Self guided Tour

Reaxys Medicinal Chemistry

WHICH ARE THE KNOWN ACTIVITIES OF MY CHEMOTYPE ON OTHER TARGET CLASSES ?

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1.1 Scenario (Hit to lead)

An Apoptosis inducer 'chemotype' from a cell- and caspase-based apoptosis high-throughput screening was found (Compound 1). A structure activity relationship expansion lead to compound 2 (Schema1)

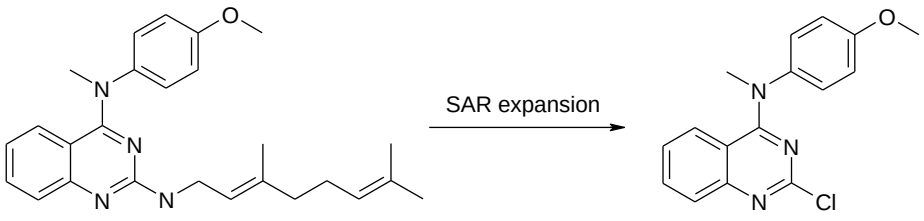


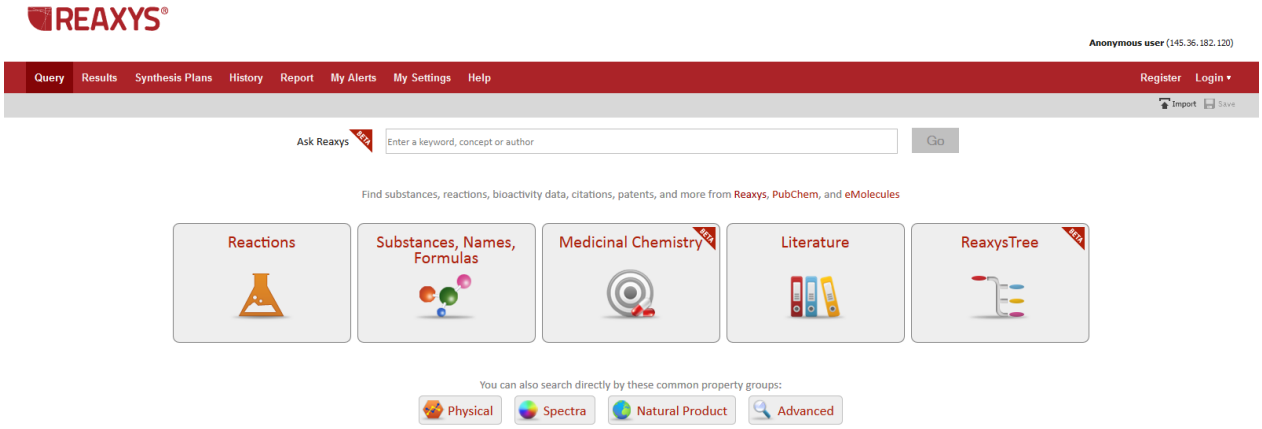
Figure 1 : Apotosis inducer : From HTS hit to new chemotype

Which are the known activities of my Chemotype on other target classes in Reaxys Medicinal Chemistry?

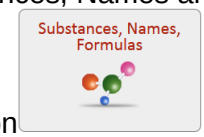
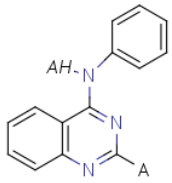
1.2 Overview

