FORECASTER Suite 2016 Tutorial

Virtual Chemist – REACT

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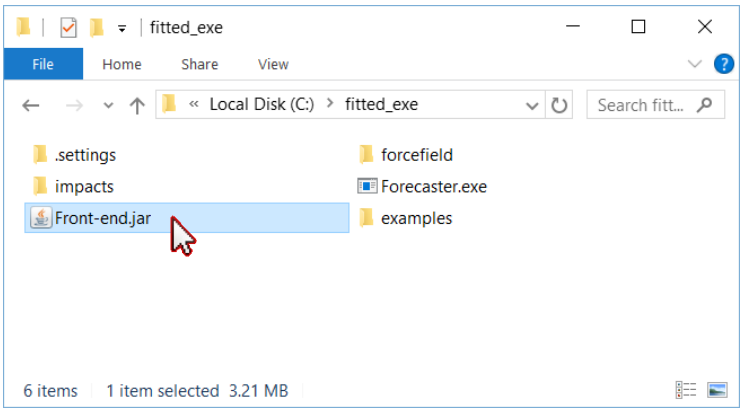
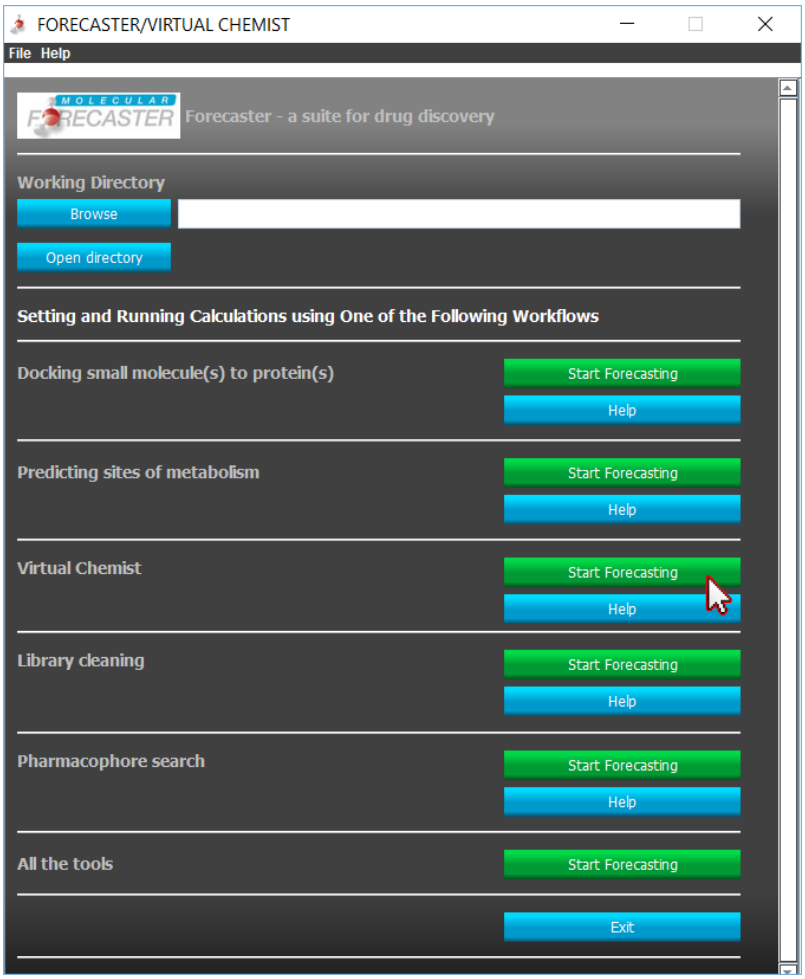
I. Running FORECASTER in Windows with the GUI

