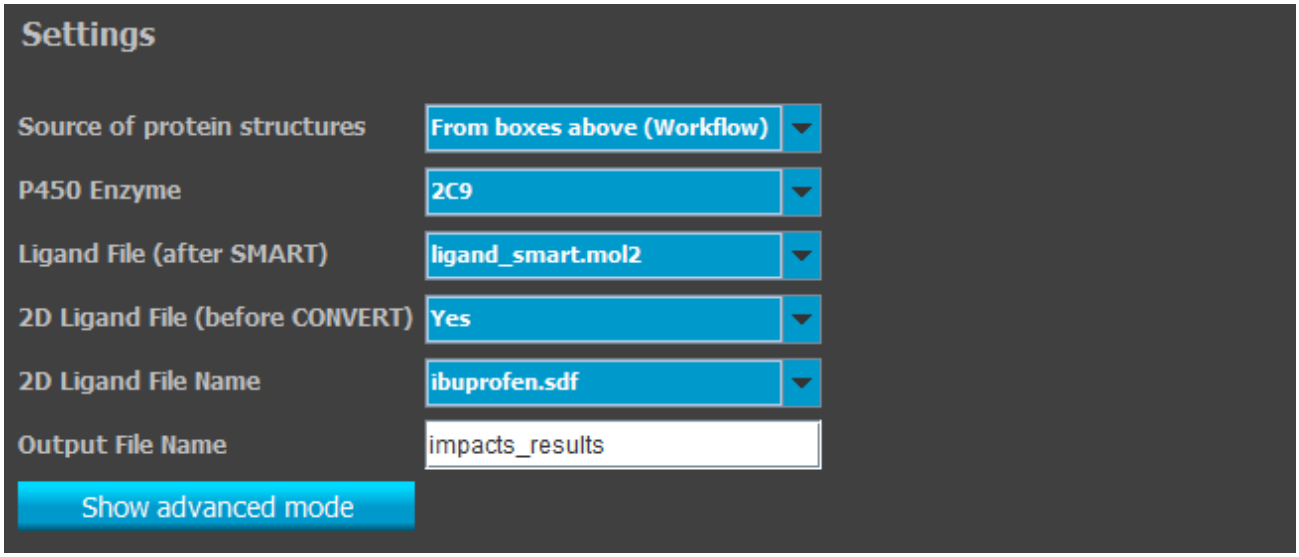


Once the settings are complete, the keyword file needs to be written by clicking the **Write keyword file** button. Clicking the **Exit** button will close the SMART parameters section and return to the main workflow. A green check should now appear in the SMART box.

IMPACTS: Sites of metabolism predictions

The **Source of structures** should be set to "From working directory". The required P450 enzyme (CYP) protein structures will be copied automatically to the working directory when the workflow is started. For this tutorial, the **P450 Enzyme** should be set to "2C9". The **Ligand file** is the ligand prepared by SMART (`ligand_smart.mol2`, if the default name was used). The **2D Ligand File** should be set to "yes" and **2D Ligand File Name** to the input 2D molecule (`.sdf`). This 2D file (when available) will be used to create the metabolite representations in 2D (can be viewed

in the sketcher). The **Output File Name** can be filled with any desired name; “impacts_results” is suggested.



The keyword may then be written by clicking the **Write keyword file** button. Click the **Exit** button to return to the main workflow. A green check should now appear in the IMPACTS box.

Workflow: Running the sites of metabolism workflow

Once all the included steps are ready, the workflow can be executed by clicking the **Run workflow** button.

