

## Self guided Tour

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### Reaxys Medicinal Chemistry

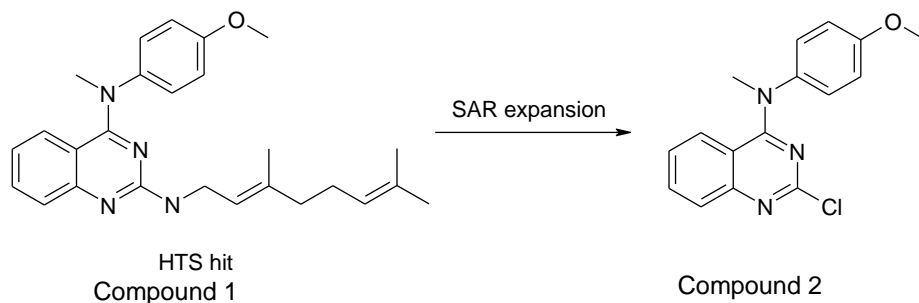
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**WHICH ARE THE KNOWN ACTIVITIES OF MY CHEMOTYPE ON  
OTHER TARGET CLASSES ?**

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

## 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 : Apoptosis 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, then click on 'Limit to'
14	Go to Heatmap tab	Click 'Heatmap' tab

## 1.3 Step by step

REAXYS®

Anonymous user (145.36.182.120)

Query Results Synthesis Plans History Report My Alerts My Settings Help Register Login

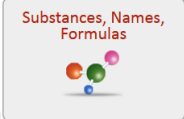
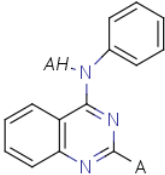
Ask Reaxys Enter a keyword, concept or author Go

Find substances, reactions, bioactivity data, citations, patents, and more from Reaxys, PubChem, and eMolecules

Reactions Substances, Names, Formulas Medicinal Chemistry Literature ReaxysTree

You can also search directly by these common property groups: Physical Spectra Natural Product Advanced

### 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

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Query Results Synthesis Plans History Report My Alerts My Settings Help Register Login

Start Over Import Save

Ask Reaxys <sup>BETA</sup> Enter a keyword, concept or author Go

Reactions **Substances** MedChemistry Literature ReaxysTree Physical Spectra Natural Product Advanced

Structure

C1=CC=C(C=C1)N(A)C2=NC3=CC=CC=C3N=C2

As drawn  
 Substructure  
 on heteroatoms  
 on all atoms  
 Similarity

Include tautomers  
 Ignore stereo  
 No salts  
 No mixtures  
 No isotopes  
 No charges  
 No radicals  
 No ring closures  
 Align results with query

More options

Identification

Reaxys Registry Number =  Lookup X

CAS Registry Number is  Lookup X

Chemical Name is  Lookup X

Element Symbols is  Lookup X

Show AND Buttons

Add to Query: Structure Molecular Formula <sup>BETA</sup> Alloy Add/Remove Fields... Search Substances

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

4621 substances out of 4546 reactions and 12426 bioactivities and 459 targets and 464 citations

Heatmap <sup>B</sup> Reactions Substances (Grid) Substances (Report) Targets <sup>B</sup> Citations

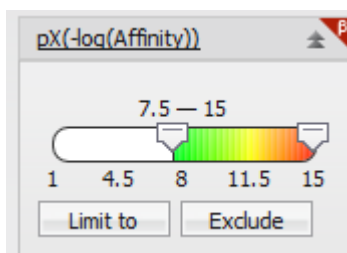
Limit to Exclude Thumbnail X-axis: Targets Y-axis: Substances Select value type MAX pX

