

## Self guided Tour

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Reaxys Medicinal Chemistry

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**WHICH SUBSTANCES ARE DUAL INHIBITORS OF TARGETS?**

# WHICH SUBSTANCES ARE DUAL INHIBITORS OF TARGETS?

## 1.1 Scenario

Dual inhibitors of PI3K/mTOR?

The phosphatidylinositol-3-kinase (PI3K)/AKT/mTOR signaling pathway is a central regulator in cell proliferation, growth, and angiogenesis. Inhibition of this pathway therefore is a major strategy for cancer chemotherapy. In order to induce the maximal therapeutic outcome in cancer treatment, development of dual inhibitors of PI3K and mTOR is of great interest..

**Search for inhibitors active on PI3K and mTOR (FRAP)?**

## 1.2 Overview

Major Steps	Steps and description	Action
1	Search by Bioactivity	Click 'Bioactivity' button
2	Select 'Target Name'	Type 'PI3K' in the 'Target Name' field and select 'PI3K', and Select pX>8 then push 'Search Bioactivities' button
3	Select 'Target Name'	Type 'mTOR' in the 'Target Name' field and select 'mtorc1' And 'mtorc2'and Select pX>8 then push 'Search Bioactivities' button
4	Go to the History menu	Select substance on the two queries and click on combine hitset. Select Overlap.
5	Click on the Heatmap Tab	Select the PI3K and mTORC1 and mTORC2

## 1.3 Step by step



Anonymous user (145.36.182.120)

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

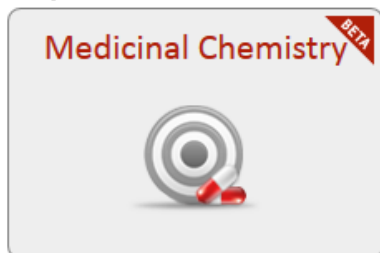
Ask Reaxys Enter a keyword, concept or author Go

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 Medicinal Chemistry



## Step 2 Select a Target

On target Name click on “look up”

Bioactivities

Substance Route	is	<input type="text"/>	Lookup X
Bioassay Category	is	<input type="text"/>	Lookup X
Putative action on target	is	<input type="text"/>	Lookup X
Effect	is	<input type="text"/>	Lookup X
Cells/Cell lines	is	<input type="text"/>	Lookup X
Organs/Tissues	is	<input type="text"/>	Lookup X
<b>Target Name</b>	is	<input type="text"/>	<b>Lookup X</b>
Target Subunit Name	is	<input type="text"/>	Lookup X
Target Nature	is	<input type="text"/>	Lookup X
Species	is	<input type="text"/>	Lookup X
pX	=	<input type="text"/>	Lookup X

Show AND Buttons

A new popup appear and Search for PI3K  
Select PI3K and Click on transfer

Select index items and click 'Transfer'

Reaxys

Search for: pi3

- pi3k (131613)
- pi4k (386)
- pi4k2a (14)
- pi4k2b (8)
- pi4k3a (46)
- pi4k3b (153)
- pi4ka (1255)
- pi4kap2 (12)
- pi4kb (407)
- pick1 (35)
- picornain 2a (13)
- picornain 3c (2956)
- piezo-type mechanosensitive ion channel component 1 (5)
- pik3p110d/p85a (3)
- pikc cytochrome p450 (19)
- pim (236)
- pim1 (18203)
- pim2 (11916)
- pim3 (8150)
- pin-1 (92)

