VIRTUAL CHEMIST Suite 2019

FINDERS and REACT2D

Tutorial

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I. What will be Covered in this Tutorial

This example demonstrates the design of a combinatorial library in two ways, using substructures and reaction schemes. The two modules used are FINDERS and REACT2D.

First, you will build a library from a provided library of scaffolds and a collection of different amines using the S_NAr reaction. Since the amine collection was already filtered to keep only the desired amines, no filtering step is required. Therefore, **only the REACT2D step** will be used for this example.

Second, you will build a library from a defined synthetic scheme using a large library of chemicals. Contrary to the first section of this tutorial, we will use the FINDERS program to search for compatible reagents based on the chemical transformation.

Why use this workflow? Our combichem tools allow you to design your own virtual libraries with any chemical reaction you may have at your disposal. We have encoded ~60 commonly used reactions, but you will learn here to **draw your own reactions** compatible with our software. Additionally, you could create a workflow to carry your virtual library into docking experiments, metabolism experiments, or catalyst design.

How long will the tutorial take? The tutorial itself is run at your own pace. The workflow takes less than a minute to complete. A standard laptop should handle the experiment in seconds. A substantially larger input library will understandably increase this time.

FAQ.

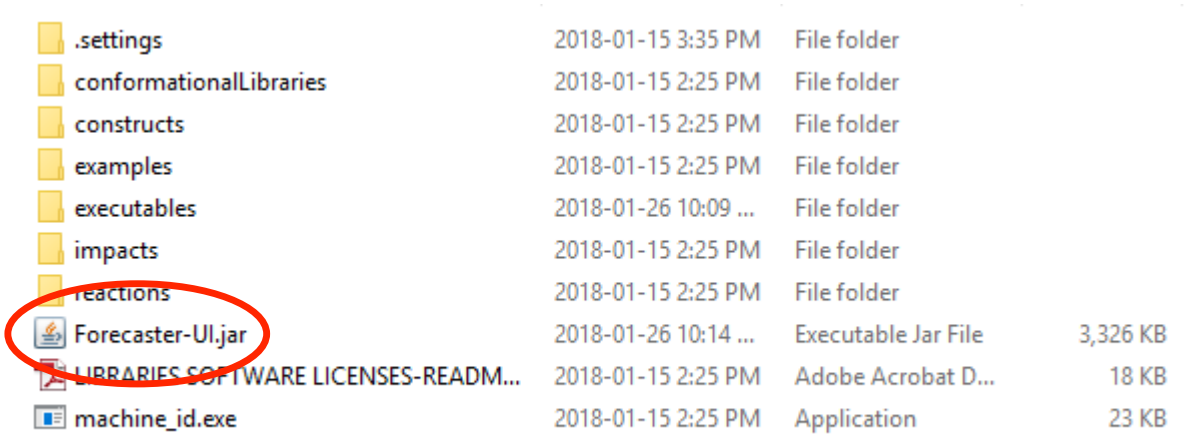
1. REACT2D considers protecting group and leaving group chemistries. Moreover, stereochemistry and ring chemistry are often crucial and are thus handled carefully and appropriately.
2. Duplicate reagents/products can be optionally removed. Depending on library sizes, there is an optimal decision to remove them at the reagent input stage, or at the product stage.

II. 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. For this tutorial, go to “examples” and then to “virtual-chemist-CombiChem”.

All the necessary files will be written there. The molecules can be drawn using the FORECASTER sketcher and the molecule/reaction files will be written there as well. If you are planning to run calculation from an external library (e.g., a catalog of chemicals, a file from the ZINC database,…), a copy should be in your working directory.

III. Combinatorial Chemistry with REACT2D

When your working directory has been selected, click the **Start Forecasting** button to expand the virtual chemist workflow.

