

Self guided Tour

Reaxys Medicinal Chemistry

WHICH SUBSTANCES ARE POTENT AND SELECTIVE INHIBITORS OF TARGET?

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WHICH SUBSTANCES ARE POTENT AND SELECTIVE INHIBITORS OF TARGET?

1.1 Scenario

Potent and Selective COX-2

It is clear that COX-2 plays an important role in tumor and endothelial cell biology. Increased expression of COX-2 occurs in multiple cells within the tumor microenvironment that can impact on angiogenesis. COX-2 appears to:

(a) play a key role in the release and activity of proangiogenic proteins;

(b) result in the production of eicosanoid products TXA2, PGI2, PGE2 that directly stimulate endothelial cell migration and angiogenesis in vivo, and

(c) result in enhanced tumor cell, and possibly, vascular endothelial cell survival by upregulation of the antiapoptotic proteins Bcl-2 and/or activation of PI3K-Akt.

Selective pharmacologic inhibition of COX-2 represents a viable therapeutic option for the treatment of malignancies. Agents that selectively inhibit COX-2 demonstrate that chronic treatment for angiogenesis inhibition is feasible.

As a continuous research for discovery of new COX-2 inhibitors, new synthetic potent and selective inhibitors of COX-2

Search for Potent and selective inhibitors of Cyclooxygenase 2 (COX-2) versus COX-1

1.2 Overview

Major Steps	Steps and description	Action
1	Search by Bioactivity	Click 'Bioactivity' button
2	Select 'Target Name'	Type cox-2 in the 'Target Name' field, Select pX=>9 then push 'Search Bioactivities' button
5	Select 'Target Name'	Type cox-1 in the 'Target Name' field and Select pX<6 then push 'Search Bioactivities' button
7	Go to the History menu	Select Bioactivities on the two queries and click on combine hitsets. Select "Heatmap Overlay".

1.3 Step by step

Query Results Synthesis Pla	ans History Report My Alerts	My Settings Help		Live Chat Logout
				Timport 🔚 Save
Ask Reaxys	Enter a keyword, concept or author			Go
Reactions	Find substances, reactions, bioactivit	y data, citations, patents, and more fro	m Reaxys, PubChem, and eMolecules	ReaxysTree
Å		Q		
	You can also	search directly by these common prop Spectra Natural Produc	t Advanced	

Step 1 Search Medicinal Chemistry



Step 2 Select a Target

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

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

A new popup displays the Target Taxonomy then Search for 'Cox-2' in Enter.

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

And then on "Transfer" to select all Cyclooxygenase 2 (Human, Rat, mouse etc...)

Select index items and click 'Transfer'	Select index items and click 'Transfer'
Reaxys Enter search term: cox-2	Reaxys Enter search term: cox-2
 Targets Atrial natriuretic peptide (AII) Claudin (AII) Enzyme (AII) Enzyme (AII) Enzyme (AII) Integrin AII) Integrin AII) Interleukin/Cytokine (AII) Inchanels (AII) Nuclear receptor (AII) Fattern recognition receptors (AII) Sigma (AII) Transporter (AII) Unclassified Targets 	
Terms selected: (Transfer) Reset Cancel	Terms selected: 'Cydooxygenase 2' Transfer Reset Cancel

Remark : to see Cox-2 Species click on the plus Vectooxygenase 2

Then select >= in the pX querylet and enter 9 (Affinity less than 1 nM)

Bioactivities			
	Target Name	is Cydooxygenase 2'	Lookup ×
	Substance Action on Target	is 💌	Lookup X
	Substance Highest Clin. Phase	is 💌	Lookup X
	Bioassay Category	is 💌	Lookup ×
	Bioassay Animal Model	is 💌	Lookup X
	Biological Species	is 💌	Lookup ×
	Cells/Cell Lines	is 💌	Lookup X
	Measurement pX	>= 9	Lookup X
Show AND Buttons			

Step 3 : Search for bioactivities an Heatmap appears with COX-2 potent inhibitors

