

Which Substances are Potent and Selective Inhibitors of Target?

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:

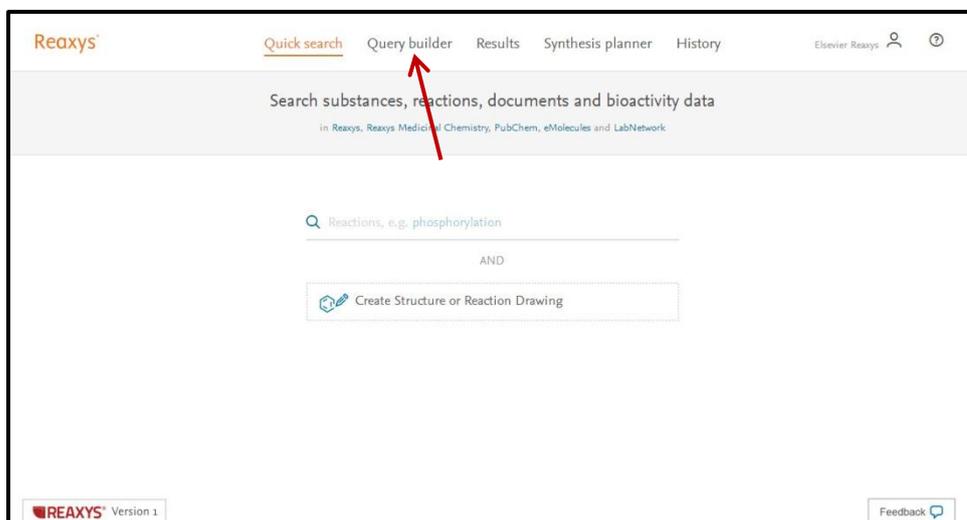
- Play a key role in the release and activity of proangiogenic proteins;
- Result in the production of eicosanoid products TXA2, PGI2, PGE2 that directly stimulate endothelial cell migration and angiogenesis in vivo, and
- Result in enhanced tumor cell, and possibly, vascular endothelial cell survival 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 are of great interest as antiangiogenic agent.

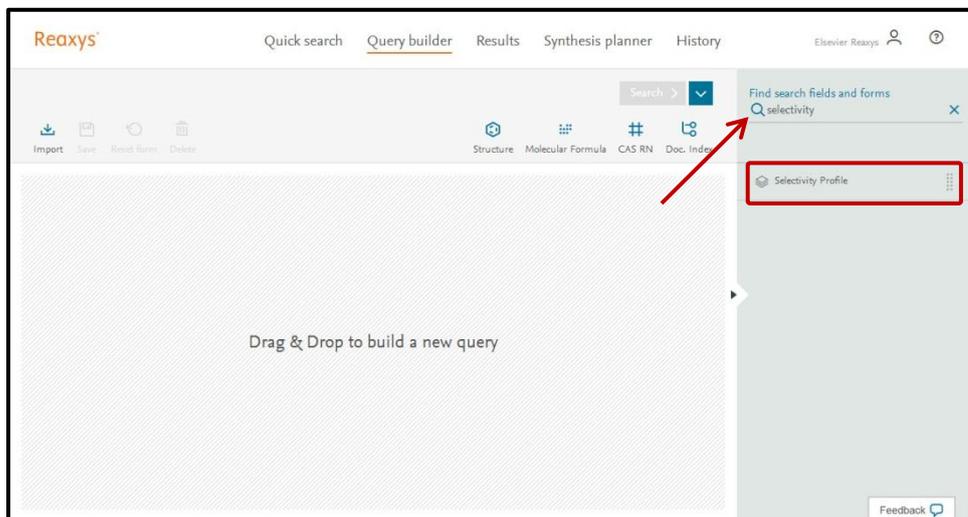
Let's search for potent and selective inhibitors of Cyclooxygenase 2 (COX-2) versus Cyclooxygenase COX-1.

