

Self guided Tour

Reaxys Medicinal Chemistry

**WHICH SUBSTANCES ARE POTENT AND SELECTIVE
INHIBITORS OF TARGET?**

<http://beta.reaxys.com>

 **REAXYS**[®]
Medicinal Chemistry

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

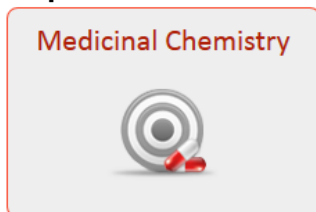
1.2 Overview

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

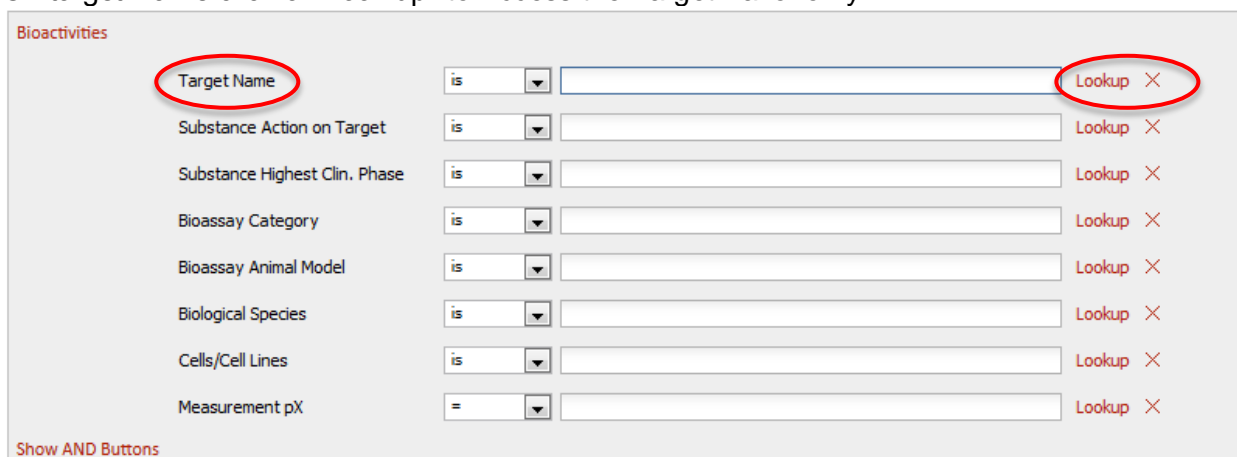
The screenshot displays the Reaxys search interface. At the top, there is a navigation bar with links for Query, Results, Synthesis Plans, History, Report, My Alerts, My Settings, and Help. On the right side of the navigation bar, there are links for Live Chat and Logout. Below the navigation bar, there is a search bar with the placeholder text "Enter a keyword, concept or author" and a "Go" button. Below the search bar, there is a section titled "Find substances, reactions, bioactivity data, citations, patents, and more from Reaxys, PubChem, and eMolecules". Below this section, there are five main search categories: Reactions (represented by a flask icon), Substances, Names, Formulas (represented by a molecular structure icon), Medicinal Chemistry (represented by a target icon), Literature (represented by a book icon), and ReaxysTree (represented by a tree icon). Below these categories, there is a section titled "You can also search directly by these common property groups:" with four sub-categories: Physical (represented by a cube icon), Spectra (represented by a spectrum icon), Natural Product (represented by a globe icon), and Advanced (represented by a magnifying glass icon).