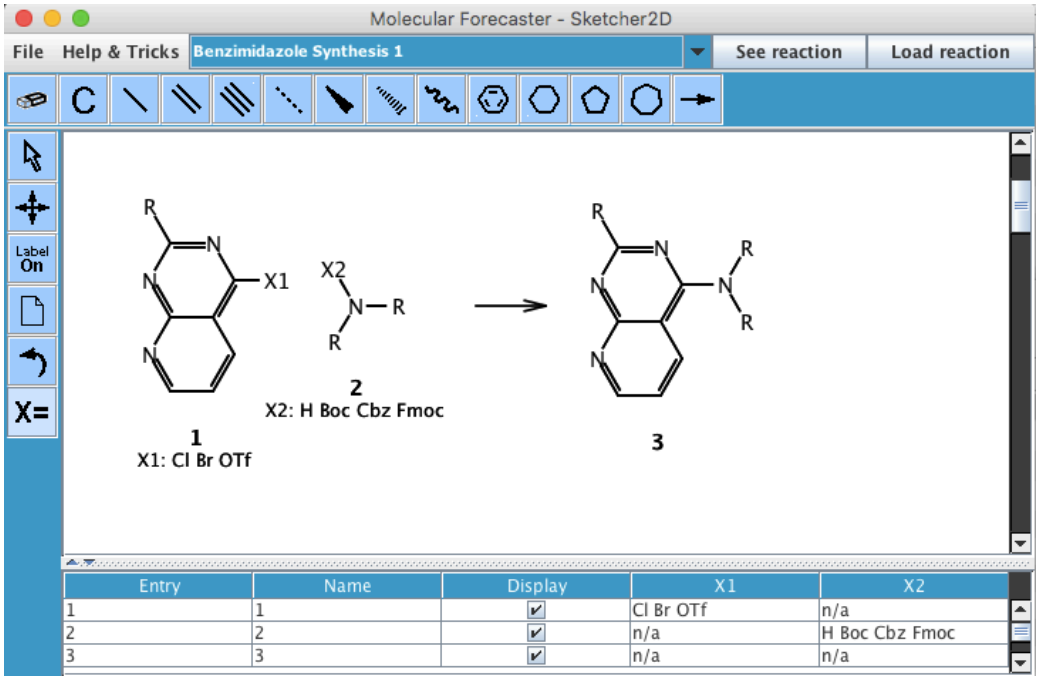
1. SKETCHER 2D: Drawing the chemical reaction

Using the sketcher, you will now need to define the reaction. Click on the gear icon to open SKETCHER2D. We will be building a library from a list of scaffolds and a collection of different amines using the S_NAr reaction. Dozens of predefined reactions can also be used as described throughout this tutorial.

Drawing the reaction should be done following some rules to ensure the programs will encode them properly. The reaction is drawn from left to right with the reactant(s) and product(s) separated by an arrow. The simplest substructure needs to be drawn and points of diversity encoded with the R, G or Ar groups (for definition click on the “Help & tricks” menu). You will be able to save your reactions and then load them using **File**, **Open reaction scheme (rxn)**.

In our example, the pyridopyrimidine scaffold is the common substructure with variations at the R position. The reactive center can either be specified (i.e. Cl) or included as a list of possible groups, X1. In our example, we will define X1 as being Cl, Br, or OTf. To define an X group on the molecule, the atom tool (“C” at the top) is used to type the X1 (or X2, …) at the desired position. Once the scheme is complete and the X groups are all specified, you will need to click the “X=” icon on the left toolbar for each X in the scheme and type the group names under the corresponding entry to enumerate them in the table.

Note: It is important to keep the same substructures for the reactants and the product for the transformation to be correctly identified by the REACT2D program.



Once the reaction scheme is complete, the reaction can be saved using the **File**, **Save reaction (rxn)** option from the sketcher and providing the `SNAr.rxn` filename.

For any other application, you may also load one of the ca. 60 reactions already listed using the drop-down menu at the top of the sketcher and then click **Load reaction**.

Small libraries of amines and scaffolds are provided in the tutorial folder. You can view them by using **File**, **Open structure file (sdf)**. You could draw your own libraries and save them using the **File**, **Save structure (sdf)** or you could use large libraries of chemicals downloaded from vendor websites as well.

