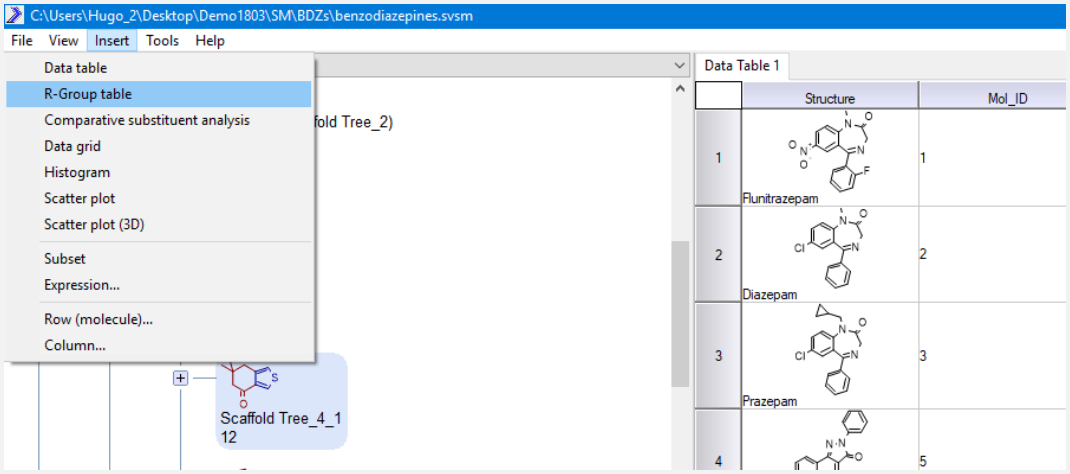
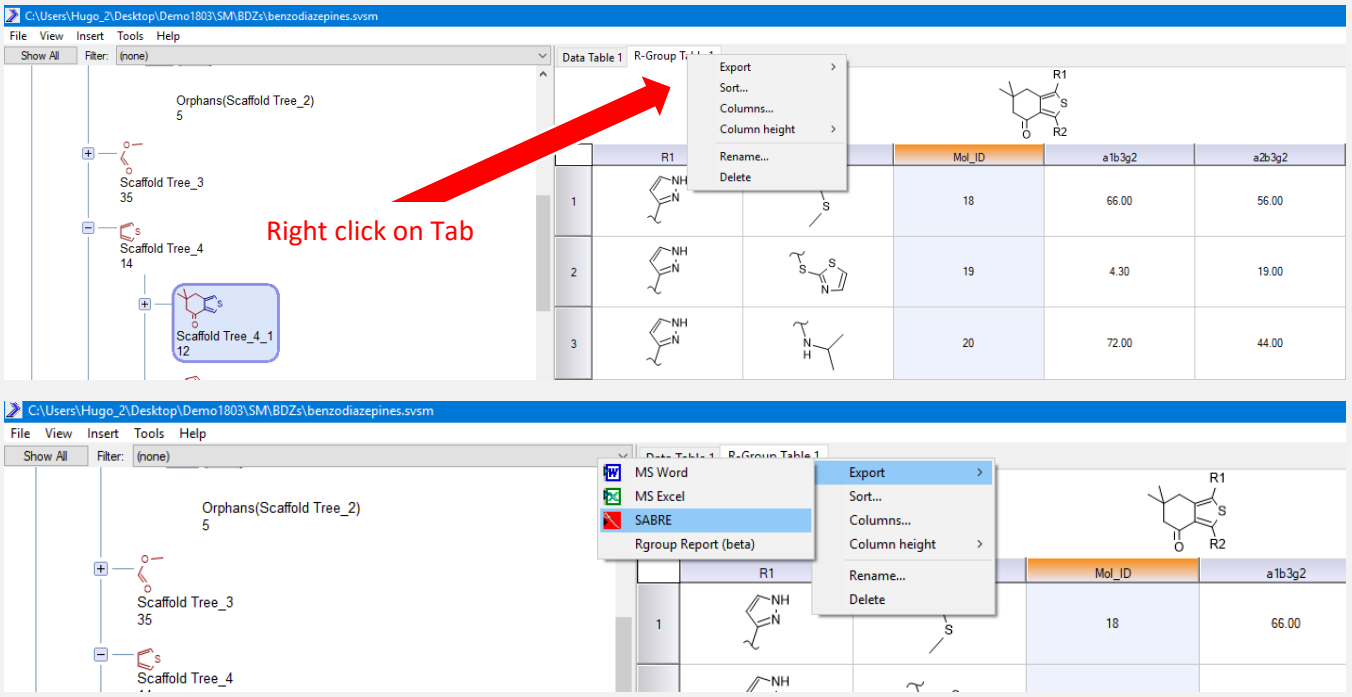
Reaching into ChemSABRE: RxR tables

