Self guided Tour

Reaxys Medicinal Chemistry

WHICH SUBSTANCES ARE POTENT AND SELECTIVE INHIBITORS OF TARGET?

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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.

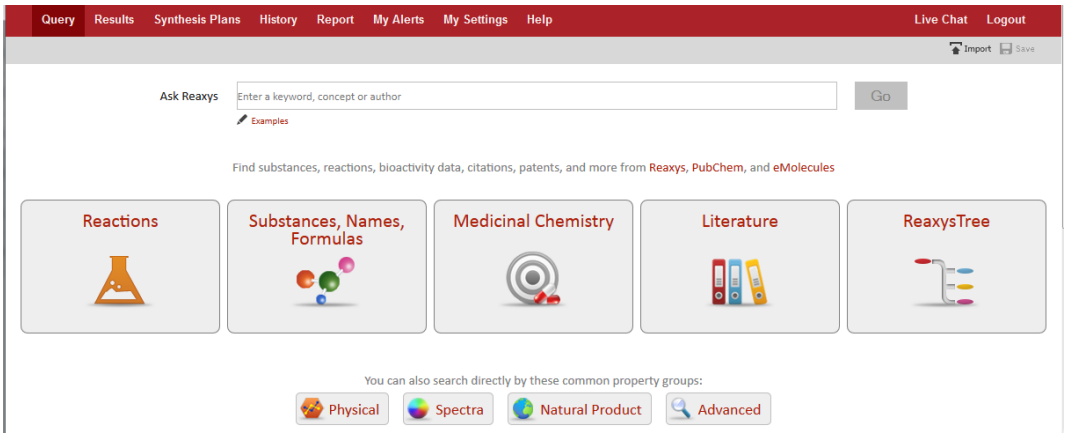
Selective pharmacologic inhibition of COX-2 represents a viable therapeutic option for the treatment of malignancies. Agents that selectively inhibit COX-2 demonstrate that chronic treatment for angiogenesis inhibition is feasible.
As a continuous research for discovery of new COX-2 inhibitors, new synthetic 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”.