❖ Define the Search Query using the Query builder

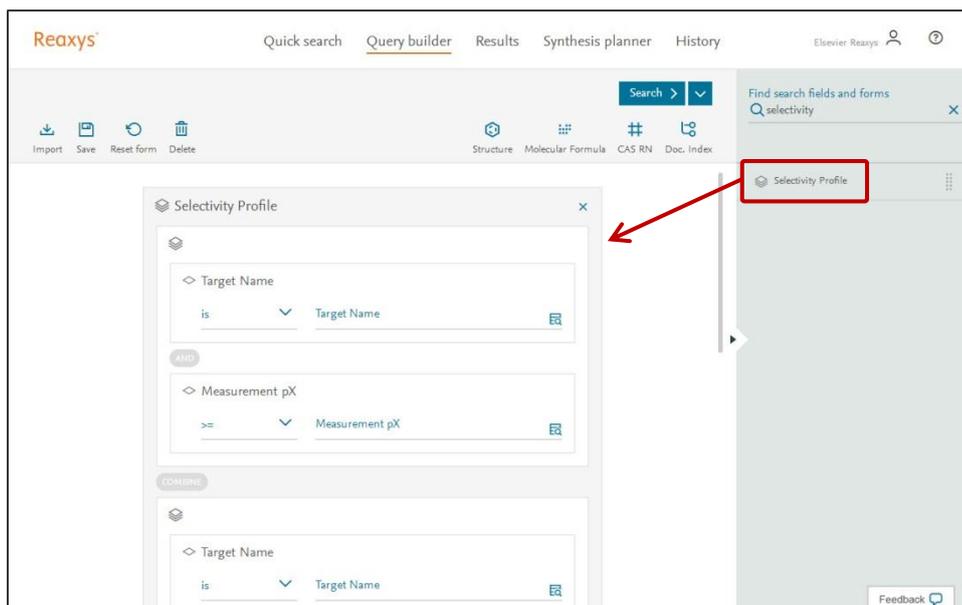
1. On the Reaxys home page, click **Query builder**



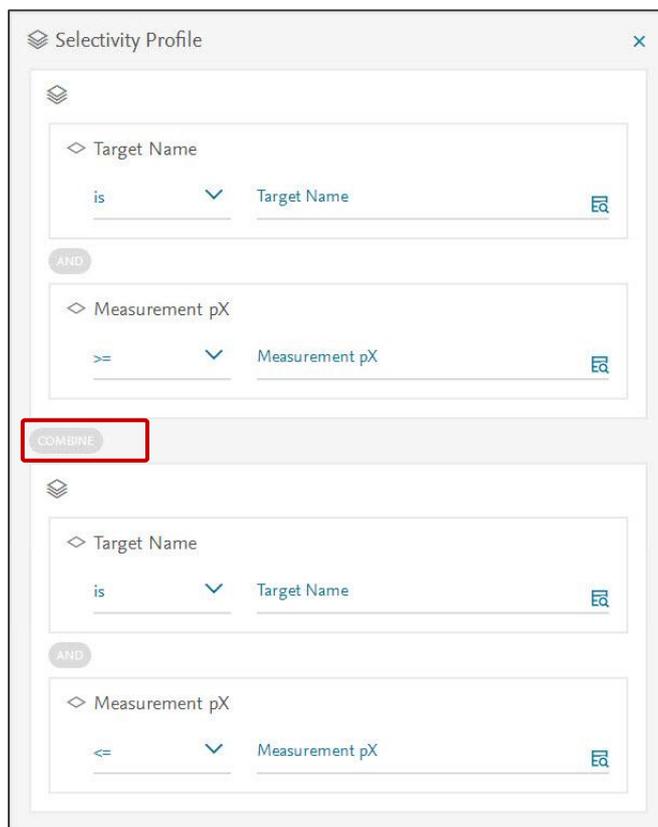
2. In the **Find search fields and forms** box, type **selectivity**
The list is filtered to include fields and forms that include the word selectivity. In this case the **Selectivity Profile** form is displayed.



- a. Drag and Drop the **Selectivity Profile** form onto the query builder.



The *Selectivity Profile* form is displayed with the *combine operator*. The *combine operator* will allow users to search for substances tested on two targets whatever the origin of the targets (same or different bioassays, same or different publication).