Bioactiv	ities (21	4)	Rea	actions (0)	Subs	tances (107)	Ta	rgets (5)	Citat	tions (61)						
DISPLAY:	Structure		107 Junor	xy AxisValues	DataDensity	SELECTED DATA:	Limit to	Exclude	FILTER:	0.0 min	pX Value:	15.0 max	Apply	Exclude GoSTAR data	Legend	-
X-axis: Targets Y-axis: Substar	nces									 cy clooxy genase 2 						
3-Benziloylo	xyqui									9.2			Thumb	nail Panel	X	*
[1-(4-chloro	benzo									9.3					1	7
	Hispidin									9.1						
(E)=1=(3,5=d	ibydr	.								9.4						
sodium 2-[()	6-dic									9.4						
4-hvdroxy-2	-met	•								12.8						
scopolamine	meth	•								9.3						
N-(2-(cycloh	exylo	•								9.3						
5-(4-chlorop	henyl	•								9						
4-[6-(4-chlo	rophe	•								9						
4-[6-(4-met	юхур	•								9						
4-(6-(3,4-di	hloro	•								9						J
4-[6-(4-triflu	iorom	V								9						
N-[4-[5-(4-n	nethyl									10.8						
4-(4-methyl	sulfon	•								9.2						
8	639888	•								9						
8	640106	•								9						
8	640398									9						
8	644185									9						
8	650184									9						
8	650185									9						
1,3-dipheny	-2,4,									9.1						
8	796634	-								9.9						

Step 4 : Go Back to the query and search for Substances tested on COX-1

	Query	Results	Synthesis Plans	History	Report	My Alerts	My Settings	Help
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Step 5 Select a Target Name

On Target Name click on "look up" type 'Cox-1' and Search, then Click on transfer. Select <= in the pX querylet and enter 6 (1000 fold Selectivity)

Bioactivities (1607	78)	Reactions	(0) Sub	stances (99:	14)	Targets ((12)	Citations	(1014)						
DISPLAY: C Structure	() Navigat	xy or AxisValues	DataDensity	SELECTED DATA:	Limit to	Exclude	FILTER:	0.0 min		pX Value:	15.0 max	Apply	Exclude GoSTAR dat	a Leg	jend
X-axis: Targets Y-axis: Substances								 cy clooxy genase 1 							
(E)-3-(5-methyl-2 토]							4.4				Thumb	nail Panel	2	(🚖
(E)-3-(3-methyl-t 💌								3.7							Ô
2-amino-nicotinoh 💌								4							
(E)-3-Phenyl-1-(p								4.4							
(E)-1-phenyl-3-(t								4.3							
(E)-1,3-bis(furan								4							
(2E)-3-(furan-2-yl								4.2							
1-(2-thienyl)-3-(2								5							
4-amino-1-phenyl	<u>ا</u>							4.4							
2-methylthiazolo[3.6							
Loliolide 🗵								3.2							
thiazolo<4,5-f>q								1							
N-phenyl phthalim								1							
atractylone	1							1							
1-(5-chioro-[2]thi	1							4.2							
								4.1							
E 6 dibudravu 7								5.1							
s,o-uiriyuroxy-/								4.7							
1 phopyl 2 mothy	7							1							
thalidomide]							3.5							

Step 6 : Search for bioactivities an Heatmap appears containing COX-1 non potent inhibitors

Step 7 : Go to the History and combine Hitsets

Query	Results	Synthesis Plans	History	Report	My Alerts	My Settings	Help	
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For each query select the Bioactivies and click on combine hitsets then click on Heatmap Overlay to retrieve potent and selective inhibitors of COX2 versus COX-1

Merge 16 with	h 12 Overlap 16 with 12	Exclude 16 from 12 Exclude 12 from 16)		
s s	Combine hitsets	19			Print
	Query	Temporary result description			Date
	Edit Create Alert Bioactivities: Target Name = "Cyclooxygenase 1" AND Measurement pX < 6.	16078 bioactivities Bioactivities: Target Name = "Cyclooxygenase 1" AND Measurement pX < 6	View	Store	2015-05-22 15:12
15	Clearence provide and	9914 substances	View	Store	
14		12 targets	View	Store	
13		1014 citations	View	Store	
	Edit Create Alert Bioactivities: Target Name = "Cyclooxygenase 2" AND Meacurement py >= 9	214 bioactivities Bioactivities: Taron Name = "Cyclooxygenase 2" AND Measurement pX >= 9	View	Store	2015-05-22 15:10
11	Meddul ellerit px 7 = 3	107 substances	View	Store	
10		5 targets	View	Store	
9		61 citations	View	Store	

Step 8 : Selective and potent inhibitors of COX-2 versus COX-1

The following Heatmap displays potent (affinity less than 1nM) and selective (SI> 1000) of COX-2 versus COX-1

Bioactivities (796	5) Reactions (0) Substances (56) Targets (11) C	itations (377)
DISPLAY: C Structure	Navigator AxisValues DataDensity DATA:	ER: 0.0 D Exclude Exclude Legend
X-axis: Targets Y-axis: Substances	 cy clooxy genase 1 	ه c clooxy genase 2
497341 💌	5.9	9. Thumbnail Panel X 🖈
2146626		
2140030 E	5.0	
5000309	5.0	
7400745	5.7	9.
7400715	5.5	
7495520	5.5	10
9260007	5,5 E 7	
8706634		3.
9019027	4.5	3.
9020949	1	
9217946	1	9
9226163	4.5	9,3
9418980 💌	1	10.2
9421133 💌	1	10.6
9421235 💌	1	10
9421809 💌	1	10
9423250 💌	1	9.4
9423969 💌	1	10.7
9424906 💌	1	9.4
9424992 💌	5.1	10.7
9426350 💌	1	10.7
9426436 💌	1	10.2
9426520 💌	1	11.2
9427586 💌	1	9.8
9427985	1	9.7

Step 9 : Sort compounds by descending bioactivities on COX-2

Click on the COX-2 button 🖃 and select "sort descending on this column" See Below.