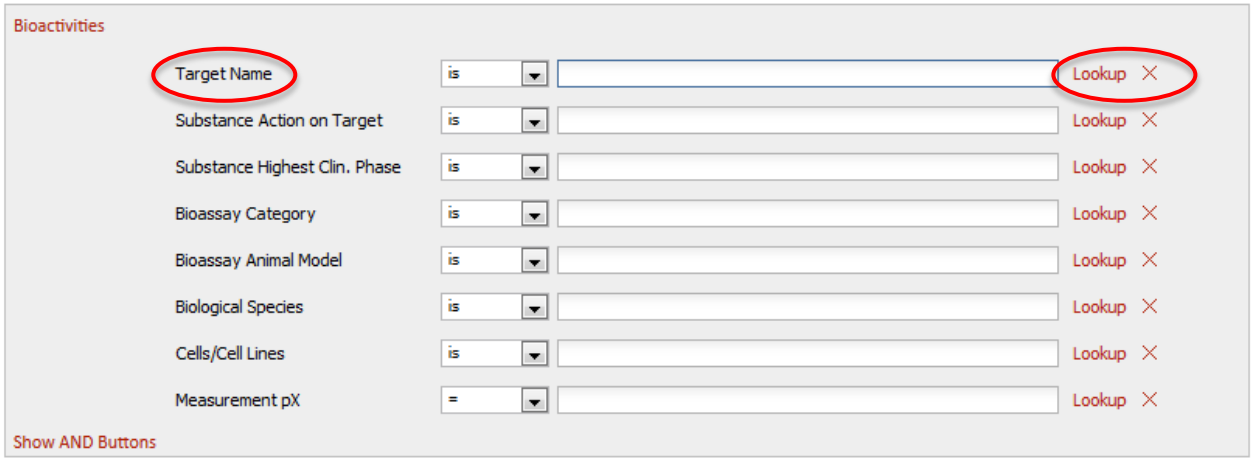
1.3 Step by step



Step 1 Search Medicinal Chemistry

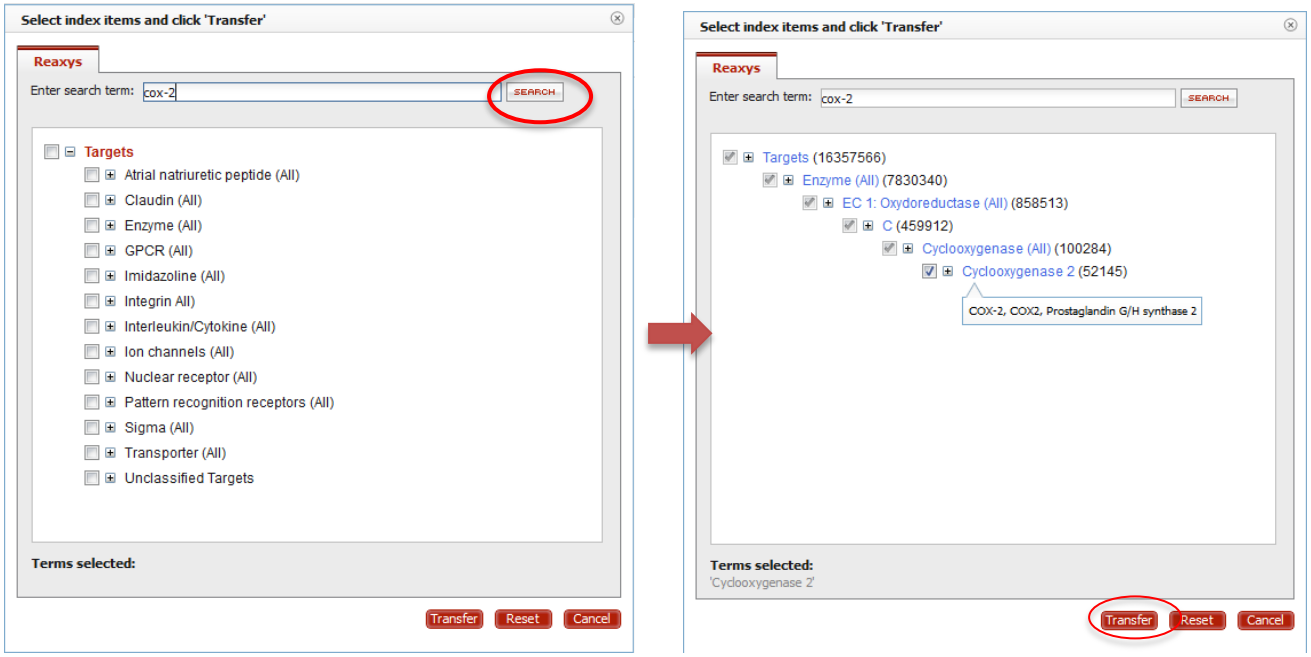
Step 2 Select a Target

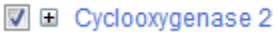
On target Name click on “look up” to Access the Target Taxonomy



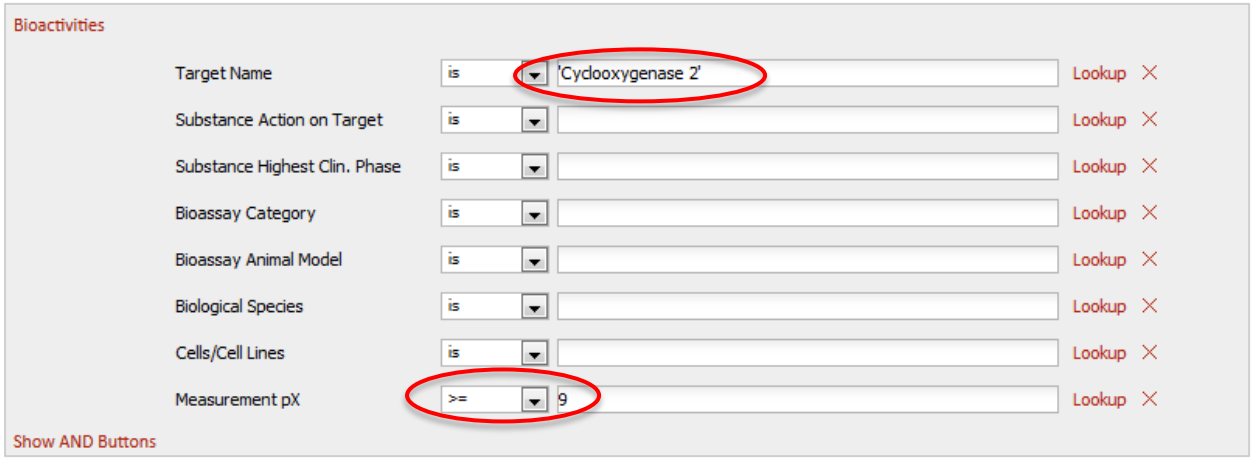
A new popup displays the Target Taxonomy then Search for ‘Cox-2’ in Enter.
Preferred term “Cyclooxygenase 2” is selected because Cox-2 was found as synonym (to display synonyms move the mouse pointer on the node name.)