Step 1 Search Medicinal Chemistry



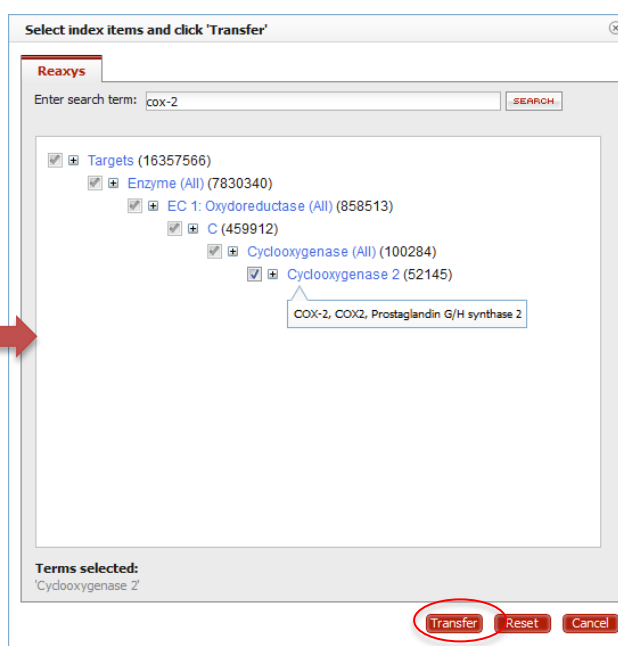
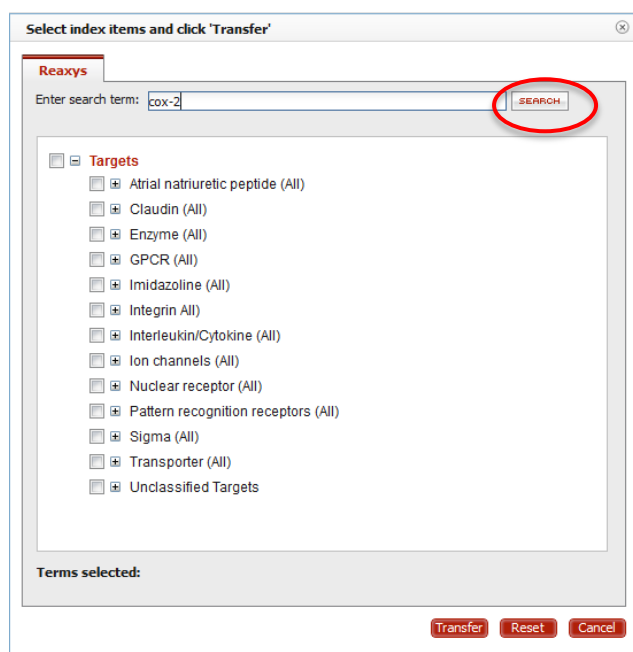
Step 2 Select a Target

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



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...)



Remark : to see Cox-2 Species click on the plus [Cyclooxygenase 2](#)

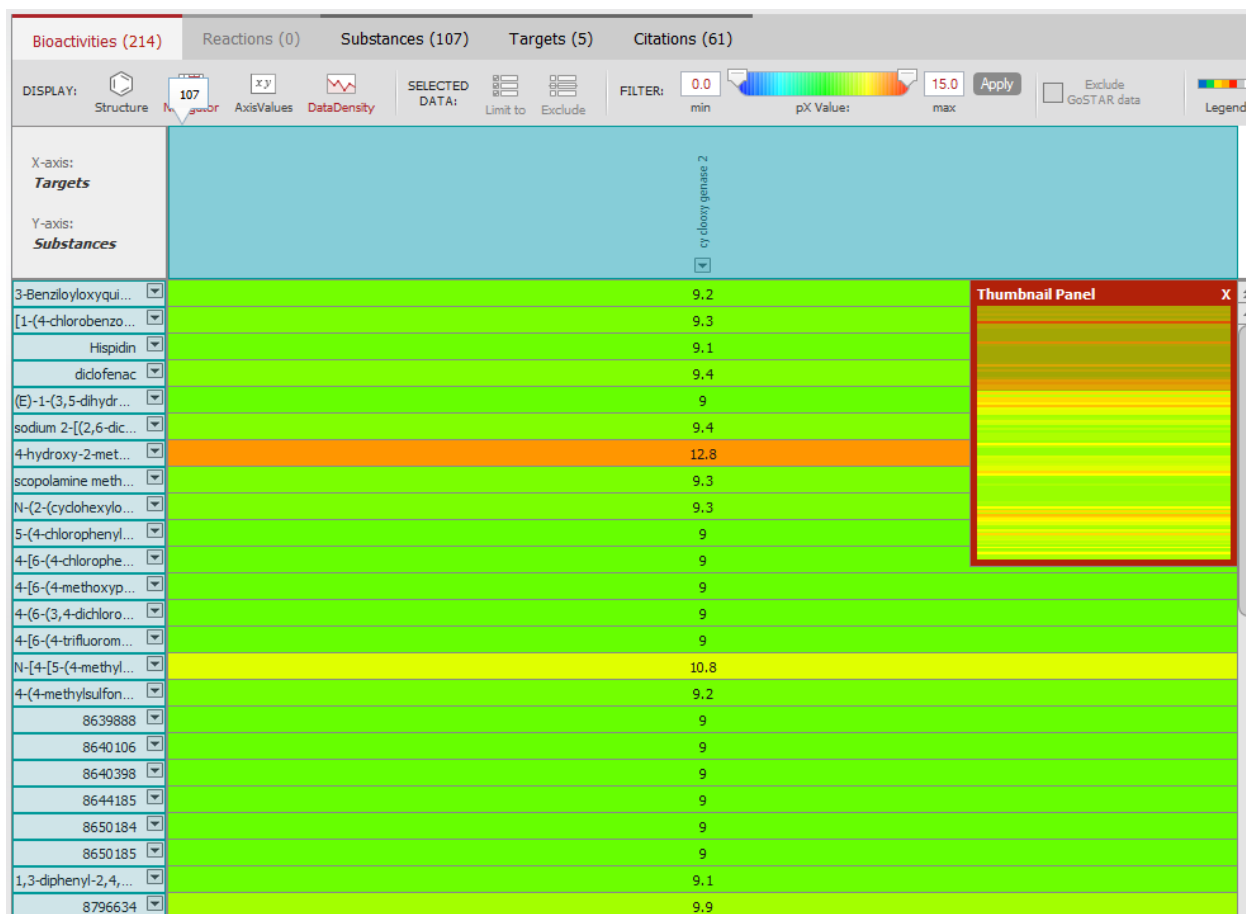
Then select \geq in the pX querylet and enter 9 (Affinity less than 1 nM)