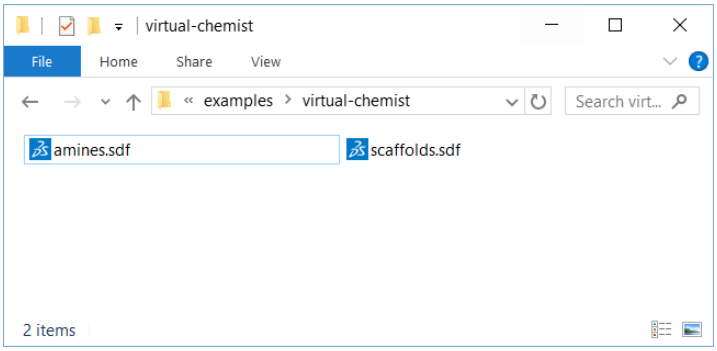
In this example, we will show how to use the in silico combinatorial chemistry program REACT to build a virtual library based a chemical reaction. Under windows, the graphical user interface (GUI) can be started by double clicking on the `Front-end.jar` file in the `fitted_exe` folder.



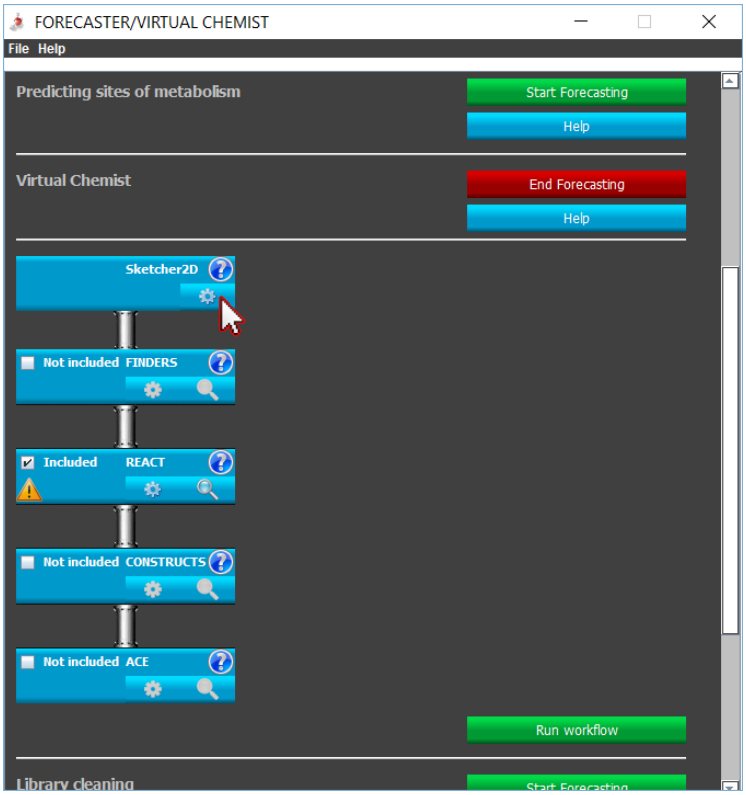
The GUI will open with Java and a list of workflows will be available. Clicking the **Start Forecasting** button will expand the virtual chemist workflow.



a. In silico combinatorial library using REACT only



The first step is to set the working directory. This is done by clicking the ***Browse*** button at the top left of the GUI. You will be prompted to navigate to the desired folder. We will be using `C:\fitted_exe\examples\virtual-chemist` for the current example. You should have the `amines.sdf` and `scaffolds.sdf` structure files in the folder.