Transfer  
Reset  
Cancel

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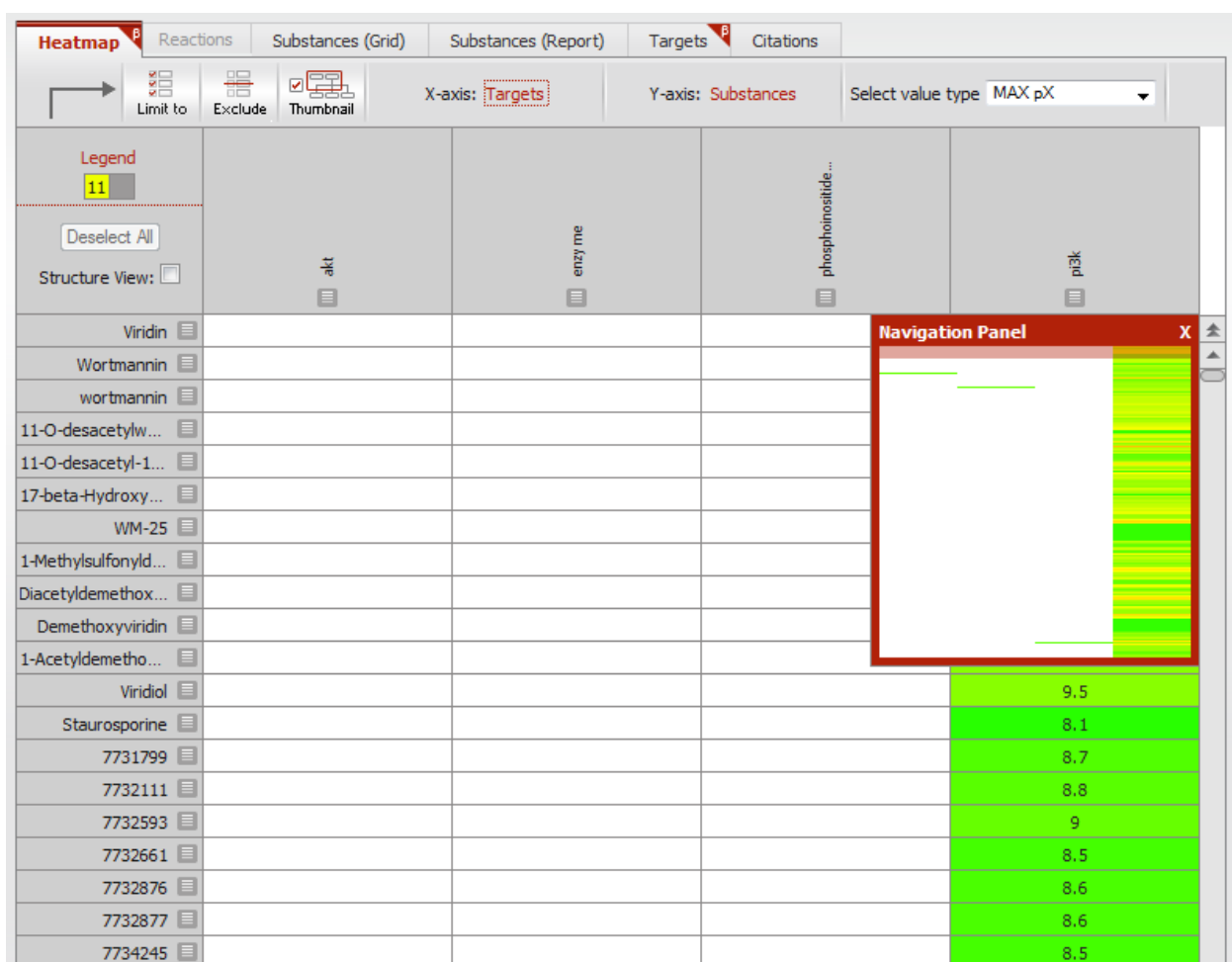
Then select  $\geq$  in the pX querylet and enter 8 (Affinity less than 10 nM)