Bioactivities

Target Name	is	'Cyclooxygenase 2'	Lookup	×
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	\geq	9	Lookup	×

Show AND Buttons

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



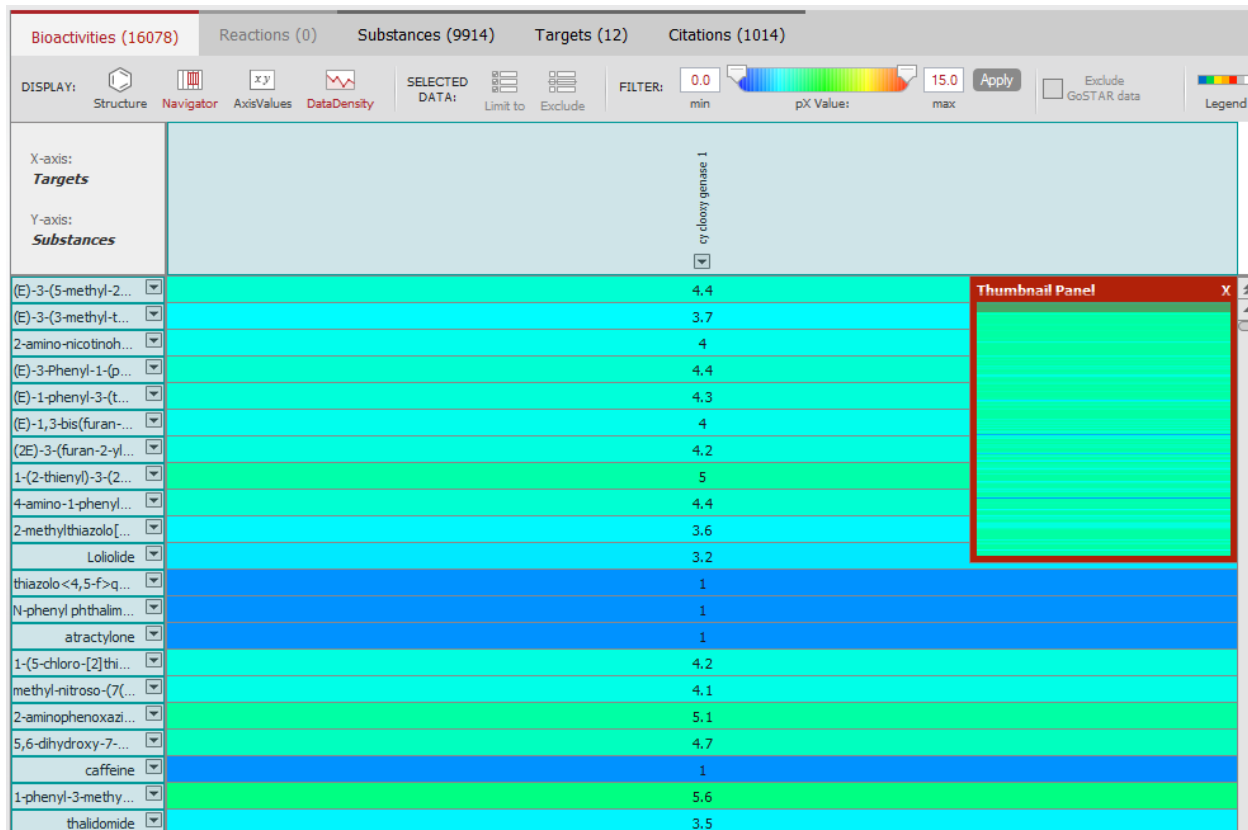
Step 4 : Go Back to the query and search for Substances tested on COX-1