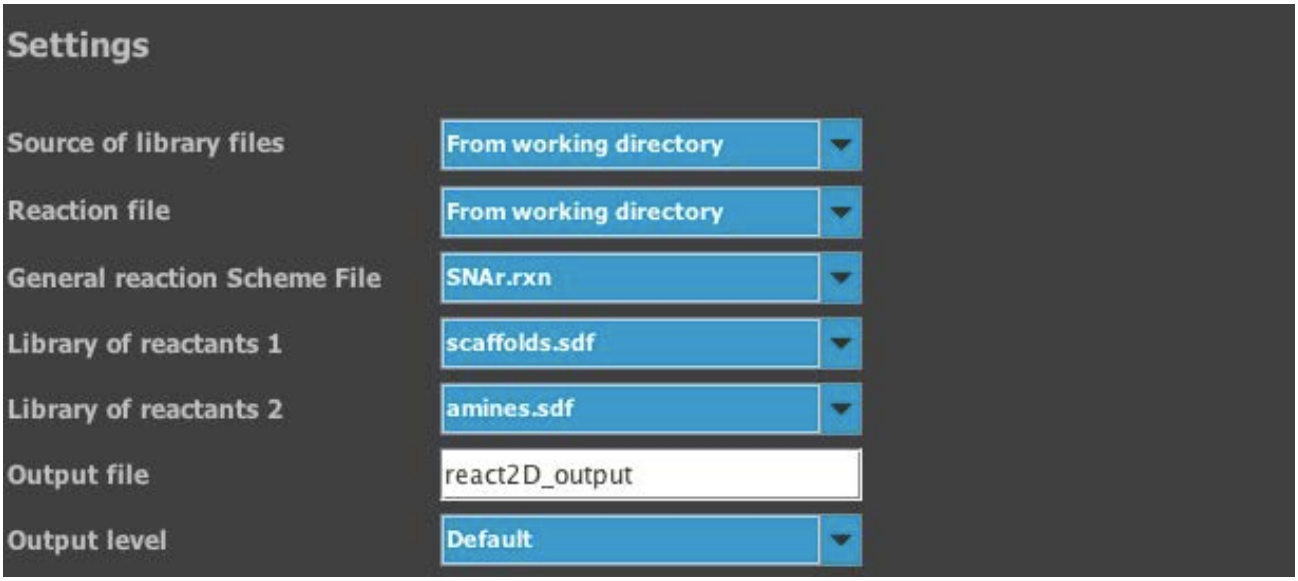
You can now exit the sketcher.

Since the provided amine collection was already filtered to keep only the desired amines, no filtering step is required. Therefore, the FINDERS step should be excluded (see next example for its use). The CONTRUCTS and ACE program are also excluded for this tutorial.

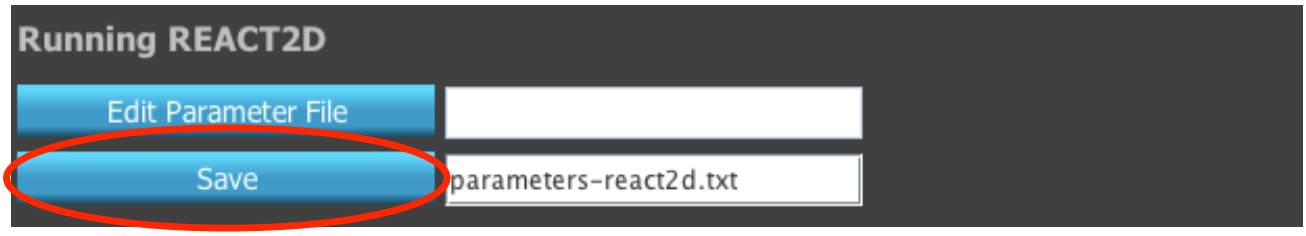
2. REACT2D: In silico combinatorial chemistry

Once the reaction scheme is defined, clicking on the gear icon of the REACT2D box will open the parameters section.