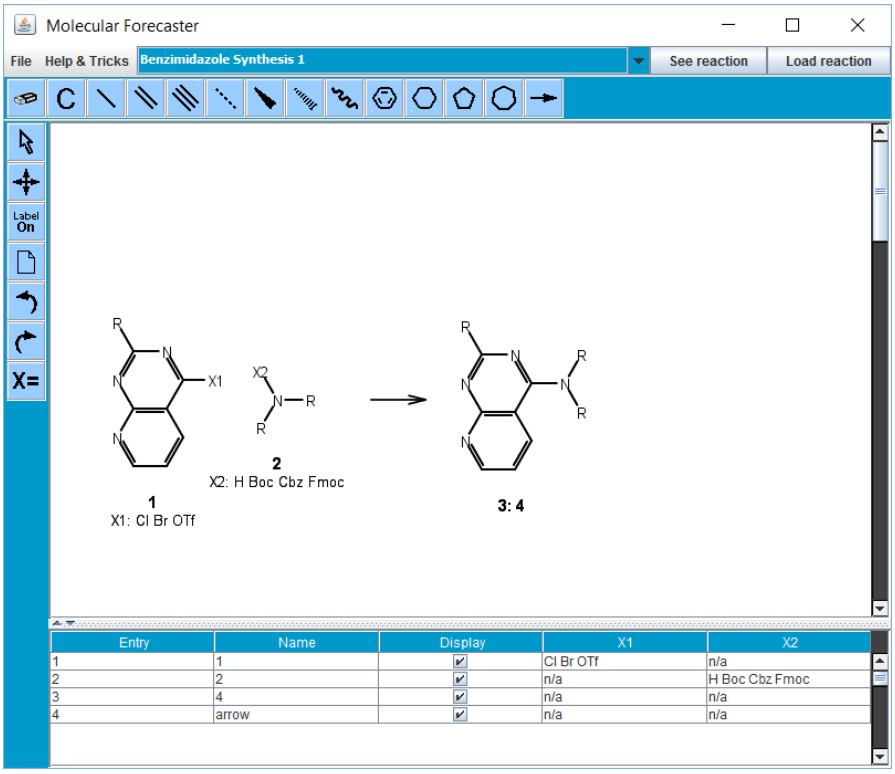
We will be building a library from a list of scaffolds and a collection of different amines using the S_NAr reaction. **Since the provided amine collection was already filtered to keep only the desired amines, no filtering step is required. Therefore, the FINDERS step should be excluded (see next example for its use)**. The CONTRUCTS and ACE program are still under development and are unavailable for the moment. In this workflow, we will use only the REACT step, therefore all the other steps will be excluded. It is important to set the parameters in the correct order.

SKETCHER 2D: Drawing the chemical reaction

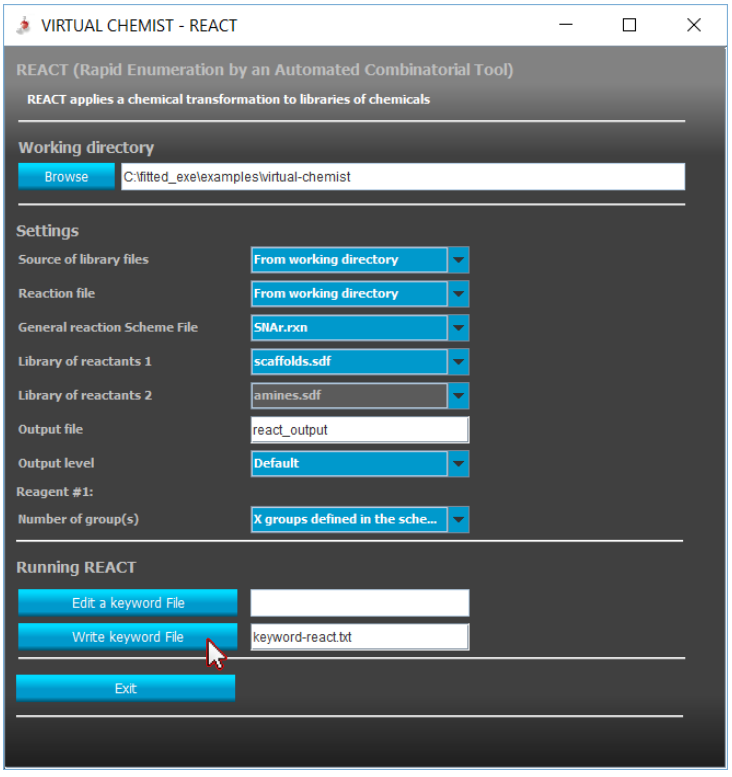
The first step requires to define the chemical reaction using the Sketcher2D. Clicking on the gear icon will open the sketcher2D. The way of drawing the reaction is critical and very important.