Legend	5-hydroxytryptamin...	5-hydroxytryptamin...	5-hydroxytryptamin...	5-hydroxytryptamin...	5-hydroxytryptamin...	5-hydroxytryptamin...	5-hydroxytryptamin...	abl	abl (e255k)	abl (315f)	acid-sensing proto...	acid-sensing ion ch...	ack1	adp-ribosyltransfer...	akt	akt1	akt2	akt3	alk	alk2	alpha 1 adrenergic...	alpha 1a adrenergic...	alpha 1b adrenergic...	alpha 1d adrenergic...	alpha 2a adrenergic...	alpha 2b adrenergic...	alpha 2c adrenergic...	ampk	ampk2	androgen receptor	angiotensin ii receptor	app	aura	aurb	aurc					
N2,N4-diphenyl-quinazolin...																																								
N2,N4-bis-(4-chloro-pheny...																																								
[2-(2-furyl-quinazolin-4-yl)-...																																								
[2-(2-chloro-phenyl)-quinaz...																																								
[4-ethoxy-phenyl]-[2-(2-chl...																																								
[2-methyl-1-(2-methyl-qui...																																								
[5-methoxy-2-methyl-1-(2-...																																								
N6-(3,4-dichloro-benzyl)-N...																																								
N2,N4-diphenyl-quinazolin...	4.5	5.3	5.4	5.3	6.3	6.2																6.1	6.2	6.2	6.2															
N2,N4-bis-(4-chloro-pheny...																																								
2-chloro-N-methyl-N-phen...																																								
7381403																																								
2-(2-methylphenylamino)-...																																								
7385614																																								
2-(2-methylphenylamino)-...																																								
7387183																																								
N2,N4-diphenyl-N2,N4-d...																																								

Navigation Panel



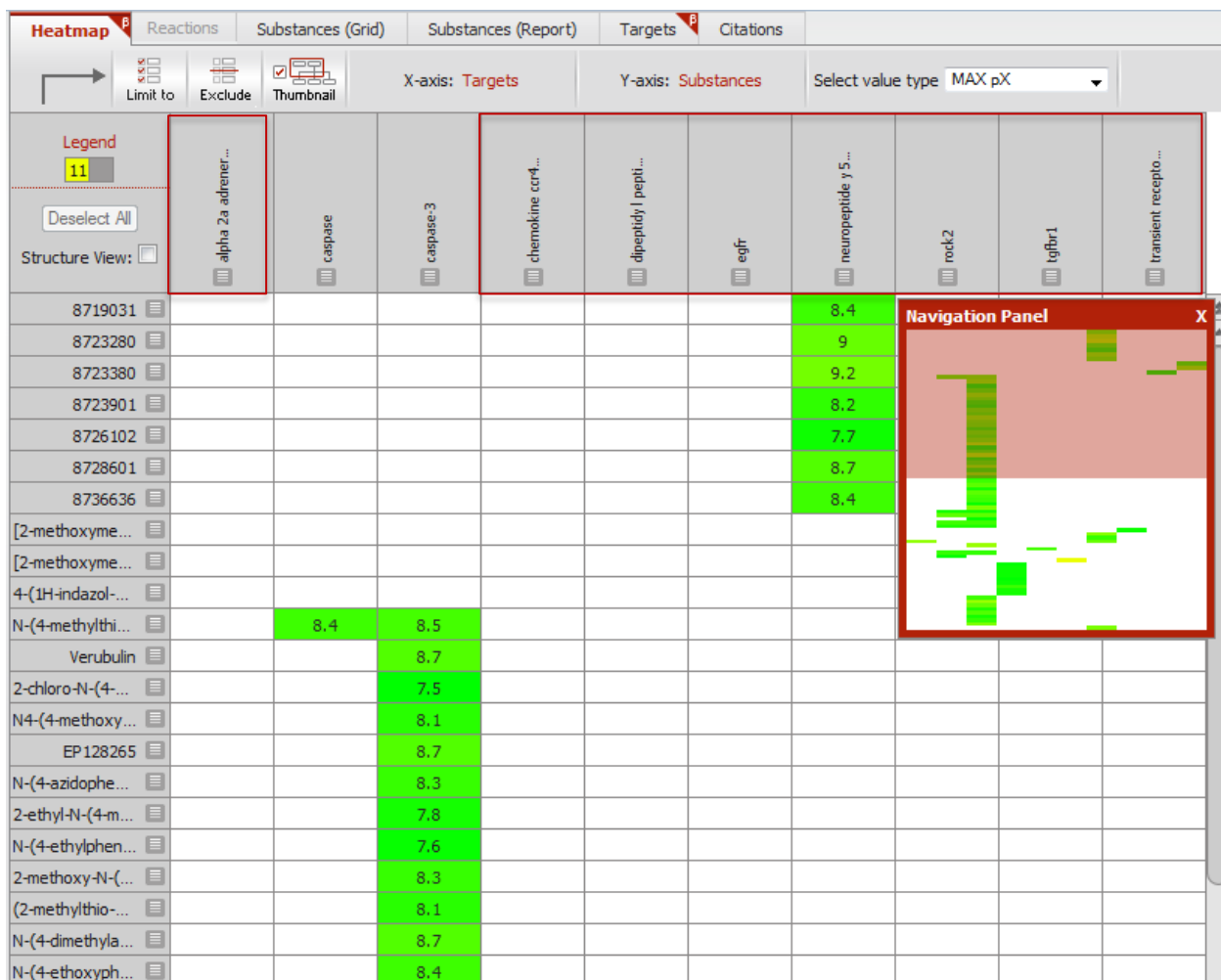
Move the slider on the right to 7.5 (0.1  $\mu\text{M}$ ) to select active compounds and click on Limit to