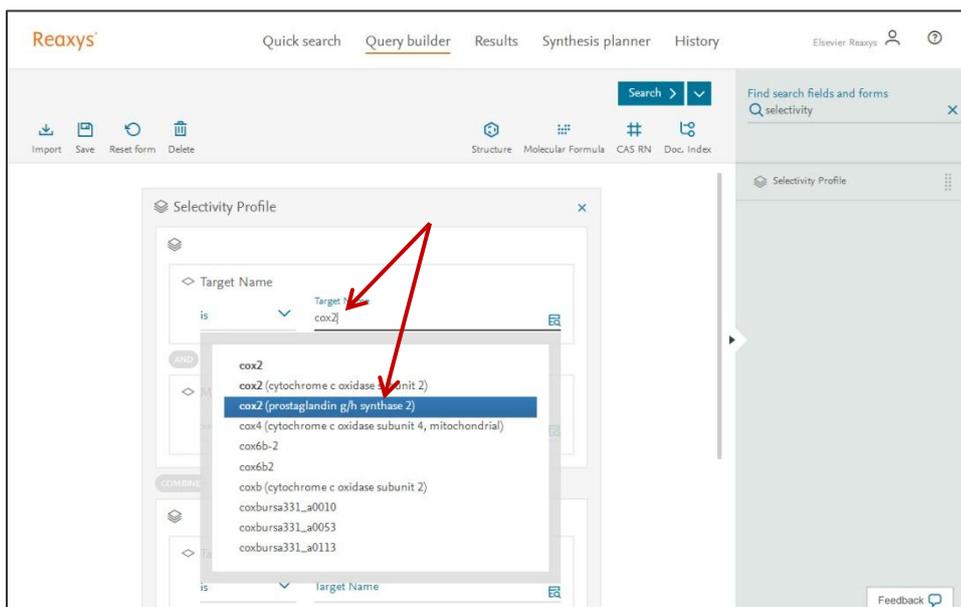
The screenshot shows a 'Selectivity Profile' window with two search criteria blocks. Each block contains a 'Target Name' field with the operator 'is' and a 'Measurement pX' field with the operator '>=' (for the first block) and '<=' (for the second block). A 'COMBINE' button is highlighted with a red box between the two blocks, indicating that the search results will be combined.

Next, let's complete the *Selectivity Profile* form with:

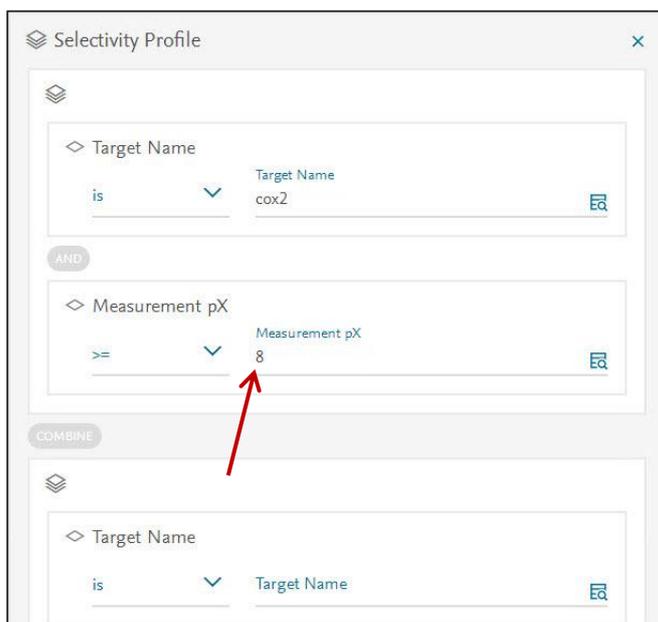
- The first target as Prostaglandin G/H synthase 2 (COX-2) and the associated pX greater than or equal to 8 (below 10 nM).
- The second target as Prostaglandin G/H synthase 1 (COX-1) and the associated pX with lower than or equal to 6 (over 1 μ M) and search for Substances.

3. Define the first *Target name* to be *cox2 (prostaglandin g/h synthase 2)*:

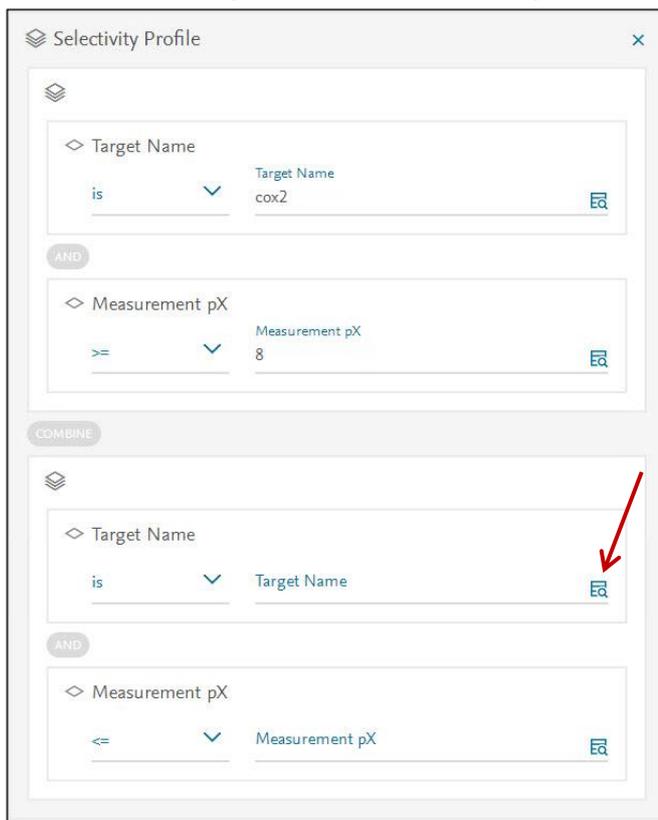
- Click the first **Target Name** field and type **cox2**.
- Click **cox2 (prostaglandin g/h synthase 2)** from the suggestion list.



