REAXYS®

Reaxys Training

Reaxys Medicinal Chemistry

March 2015

ELSEVIER

Reaxys application version: 2.19790.2

MarvinSketch version 6.0.6

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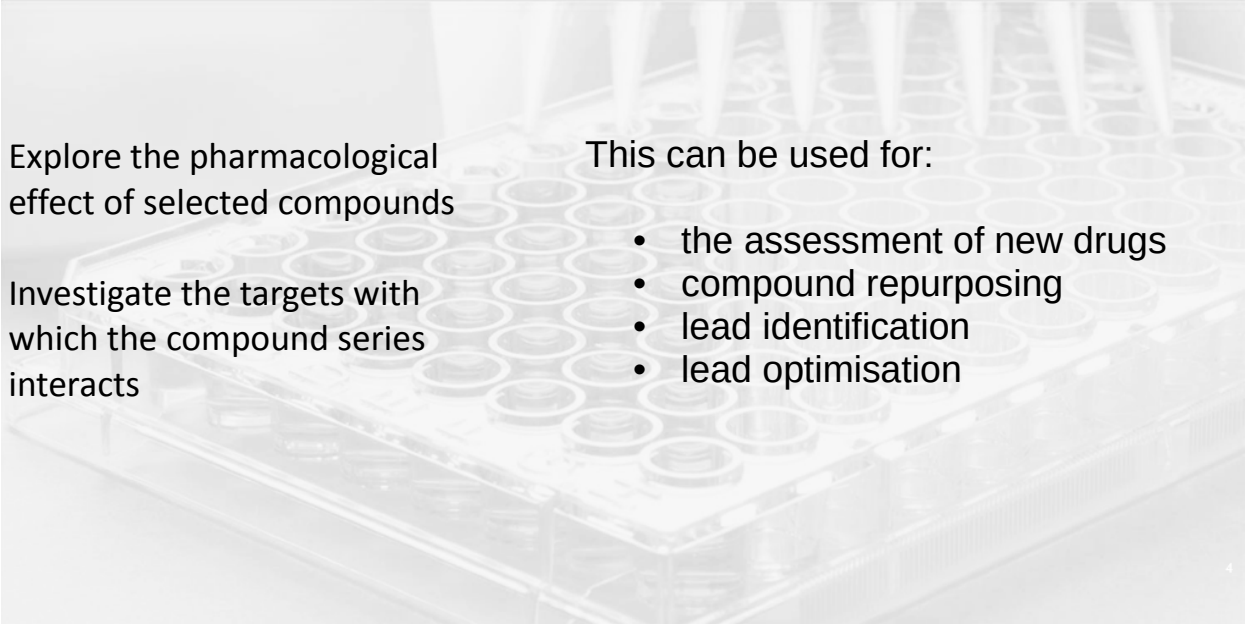
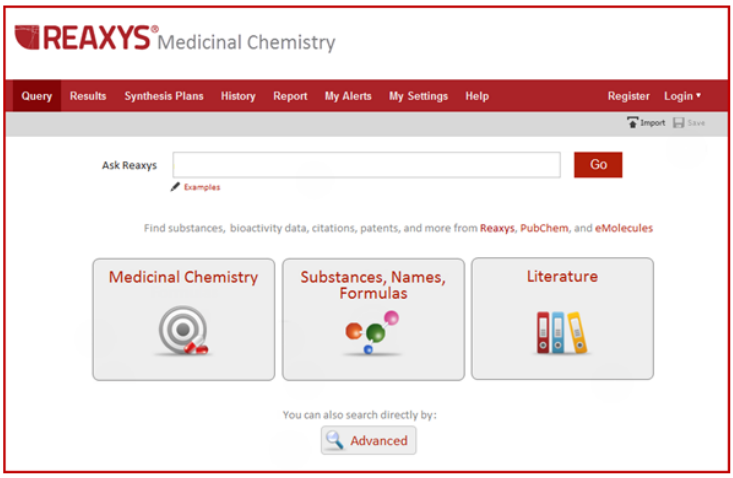
What is Reaxys Medicinal Chemistry?

Reaxys Medicinal Chemistry is a product that enables you to better select the most promising compounds to advance in the Drug Discovery process and abandon the wrong compounds earlier



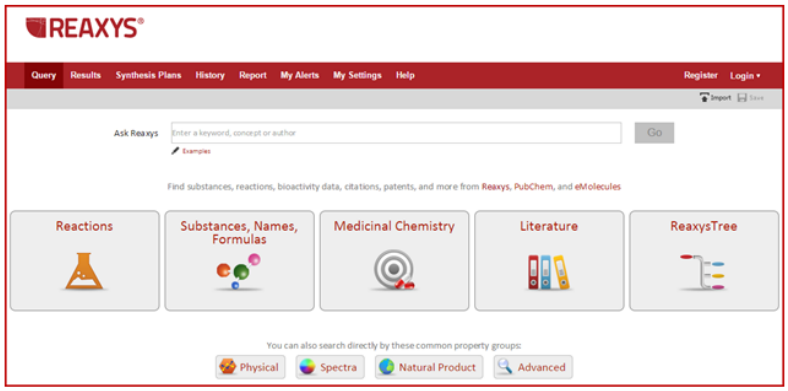
- **Reaxys Medicinal Chemistry** is all about connections between the bioactivity of compounds and their targets and helps you choose the right compound to develop during your preclinical work. We extract and index the following:
- The **chemical structure**, name, code, synonym of a **compound**
- **Target information** so you can explore **Target** affinity patterns of chemical compounds
- **In vitro assays** (binding, second messenger etc..) and **Cell based assays** for example : Aggregation, Angiogenesis, Apoptosis, Cell differentiation, Cellular Cycle,
- **Animal models of disease**, like ovariectomized rat in osteoporosis, treatment of glaucoma, Xenografted animals with tumors to test and develop antineplastic drugs
- **Pharmacokinetic and ADME Properties**, like metabolic stability, Intrinsic clearance, half life of elimination, bioavailability, In vivo clearance
- **Toxicity**, like, Cytotoxicity, cardiotoxicity, chronic toxicity

User Interface



Reaxys Medicinal Chemistry

- Searches over 5 million unique substances
- 25 million biological datapoints
- from over 5,000 journals and over 90,000 Patents

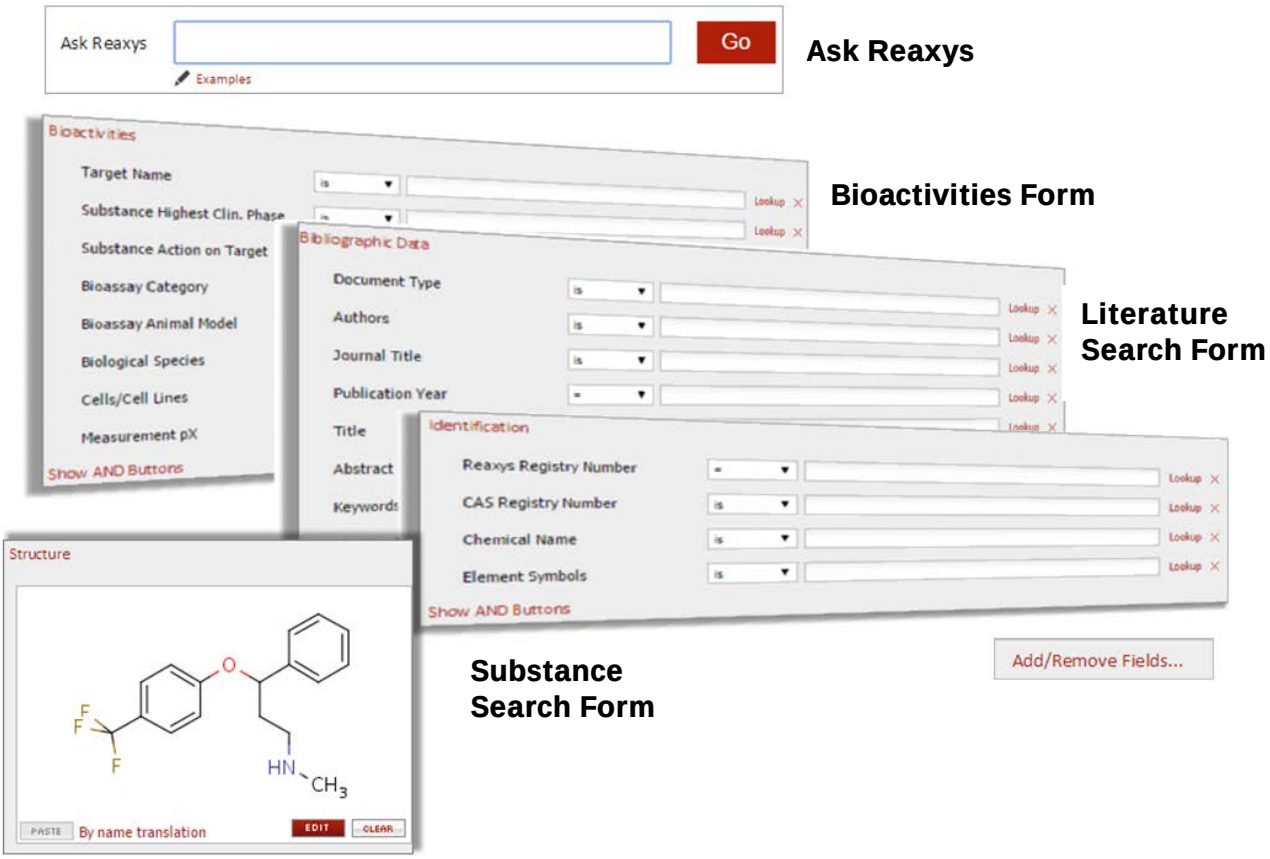


When combined with Reaxys

- Searches over 50 million unique substances
- Physical properties
- Spectra data
- Reaction information
- Plus all of the information in **Reaxys Medicinal Chemistry**