And then on “Transfer” to select all Cyclooxygenase 2 (Human, Rat, mouse etc…)

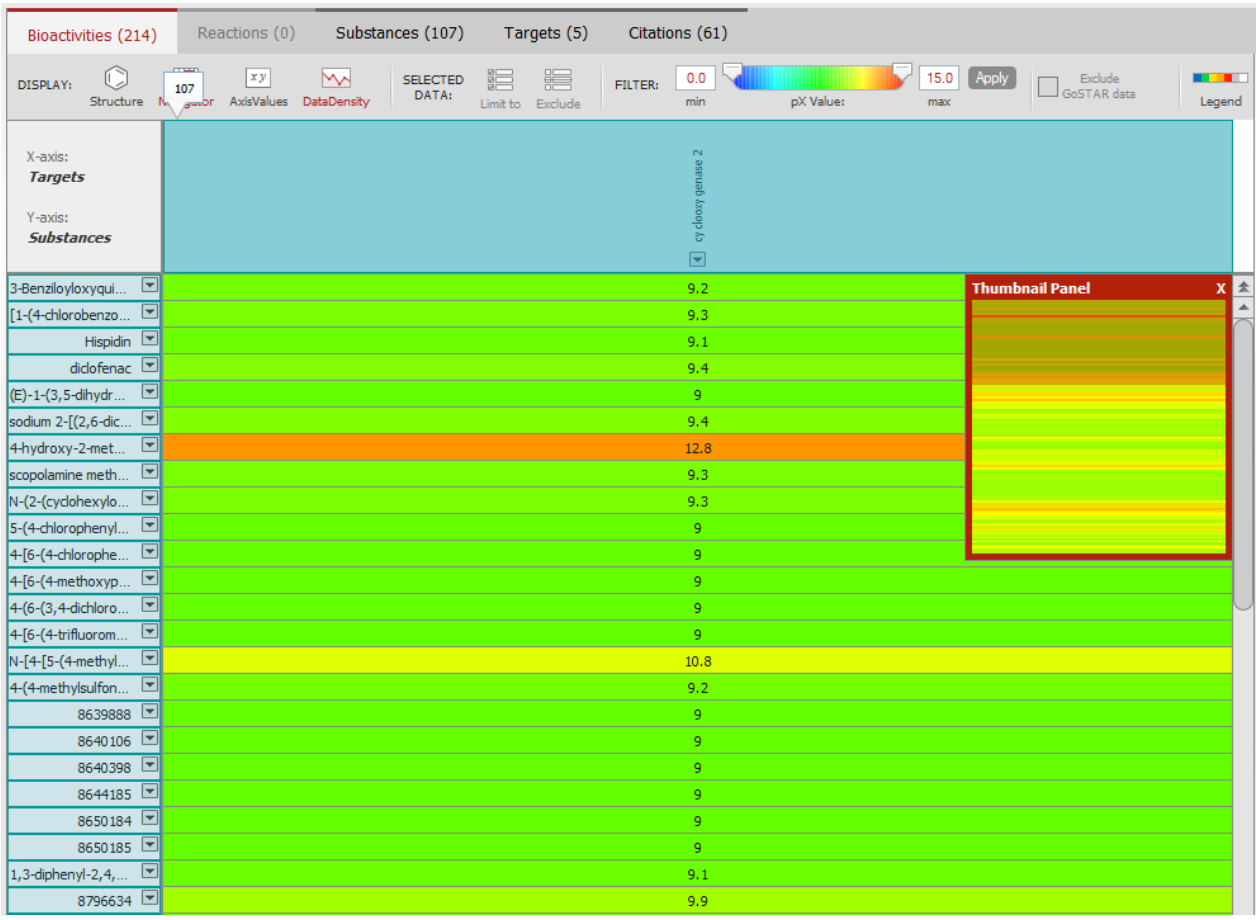


Remark : to see Cox-2 Species click on the plus 

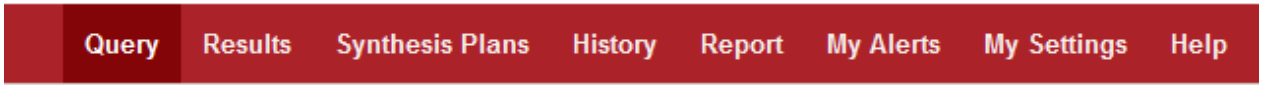