The reaction is drawn from left to right with the reactants and the product separated by the arrow. The simplest substructure needs to be drawn and points of diversity encoded with the R group (R can be anything including H). 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 either Cl, Br, or OTf. To define an X group on the molecule, the atom tool is used to type the X1 at the desired

position. Once the scheme is complete and the X groups are all specified in the scheme, they need to be enumerated in the table. This is done by clicking the X= icon on the left toolbar and listing the groups under the corresponding entry. It is important to keep the same substructures for the reactants and the product for the transformation to be correctly identified by the REACT 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.

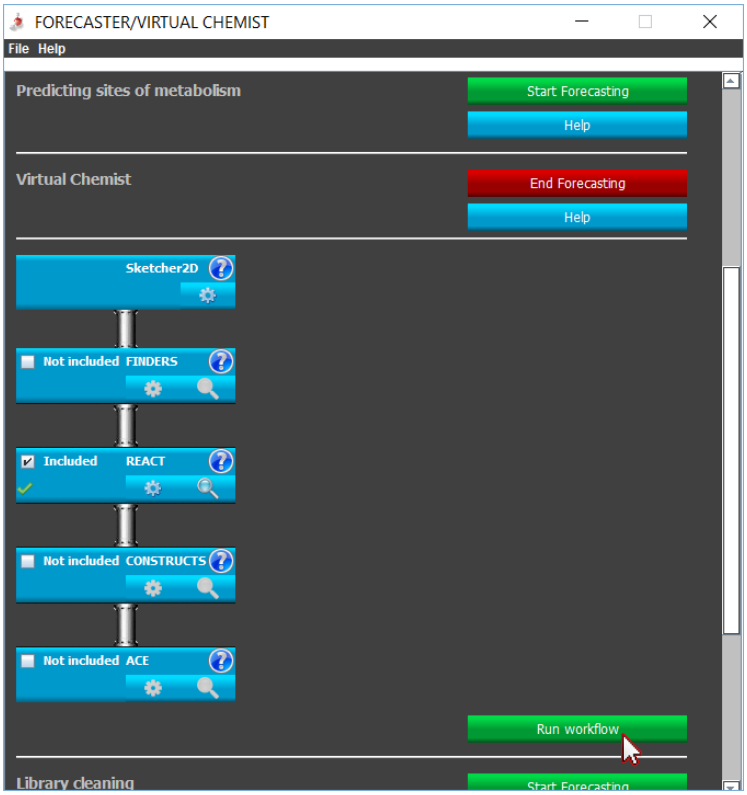


REACT: In silico combinatorial chemistry

Once the reaction scheme is defined, clicking on the gear icon of the REACT 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, "react-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".



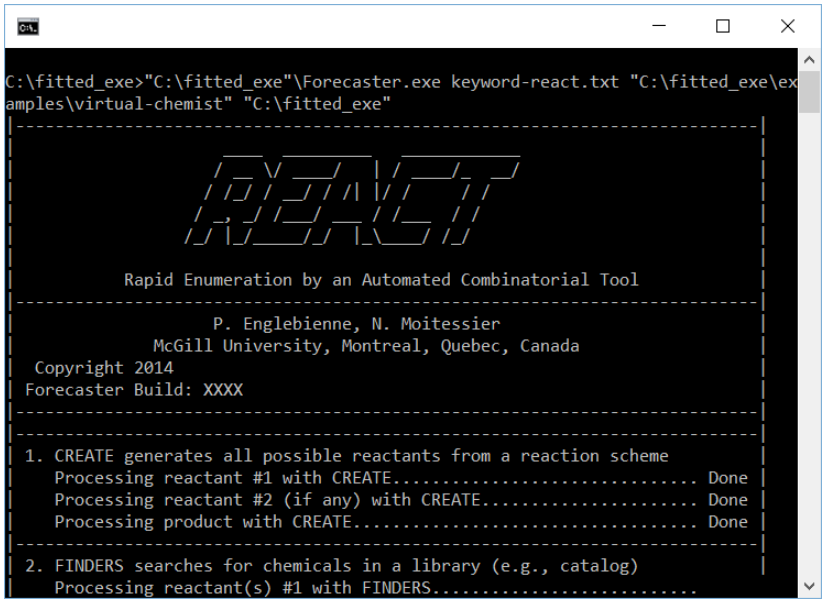
Once all the parameters are set, the keyword file needs to be written by clicking the **Write keyword file** button. Clicking the **Exit** button will close the REACT parameters section and return to the main workflow. A green check should now appear in the REACT box. The program will not run until the complete workflow is ready.