Step no.	Steps and description	Action
1	Search By Substances	Click on substance button
2	Draw your Substance	Use Marvin Sketch and draw structure
3	Search using Substructure, on all atoms option	Click on 'Substructure' and 'All atoms option'
4	Filter by Target Species	Filter by 'Target Species', select 'human', then click on 'Limit to'
5	Filter by pX	Filter by 'pX(-log(Affinity), move the bar to ca. 7.5, then click on 'Limit to'
6	Go to Heatmap tab	Click 'Heatmap' tab
7	Sort compounds by descending bioactivities on Target	Click on Caspase 3 column and sort descending
8	Check for common compound feature acting on caspase	Check the chemical structure of compounds acting on caspase
9	Check if this CH3 group is special, Go back to Query	Click on Query
10	Use Sketch to modify the structure	Click Edit on Sketch
11	Performed a new search on modified structure	Click on 'Search Substances'
12	Filter by 'Target Species'	Filter by 'Target Species', select 'human', then click on 'Limit to'
13	Filter by 'pX'	Filter by 'pX(-log(Affinity), move the bar to ca. 7.5, them click on 'Limit to'
14	Go to Heatmap tab	Click 'Heatmap' tab

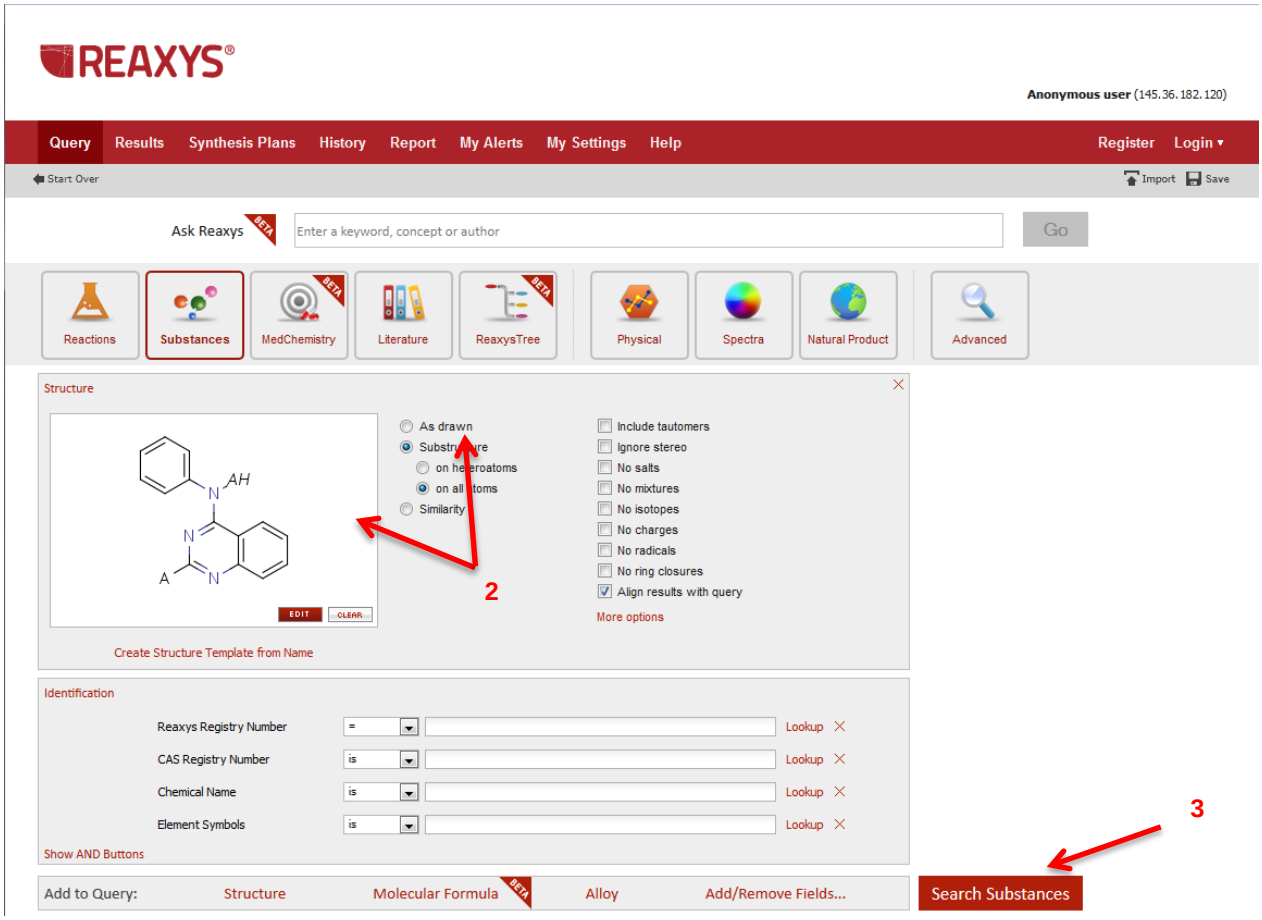
1.3 Step by step



Step 1 Search By substances and Chemical drawing

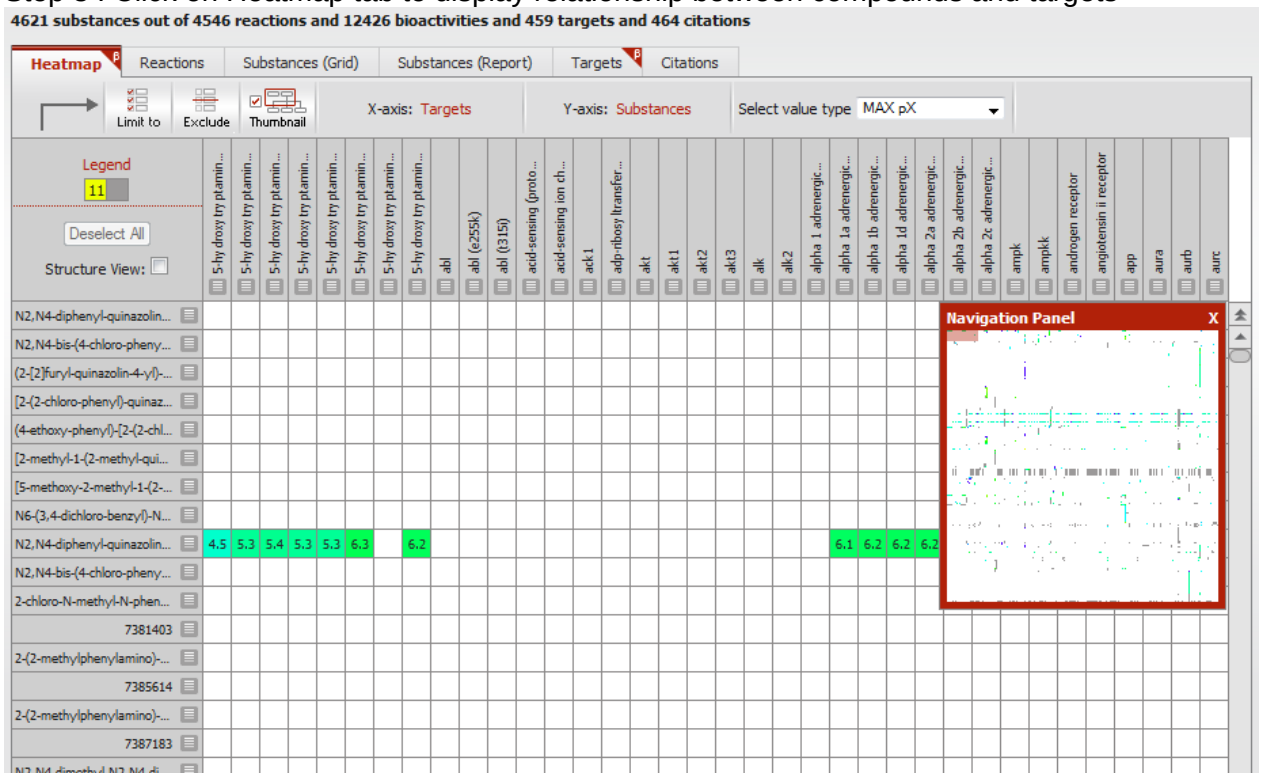
Step	Action	Comment
1	Click on Substances, Names and Formulas Button 	A new query Page dedicated to Substance will appear where you will be able to draw Compound 2 Scaffold
2	Draw the chemical Structure and Select Substructure all element in the option on the right 	Don't forget to transfer the query before closing the sketcher