Then select >= in the pX querylet and enter 9 (Affinity less than 1 nM)



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



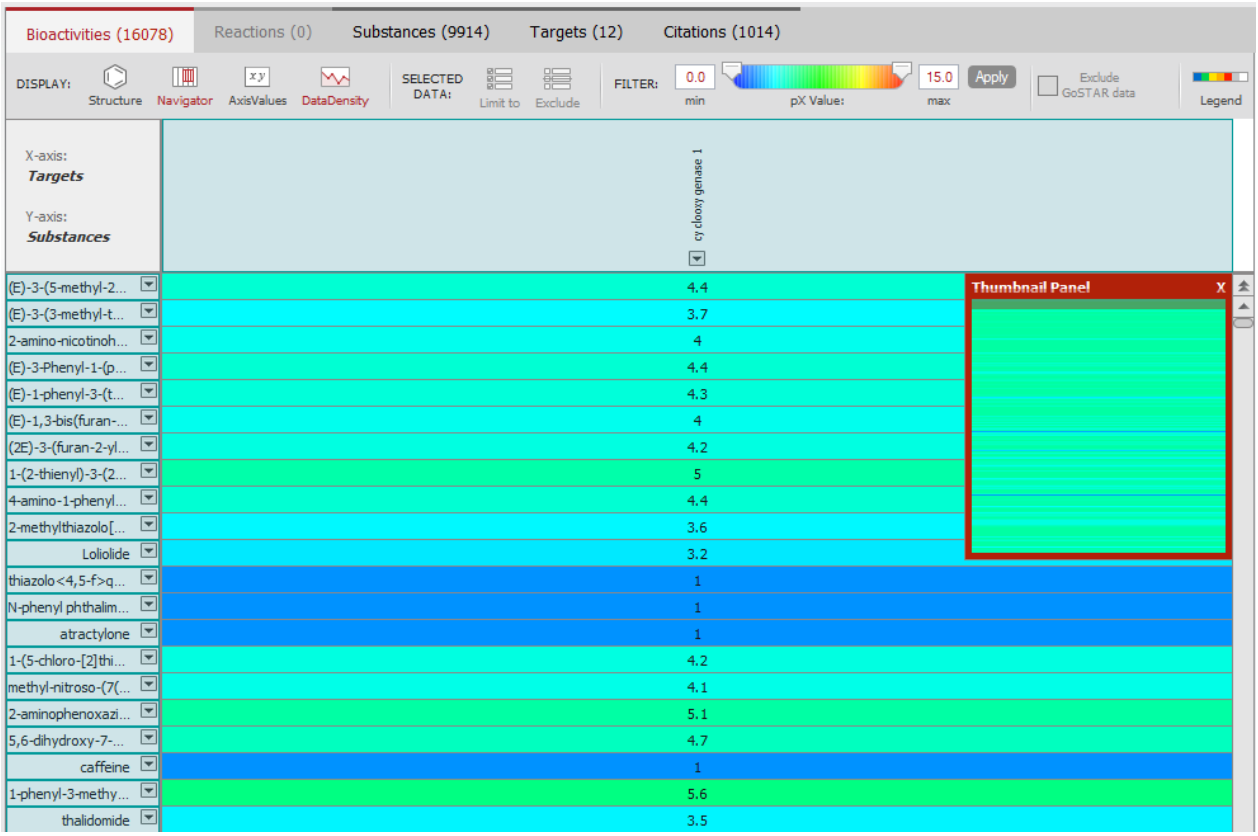
Step 4 : Go Back to the query and search for Substances tested on COX-1