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.

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

The `react-output.sdf` file contains the entire library with the 2D structure. It can be visualized in your favorite graphical program.



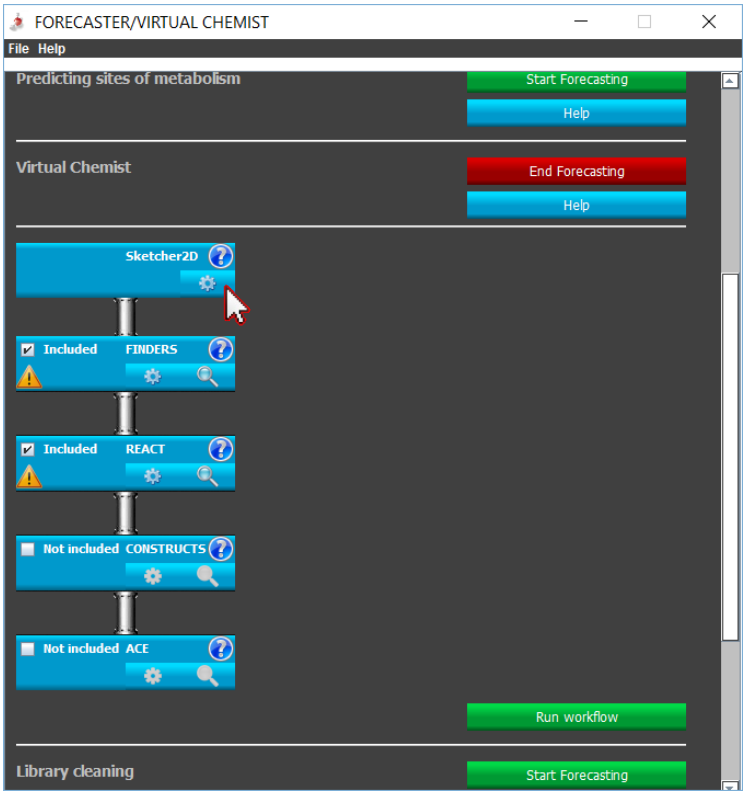
Alternatively, the output library can be visualized by clicking the magnifier icon in the REACT box. Clicking the **2D structure** button will open the library within the sketcher while the **Text file** button will open the library as a text file.

Although the program REACT has been validated on multiple

reactions, it has not yet been tested extensively and some problem might occurs. For any problem, please contact our team.

b. In silico combinatorial library using FINDERS and REACT

In this example, we 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.