Step 2 : Search by Substructure

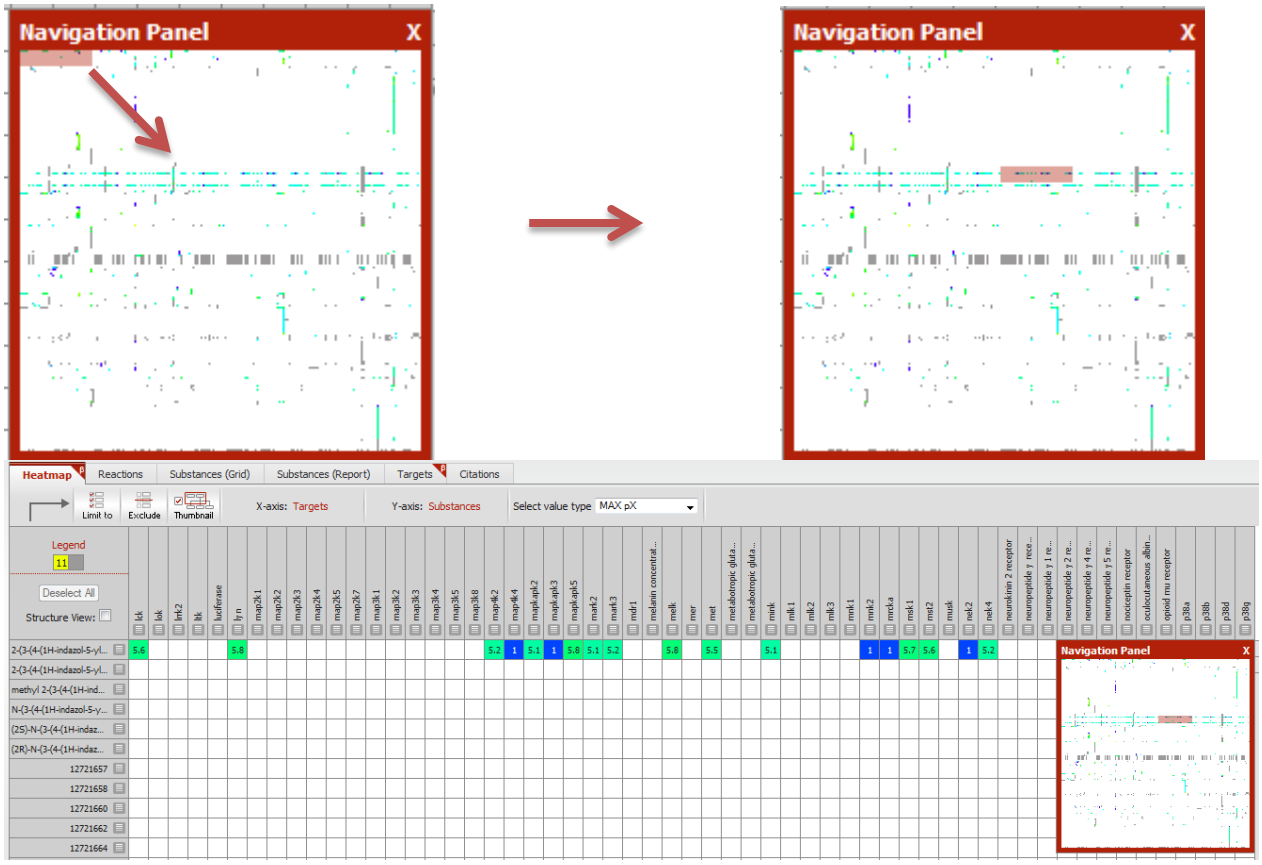


Substances report will be displayed (Default view when a search is performed by substance)