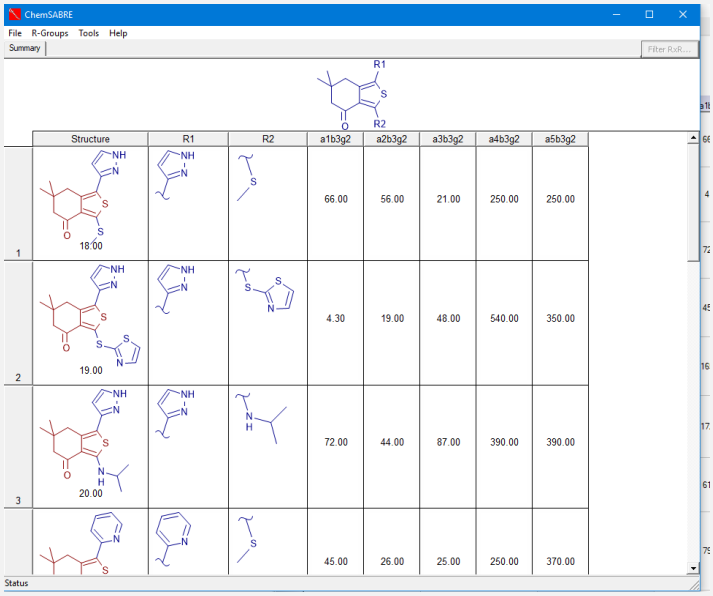
1. **Create an R-group Table.** If you do not know how to, find our video on creating R-group tables in our ChemAPPS channel on YouTube (https://youtu.be/Ip755bKojZU).