The **Source of reaction and library files** should be "From working directory". The **General reaction Scheme file** should point to "SNAr.rxn". The **Library of reactants 1** should be the first reactant as defined in the scheme, the scaffolds in our case (`scaffolds.sdf`). The **Library of reactants 2** should be the second reactant in the scheme, the list of amines (`amines.sdf`). The **output file** can be filled with anything, "`react2D-output`" is suggested. Since we have already defined the X groups directly in the scheme, the **Number of group(s)** settings for both reactants should be set to "X groups defined in the scheme".



The parameter file needs to be written by clicking the **Save** button. Clicking the **Exit** button will close the REACT2D parameters section and return to the main workflow.



A green check-mark should now appear in the REACT2D box.

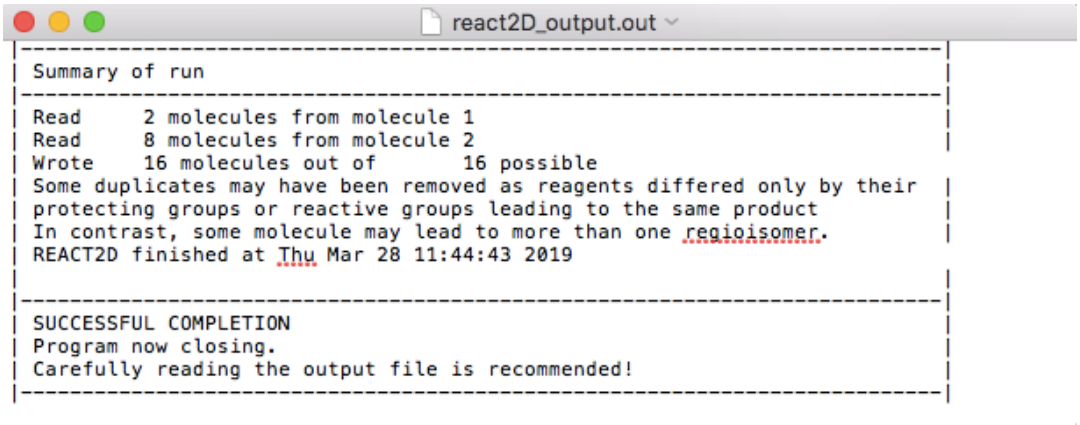
3. Workflow: Running the VIRTUAL CHEMIST

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) and once the complete workflow is complete, the terminal window will close.

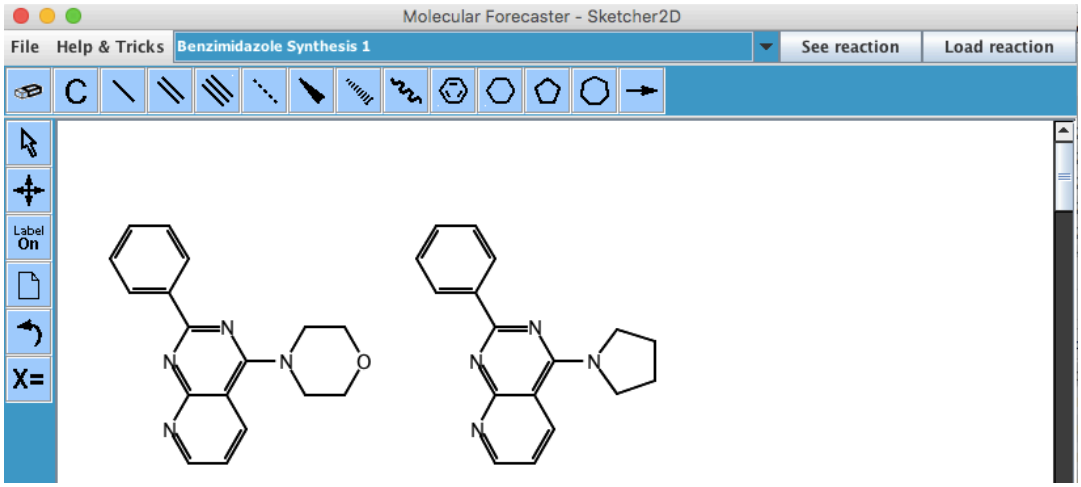
4. Analyzing the results

Once the combinatorial chemistry is complete, multiple files will be created. The files are `react2D-output.out` (output file) and `react2D-output.sdf` (sdf file with the new library).