Step 6 Click on The Heatmap tab

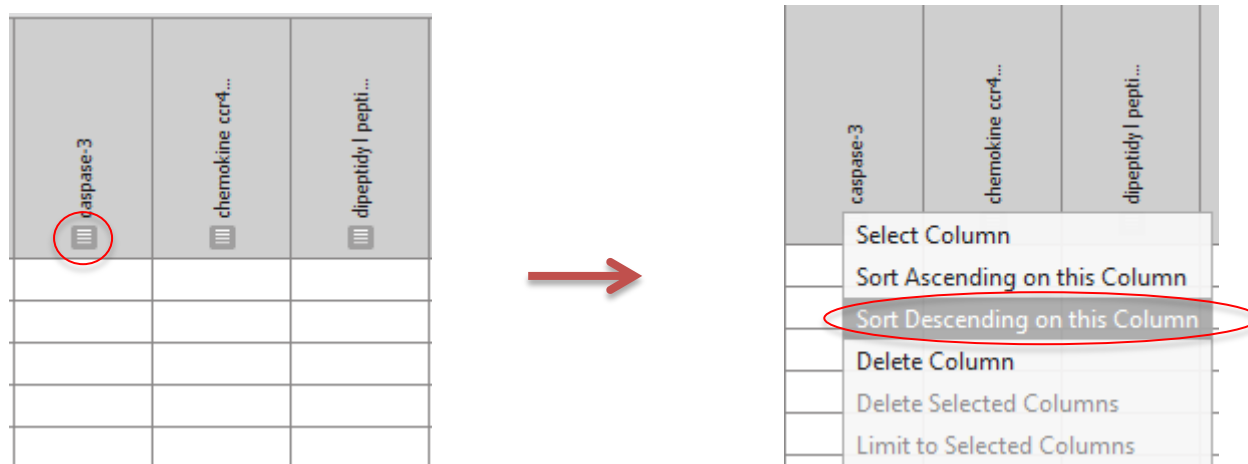
The chemotype potentially bind on the following targets :

- GPCR : Alpha2a Adrenergic, Chemokine CCR4, Neuropeptide Y5
- Kinase : EGFR, Rock2, tgfb1
- 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.



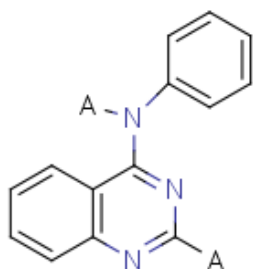
If look you into the chemical compounds carefully, you can see that compounds active on caspase have a methyl group on the aniline nitrogen whereas all the others active compounds on non caspase target have no methyl substituent in the same position.

