

# **Self guided Tour**

## **Reaxys Medicinal Chemistry**

### WHICH SUBSTANCES ARE THE MOST ACTIVE ON MY TARGET (HUMAN) OF INTEREST ?

http://beta.reaxys.com



# WHICH SUBSTANCES ARE THE MOST ACTIVE ON MY TARGET (HUMAN) OF INTEREST ?

#### 1.1 Scenario (New Project)

New project focused on finding new AKT1 inhibitors with less affinity on AKT2 (minimizing adverse effect)

- Akt is associated with tumor cell survival, proliferation, and invasiveness.
- The activation of Akt is also one of the most frequent alterations observed in human cancer and tumor cells.
  - Akt1 has been implicated as a major factor in many types of cancer
  - Akt2 is an important signaling molecule in the Insulin signaling pathway
  - The role of Akt3 is less clear, though it appears to be predominantly expressed in the brain

Therefore, understanding Akt and its pathways is important for the creation of better therapies to treat cancer and tumor cells.

#### Search for active chemotype on AKT1?

#### 1.2 Overview

Step no.	Steps and description	Action
1	Search Bioactivities	Ask Reaxys or Medicinal chemistry Query
•		
2	Heatmap is displayed'	Click on Search Bioactivities
3	Filter by 'Target Species'	Filter by 'Target Species', select 'human', then click on 'Limit to'
4	Filter by 'pX'	Filter by 'pX(-log(Affinity), move the bar to ca > 9, then click on 'Limit to'
5	Display Structure in the Heatmap	Click on Structure
6	Select compounds in the Heatmap	Click on the row
7	Find Similar compounds	Will display similar compounds as well as pharmacology profile.

#### 1.3 Step by step

There is two ways of Searching AKT 1 potent Inhibitors using "Ask Reaxys" or using the medicinal chemistry query theme. The two ways are providing the same results.

Query Results Synthesis Pl	ans History Report My Alerts	My Settings Help		Live Chat Logout
				Timport 🔛 Save
Ask Reaxys	Enter a keyword, concept or author  Examples			Go
	Find substances, reactions, bioactivit	y data, citations, patents, and more fro	m Reaxys, PubChem, and eMolecules	
Reactions	Substances, Names, Formulas	Medicinal Chemistry	Literature	ReaxysTree
	• •	Q		
	You can also	search directly by these common prop	erty groups:	
	🤡 Physical 🧶	Spectra 💽 Natural Produc	t Advanced	

Step 1 : Search substances tested on AKT1

#### Using Ask reaxys

Ask Reaxys	AKT1	Go
	Examples	

Ask Reaxys recognize the abbreviated terms as a target by using the target taxonomy (main terms as well as synonyms are searched) to retrieve substance tested on the corresponding target.

#### Using the Medicinal chemistry Query theme

On target Name click on "look up" to Access the Target Taxonomy

Target Name	is 💌	Lookup X
Substance Action on Target	is	Lookup ×
Substance Highest Clin. Phase	is 💌	Lookup X
Bioassay Category	is	Lookup X
Bioassay Animal Model	is	Lookup ×
Biological Species	is 💌	Lookup ×
Cells/Cell Lines	is 💌	Lookup ×
Measurement pX	=	Lookup ×
how AND Buttons		

A new popup displays the Target Taxonomy then Search for 'AKT1' in .

Preferred term "Cyclooxygenase 2" is selected because Cox-2 was found as synonym (to display synonyms move the mouse pointer on the node name.)