The `react2D-output.sdf` file contains the entire library with the 2D structures. The output library can be visualized by clicking the **magnifier icon** in the REACT2D box. Clicking the **2D structure** button will open the library within the sketcher while the **Text file** button will open the library as a text file. Alternatively, the structures can be visualized within any graphical program.



Although REACT2D has been validated on numerous reactions, it is possible that some chemistry causes problems. Please contact our team if you observe anything unexpected.



IV. In silico combinatorial library using FINDERS and REACT2D

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. For this tutorial, go to “examples” and then to “virtual-chemist-CombiChem2”.

We will be searching within a large library of chemicals the reactants that are compatible with the pyrimidine cyclization reaction using a single predefined scaffold. Therefore, the workflow will use both the FINDERS and REACT2D steps. It is important to set the parameters in the correct order.

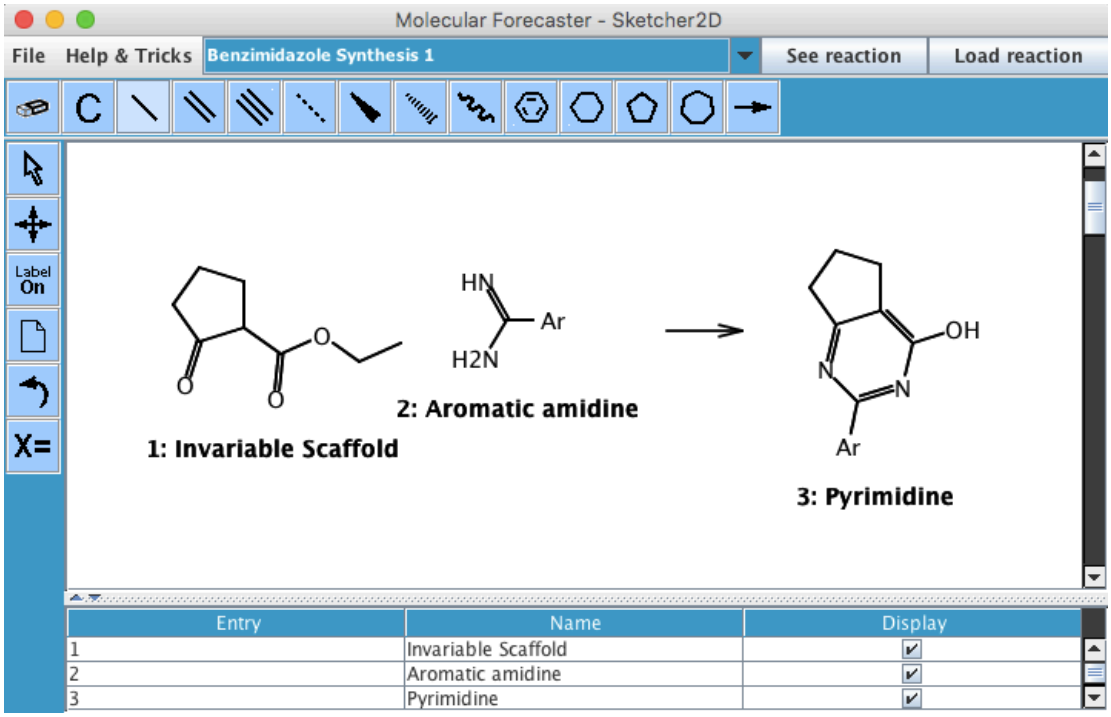
1. SKETCHER 2D: Drawing the chemical reaction

The first step requires to define the chemical reaction using the SKETCHER2D. Clicking on the gear icon will open the SKETCHER2D. The way of drawing the reaction is critical and very important.

Drawing the reaction should be done following some rules to ensure the programs will encode them properly. The reaction is drawn from left to right with the reactant(s) and product(s) separated by an arrow. The simplest substructure needs to be drawn and points of diversity encoded with the R, G or Ar groups (for definition click on the "Help & tricks" menu). You will be able to save your reactions and then load them using **File**, **Open reaction scheme (rxn)**.