2. Select a scaffold that you are interested in and export it to ChemSABRE.

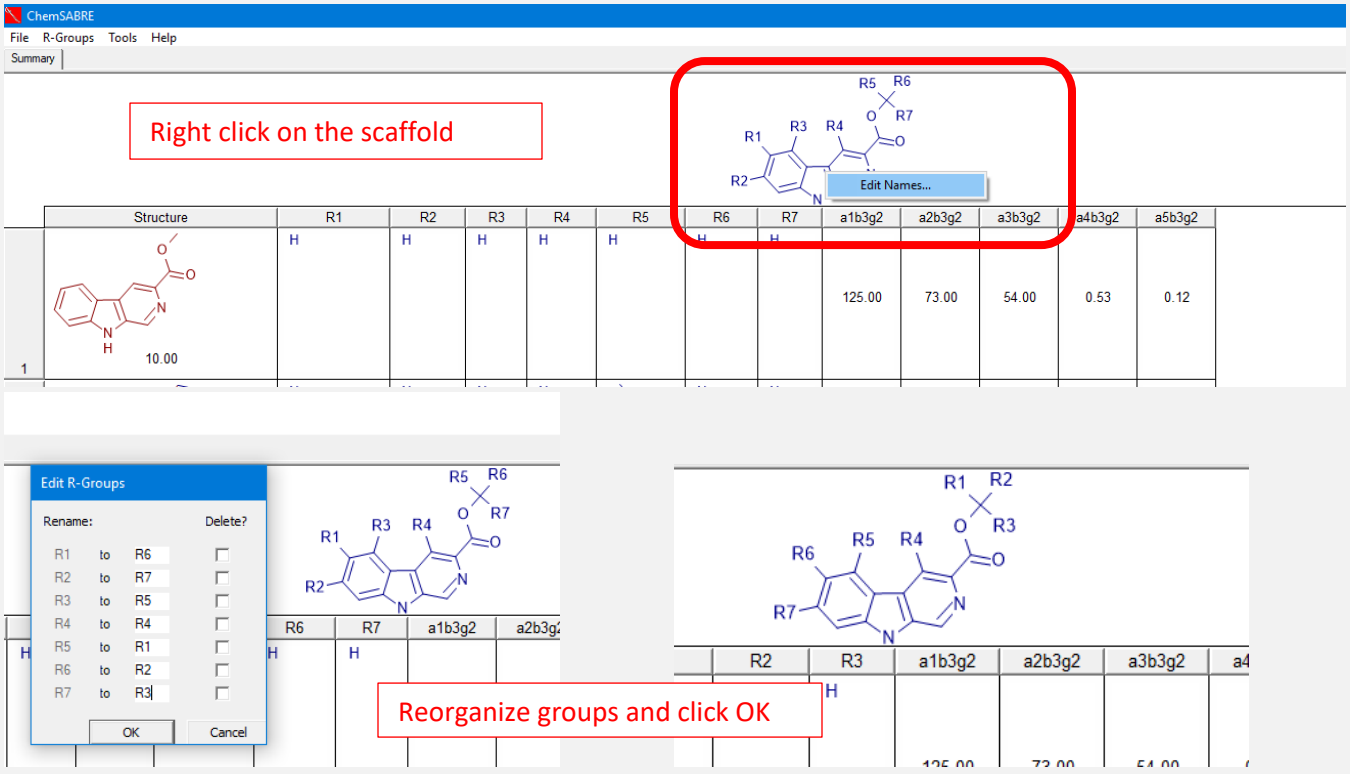


This will **open ChemSABRE** in a pop-up window



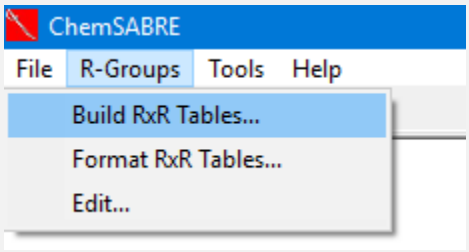
When ChemSABRE opens, it will look similar to the R-group table. However, you can see the molecule in the first column.

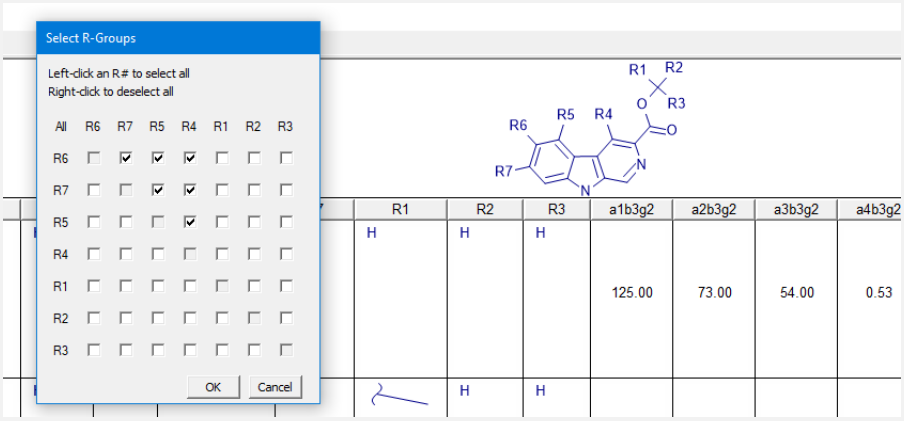
3. **Reorder the numbering of R groups**: ChemSABRE was developed to carry out a deeper analysis of R-groups to aid in lead optimization. When multiple R-groups are present, you can reorder them:



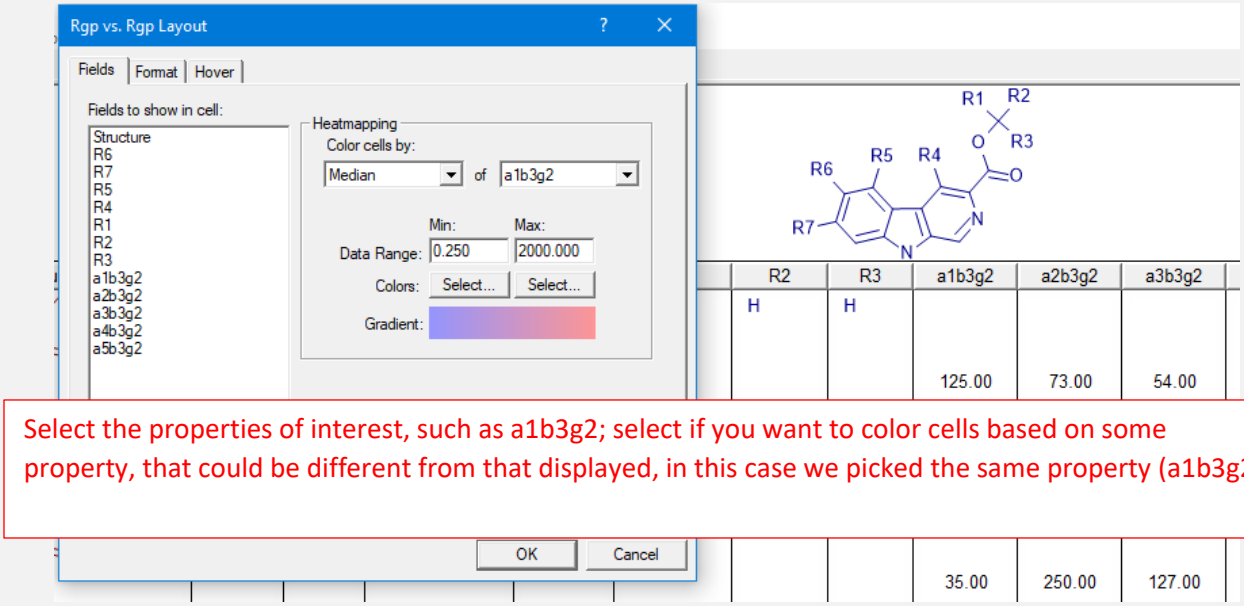
4. To reorganize the columns in the table simply drag the header of the table to the position that you are interested in.