4. Set the first **Measurement pX** to **≥ 8** (e.g. user searched for substances highly potent on COX-2 with a potency below 10 nM using IC50, Ki, EC50 etc.).

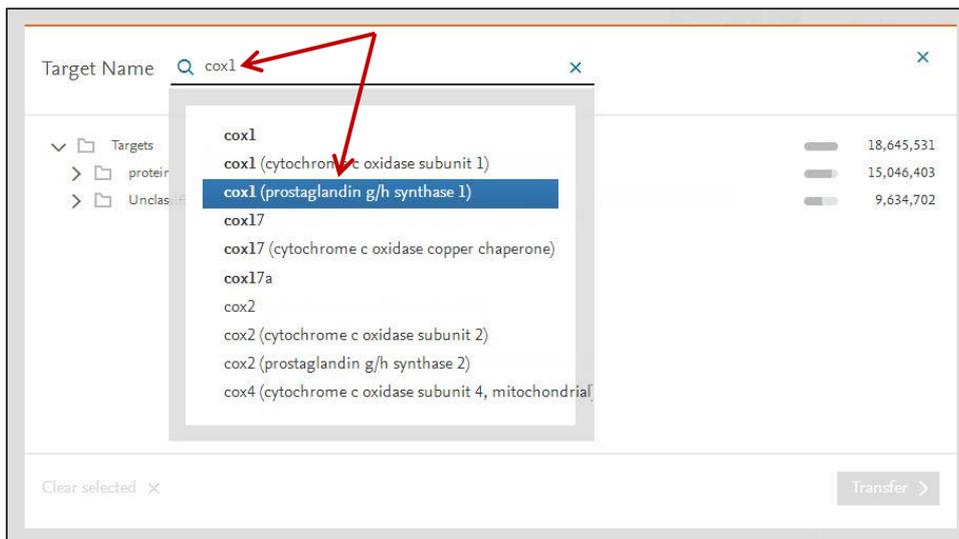


5. Define the second *Target name* using the *Lookup tool*:
 - a. For the second **Target Name** click the **Lookup tool**



The screenshot shows the 'Selectivity Profile' interface. It contains two target definition blocks. The first block has 'Target Name' set to 'is' and 'cox2', and 'Measurement pX' set to '>=' and '8'. The second block has 'Target Name' set to 'is' and 'Target Name', and 'Measurement pX' set to '<=' and 'Measurement pX'. A red arrow points to the 'Lookup tool' icon (a magnifying glass) next to the 'Target Name' field in the second block.