The most potent COX-2 inhibitors will be on the top of the Heatmap.

Bioactiv	rities (796)	Re	action	s (0)		Subs	tand	es (56)	Tar	gets	(11)		Citat	ions (377)	_														
DISPLAY:	Struct) ure N	avigator	x; AxisV	y alues	Data D	v ensity	,	SELECTE DATA:	mit to	Exc	lude	F	FILTER:	0.0 mir) '		pX V	alue:		7	15.0 max		Apply		GoST	clude 'AR dat	a		Lege	nd
X-axis: Targets Y-axis: Substa i	s nces							C clooxy genase 1															 cy clooxy genase 2 								
4-hydro								5.8	3													1	2.8	Thum	bnai	Pane	el			х	*
2-[4-(a								1														1	1.2								$\overline{\cap}$
N-[4-[5								5.5	,													1	0.8								
3-(4-flu								5.0	1													1	0.7		_	_					
2-(4-ami								1														1	0.7		_						
H-Trp-T								4.3	2													1	0.7								
2-(4-me								1														1	0.6		_	_					
2-(4-Me								1														1	0.2								
2 -(4-ami								1														1	0.2		-	_					
2-(4-me								1															10								
2-(4-ami								1															10								
N-cyclop								1															10								
8796634								4.	5														9.9								
2-(4-ami								1															9.8 . 7							-	
2-(4-me								1									_		_	_	_		9.7 9.7		_	_	_	_	_	_	
4-(2-hv								5.1	1																						
H-Trp-C								5.3	2														9.7								
2-pheny								1														9	9.6								
N-(benz								4.4	1													9	9.6								
3 -(4-(4-								4.3	5													9	9.5								
2-pheny								1														9	9.5								U

Bioactivities contain in the cell are displayed by clicking directly in the cell (Right click). The corresponding substances and bioactivities are then available on the screen.

	-axis: Targ	jets		Y-axis: Substan	ices	Select value type: MAX			1 substances and 3 bioactivities			
					Hide	CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ Details						Che 2-(4 Rez Typ Mol Line Mol InC
- (., - (-,										
▼ Druglik ★ Bioactive ★ In vite Quantitation	ity o: Efficacy (ve Results	(3) Value			Tarnet	Tarnet						
¥ Druglik ★ Bioactiv ★ In viti Quantitati Paramet	ity o: Efficacy (ve Results er Value (qual)	(3) Value (quant)	Unit	Target	Target subunit	Target Species	Tissue/Organ	Cell	Bioassay	Dose	Effect	Reference
 ➤ Druglik ★ Bioactive ★ In vite Quantitati Paramet IC50 	ity o: Efficacy (ve Results er Value (qual)	(3) Value (quant) 0.17	Unit nM	Target Cydooxygenase 2	Target subunit	Target Species mouse	Tissue/Organ Peritoneal cavity	Cell Macrophage	Bioassay Enzymology inhibition	Dose	Effect	Reference Bioorganic Title/Abstr
▼ Druglik ★ Bioactin ★ In vitic Quantitatin Parameter IC50	ity o: Efficacy (ve Results er Value (qual) =	 3) Value (quant) 0.17 0.17 	Unit nM nM	Target Cyclooxygenase 2 Cyclooxygenase 2	Target subunit	Target Species mouse	Tissue/Organ Peritoneal cavity	Cell Macrophage Macrophage	Bioassay Enzymology inhibition	Dose	Effect	Referen Bioorgania Title/Abst Current M Title/Abst
➤ Druglik ★ Bioactin ★ In vit: Quantitati Paramet IC50 IC50	ness ity o: Efficacy (ve Results er Value (qual) = = =	 (3) Value (quant) 0.17 0.17 0.17 	Unit nM nM	Target Cyclooxygenase 2 Cyclooxygenase 2 Cyclooxygenase 2	Target subunit	Target Species mouse	Tissue/Organ Peritoneal cavity	Cell Macrophage Macrophage	Bioassay Enzymology inhibition	Dose	Effect	Reference Bioorganic Title/Absti Current M Title/Absti European Title/Absti

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