- Reaxys and Reaxys Medicinal Chemistry are 2 separate databases
- Reaxys (without Reaxys Medicinal Chemistry) Searches over 50 million unique substances, physical properties, spectra data, and reaction information
- Reaxys Medicinal Chemistry (without Reaxys) contains over 5 million substances, and 25 million biological data points from over 5,000 journals and over 90,000 Patents
- There is a combined interface for searching both databases at once.

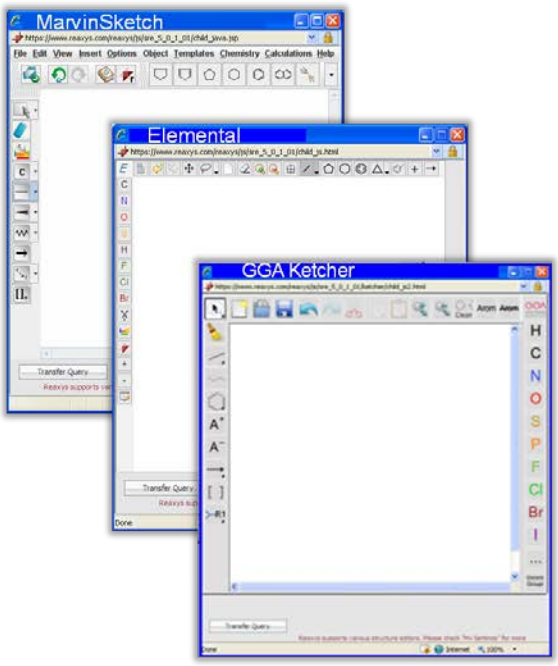
Search Forms



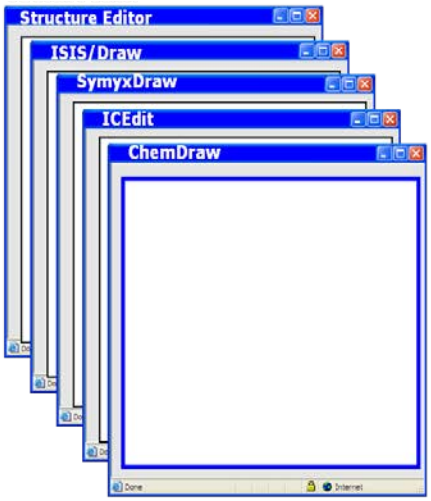
- **Ask Reaxys** allows you to type in terms and then interprets the query and performs either a substance or literature search*.
- Search forms can be customized with hundreds of different search fields by clicking the Add/Remove Fields link.
- Perform a structure search by drawing the structure with one of 7 different Structure Editors, or use the Generate Structure Template from Name link below the substance box to generate a structure.

*Ask Reaxys will also perform a Reaction search if you license both **Reaxys** and **Reaxys Medicinal Chemistry**