5. To **create an RxR table** select from the R-groups pulldown Build RxR Tables…



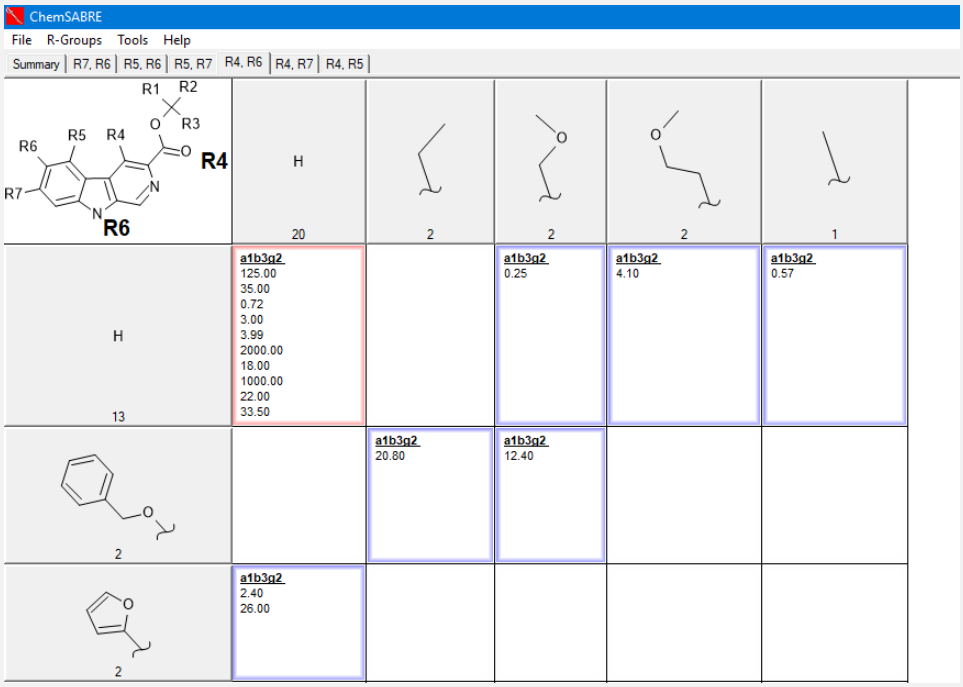


Then choose the pairs of RxR tables you are interested and select what information you would like to see in the two way table, you may want to create a heatmap for the cells:



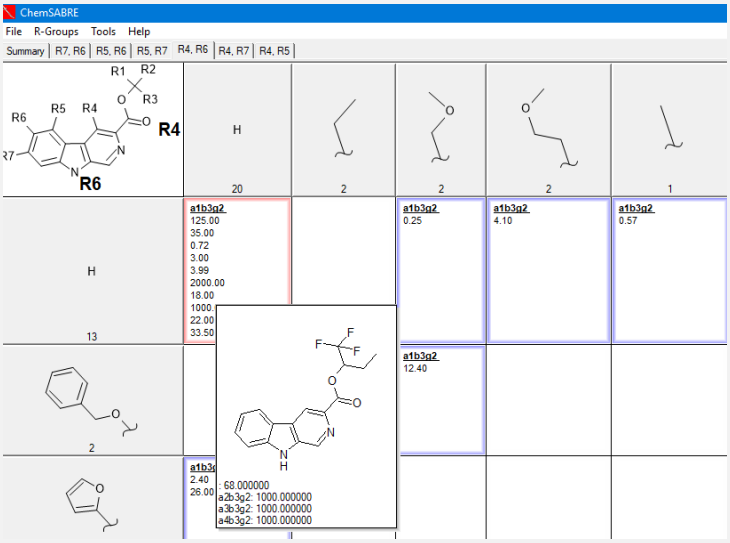
Select the properties of interest, such as a1b3g2; select if you want to color cells based on some property, that could be different from that displayed, in this case we picked the same property (a1b3g2).

A set of new tabs will be created for each pair selected. In the tab you will find a two way entry table that displays the data as you selected it.



In the table you can see the list of R-groups in each of the two positions and in each cell the values of the property selected as a list. If you prefer to see averages, minimum or maximum values you can simply reformat the table selecting form the pull-down menu Format RxR tables.

In the format as well as the pop-up menu where you select the RxR layout, there is the possibility to choose properties to be displayed when you hover over a number with your mouse.