Step 5 Select a Target Name

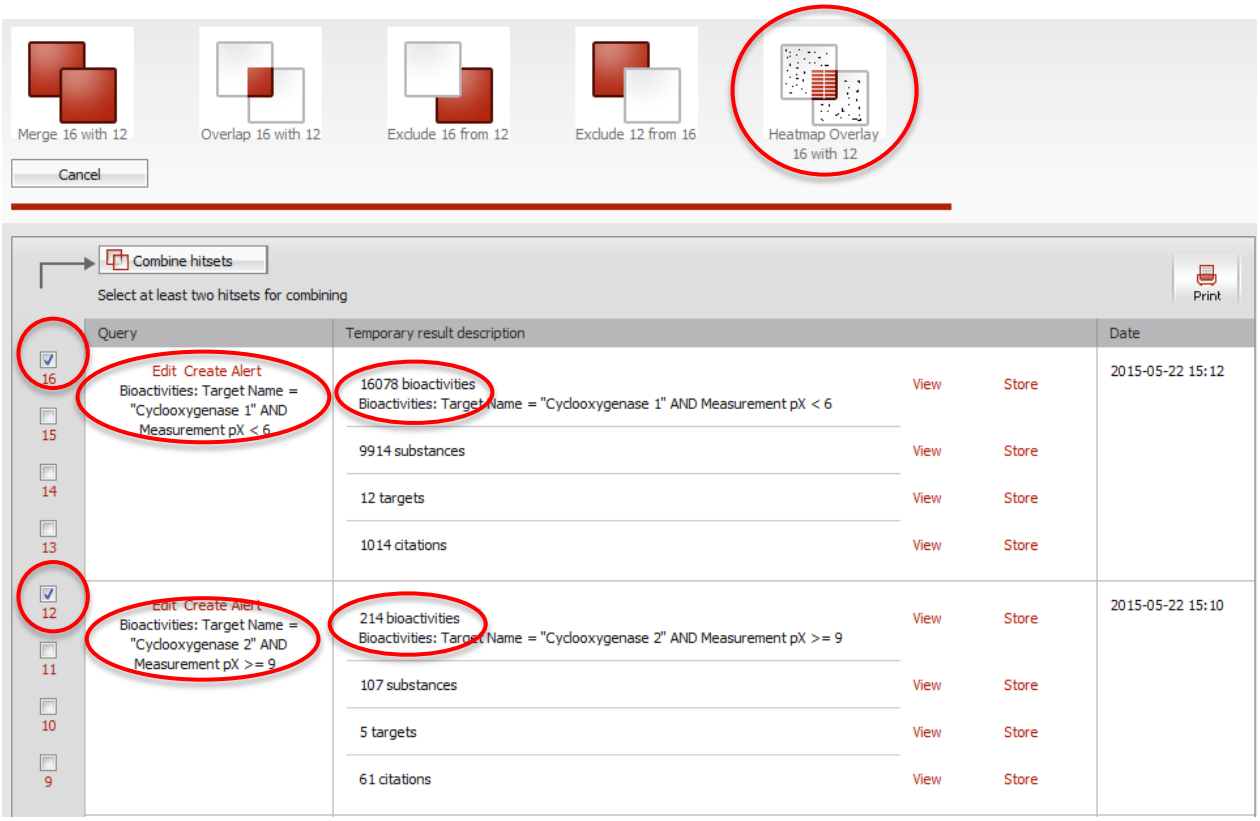
On Target Name click on “look up” type ‘Cox-1’ and Search, then Click on transfer.
Select <= in the pX querylet and enter 6 (1000 fold Selectivity)