Step 3 : Click on Heatmap tab to display relationship between compounds and targets

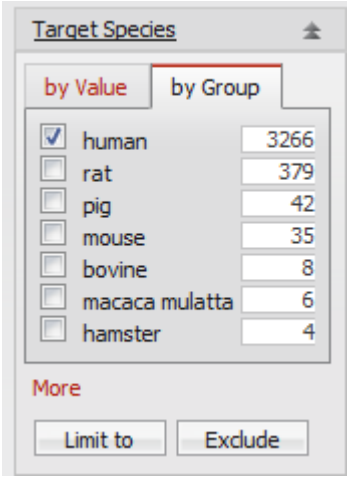


As many compounds and targets were retrieved by the search the screen display only a subset of the whole heatmap. The whole heatmap is shown in the thumbnail and what is seen on the screen is outlined by a red rectangle.
By dragging and dropping this red rectangle user are able to explore the whole heatmap.
Nevertheless in order to focus on the most interesting compounds Filters on the left hand side are available.



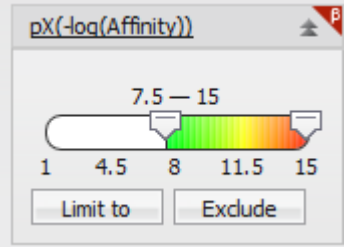
Nevertheless in order to focus on the most interesting compounds Filters on the left hand side are available.
Step 4: Filter by Target species

Select Human and click on limit to.