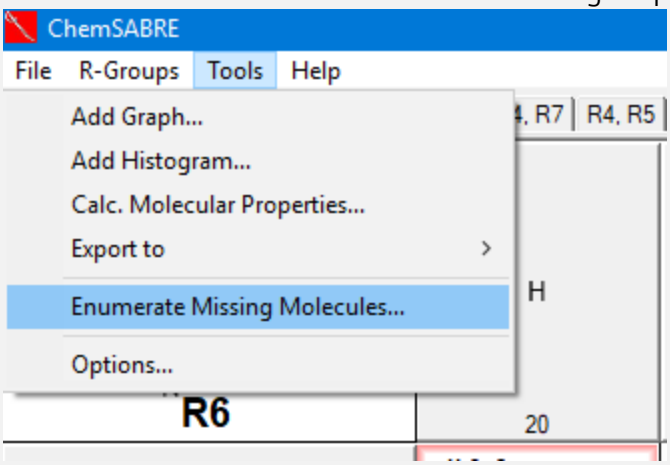


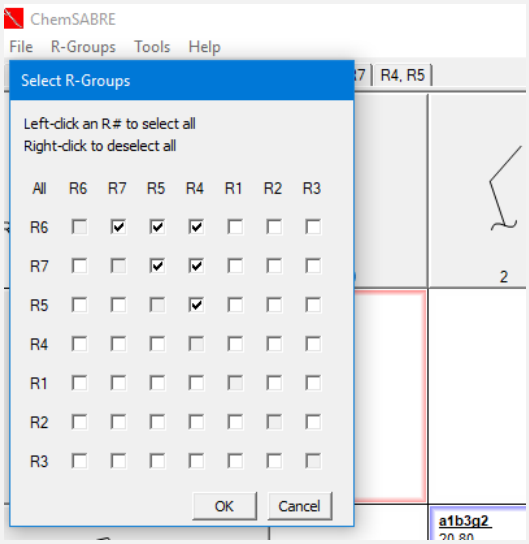
Note that in the H vs H cell there are a number of values for the a1b3g2 IC50s. While we are fixing in the two way entry table the values for R4 and R6, the substitution patterns in all other positions can be changing, therefore there are many possible compounds.

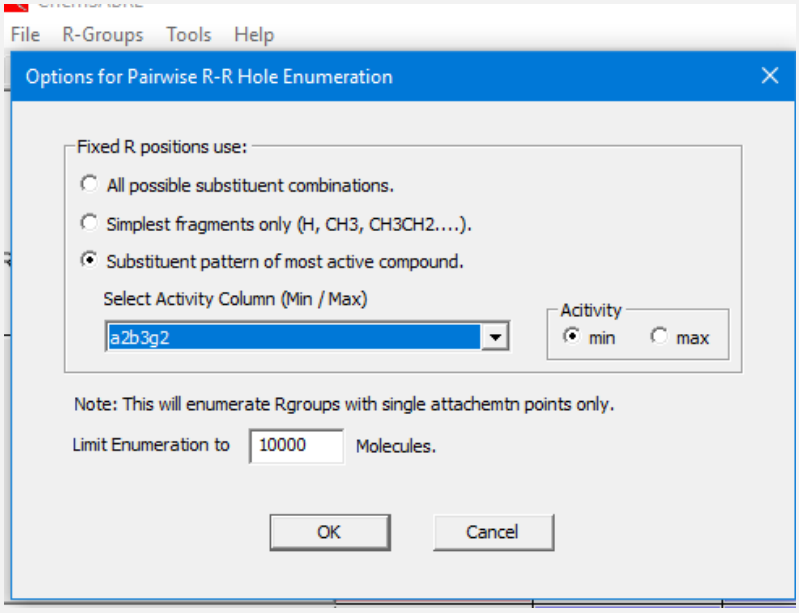
6. **Identify holes in your SAR**.