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



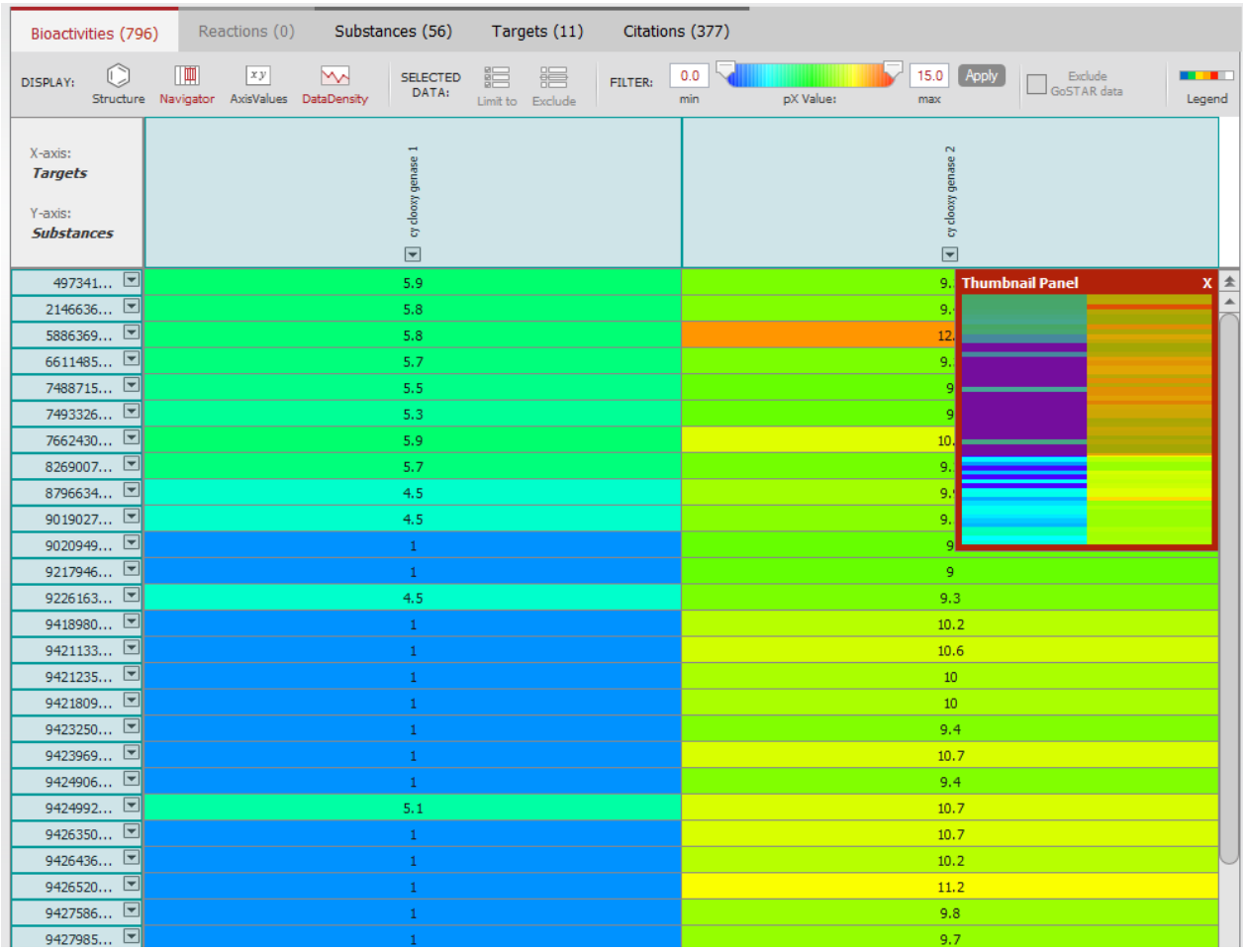
Step 7 : Go to the History and combine Hitsets