Structure Editors

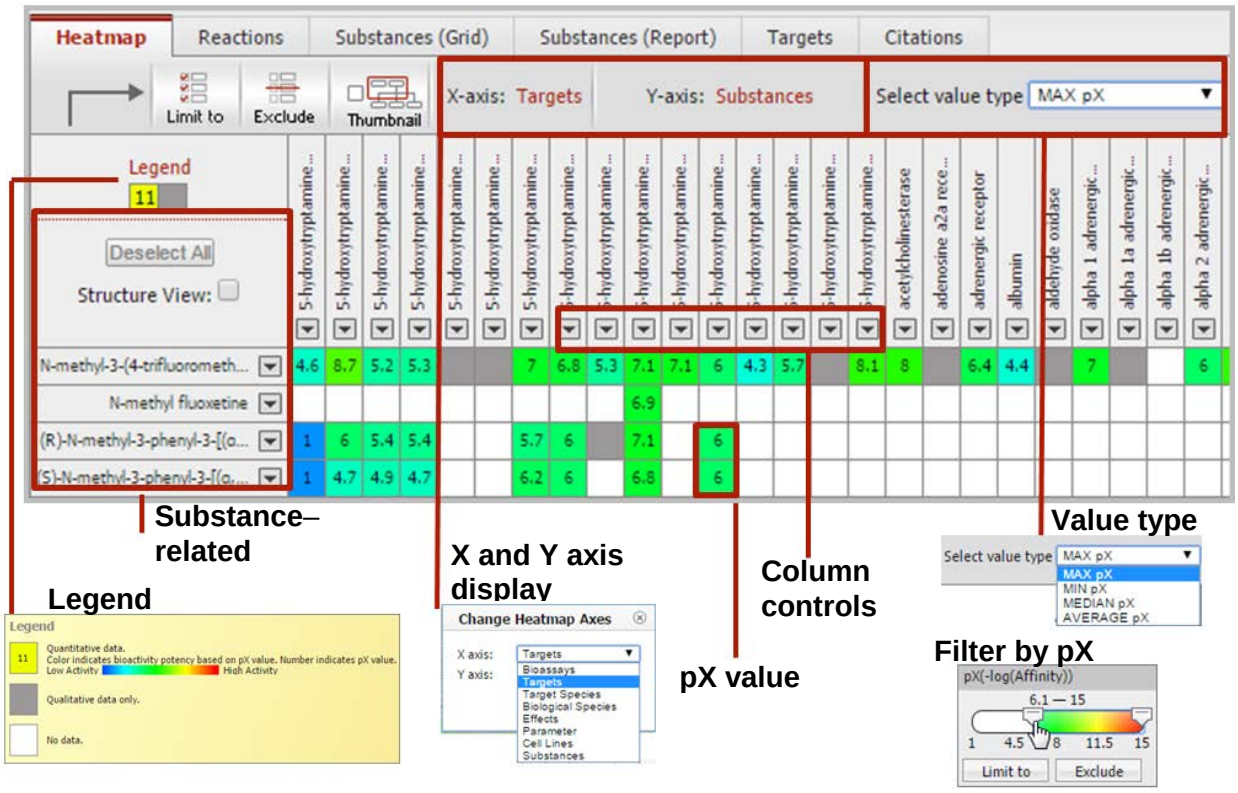


www.reaxys.com/info/support/downloads



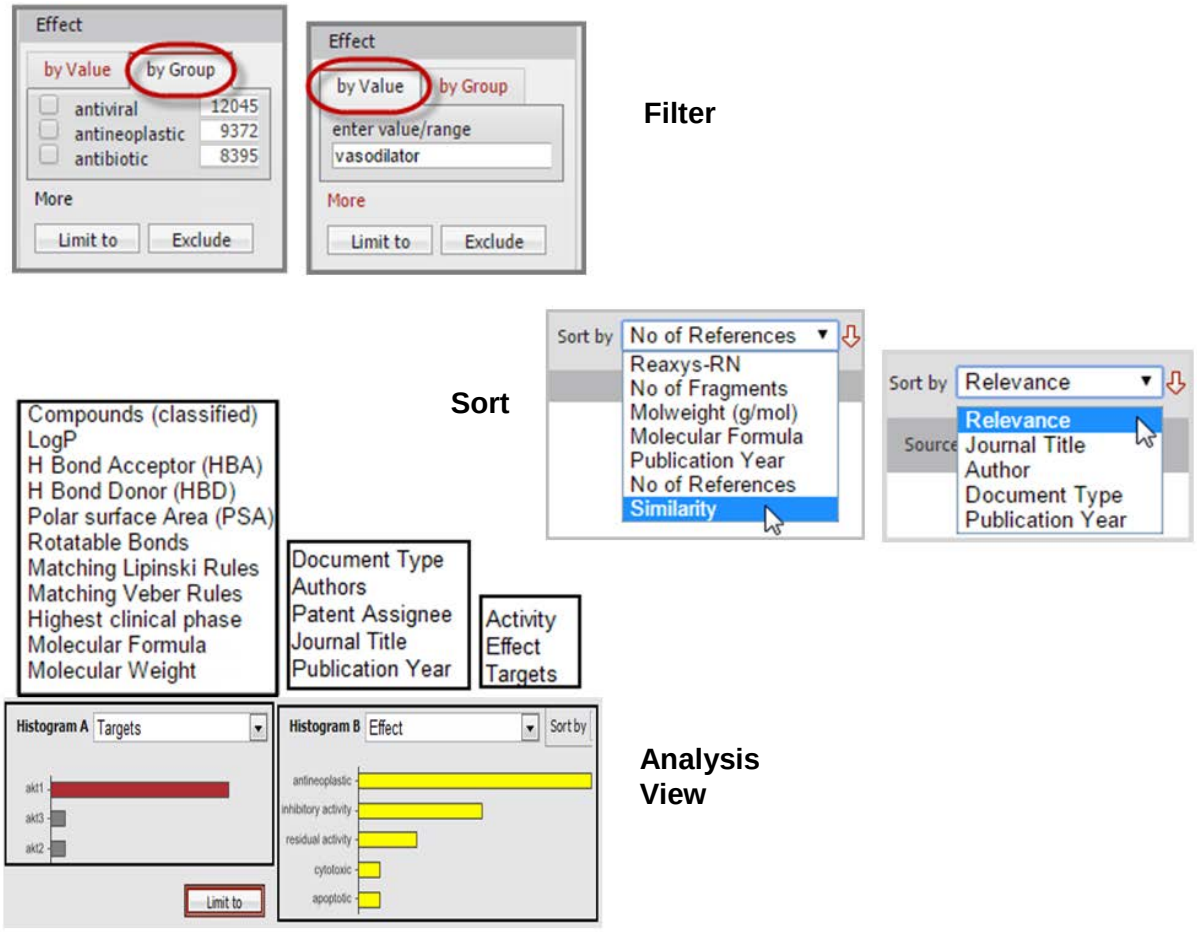
- Structural queries can consist of complete structures or fragments and can contain **atom** and **bond** query features.
- There are 3 structure editors that come with Reaxys and require no installation: MarvinSketch, Elemental, and GGA Ketcher shown on the left.
- Reaxys can also be used with the 5 structure editors shown on the right. Connection software is required and can be downloaded from the Reaxys infosite. www.reaxys.com/info/support_downloads.
- **MarvinSketch** will be used for the examples in this document.
- Consult the **Reaxys Help file** for more drawing tips.

Heatmap



- **Substances** – Click the **Structure View** box to display the structures. Click the dropdown menu for details about the substance and for copy options.
- **X and Y Axis Display -** Substances are displayed on the **Y** axis and Targets are displayed on the **X** axis by default. Select different options in the dropdown menu.
- **Column Controls –** Click the dropdown arrow for deleting and sorting options.
- **Legend –** View color coding legend.
- **Value Type** – Px values are calculated from data points. If multiple data points are available for an assay/target you can select Max, Min, Median, or Average.
- **pX value** - A value calculated from experimental data points. This allows you to compare data from different sources, different assays, or with different parameters. The Px value is hyperlinked to the real data.
- **Filter by pX value** - **Filter by Px value** – Use the filter on the left side of the Results page. Use the slider on the filter to limit results to a particular Px range.

Sort, Filter and Analyze



- **Filter** - **Filter by** categories are displayed on the left side of the results page. Some filters offer a **By Value tab** that allows you to type in a term. Some filters offer a More link that allows you to refine using more details.

- **Sort** – Click to view and select sorting options.

- **Analysis View** – Click the **Analysis View** button on the **Results** page (above the results list). **Analyze** results by any of the categories shown using histograms to see how one category may relate to another.

Step 1 – Select a category for **Histogram A** from the dropdown menu(the bar will be displayed in red and shows the number of relevant hits in your result list).
Step 2 –Select a category for **Histogram B** (the bars will be displayed in yellow and show the numbers of hits per category in your result list that are a subset of the **Histogram A** list**.**
Step 3 - After analyzing various combinations, click **Limit to** (or **Exclude**).

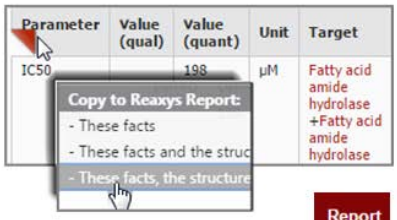
Save, Print, Export, and Report

1. **Save a Query** – Click **Save** in the upper right corner of the **Query page**. This saves the query as an xml file on your computer.

2. **Save a Result list –** Click the **History** button. Click the Store link on the right side of the page. This saves the result list to your Reaxys account. You can open the list again from the **History** page.

3. **Print the current page –** Click the **Print** button located on the button bar towards the left side. This will print the current screen.

4. **Export Results –** Click the **Export** button. Select options for format, range, and content. Available formats are xml, SD file, and Excel. These files will be saved to your computer.



5. **Add Data to a Report** – Mouse over the results. Click the red triangle that appears near individual data points and structures. Choose from the options that appear. You can select different types of data from different searches and add them to the same **Report**.

6. **View a Report** - Click the **Report** button. Arrange items with the Show, Move up, Move Down, Remove links. Add text using the Annotate link.

7. **Send Report through email** – Click the **Send** button on the **Report** page and fill in the form. The report will be sent as a zipped html attachment.

- Saving can be done from the **Query Page**, **Reports page** and **History page**. The results are saved as xml files from the **Query page** and the **Reports page**. In the **History page**, results are saved in Reaxys.
- Your results can be printed and exported in a variety of formats
- Exported documents contain the hyperlinked phrase **View in Reaxys** next to references and Reaxys substance and reaction ID numbers. Clicking the link will automatically open Reaxys and begin a search.
- The **Report** feature lets you instantly select specific results of interest and copy them to the clipboard. These results can be annotated and immediately emailed to colleagues. (Note: colleagues ***do not*** need to have a Reaxys license in order to view the reports).