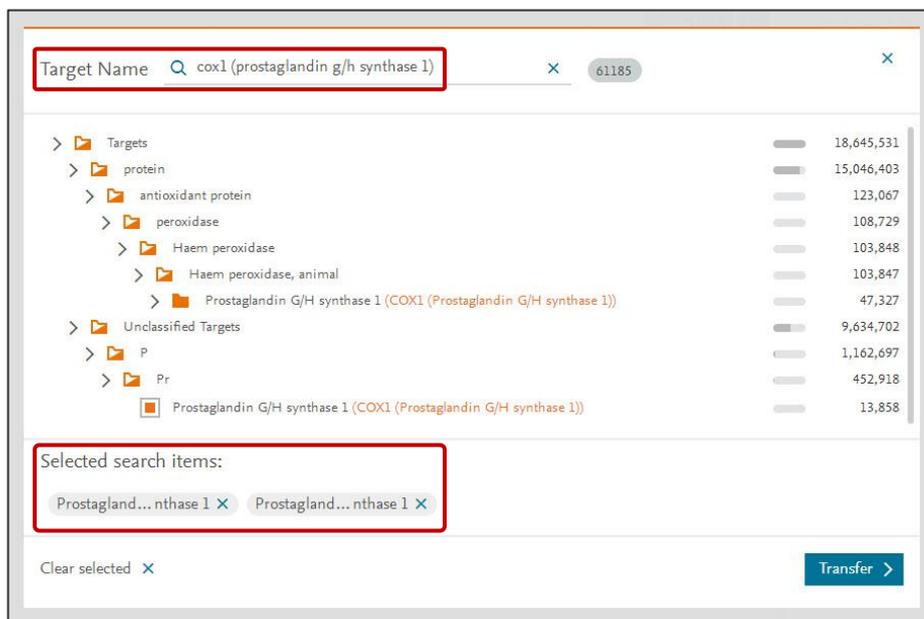
- b. Type **cox1** (do NOT press the Enter key)
 - c. Click **cox1(prostaglandin g/h synthase 1)** from the suggestion list and press the **Enter key**



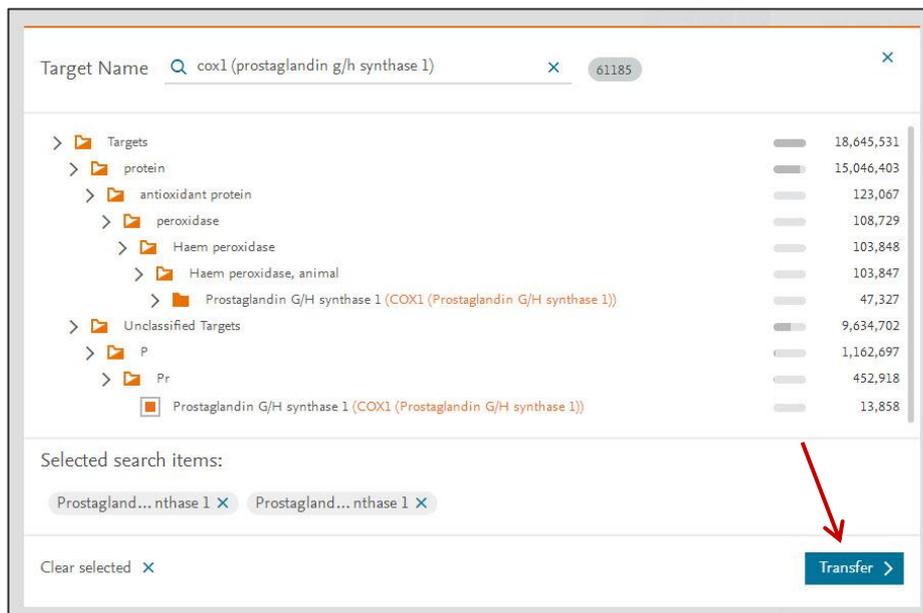
The screenshot shows the 'Target Name' lookup tool. The search input is 'cox1'. A list of suggestions is displayed, including 'cox1', 'cox1 (cytochrome c oxidase subunit 1)', 'cox1 (prostaglandin g/h synthase 1)', 'cox17', 'cox17 (cytochrome c oxidase copper chaperone)', 'cox17a', 'cox2', 'cox2 (cytochrome c oxidase subunit 2)', 'cox2 (prostaglandin g/h synthase 2)', and 'cox4 (cytochrome c oxidase subunit 4, mitochondrial)'. The suggestion 'cox1 (prostaglandin g/h synthase 1)' is highlighted with a blue background. A red arrow points to this highlighted suggestion. The interface also shows a 'Clear selected' button and a 'Transfer >' button.

Note: The search in the Taxonomy is performed using a substring within the full name and the associated synonyms of the target. The searched term is highlighted in orange when found in synonyms and corresponding main terms are displayed as a flat list at the bottom of the page. In the *Selected search items* section the terms can be deleted by clicking on the blue X.