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



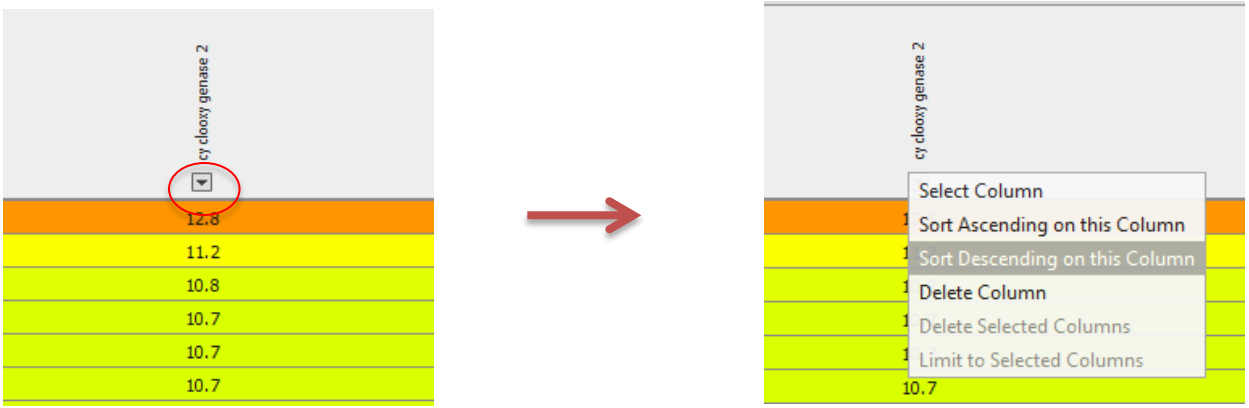
Step 8 : Selective and potent inhibitors of COX-2 versus COX-1