Pharmacokinetic Content Overview

PK Substances and citations

- **>71000 Substances**
- **>33000 Citations**

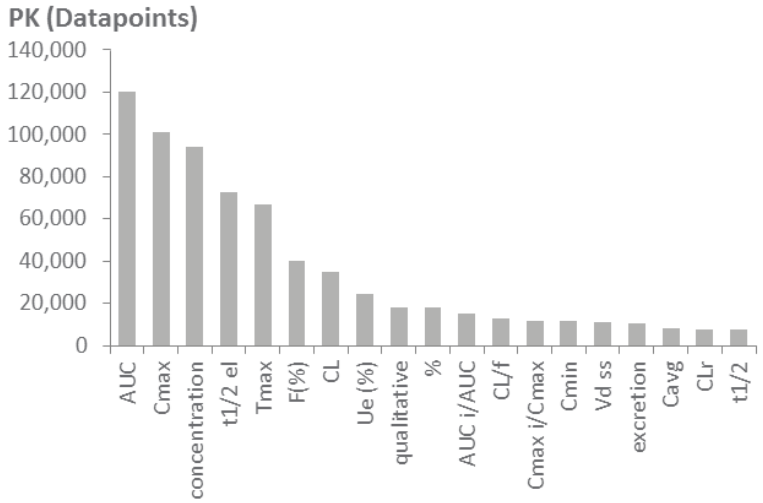
PK Parameters

- **>250 Parameters**
- **>780000 Data points**

Species

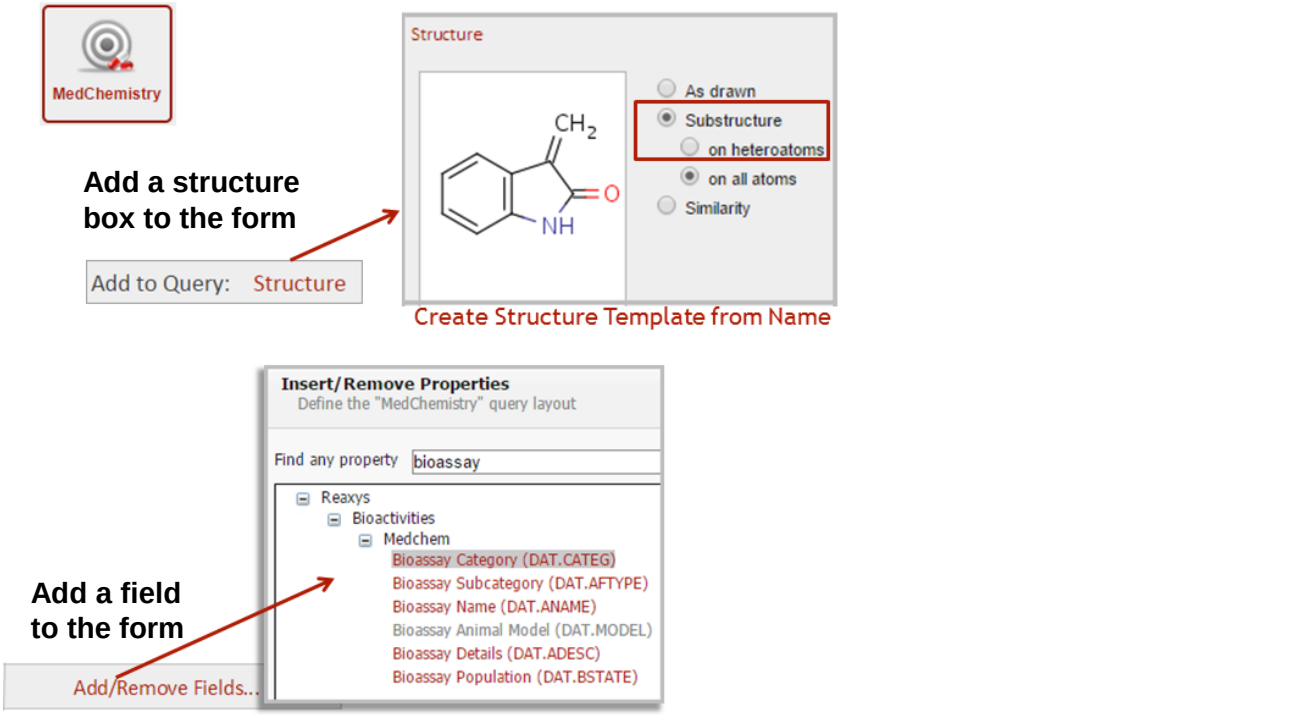
Humann, rat, mouse, Guinea pig, e.coli, rabbit, swine, etc.

«RMC PK content datapoints breakdown by Parameters (top 20)»



- Reaxys Medicinal Chemistry covers over 250 different PK parameters and over 780000 data points
- This covers over 71000 substances and over 33000 citations
- The species covered includes Human, rat, mouse, bovine, guinea pig, etc.
- The relevant search fields are **Measurement Parameter** and **Bioassay Category**.

Search for Pharmacokinetic Data

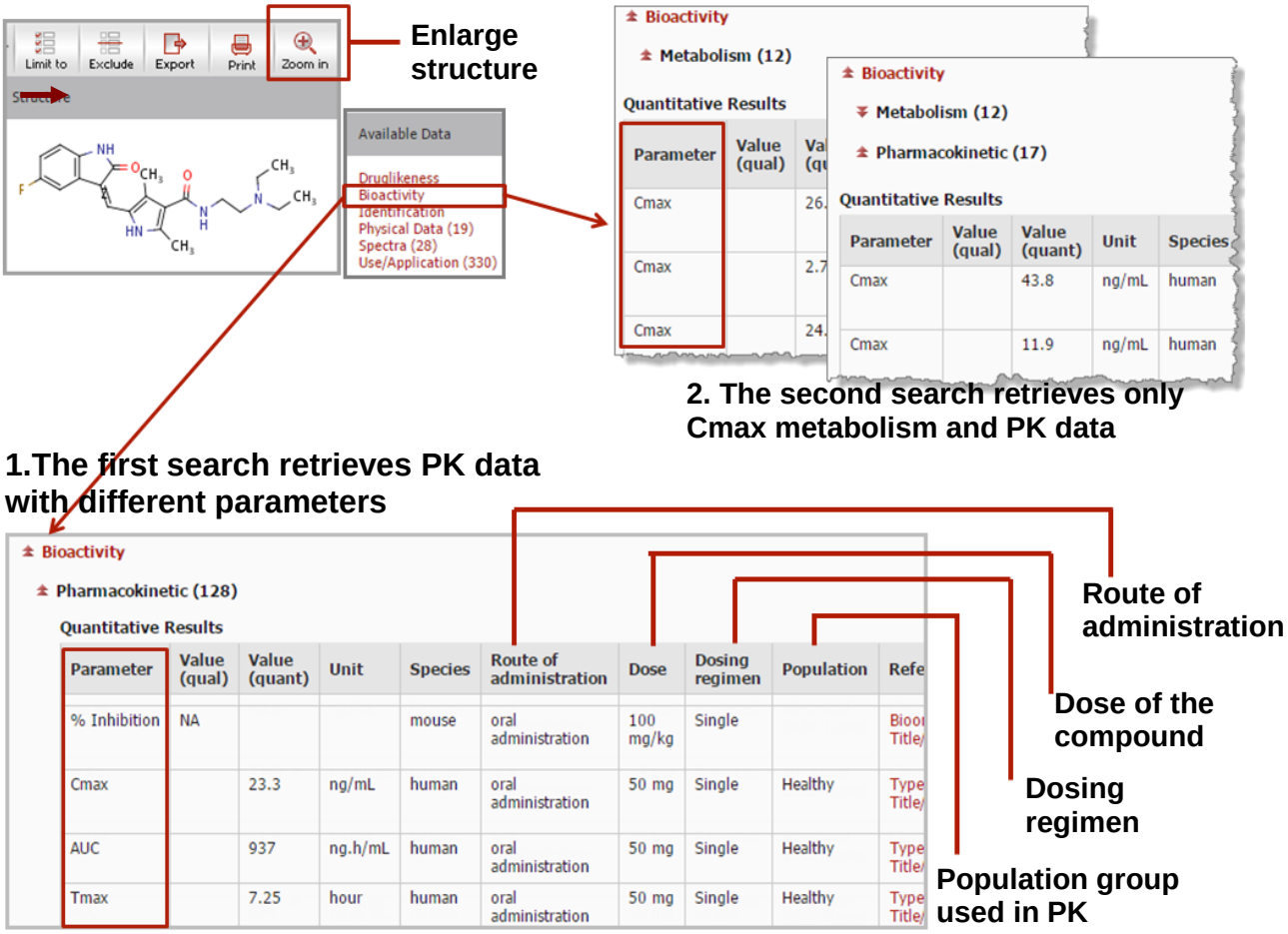


Query #1
Substructure + 'Bioassay Category' field

Query #2
Substructure + 'Measurement Parameter' field

- Perform 2 searches using the same structure and 2 different search fields (**Bioassay Category** field and **Measurement Parameter** field)
- Click the **Medicinal Chemistry** button to open the **Bioactivities** form.
- Add a structure box to the form by clicking the Structure link on the **Add to Query** bar below the form. Draw the structure shown above. *(Alternatively, you can use the Create Structure Template from Name link below the structure box and cut/paste the following name **3-methylideneoxindole**).* Select **Substructure on all** next to the structure box.
- From the **Bioassay Category** field, click the Lookup link and then select **Pharmacokinetic** from the pop-up box. Click **Transfer**. (If you do not see the field on the form, click the Add/Remove fields link below the form, search for the field in the pop-up box, click the fieldname, click the **Add** button, and then click the **Save** button.)
- For the second query, use the same structure, but delete the entry in the **Bioassay Category** field, and then type *cmax* into the **Measurement Parameter** field.

View Pharmacokinetic Results



Here are the results of the 2 queries shown on the previous page

- When you perform a query from the Bioactivities form, the results appear in **Heatmap** view by default. Click the tab for **Substance Report** view to see substances and their properties. You can enlarge the substance display by clicking **Zoom**.
- Click the Bioactivities link to view the data.
- Notice that the results of the first query retrieved only PK data and different parameters.
- The results of the second query were limited to only Cmax data and covered PK and metabolism.