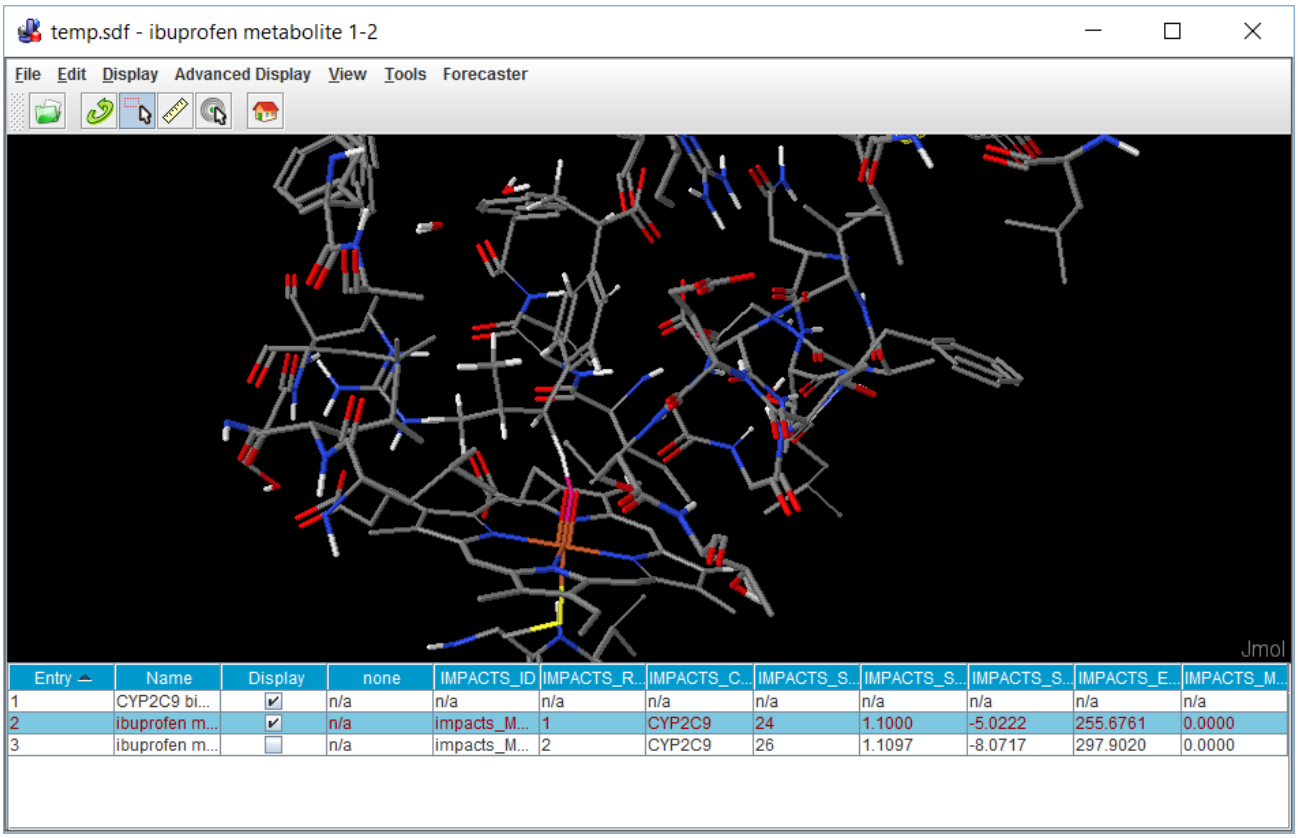
The programs run in a terminal (e.g., dos in Windows) and once the complete workflow is complete, the terminal window will close automatically. Do not close it manually.

III. Results Analysis

During the prediction process, several files will be generated. CONVERT will generate a new ligand. Smart will generate a new ligand (in FITTED mol2 format) and an output file (out format). To verify the integrity of any of these files, click the magnifying glass of the corresponding step.

IMPACTS will generate two structural files. The file `impacts_Metabolites3D.sdf` contains the 3D conformation of the oxidized molecule in complex with the heme's iron. This file can be visualized in your favorite 3D graphical program along with the corresponding P450 protein structure. The file `impacts_Metabolites2D.sdf` contains 2D structures of the 2 possible metabolites. This file can be visualized in your favorite 2D sketcher program. The other output files generated are `impacts.log` (log file for potential errors), `impacts.out` (detailed output file), and `impacts-results.txt` (summary results text file).

Alternatively, the results can be visualized by clicking the magnifier icon in the IMPACTS box. Clicking the **Metaboolites in 3D / Binding site** button will open the results in the 3D viewer. Within this 3D viewer, a table of data with the corresponding sites of metabolism will be available to easily visualize and analyze the predicted 3D poses.



Entry	Name	Display	none	IMPACTS_ID	IMPACTS_R...	IMPACTS_C...	IMPACTS_S...	IMPACTS_S...	IMPACTS_S...	IMPACTS_E...	IMPACTS_M...
1	CYP2C9 bi...	☑	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
2	ibuprofen m...	☑	n/a	impacts_M...	1	CYP2C9	24	1.1000	-5.0222	255.6761	0.0000
3	ibuprofen m...	☐	n/a	impacts_M...	2	CYP2C9	26	1.1097	-8.0717	297.9020	0.0000

In addition, clicking the **Metabolites in 2D** button will open the results in a 2D viewer. Within this 2D viewer, a table of data with the score and energy values of the corresponding sites of metabolism will be available to easily visualize the results.