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

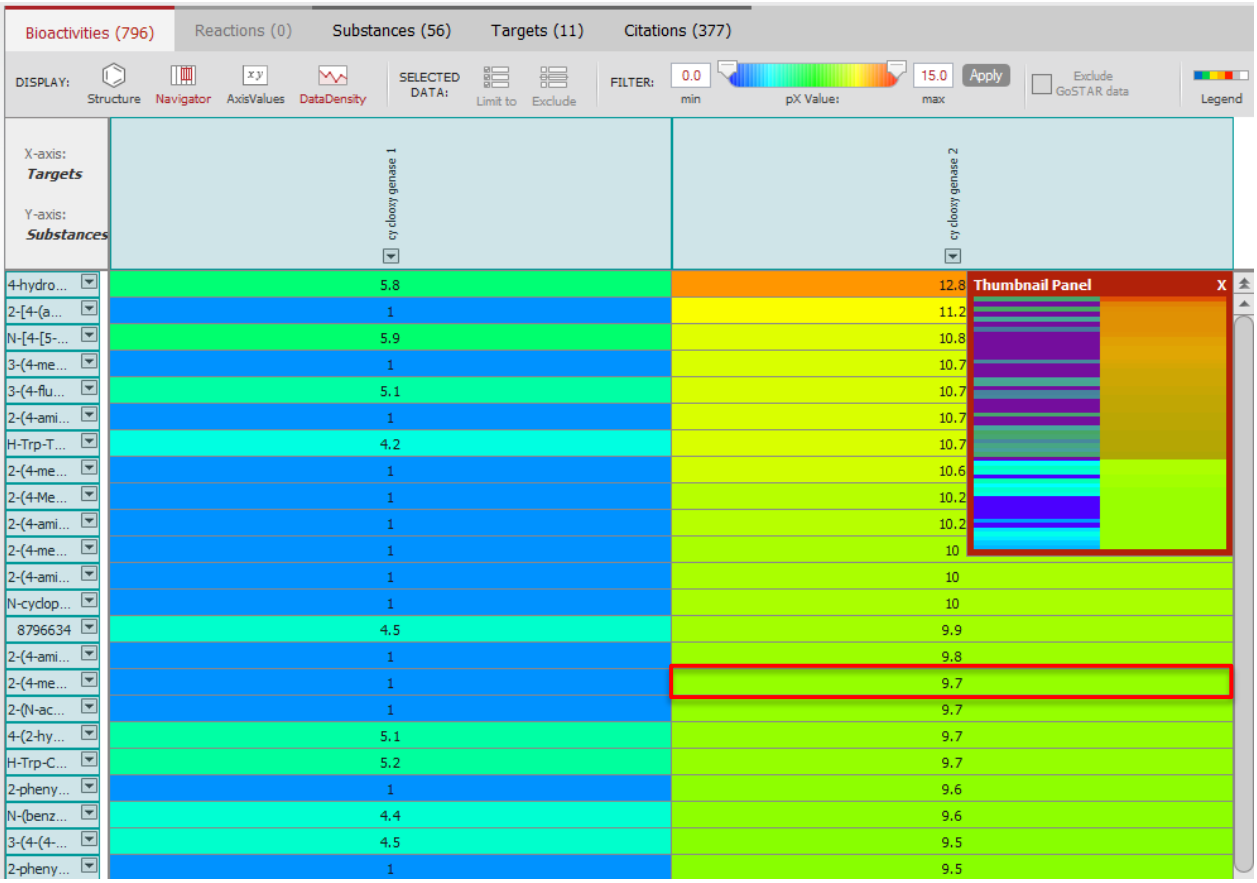


Step 9 : Sort compounds by descending bioactivities on COX-2

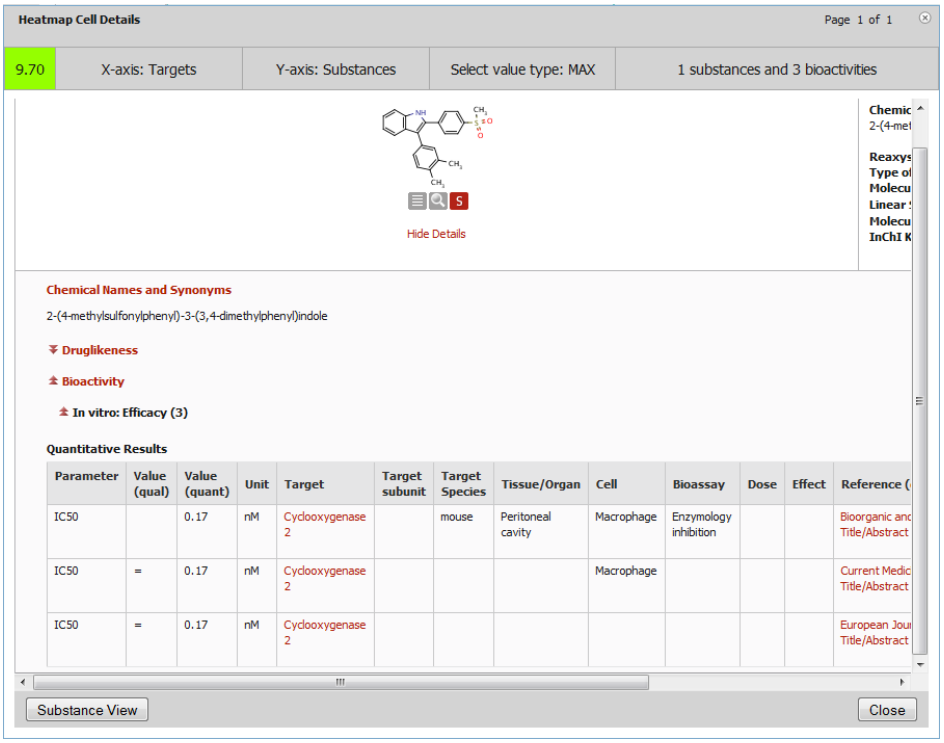
Click on the COX-2 button  and select “sort descending on this column” See Below.



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.



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