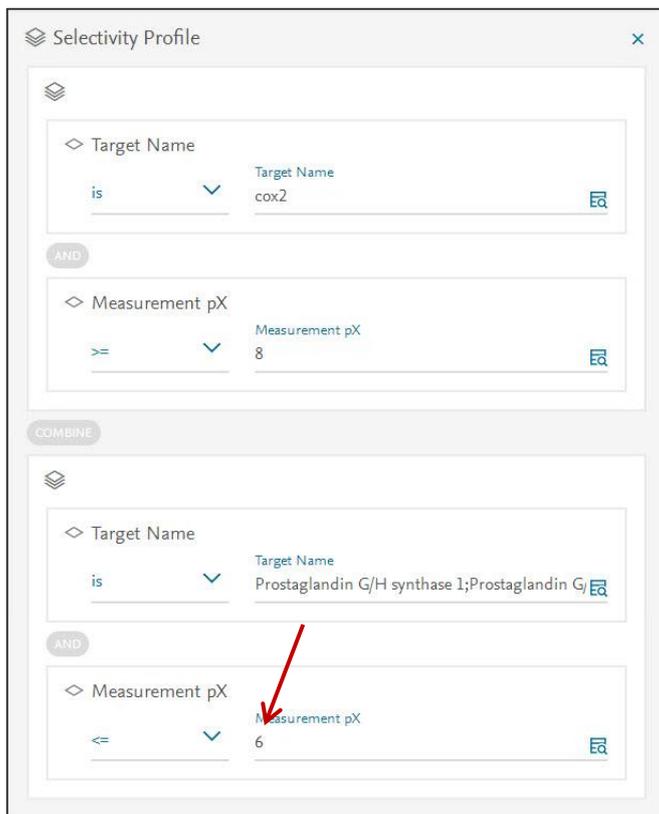
Numbers on the right hand side of the windows are counting bioactivities (data points) on the corresponding target or family of target.



d. Click **Transfer**



- Set the second **Measurement pX** to **<= 6** (e.g. user searched for substances less potent on COX-1 with a potency over 1 μ M using IC50, Ki, EC50 etc.).



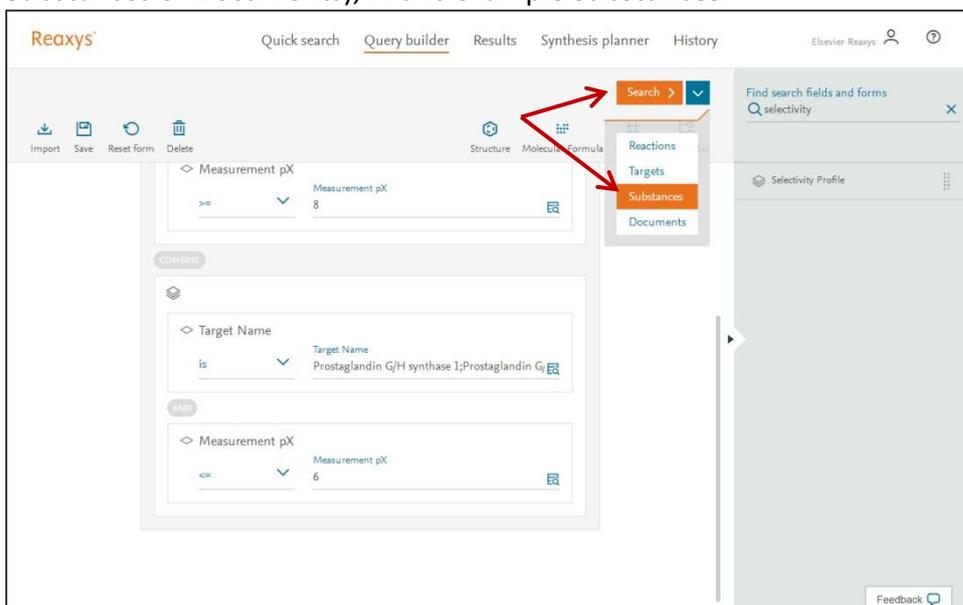
Selectivity Profile

Target Name is cox2 Measurement pX >= 8

AND

Target Name is Prostaglandin G/H synthase 1;Prostaglandin G Measurement pX <= 6

- Click **Search** on the top of the screen and click the desired content (Reactions, Targets, Substances or Documents), in this example **Substances**.



Reaxys Quick search Query builder Results Synthesis planner History Elsevier Reaxys

Import Save Reset form Delete Structure Molecule Formula

Search >

- Reactions
- Targets
- Substances
- Documents

Find search fields and forms Q selectivity

Selectivity Profile

Feedback

The Results Page is displayed. Reaxys Medicinal Chemistry will retrieve substances tested on the above-mentioned targets with a 100 selectivity fold COX-2 versus COX-1.