Bioactivities

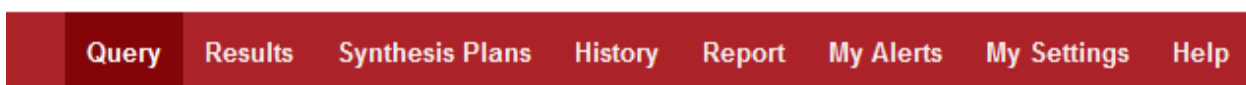
Substance Route	is		Lookup	X
Bioassay Category	is		Lookup	X
Putative action on target	is		Lookup	X
Effect	is		Lookup	X
Cells/Cell lines	is		Lookup	X
Organs/Tissues	is		Lookup	X
Target Name	is	pi3k	Lookup	X
Target Subunit Name	is		Lookup	X
Target Nature	is		Lookup	X
Species	is		Lookup	X
pX	$\geq$	8	Lookup	X

Show AND Buttons

Step 3 : Search for bioactivities an Heatmap appears with PI3K potent inhibitors



Step 4 : Go Back to the query and search for Substances tested on mTOR



## Step 5 Select a Target Name

On Target Name click on “look up” type mTOR and Select ‘mtorc1’ and mtorc2 then Click on transfer.

Click again on look up and type FRAP then select FRAP and click on transfer.

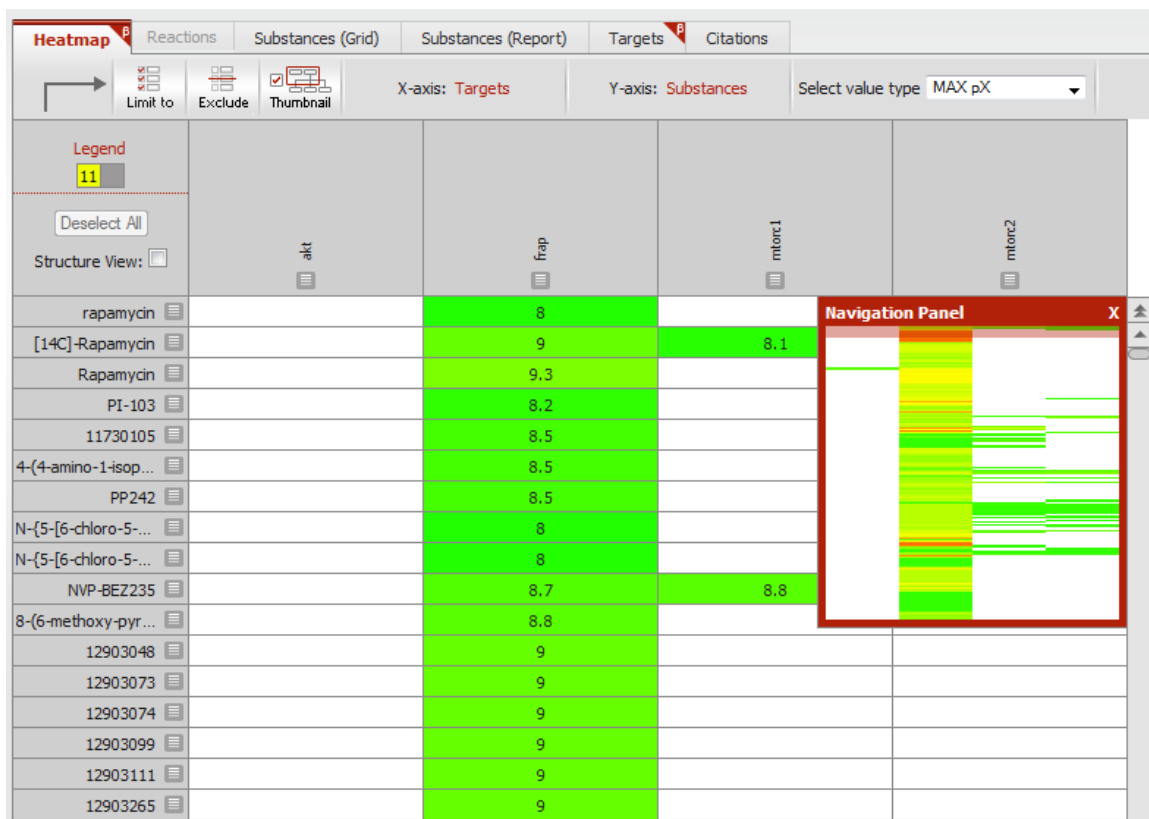
Select >= in the pX querylet and enter 8 (Affinity less than 10 nM)