In our example, we will search for compatible benzamidines from a reduced Aldrich catalog, which is included in the tutorial folder. The pyrimidine reaction we will draw involves the condensation of a 1,3-keto ester with different aromatic benzamidines. The 1,3-keto ester doesn't include any generic groups and thus will be considered as invariable (still must be drawn as part of the reaction). The aromatic benzamidines will be queried by the software for compatible reactants within the provided catalog. To define an Ar group on the molecule, the atom tool ("C" at the top) is used to type the Ar at the desired position. The reaction scheme should look like the following image.

Note: It is important to keep the same substructures for the reactants and the product for the transformation to be correctly identified by the REACT2D program.



Once the reaction scheme is complete, the reaction can be saved using the **File**, **Save reaction (rxn)** option from the sketcher and providing the `pyrimidines.rxn` filename. You can now exit the sketcher.

2. FINDERS: Searching libraries for compatible chemicals

Once the reaction scheme is defined, clicking on the gear icon of the FINDERS box will open the parameters section.

The **Catalog to be searched** should be "`Aldrich1125.sdf`", the **reaction file** "From working directory", and the **Reaction Scheme** "`pyrimidines.rxn`". Since the catalog might contain aromatic benzamidines with incompatible functional groups, we will change the **Check for compatibility** to "Yes" and check the boxes for the following groups: aldehyde, amine, ammonium, aniline, carboxylic acid, carboxylate, imine, isocyanate, and thiol. The remaining settings should be left to their default settings.

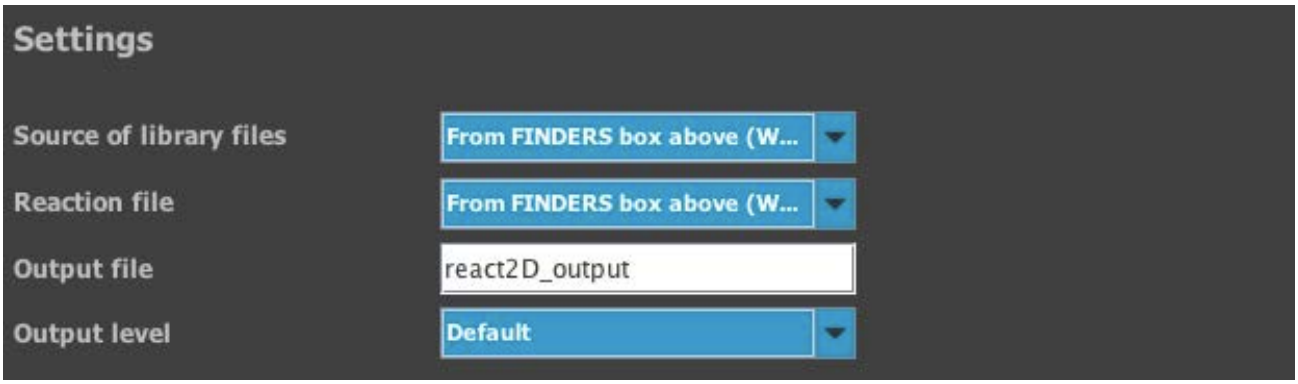

Settings
Source of molecule structures
From working directory
Search mode
From a reaction scheme
Catalog to be searched
Aldrich1125.sdf
Substructure Scheme
Reaction file
From working directory
Reaction Scheme
pyrimidines.rxn
Output file
finders_output
X1, X2, X3: groups such as protecting groups and leaving groups that can be defined belowEx.:
R-CH2-OX with R=everything but aldehyde and X being a protecting group
Restrict chemical library size
2000
Check for size
No - Any R group would be compa...
Check for compatibility
Yes - Some R groups may not be c...
Check the incompatible groups
acyl chloride
alcohol
aldehyde
alkene
alkyl chloride
alkyl bromide
alkyl iodide
amide
terminal amide
anhydride
amine
primary amine
secondary amine
tertiary amine
quat ammonium
aniline
aromatic
azide
boronic acid
boronate
carbamate
carboxylic acid
carboxylate
ester
hydroxamic acid
imine
isocyanate
ketone
lactone
lactame
michael acceptor
nitrile
nitro
oxime
silicon
sulphonamide
sulfonyl chloride
thiol
vinyl bromide
vinyl chloride
vinyl iodide

Once all the parameters are set, the parameter file needs to be written by clicking the **Save** button. Clicking the **Exit** button will close the FINDERS parameters section and return to the main workflow.