The screenshot shows the Reaxys interface with the following details:

- Navigation:** Quick search, Query builder, Results (selected), Synthesis planner, History.
- Filters and Analysis (Left Sidebar):** By Structure, Measurement pX, Highest Clinical Phases, Targets, Parameters, Substance Classes, Molecular Weight, Availability, Availability in other databases, Available Data, Document Type.
- Main Content:**
 - 427 Substances out of 587 Documents, containing 1,783 Reactions, 12 Targets.
 - Buttons: Limit To, Exclude, Export.
 - Heatmap button: Heatmap
 - Substance 1: [1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetic acid. C₁₉H₁₄ClNO₄. 357,793 497341 53-86-1. Data: Physical Data - 492, Preparations - 61, Reactions - 852, Spectra - 155, Targets - 703, Documents - 6,657.
 - Substance 2: [2-(2,6-dichloroanilino)phenyl]acetic acid. C₁₄H₁₁Cl₂NO₂. 296,153 2146636 15307-86-5. Data: Physical Data - 159, Preparations - 28, Reactions - 419, Spectra - 67, Targets - 339, Documents - 4,041.

❖ View the Heatmap

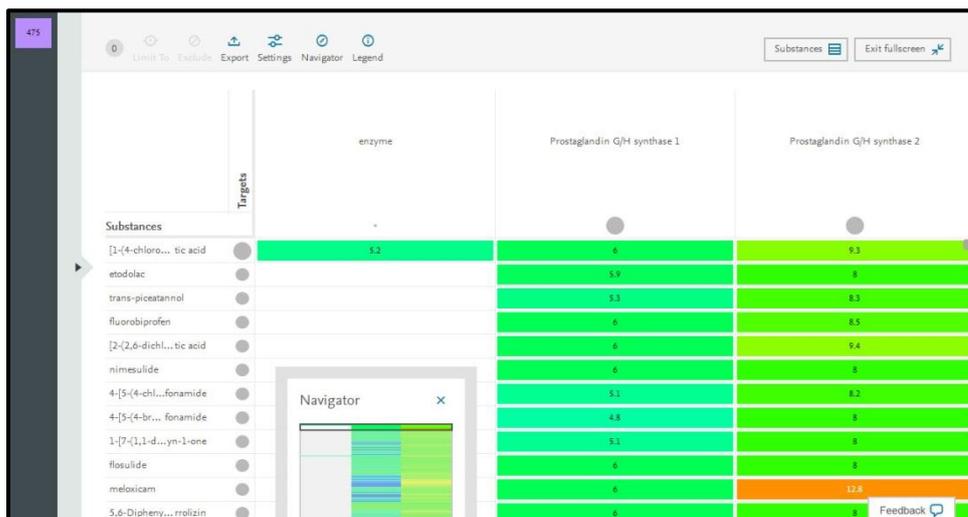
1. Click **Heatmap**.
 - a. Review the Settings and click **Apply**.

The screenshot shows the Reaxys interface with the Heatmap settings dialog box open. The dialog box contains the following settings:

- Value of X-axis: Targets
- Value of Y-axis: Substances
- Value of Cells: Maximum of pX
- Show substances: Names Structure drawing
- Display mode: Normal Full Screen
- Always show settings:
- Buttons: Apply

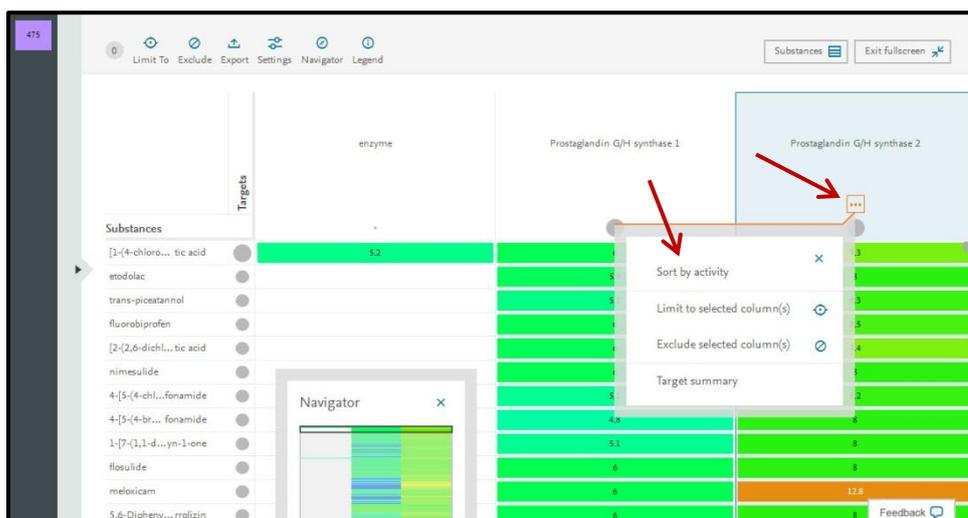
Red arrows in the image point to the Heatmap button in the top right of the main content area and the Apply button in the Heatmap settings dialog box.