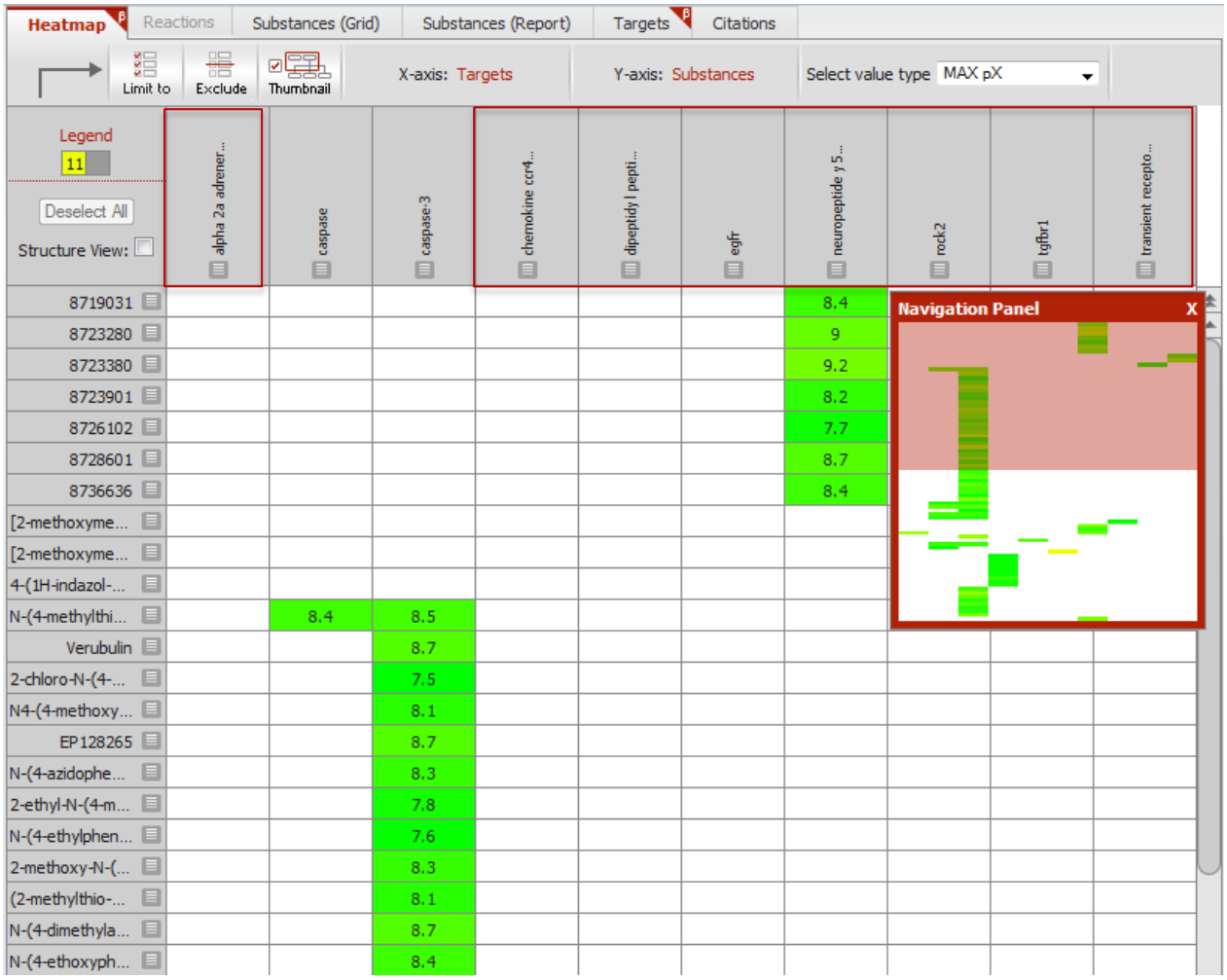
Step 5 filter by pX Values

Move the slider on the right to 7.5 (0.1 µM) to select active compounds and click on Limit to



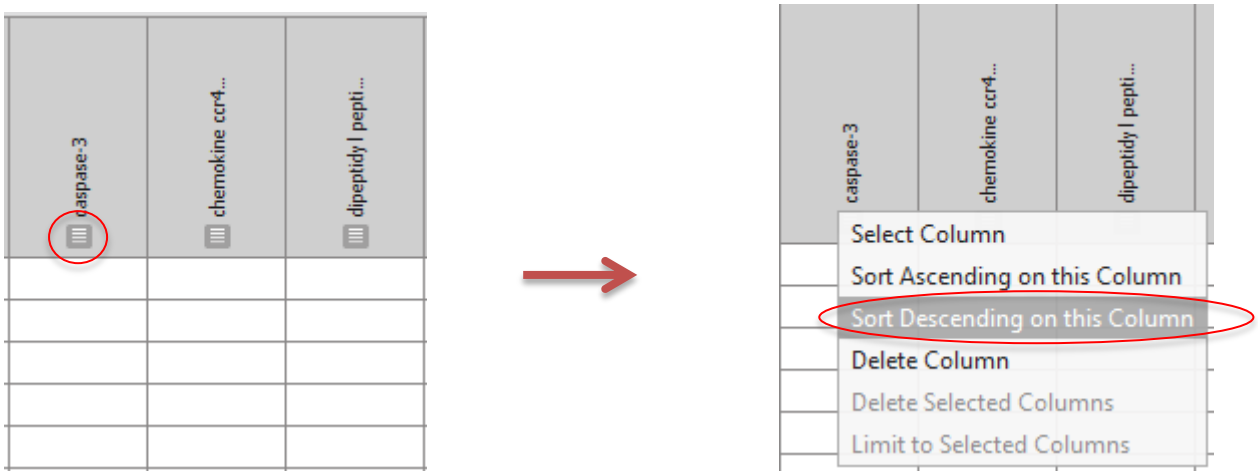
Step 6 Click on The Heatmap tab
The chemotype potentially bind on the following targets :

- GPCR : Alpha2a Adrenergic, Chemokine CCR4, Neuropeptide Y5
- Kinase : EGFR, Rock2,tgfbr1
- Histone : Histone deacetylase
- Peptidase : Dipeptidyl peptidase 4
- Ion Channel : Transient receptor Vanilloid 1