Metabolism Content Overview

substances & citations

>120000 Substances
>29000 Citations

Parameters & data pts

>400 Parameters
609000 Data Points

Targets

>2200 Targets
***Plus* Target Species & Cell Lines**

Parameters	Occurrence
ic50	71086
x0025; inhibition	48082
qualitative	46591
t1/2 el	45043
clint	36569
biodistribution	36556
x0025;	22639
x0025; metabolic stability	20980
papp (transport)	20203
km	19756
t1/2	18667
rate	17939
ki	16986
vmax	15219
fu	14990
activity	14305
cl	13323
concentration	11920
fold-increase	11507
transport ratio	8218
ratio	7837
protein binding (x0025;)	7678

Quantitative information

Qualitative Information

Metabolism (17)

Quantitative Results

Parameter	Value (qual)	Value (quant)	Unit	Target	Species	Tissue/Orga
Vmax		4.7	pmol/min/mg protein	Cytochrome P450 2C	human	liver
Km		19.57	µM	Cytochrome P450 2C	human	liver
Clint		0.2402	µL/min/mg protein	Cytochrome P450 2C	human	liver
t1/2	=	32	hour		human	
Ki		33	µM	Cytochrome P450 2C19	human	liver

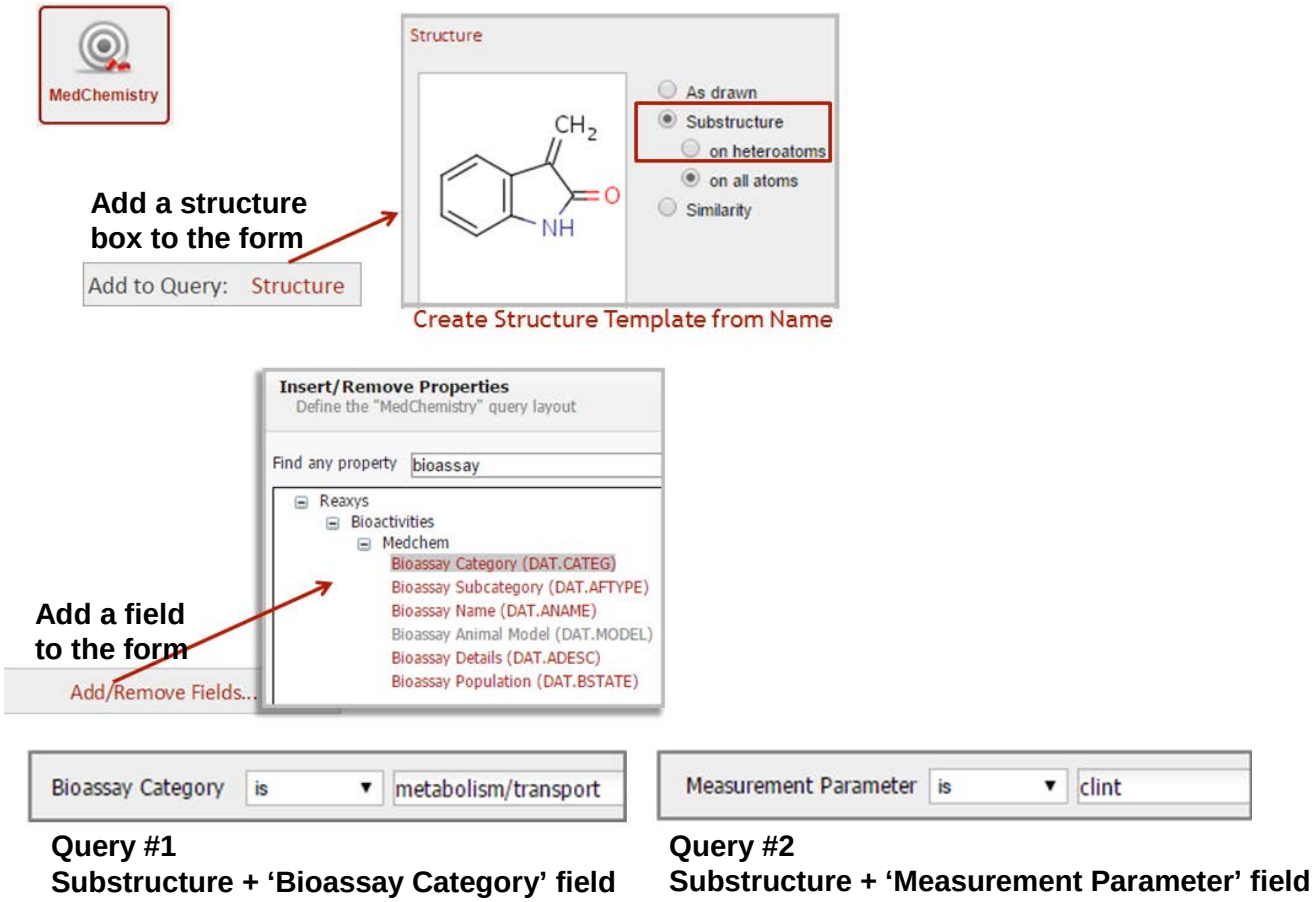
Metabolism (2)

Qualitative Information

1 of 2	Assay Description	Partition Coefficient of the compound was determinec
	Citation	**Quinn; Neiman; Beisler** Journal of Medicinal Chemistry, 1981 , vol. 24, # 5 p Title/Abstract Full Text Show Details
2 of 2	Assay Description	Partition Coefficient of the compound was determinec
	Citation	**S. P. Gupta** Chemical reviews, 1994 , vol. 94, # 6 p. 1507 - 1551 Title/Abstract Full Text Show Details

- Reaxys Medicinal Chemistry covers > 400 different metabolism parameters and over 609000 data points.
- This covers over 120000 substances, over 2200 Targets and over 29000 citations
- The species covered includes Human, rat, mouse, bovine, guinea pig, etc.
- The relevant search fields are **Measurement Parameter** and **Bioassay Category**.

Search for Metabolism Data

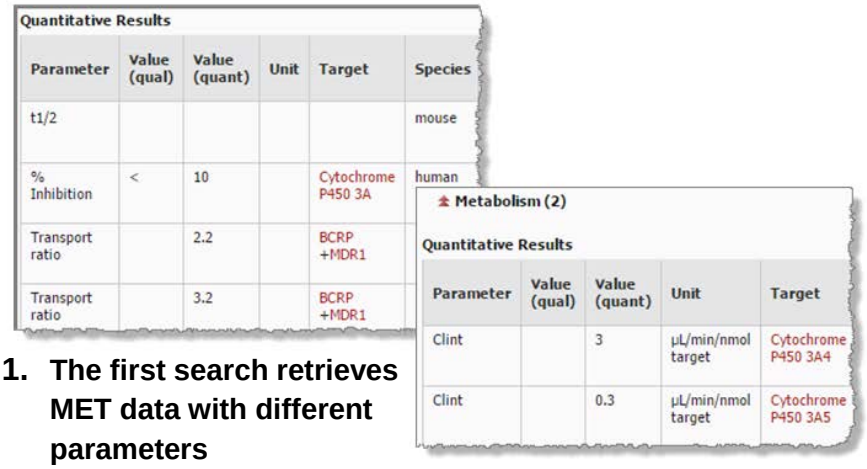


Query #1
Substructure + 'Bioassay Category' field

Query #2
Substructure + 'Measurement Parameter' field

- Perform 2 searches using the same structure and 2 different search fields (**Bioassay Category** field and **Measurement Parameter** field)
- Click the **Medicinal Chemistry** button to open the **Bioactivities** form.
- Add a structure box to the form by clicking the Structure link on the **Add to Query** bar below the form. Draw the structure shown above. *(Alternatively, you can use the Create Structure Template from Name link below the structure box and cut/paste the following name **3-methylideneoxindole**).* Select **Substructure on all** next to the structure box.
- From the **Bioassay Category** field, click the Lookup link and then select **Metabolism/transport** from the pop-up box. Click **Transfer**. (If you do not see the field on the form, click the Add/Remove fields link below the form, search for the field in the pop-up box, click the fieldname, click the **Add** button, and then click the **Save** button.)
- For the second query, use the same structure, but delete the entry in the **Bioassay Category** field, and then type *clint* into the **Measurement Parameter** field.

View Metabolism Results-(Filter)



History – Display the results of the previous search

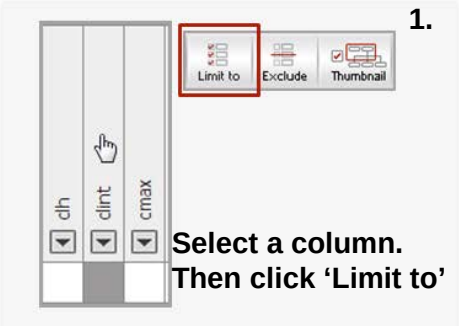
History

1. The first search retrieves MET data with different parameters

2. The second search retrieves only Clint metabolism data

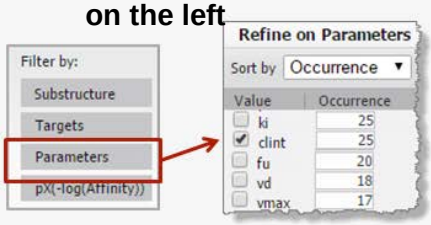
Two ways to filter by parameter

1.