The Heatmap is displayed showing selective compounds in a graphical way.

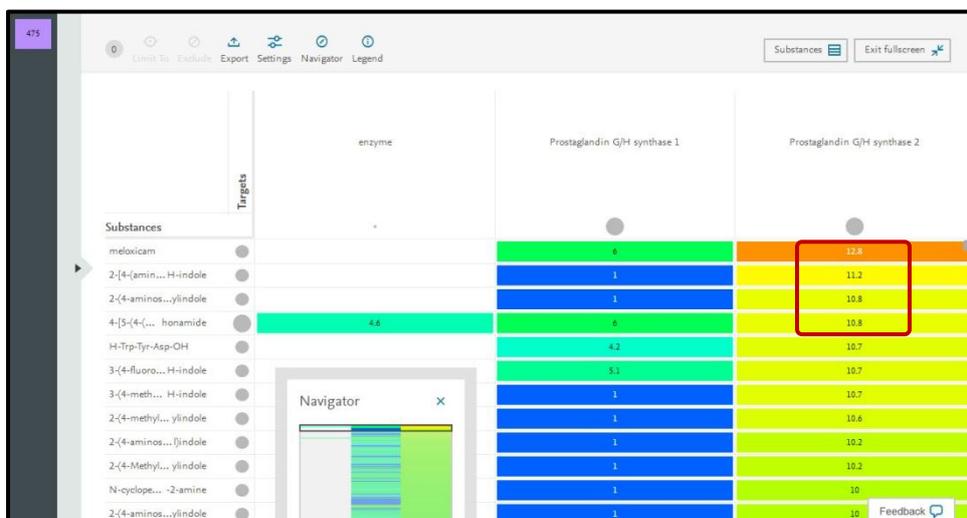


Sort compounds by descending bioactivities on COX-2:

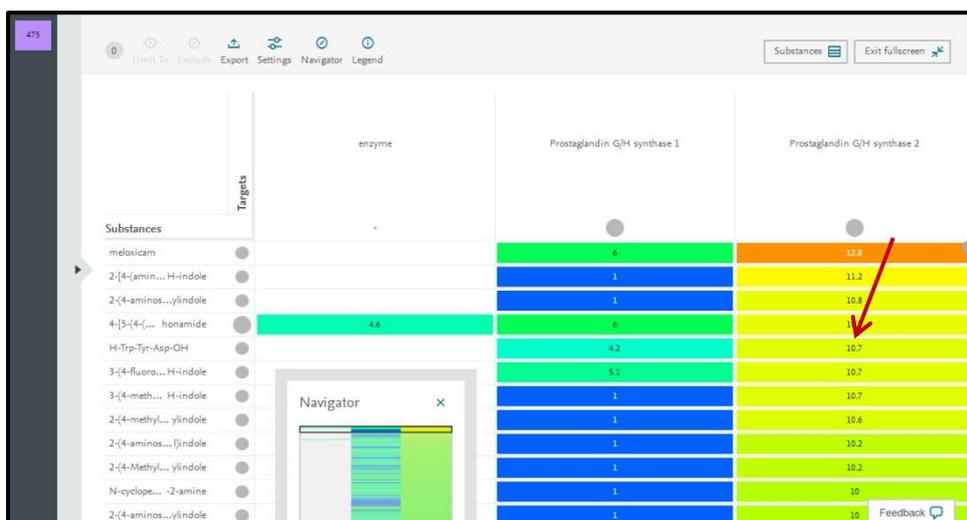
2. Click the **COX-2 three dots** and **Sort by activity**.



This will rank the compounds by decreasing potency on the COX-2 target. The most potent COX-2 inhibitors will be at the top of the Heatmap.



Bioactivities contained in the cell are displayed by clicking directly in the cell.



The corresponding substances and bioactivities are then displayed on the screen