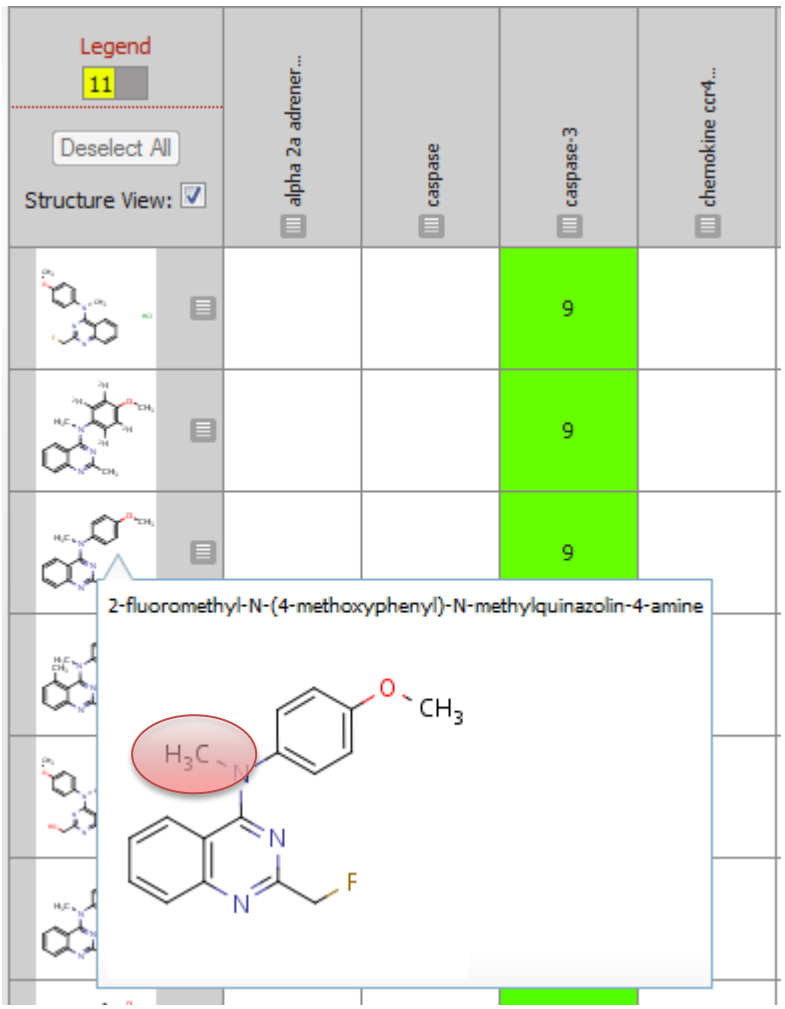
Step 7 : Sort compounds by descending bioactivities on Caspase 3

Click on the caspase 3 button  and select “sort descending on this column” See Below.



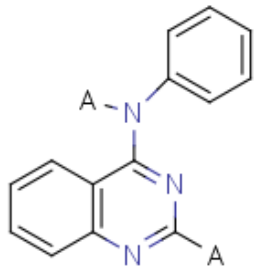
If look you into the chemical compounds carefully, you can see that compounds active on caspase have a methyl group on the aniline nitrogen whereas all the others active compounds on non caspase target have no methyl substituent in the same position.