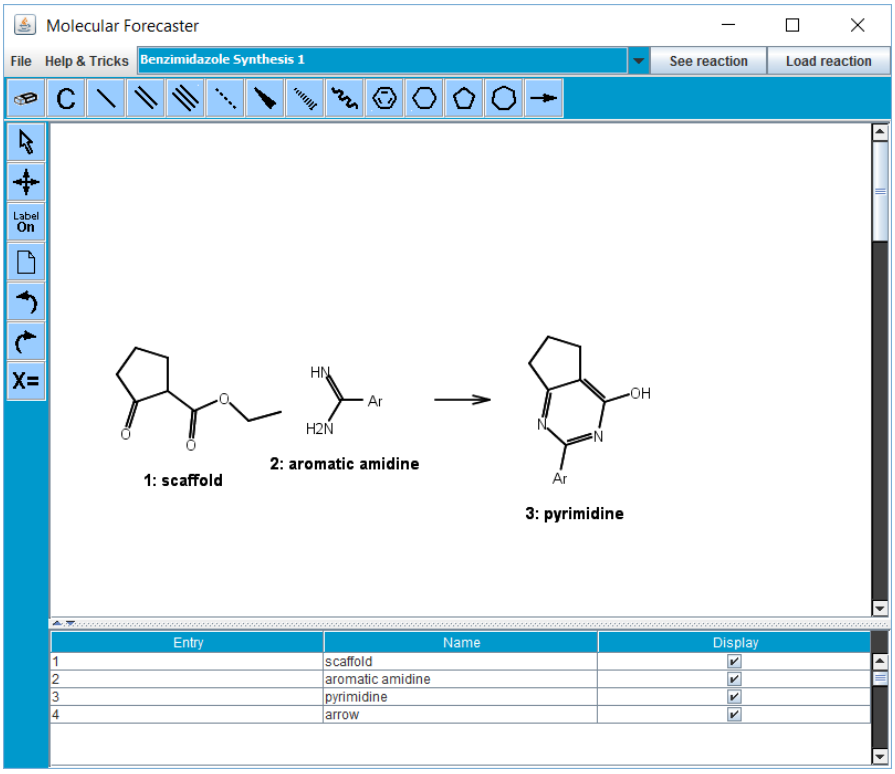
The first step is to set the working directory. This is done by clicking the ***Browse*** button at the top left of the GUI. You will be prompted to navigate and create the desired folder. We will be using `C:\fitted_exe\examples\virtual-chemist2` for the current example.

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 REACT steps. It is important to set the parameters in the correct order.

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.

The reaction is drawn from left to right with the reactants and the product separated by the arrow. The simplest substructure needs to be drawn and points of diversity encoded with the R group (R can be anything including H). In our example, we will search for compatible benzamidines from a reduced Aldrich catalog (http://fitted.ca/docs/Aldrich1125.sdf). Thus, the scaffold is drawn as the reactant and since the structure doesn't include any generic groups such as R, G, or Ar, it will be considered as invariable. When such groups are used in the structure, the software will search for compatible reactants within the provided catalog. The pyrimidine reaction involves the condensation of a 1,3-keto ester with different aromatic benzamidines. In this example, we will be



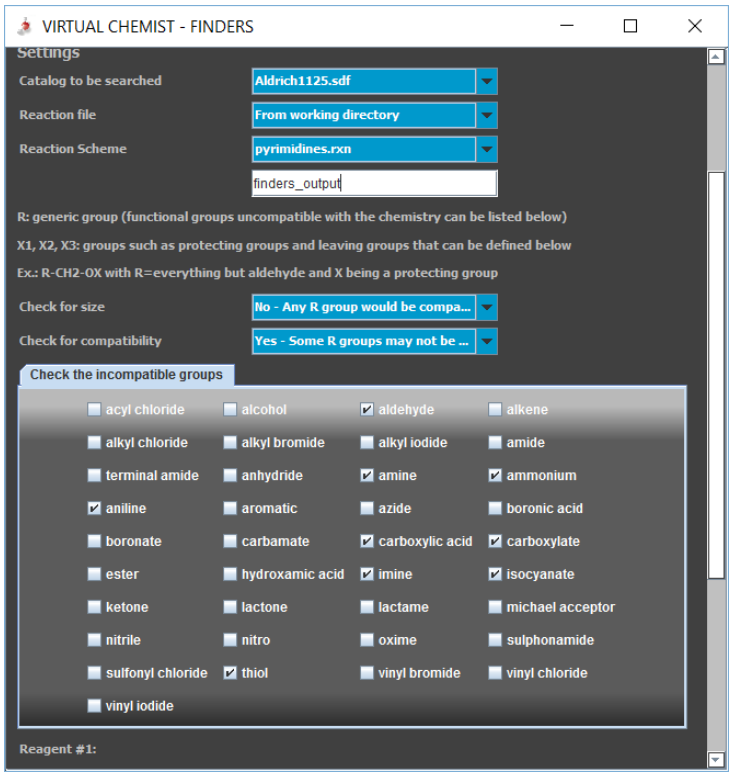
searching only for aromatic benzamidines and the reaction scheme should look like the following image. It is important to keep the same substructures for the reactants and the product for the transformation to be correctly identified by the REACT program.