A green check should now appear in the FINDERS box.

3. REACT2D: In silico combinatorial chemistry

Once the FINDERS settings are set, clicking on the gear icon of the REACT box will open the parameters section. The **Source of library files and reaction file** should be "From FINDERS box above". The **output file** can be filled with anything, "`react2D-output`" is suggested.



Once all the parameters are set, the parameter file needs to be written by clicking the **Save** button. Clicking the **Exit** button will close the REACT2D parameters section and return to the main workflow.

A green check should now appear in the REACT2D box.

4. Workflow: Running the VIRTUAL CHEMIST

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) and once the complete workflow is complete, the terminal window will close.

5. Analyzing the results

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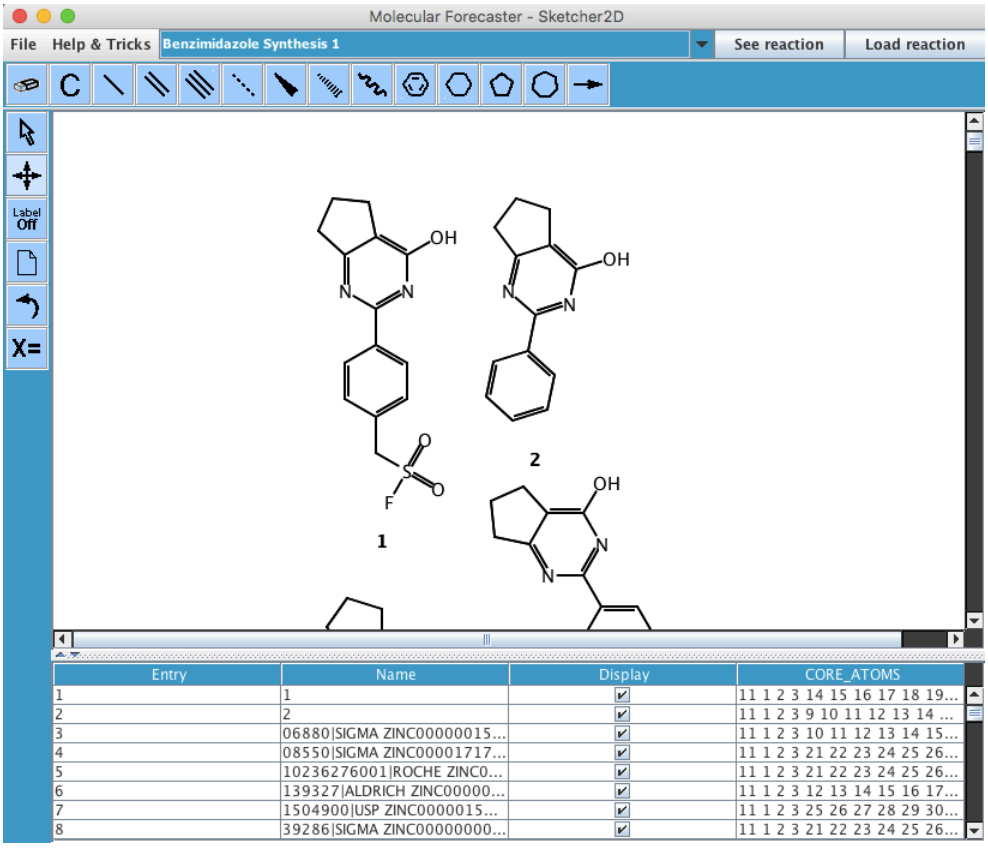

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