**Bioactivities**

Substance Route	is		Lookup	×
Bioassay Category	is		Lookup	×
Putative action on target	is		Lookup	×
Effect	is		Lookup	×
Cells/Cell lines	is		Lookup	×
Organs/Tissues	is		Lookup	×
Target Name	is	'frap';mtorc1';mtorc2'	Lookup	×
Target Subunit Name	is		Lookup	×
Target Nature	is		Lookup	×
Species	is		Lookup	×
pX	>=	8	Lookup	×

Show AND Buttons

## Step 6 : Search for bioactivities an Heatmap appears containing mTOR (FRAP) potent inhibitors



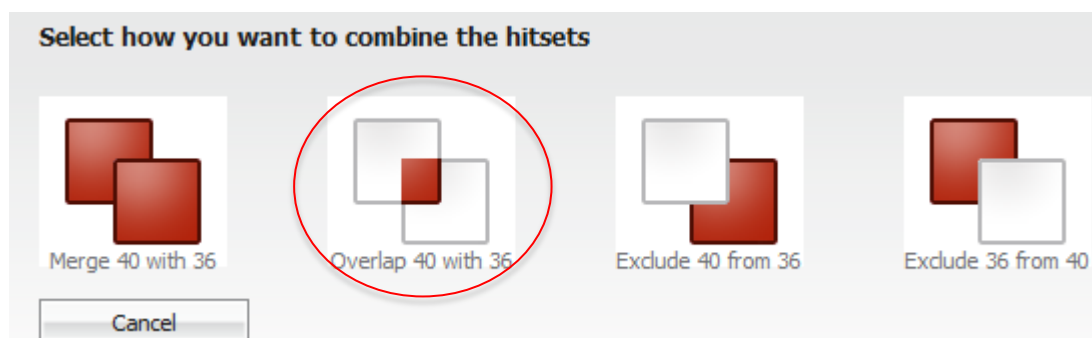
## Step 7 : Go to the History and combine Hitsets



For each query select the substances and click on combine hitsets

	Query	Temporary result description	Date
<input type="checkbox"/> 41	<a href="#">Edit</a> <a href="#">Create Alert</a> Bioactivities: Target Name = "frap";mtorc1';mtorc2" AND pX >= 8	8416 bioactivities Bioactivities: Target Name = "frap";mtorc1';mtorc2" AND pX >= 8	2014-04-02 16:06
<input checked="" type="checkbox"/> 40		6193 substances	
<input type="checkbox"/> 39		25 targets	
<input type="checkbox"/> 38		157 citations	
<input type="checkbox"/> 37	<a href="#">Edit</a> <a href="#">Create Alert</a> Bioactivities: Target Name = "pi3k" AND pX >= 8	6945 bioactivities Bioactivities: Target Name = "pi3k" AND pX >= 8	2014-04-02 15:53
<input checked="" type="checkbox"/> 36		4980 substances	
<input type="checkbox"/> 35		90 targets	
<input type="checkbox"/> 34		336 citations	