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)

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



Step 7 : Go to the History and combine Hitsets



For each query select the Bioactivities and click on combine hitsets then click on Heatmap Overlay to retrieve potent and selective inhibitors of COX2 versus COX-1

Combine hitsets

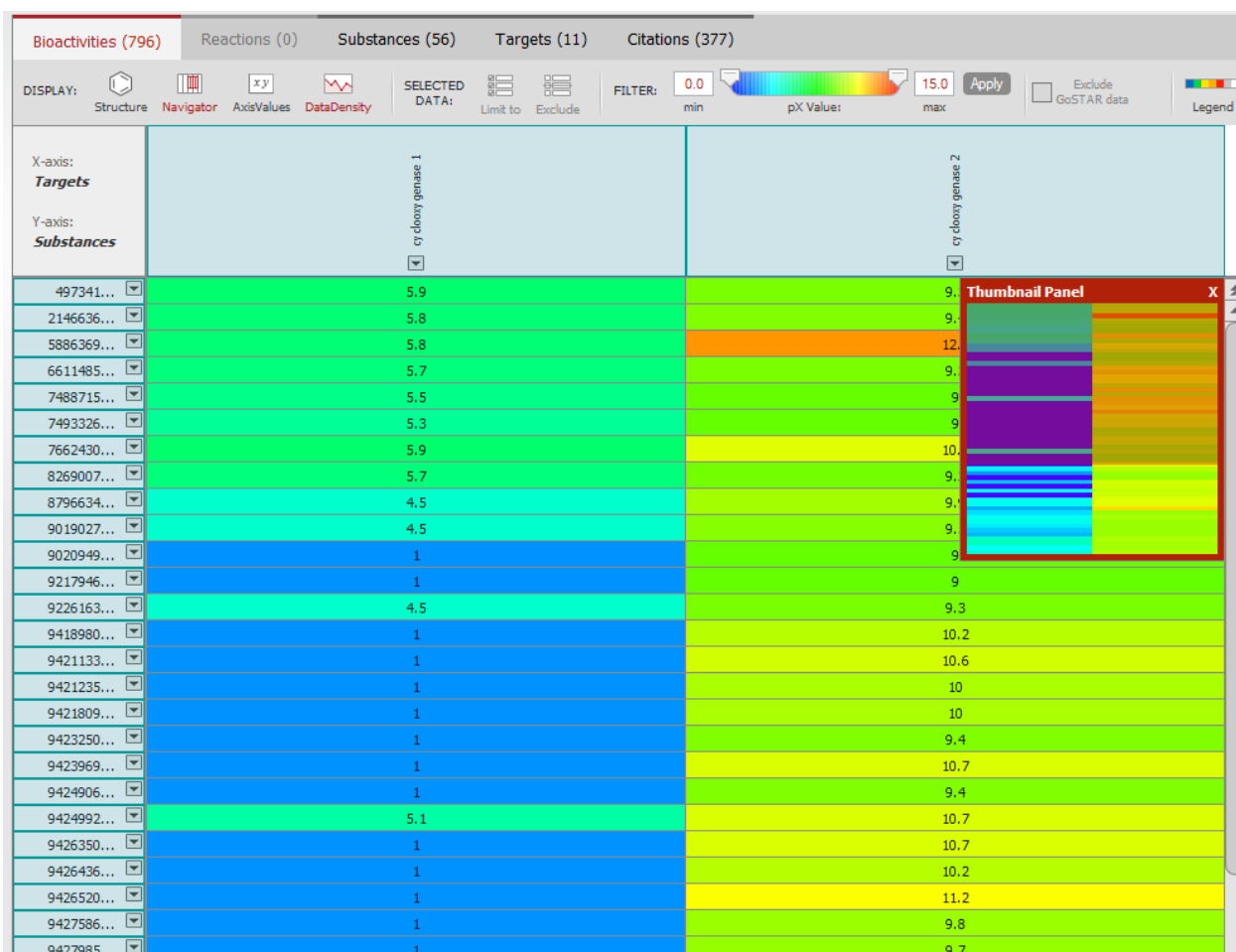
Select at least two hitsets for combining