elect index items and click 'Transfer'	Select index items and click 'Transfer'					
Reaxys	Reaxys					
Enter search term: AKT1	Enter search term: AKT1 SEARCH	]				
□		•				
🔳 🗉 Atrial natriuretic peptide (All) (2012)	I Enzyme (All) (7830340)					
🔲 🗉 Claudin (All) (8)	EC 2: Transferase (All) (4463297)					
Enzyme (All) (7830340)	✓ Imase (All) (4132887)					
GPCR (All) (4465597)	🖉 🖬 Group 1: prot. S/T-Y-kinase/ Atypical protein kinase /	1				
Imidazoline (All) (3196)	Lipid kinase / ATP-grasp (All) (3771431)	Lipid kinase / ATP-grasp (AII) (3771431)				
Integrin All) (23095)	Protein S/T-Y kinase / Atypical kinase (All)	Image: Protein S/T-Y kinase / Atypical kinase (All) (2560077)				
Interleukin/Cvtokine (All) (1765)	(3569877)	(3569877)				
In the second	Protein 5/1-1 Kinase (All) (3504804)					
Nuclear receptor (All) (576278)	■ ACC (AI) (500373) ■ AKT (AII) (81370)					
Pattern recognition receptors (All) (8290)	✓ ■ AKT1 (10460)					
E Sigma (All) (15555)	AKT1 [Bovinae]					
Transporter (All) (344524)	(8)					
Handporter (m) (644624)	🖉 AKT1 [Human]					
	(6718)					
	AKT1 [mouse]					
	(63)	*				
Terms selected:	Terms selected: 'AKT1';'Proline-rich AKT1 substrate 1 [human]';'Proline-rich AKT1 substrate 1'					
Transfe	Reset Cancel Transfer Reset	Cano				

The search is done by substring in the target name as well as in the synonyms consequently some targets may be not always relevant. To unselect these unwanted targets uncheck the corresponding node and then click on "transfer".

nter search term: AKT1	SEARCH	]
	Protein S/T-Y kinase (All) (3564864)	^
	✓	
	🖉 🗉 AKT (AII) (81370)	
	AKT1 (10460)	
	🔽 AKT1 [Bovinae]	
	(8)	
	AKT1 [Human]	
	(6718)	
	🔽 AKT1 [mouse]	
	(63)	
	AKT1 [rat] (1)	-
		-
	Targets (2122576)	
E P (226	886) B- (500.42)	
	FT (39643)	
	Proline rich A/CT substrate 1 (bumon) (12)	
	Profine-fich AKTT substrate T [numan] (12)	-

Bioactivities (10460	) Reactions (0) Substances (8422)	Targets (38) Citations (789)	
DISPLAY: Structure N	lavigator AxisValues DataDensity SELECTED Limit to	FILTER: 0.0 pX Value:	15.0 Apply Exclude max Exclude Legend
X-axis: <b>Targets</b>			
Y-axis: <i>Substances</i>	akt 1	akt2	akt 3
4,5,6,7-tetrahydr 💌	1		Thumbnail Panel X 🚖
3-Aminoindazole 💌	1		ê
NSC 10120 💌	1		
6-benzylthiopurine 💌	1		
N2,N4-diphenylpy 💌	1		
6-(p-fluorobenzylt 💌	1		
2,3,7,8-tetrahydr 💌	5.4		
Wortmannin 💌	7.2		
Epigallocatechin 🗵	1		
1-[6-(3-acetyl-2,4	1		
adenosine 5'-triph			
JNK Inhibitor II, N	1		
Indirúbin 🗹	1		
pyrroio[2,3-b]pyri	3.3		
indele 2 cartinel	1		
	1		
6-bromo-3 4-diby	43		
5.6-dichloro-1H-b	5.1		
1-(1H-indol-3-yl)			
harmane 💌	1		
2-phenyl-1,2-beh	1		
N-(pyridin-2-yl)-N' 🔽	1		

Step 2 : A full heatmap will appear with compounds tested on AKT1

#### Step 3 : Filter by Target Species

On the left had side click on "Target species" select human and click on "Limit to"

Target Species	
by Value by Grou	ab 🔤
<ul> <li>human</li> <li>mouse</li> <li>bovinae</li> <li>rat</li> <li>(no entry given)</li> </ul>	6717 86 8 1 3671
Limit to Exc	lude

A new heat map will appear with the AKT1 target

## Step 4 : Retrieve Active compounds by filtering by pX value >9 (Bioactivities Ki, IC50, Kd, etc...<1nM)

Move the cursor to the right without releasing the mouse button and click on "Apply"

FILTER:	9.0		15.0	Apply
	min	pX Value:	max	

Heatmap will appear with the most active compounds on AKT1

Click on the AKT1 arrow 🖃 and select "sort descending on this column" See Below.