Select a column. Then click 'Limit to'

2. **Use the filters on the left**



- Perform 2 searches using the same structure and 2 different search fields (**Bioassay Category** field and **Measurement Parameter** field) as shown on the previous page. Notice that the first set of results contains Clint data along with other parameters.
- **Filter results by parameter** - Click the **History** button and look for the results of the first query (**Bioassay** field).Click the View link that is aligned with the number of bioactivites (link is located on the right side of the **History** page). This will open with the **Heatmap** view.
- One way to filter is by selecting a column in the Heat map and limiting results to that column.
- From the **Bioassay Category** field, click the Lookup link and then select **Pharmacokinetic** from the pop-up box. Click **Transfer**. (If you do not see the field on the form, click the Add/Remove fields link below the form, search for the field in the pop-up box, click the fieldname, click the **Add** button, and then click the **Save** button.)

In vitro Efficacy Content Overview

Parameter
Value
Unit
Target
Species
Tissue/Organ
Cell
Bioassay
Dose
Effect

Parameter	Occurrence
qualitative	7939042
ic50	5365001
ki	1708230
x0025; inhibition	1348484
mic	950463
ec50	889608
activity	676825
x0025;	380136
pic50	293031
pki	292802
emax(x0025;)	136659
kd	132840
gi50	123937
ed50	117518
zi	104878
ratio	95888
concentration	85518
mic90	75327
pec50	71162

Qualitative Information

In vitro: Efficacy (8)

Qualitative Information

1 of 65	Assay Description	Effect : |agonist Target : Sprague-Dawley rat primary cerebellar gran Bioassay : buffer control well-plated cells incubated evaluated by measuring cAMP formation in supernata
	Results	title comp. slightly decreased cAMP formation (figure
	Citation	Fici; Wu; VonVoigtlander; Sethy, Vimala H. Life Sciences, 1997 , vol. 60, # 18 p. 1597 - 1603 Title/Abstract Full Text View citing articles Sh

Quantitative information

In vitro: Efficacy (8)

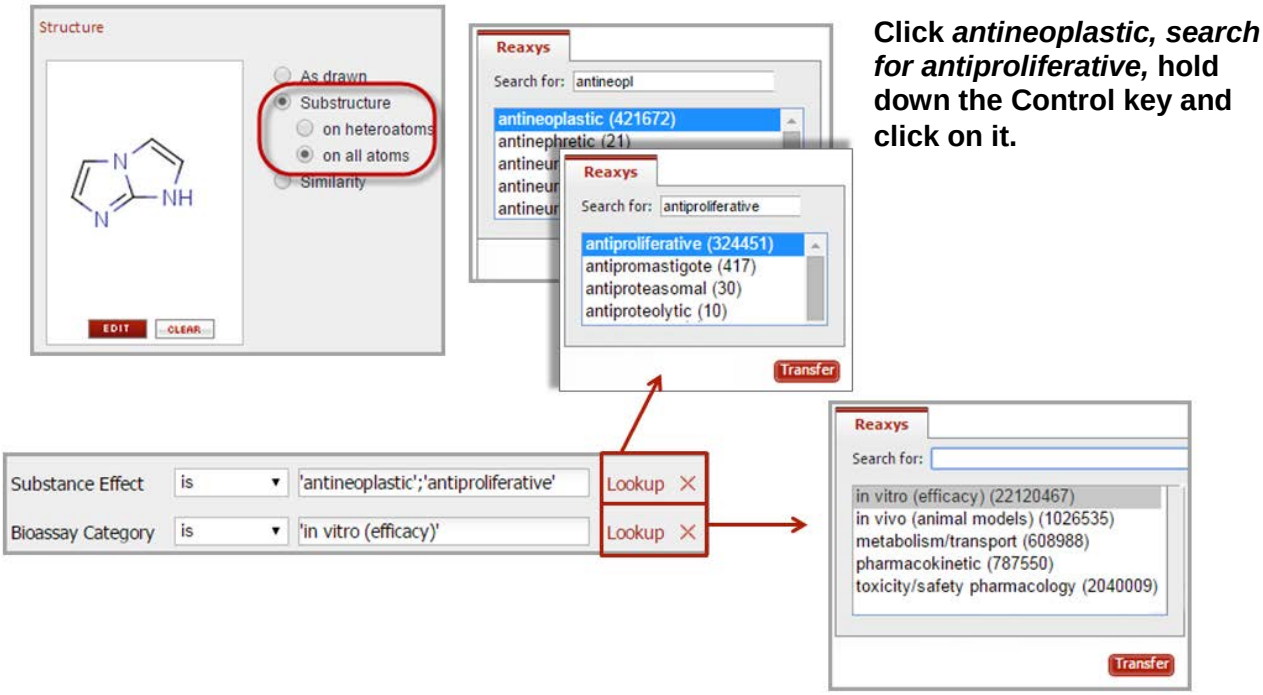
Quantitative Results

Parameter	Value (qual)	Value (quant)	Unit	Target	Target subunit	Species
EC50		510	nM	Androgen receptor		Saccharomyces cerevisiae
% Inhibition		31		Constitutive androstane receptor		
pIC50		4.65		Constitutive androstane receptor		
IC50	=	139.67	µM	Tyrosinase		mushroom

- The in vitro efficacy information comes from over 318000 citations and covers over 5 million substances and over 41000 targets. There are over 22 million data points.
- Results include parameters, unit, value, target, species, tissue/organ, cell, bioassay, dose, and effect.

Search for In Vitro Efficacy

Search for antiproliferative and antineoplastic in vitro efficacy information on this scaffold



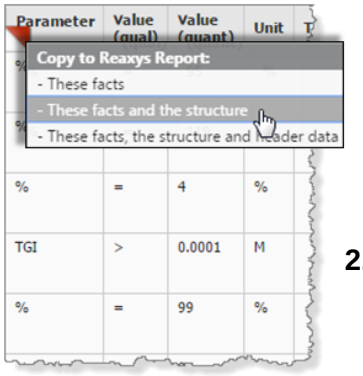
Click *antineoplastic, search for antiproliferative,* hold down the Control key and click on it.

- Search in vitro efficacy information on the scaffold shown above.
- Draw the structure and set it to **Substructure on all atoms**.
- Use the **Measurement Parameter** field and the **Effects** field.

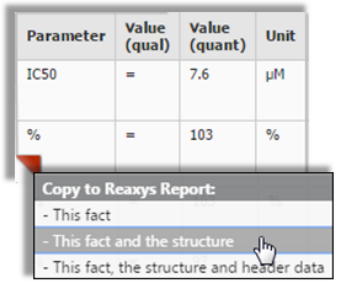
View In Vitro Efficacy Results- (Report)