Print

Query	Temporary result description	Date
<input checked="" type="checkbox"/> 16 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 9914 substances View Store 12 targets View Store 1014 citations View Store	2015-05-22 15:12
<input checked="" type="checkbox"/> 12 Edit Create Alert Bioactivities: Target Name = "Cyclooxygenase 2" AND Measurement pX >= 9	214 bioactivities Bioactivities: Target Name = "Cyclooxygenase 2" AND Measurement pX >= 9 View Store 107 substances View Store 5 targets View Store 61 citations View Store	2015-05-22 15:10

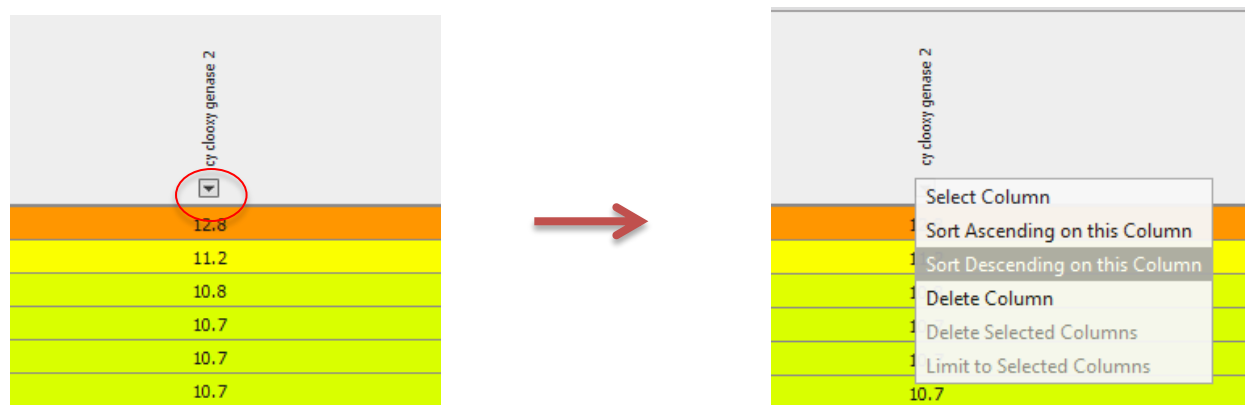
Step 8 : Selective and potent inhibitors of COX-2 versus COX-1