The most active compound will be on the top of the Heatmap

Bioactiv	ities (83)	Read	tions (0)	Substan	ces (80)	Targe	ets (5)	Citation	s (29)					
DISPLAY:	) Structure	Navigator	xy AxisValues	DataDensity	SELECTED DATA:	Limit to	Exclude	FILTER:	9.0 min	pX Value:	15.0 max	Apply	Exclude GoSTAR data	Legend
X-axis: <b>Targets</b>	5													
Y-axis: <i>Substar</i>	nces								▲ akt1					
(±)-2-amino	-1 🗵								11.1			Thumb	nail Panel	х 🕿
(±)-2-amino	-1 🗵								10.8					<u></u>
6-(4-(1-(2-(	az 💌								10					
A-44	3654 💌								9.8					
6- <b>(4-(1-(2-(</b>	az 💌								9.8					
2416	9682 💌								9.8					
2449	4707 🗵								9.7					
5-ethyl-6-{4	+-[ ▼								9.5					
2439	9398 💌								9.5					
2439	9399 💌								9.5					
(S)-1-(1H-in	dol 💌								9.4					
trans-3-amir	no 💌								9.4					
5-ethyl-6-{4	+[ 🗵								9.4					
2439	9400 🗵								9.4					
2439	9475 🗵								9.4					
(S)-N-((3-an	nin 🗵								9.3					
2439	9401 🗵								9.3					
(S)-2-amino	-1 🗵								9.3					
4-(2-(4-amir	10 💌								9.2					
GSK69	0693 🖃								9.2					
2060	4613 🗵								9.2					
C 14 14 15 1									0.0					

Step 5 : Hide data density and then click on structure to display the Chemical structure in the Heatmap



Bioactiv	ities (83)	Read	ctions (0)	Substan	ces (80)	Target	s (5)	Citation	s (29)					
DISPLAY:	Structure	Navigator	xy AxisValues	DataDensity	SELECTED DATA:	Limit to	Exclude	FILTER:	9.0 min	pX Value:	15.0 max	Apply	Exclude GoSTAR data	Legend
X-axis: <b>Targets</b>	;													
Y-axis: <i>Substar</i>	nces								▲ akt1					
, prox									11.1			Thumb	iail Panel	x 🛳
	)								10.8					
-200	> R 🖻								10					U
20 m	ک ک								9.8					
400	S I								9.8					

If chemical structures are too small grab the column line and move it to the right to resize it.



Step 6 : Then select the compound by clicking on the row header (Chemical structure) and limit to

Bioactivities (83)	Reactions	s (0) Substan	ces (80)	Targets (5)	Citations (29)				
DISPLAY: C Structure N	Iavigator Axis	xy 🔨 Values DataDensity	SELECTED DATA	Limit to Exclude	FILTER: 9.0 min	pX Value:	15.0 max	Apply Exclude GoSTAR data	Legend
X-axis: <b>Targets</b>									
Y-axis: <i>Substances</i>					▲ akt1				
$(\pm) \ \begin{array}{c} (\pm) \ (2 - \operatorname{amino} -1 \cdot (4 \cdot (6 - \operatorname{amin} \\ H^{H_2}) \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$	1 <b>V</b>				11.1			Thumbnail Panel	× *
(±)-2-amino-1-(4-(6-amin	n 🗨				10.8				

#### Cick on the substance tab

Bioactivities (1) Reactions		)) Substances (1) Targets (1) Citations (1)	go to Pag	go to Page 📃 ᅌ Page 1 of 1			
	Limit to	Print Zoom in Zoom out Hide Sort by No of References	🗸 🖡 🕇 Display as: 📕	splay as: 📕 🎆 🛛 🖂 Exclude GoSTAR dat			
	Structure	Structure/Compound Data	N° of preparations All Preps   All Reactions	Available Data	Target	N° of ref.	
1	Synthesize   Show Details Find similar	Chemical Name: (±)-2-amino-1-(4-(6-amino-5-bromopyrimidin-4-yl)piperazin-1-yl)- 3-(4-chlorophenyl) propan-1-one Reaxys Registry Number: 26585609 Molecular Formula: C1/H120BrClN60 Linear Structure Formula: C1/H120BrClN60 Molecular Weight: 439.742 InChI Key: OWZITGLREJNFEI-UHFFFAOYSA-N	4 prep out of 4 reactions.	Druglikeness Bioactivity Identification Physical Data (2) Spectra (4)	Show Targets	1	

Step 7: Is there known similar compounds and what are their pharmacology profiles?