Blank cells are clearly noticeable in the RxR table. Those are combinations of compounds that have not been made or that we have not evaluated. In the example above, we can see we never made R4 ethyl while R6 is H. There are several other combinations that have not been made. The program permits the creation of an SD file that enumerates all the missing compounds in

the SAR. That file can then be used for analysis with AMEDEO or some other technique such as docking, or pharmacophore based virtual screening to identify compounds that could be of interest. To create that list take the following steps: from the Tools pulldown select Enumerate Missing Molecules… and a pop-up to select the pairs of interest, similar to the one seen before will appear. As we select all pairs of interest, a new pop-up will appear. One point to remember is that the result will be a combinatorial expansion. Therefore it is possible to generate very large numbers of structures. Therefore the next pop-up is there to limit the number of chemicals that will be enumerated. There are three options and all refer to what should be done with the other positions that are not under study. For example, as we enumerate all possible combinations of substituents in R6xR7, what should be done about R4, R5 and the other R groups?





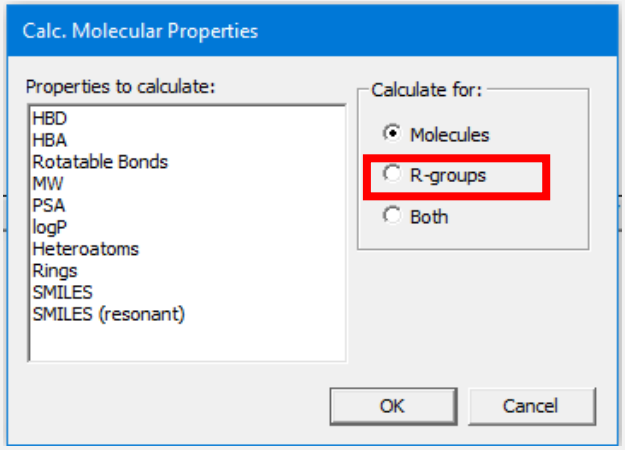


The first option is to consider all possible substituents in the other positions. The second would be to take the simplest R-group. For example in R6xR7, only the simplest substituents for R4 and 5 should be included as we vary R6 and R7. The final option is to select the substitution pattern for R4 and R5 that corresponds to that of the most active compound. R4 and R5 are therefore fixed to the R

groups in that position for the most active analog. One more safeguard is to place a limit in the total number of chemicals to be enumerated. Only selecting the name for the SD file generated remains. It could be imported into SARvision|SM for further analysis, for example filter by MW, logP or PSA or to use AMEDEO to select the compounds most likely to be of value.

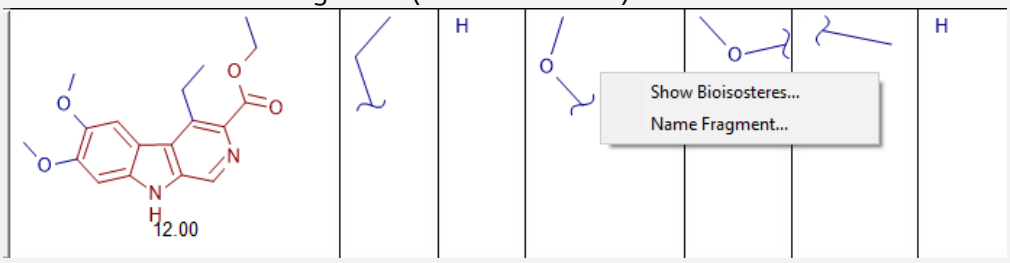
7. Beyond the RxR in ChemSABRE

ChemSABRE allows us to create scatter plots and histograms (bar plots) in the Tools pulldown.



You can calculated properties for R-groups (not just the entire molecule). Or you can combine the two and create graphs of the IC50 versus the value of the property at a given position, i.e. MW at R4.

If you right click on an R-group cell in the Summary tab, you will see a pop-up indicating that you can change the name of the fragment (-OMe or OCH3) or more interestingly you can select to see bioisosteres for the group. These are based on calculated properties for the fragments with Steric, Electronic and Entropy driving properties (Environmental). The program comes with a small database of such bioisosteric pairs based on calculations and other with a reference from the literature.



If you have any questions contact us at info@altoris.com. Our Resources area is continuously growing. We encourage you to visit it periodically. SARvision|SM is quite feature rich and not all its capabilities are easy to surface.