It appears that this methyl group is very important for the selectivity on caspase versus other targets



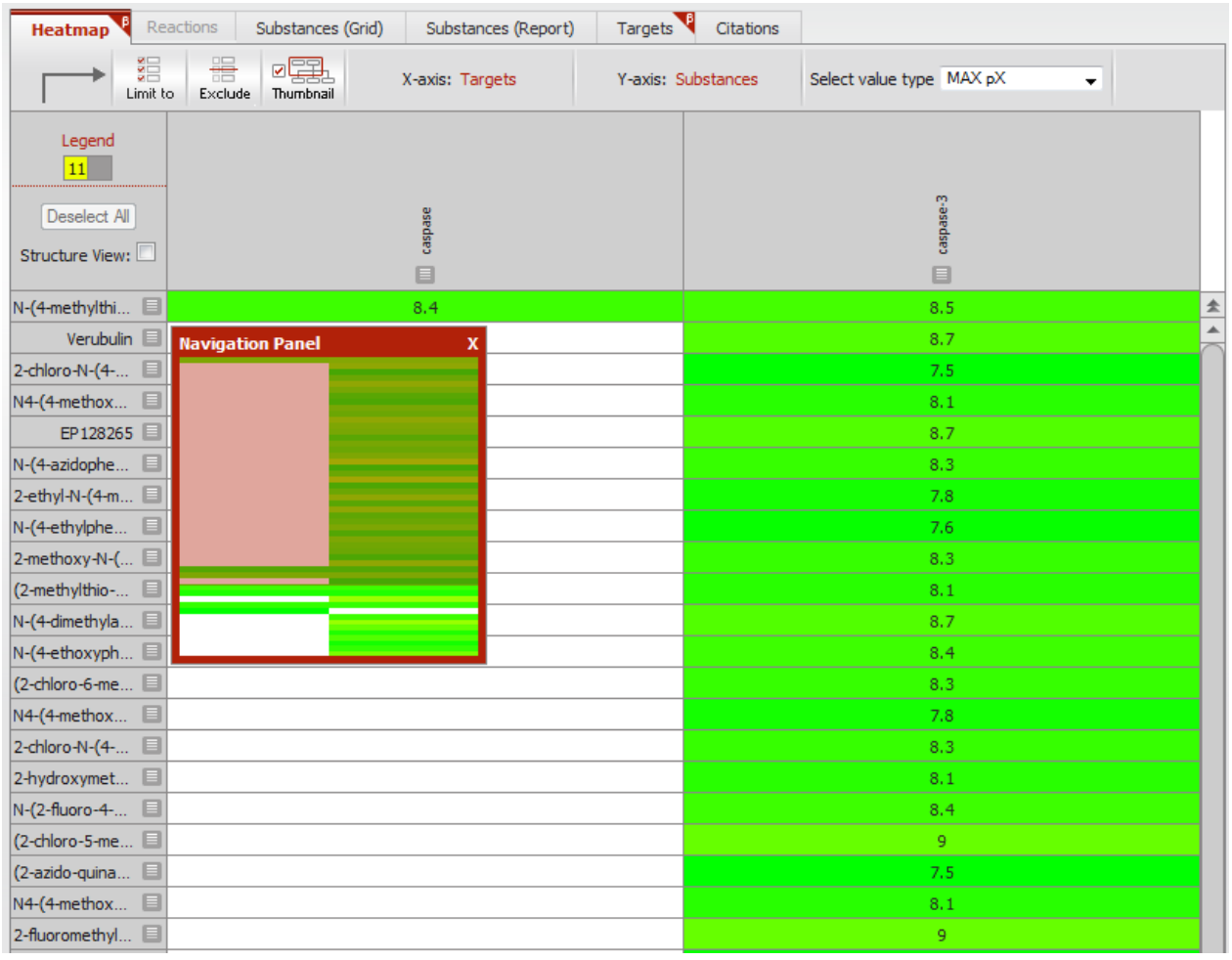
Step 8 : How to check that?

Perform a new search by changing the substructure search with



Step 9: Filter by Target Species Human

Step 10 : Filter by active compound pX>7.5



Compounds are mainly active on Caspase3, consequently methyl group on the anilino nitrogen is mandatory for caspase activity and selectivity.

For more information please Contact

E-Customer Service
Theodor-Heuss-Allee 108
60486 Frankfurt/Main, Germany
Tel: +49-69-5050 4268

Email: pharmabiotechEH@elsevier.com