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

Legend	alpha 2a adrener...	caspase	caspase-3	chemokine ccr4...
11 Deselect All Structure View: <input checked="" type="checkbox"/>				
			9	
			9	
			9	
2-fluoromethyl-N-(4-methoxyphenyl)-N-methylquinazolin-4-amine 			9	

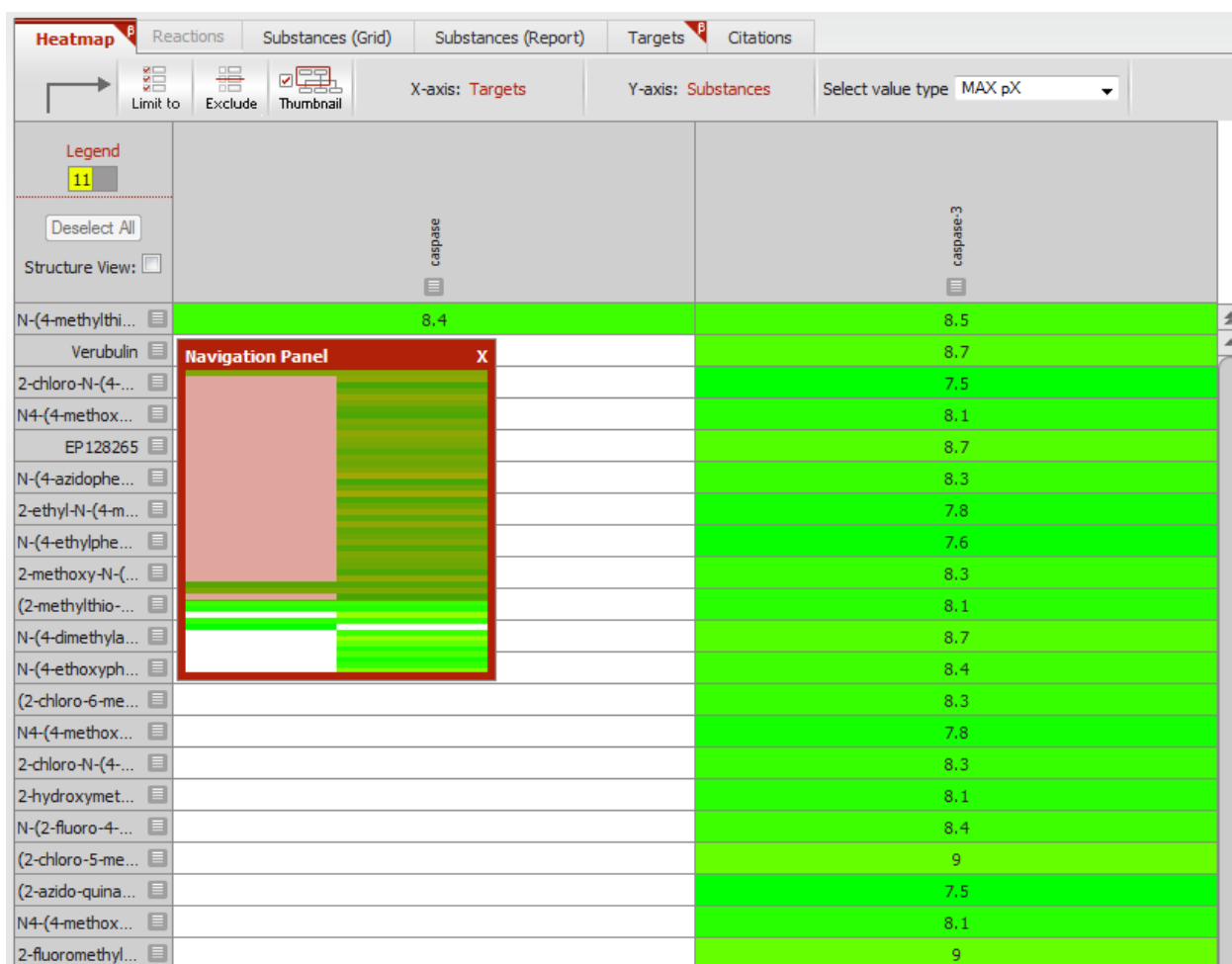
Step 8 : How to check that?

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.



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