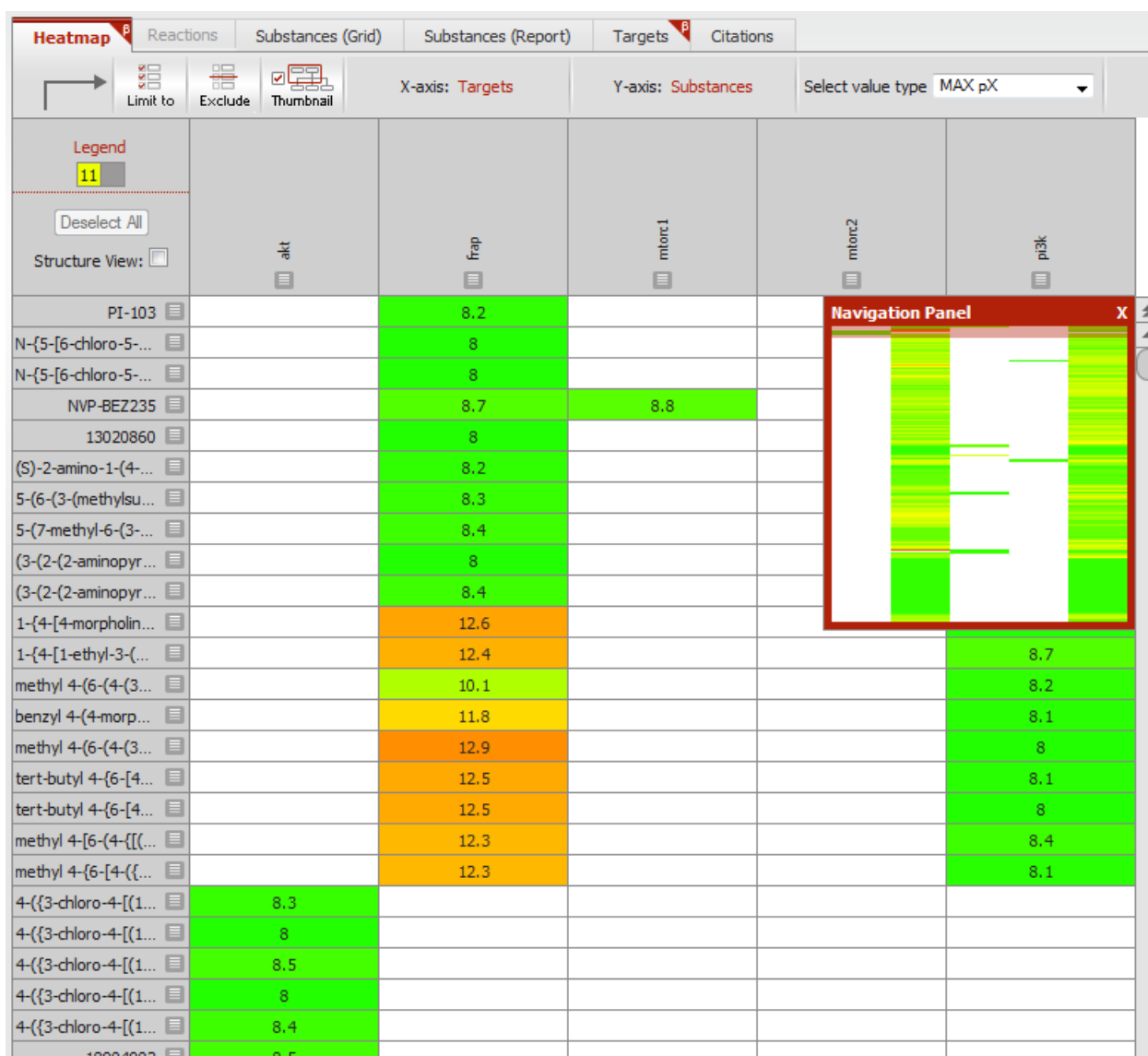
Click on overlap to retrieve dual inhibitors of PI3K and mTOR(FRAP)



Click then on the Heatmap tab

## Step 9 : Dual inhibitors of mTOR(FRAP) and Pi3K

The following Heatmap displays dual inhibitors of mTOR(FRAP) and PI3K (Affinity  $\geq 10\text{nM}$ )



*“Two hits are better than one: targeting both phosphatidylinositol 3-kinase and mammalian target of rapamycin as a therapeutic strategy”*

For more information please Contact

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