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

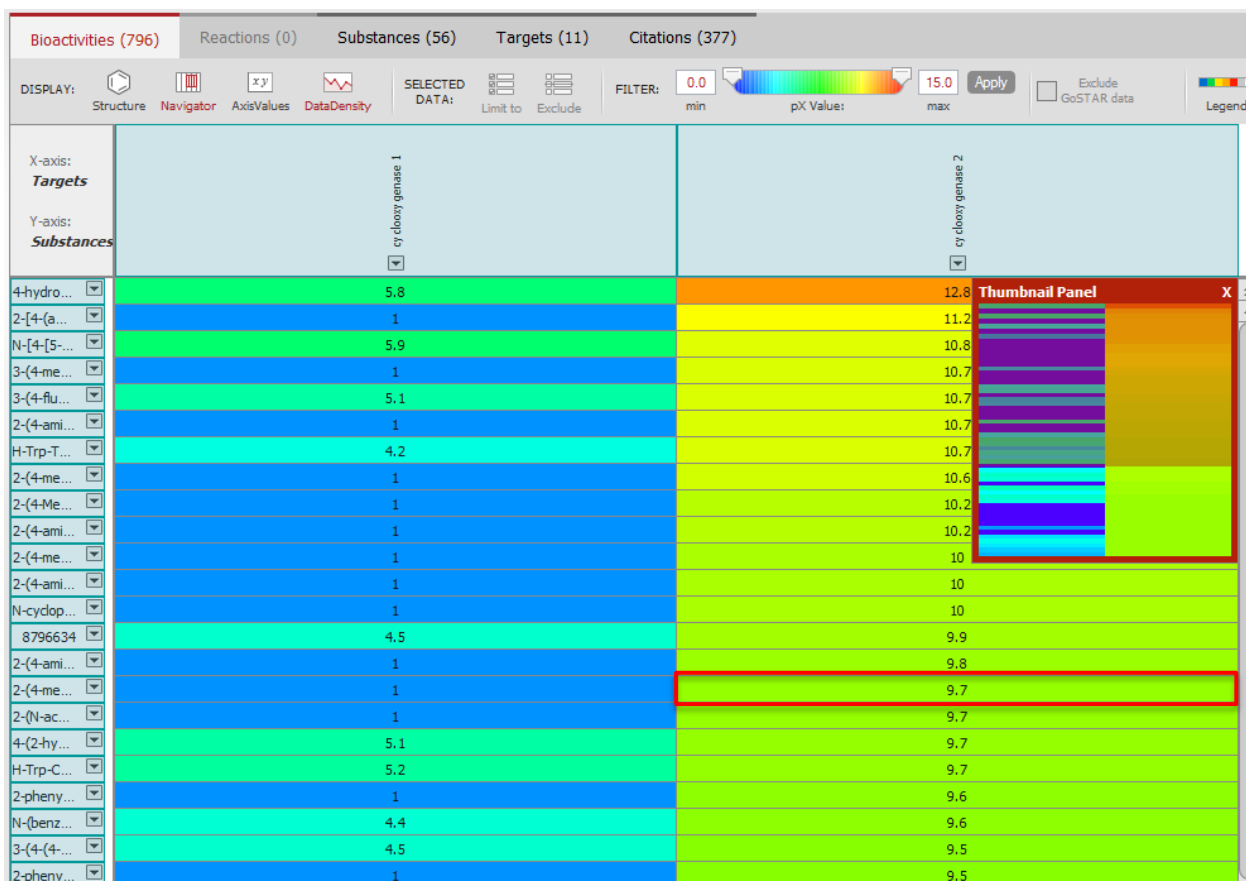


Step 9 : Sort compounds by descending bioactivities on COX-2

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.



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.

Heatmap Cell Details

9.70 X-axis: Targets Y-axis: Substances Select value type: MAX 1 substances and 3 bioactivities

Chemical structure: Cc1ccc(cc1N2C(=O)Nc3ccc(C)cc32)S(=O)(=O)c4ccc(C)cc4

Hide Details

Chemical Names and Synonyms
2-(4-methylsulfonylphenyl)-3-(3,4-dimethylphenyl)indole

Druglikeness

Bioactivity

In vitro: Efficacy (3)

Quantitative Results

Parameter	Value (qual)	Value (quant)	Unit	Target	Target subunit	Target Species	Tissue/Organ	Cell	Bioassay	Dose	Effect	Reference (Title/Abstract)
IC50		0.17	nM	Cydooxygenase 2		mouse	Peritoneal cavity	Macrophage	Enzymology inhibition			Bioorganic and Title/Abstract
IC50	=	0.17	nM	Cydooxygenase 2				Macrophage				Current Medic Title/Abstract
IC50	=	0.17	nM	Cydooxygenase 2								European Jou Title/Abstract

Substance View Close

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