Use the find similar function to do so. Similar compounds will be retrieved

Find Similar Compounds												
Click on one of the hyperlinks below for getting similar compounds according to the selected scope:												
Query Structure	Position/Stereo Isomers	Near	Medium	Wide	Widest							
	1	6	22	103	318							
	Cancel											

#### Medium category was used

Bioacti	vities (51) Reactions (	27) Sub	stances (22) Targe	ts (6) Citations (10)		go to Page [	9	Page 1 of 1
	Limit to Exclude Export	Print Zo	Or in Zoom out Hide	Sort by Similarity		GoSTAR data		
	Structure	% Similarity	Structure/Compound Data	a	N° of preparations All Preps   All Reactions	Available Data	Target	N° of ref.
1	Synthesize   Show Details	100.0%	Chemical Name: (±)-2-amino-1-(4-(6-amin 1-yl)-3-(4-chlorophenyl) p Reaxys Registry Numl Molecular Formula: C <sub>1</sub> Linear Structure Form Molecular Weight: 439 InChI Key: OWZITGLRE:	o-5-bromopyrimidin-4-yl)piperazin- ropan-1-one <b>ber:</b> 26585609 yHzgBrClNeO <b>sula</b> : C1 <sub>7</sub> HzgBrClNeO .742 JNFEI-UHFFFAOYSA-N	4 prep out of 4 reactions.	Druglikeness Bioactivity Identification Physical Data (2) Spectra (4)	Show Targets	1
2	or the second se	97.8%	Chemical Name: (±)-2-amino-1-(4-(6-amin 1-yl)-3-(4-chlorophenyl)pr Reaxys Registry Numl Molecular Formula: C <sub>1</sub> Linear Structure Form Molecular Weight: 395 InChI Key: SSFWF2BIPV	o-5-chloropyrimidin-4-yi)piperazin- ropan-1-one ber: 26585607 ;H120Cl_2N60 rula: C1;H120Cl_2N60 ;291 VHUFP-UHFFFAOYSA-N	4 prep out of 4 reactions.	Druglikeness Bioactivity Identification Physical Data (2) Spectra (4)	Show Targets	1
3		95.8%	Chemical Name: (S)-2-amino-1-(4-(6-amino 1-yl)-3-phenylpropan-1-or Reaxys Registry Numl Molecular Formula: C1 Linear Structure Form	b-5-chloropyrimidin-4-yl)piperazin- ne <b>ber:</b> 265855605 jH2jClN <sub>6</sub> O uda: C +H3+ClN <sub>6</sub> O	4 prep out of 4 reactions.	Druglikeness Bioactivity Identification Physical Data (2) Spectra (4)	Show Targets	1

Substances are ranked by decreasing similarity (Based on tanimoto metric) Clicking on the Bioactivities tab will display the phamacology profile of similar substances.

DISPLAY:	Structure	Navigator	x y AxisValues	DataDensity	SELECTED DATA:	Limit to	Exclude	FILTER:	0.0 min	pX Value:	15.0 Apply max	GoST/	lude AR data	Legen	n d
X-axis: <b>Targets</b> Y-axis: <b>Substanc</b>	ces	akt			€ akt1		<ul> <li>melanocortin 1 r</li> </ul>			Imelanocortin 3 r	Imelanocortin 4 r		Melanocotin 5 r		
۲ ۲ ۲ ۲ ۲ ۲ ۲ ۲ ۲ ۲															*
ç∕∘ <sup>β</sup> ⊾					7.3										
20 20 20 20 20							1			1	1		1		
×							5			5.3	5.6		5.4		
▼ andra															
- 90 m										5	5				
- 302 -															
Trice a							1			1	1		1		
4000 I					8.7										
20X				:	.0.8										
20X				:	1.1										
\$0%					9.3										<ul><li>▼</li><li>¥</li></ul>

## 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