1. Check the Substances (Report) tab

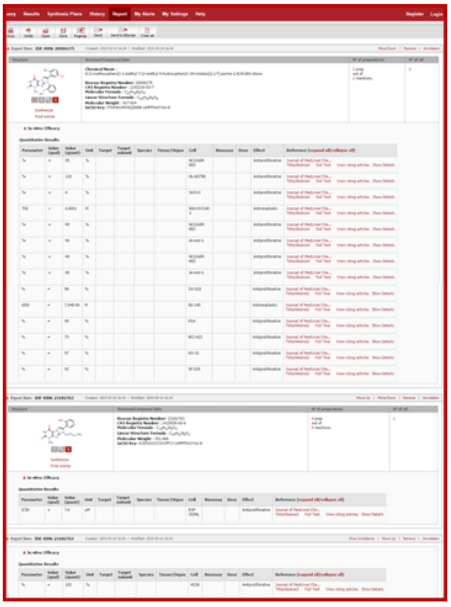
3. Click the 'Report' button



2. Select data points

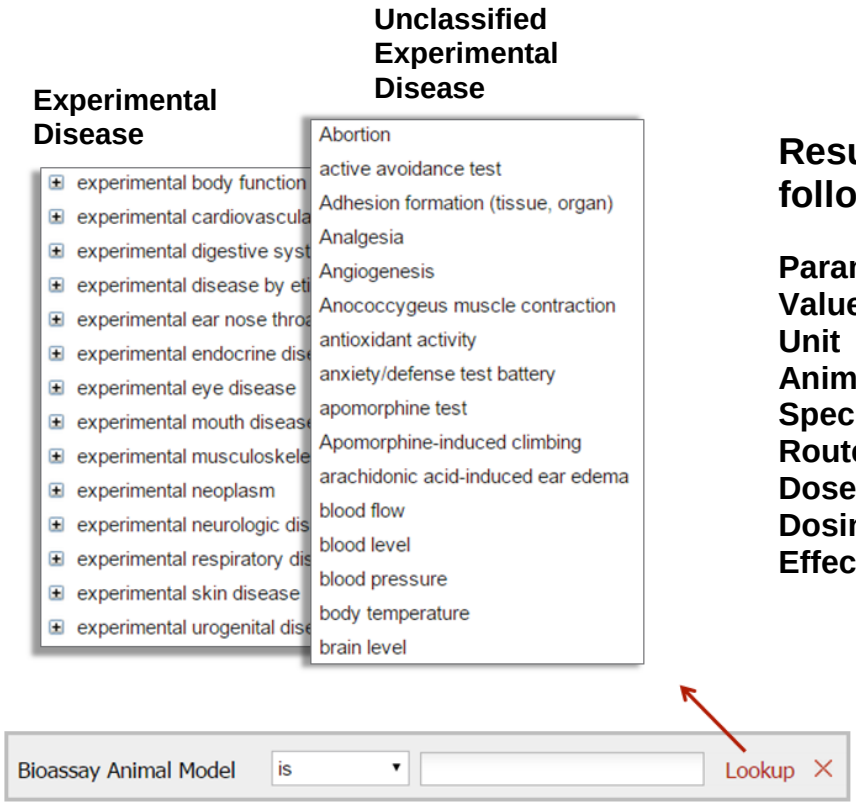


4. Edit the report and then click the 'Send' button to email the report as a zipped html file



- Click the **Substances (Report)** tab. There are only 8 hits, so you can easily create a report for these substances.
- Click the Bioactivities link for the first substance. Move the cursor to the column header near **Parameters** for the first set of in vitro Efficacy data. Click when you see the red triangle, and then select an option. This will select the whole set of data.
- Click the Bioactivities link for the 4th structure. Select only 2 rows of data this time. Move the cursor to the white box on the left side of the row. Click when you see the red triangle and select an option. Repeat with another row.
- Click the 'Report' button. Edit the report by moving, deleting, or annotating selections. Click the 'Send' button to send the report as a zipped up html file. The recipient of the file is not required to have a Reaxys license.

In Vivo Animal Model Content Overview

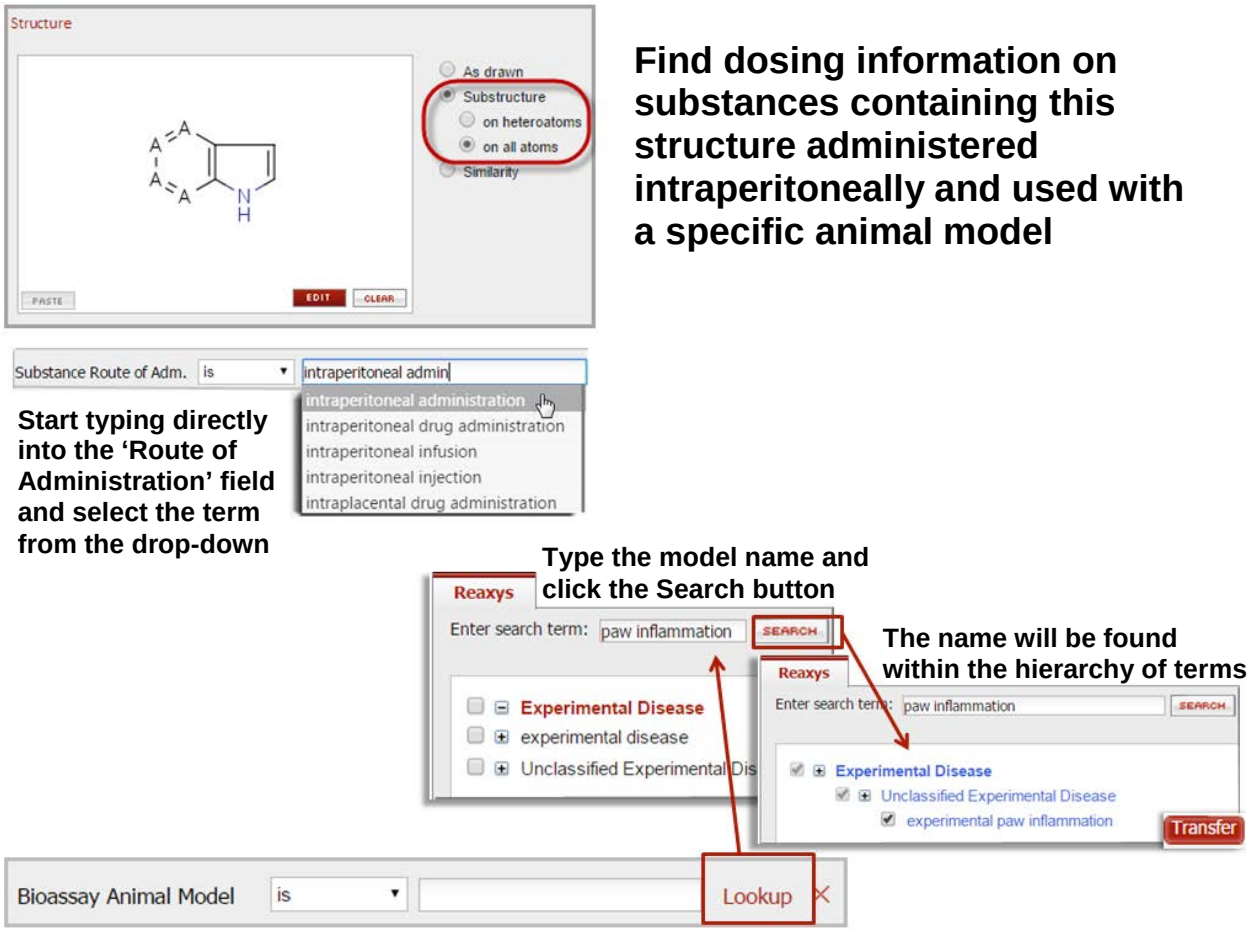


Results display the following categories:

Parameter
Value
Unit
Animal Model
Species
Route of Administration
Dose
Dosing Regimen
Effect

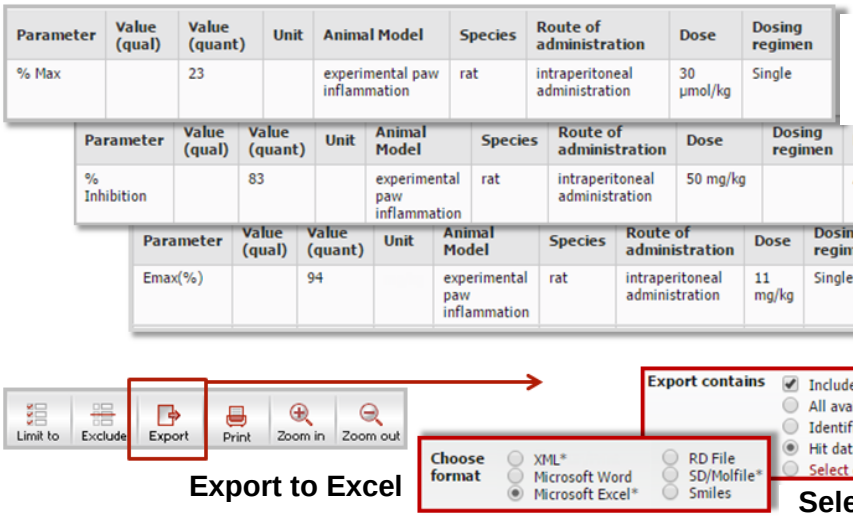
- There are about 400 different animal models in Reaxys Medicinal Chemistry.
- The in vivo information comes from over 80000 citations and covers over 330000 substances and almost 2000 targets. There are over 1 million data points.
- Results include parameters, animal models, species, route of administration, dosing, and effect.

Search for In Vivo Data



- There are several fields that can be useful when looking for in vivo data, for example: *Bioassay Category, Bioassay Animal Model, Route of Administration, Dosing Regimen, Biological Species.*
- Draw the structure above and set it to **Substructure on all atoms**.
- Use the **Route of Administration** field. Start typing *intraperitoneal* and then select *intraperitoneal administration* from the drop-down menu.
- Use the **Bioassay Animal Model** field. Click Lookup. Type *paw inflammation* and then click the **Search** button. Click **Transfer**. Click Search **Bioactivities**.