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.

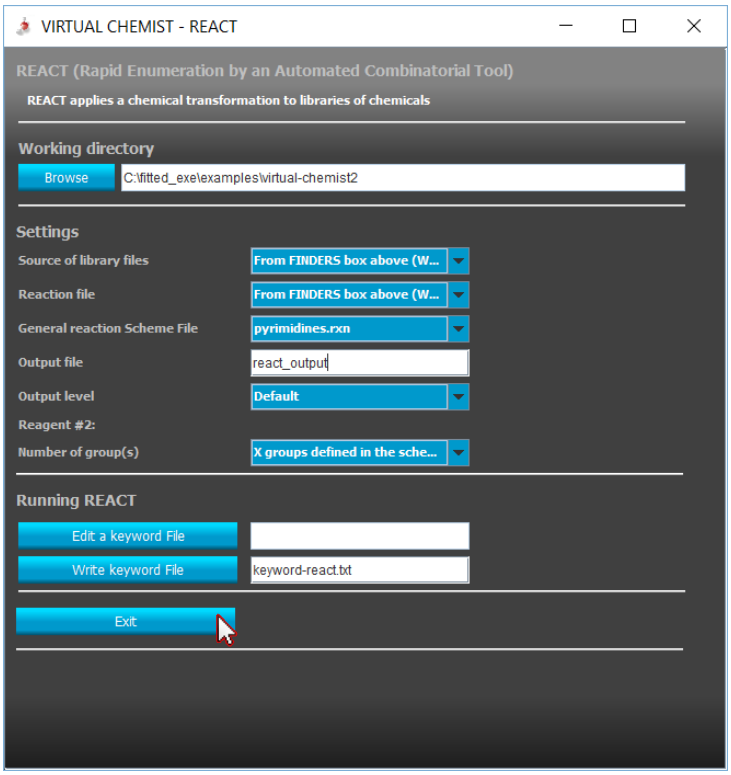
FINDERS: Searching libraries for compatible chemicals

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** to point to "`pyrimidines.rxn`". Since the catalog might contain aromatic benzamidines with incompatible 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, and imine. The remaining settings should be left to their default settings.



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 FINDERS parameters section and return to the main workflow. A green check should now appear in the FINDERS box. The program will not run until the complete workflow is ready.



REACT: 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, "react-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".

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 REACT parameters section and return to the main workflow. A green check should now appear in the REACT box. The program will not run until the complete workflow is ready.

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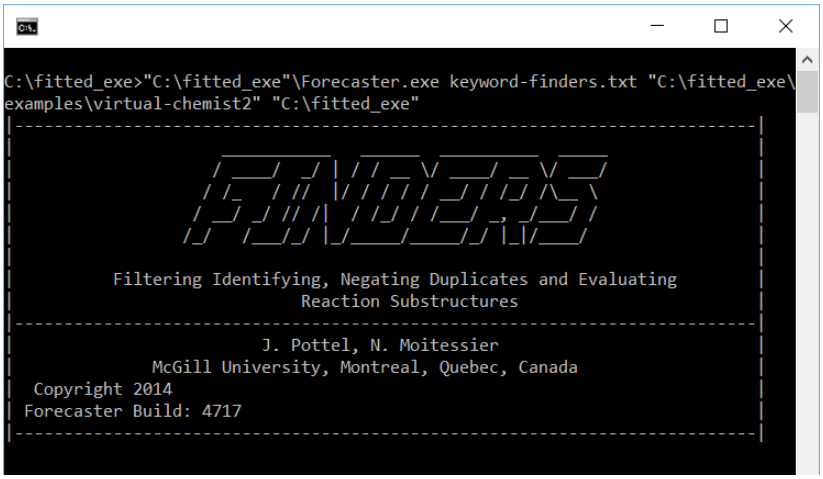

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