View In Vivo Results – (Export to Excel)



Parameter	Value (qual)	Value (quant)	Unit	Animal Model	Species	Route of administration	Dose	Dosing regimen
% Max		23		experimental paw inflammation	rat	intraperitoneal administration	30 µmol/kg	Single

Parameter	Value (qual)	Value (quant)	Unit	Animal Model	Species	Route of administration	Dose	Dosing regimen	Effect
% Inhibition		83		experimental paw inflammation	rat	intraperitoneal administration	50 mg/kg		Antiinflammatory

Parameter	Value (qual)	Value (quant)	Unit	Animal Model	Species	Route of administration	Dose	Dosing regimen
Emax(%)		94		experimental paw inflammation	rat	intraperitoneal administration	11 mg/kg	Single

Structures are displayed as smiles strings so that the data can be used in multiple applications

	A	B	C	D	E	F	G
1	Structure	Bioassay Name	Biological Species	Substance Dose	Substance Route of Adm.	Substance Dosing Regimen	Measurement Parameter
2	[H][C@@]12CC[C@H](O)[C@H](C(=O)OC)[C@@]1([H])C[C@]1([H]	In vivo Measurement	mouse	0.380000 mumol/kg	intraperitoneal administration	Single	% Inhibition
3	CN1CCN(CC1)C(=O)C1=CC2=CC(Cl)=CC=C2N1	Hot plate	rat	30 mumol/kg	intraperitoneal administration	Single	% Max
4	CN1CCN(CC1)C(=O)C1=CC2=CC(Cl)=CC=C2N1	Hot plate	rat	100 mumol/kg	intraperitoneal administration	Single	% Max
5	CN1CCN(CC1)C(=O)C1=CC2=CC(Cl)=CC=C2N1	Hot plate	rat	300 mumol/kg	intraperitoneal administration	Single	% Max

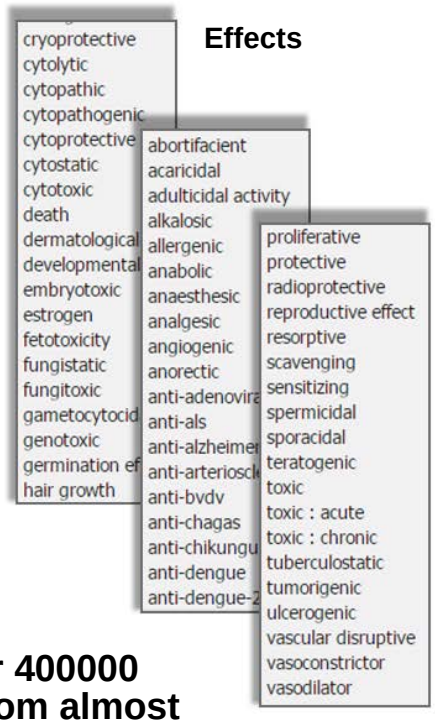
- Some of the Animal Model results are shown above.
- Export these in vivo results to Excel by clicking the **Export** button.
- Notice that the export box shows that 3 file types can be used with bioactivity data (they are marked with *). The file types are Excel, SD/MOLfile, and xml file.
- Select **Hit Data Only**. Your query included in vivo-related fields. Therefore the results display this as "Hit Data".
- Even though the form shows that "Include Structures" is checked, the export will not display the structure images. Instead they are shown as smiles strings. This makes it easier to use the exported data with several different types of applications.
- Export limits are set to 5000 for XML, SD, RD and SMILES formats, and 1000 for other file types. The Fact export limit is at 10000 occurrences.

Toxicity/Safety Pharmacology Content

ic50	573544
mic	431056
qualitative	198222
x0025; inhibition	138773
gi50	85871
ld50	70083
zi	67756
ec50	43652
cc50	32443
lc50	29467
x0025;	29036
mic90	28821
pic50	26224
mic50	25797
mortality rate	19663
tgi	18218
activity	15742
pgi50	13128
gp (x0025;)	11822

Parameters

Parameter
Value
Value
Unit
Target
Target subunit
Species
Tissue/Organ
Cell
Bioassay Dose
Effect

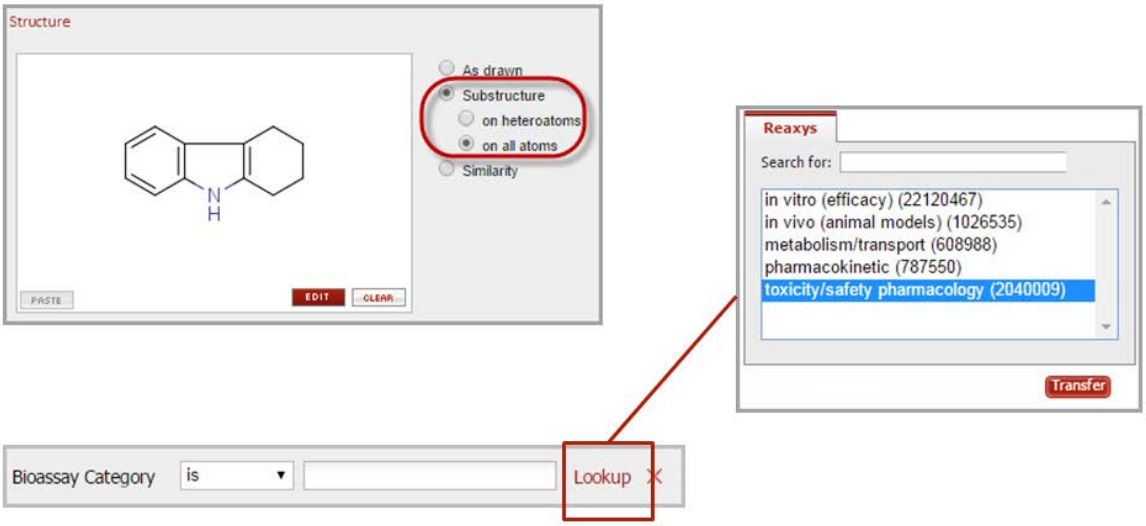


Effects

Over 2 million bioactivities from over 400000 substances with over 3000 targets from almost 70000 citations

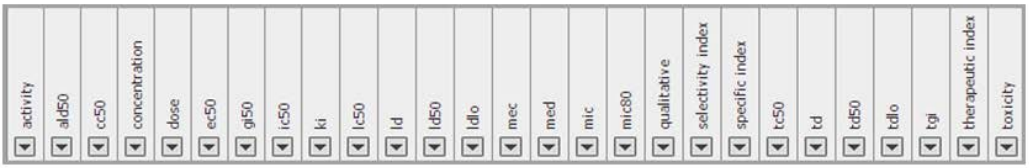
Search for Toxicity/Safety Pharmacology Data

Search for tox/safety pharmacology information on this scaffold

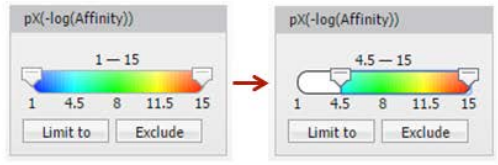


- Search in vitro efficacy information on the scaffold shown above.
- Draw the structure and set it to **Substructure on all atoms**.
- Use the **Measurement Parameter** field and the **Effects** field.

View Toxicity/Safety Pharmacology Results – (Heatmap)

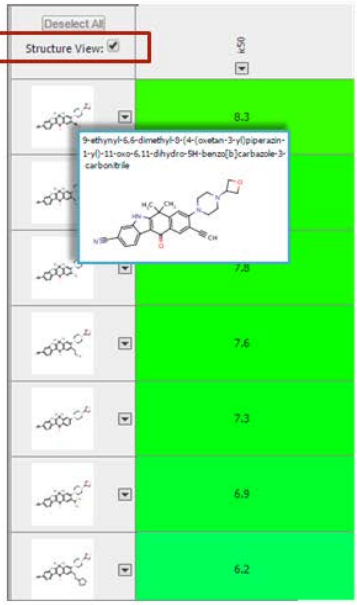


Examples of parameters

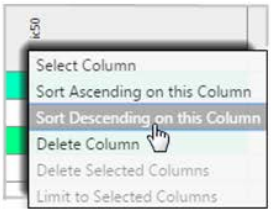


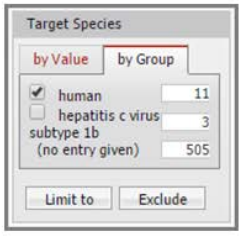
Filter to eliminate the least active compounds

Click to view the active structures



Sort the ic50 column to view the most active compounds at the top

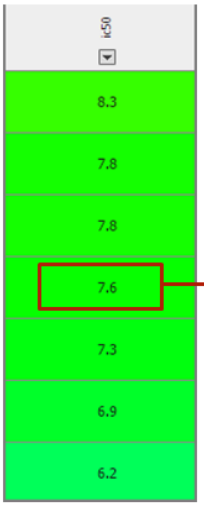




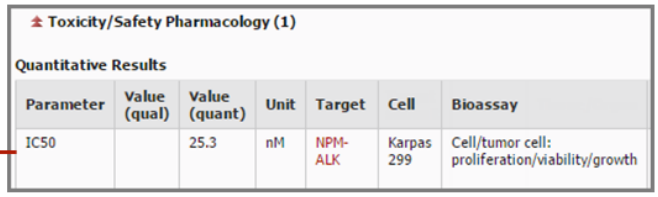
Filter to limit the list to human-related results

- View the Heat map. Set the x-axis to Parameters. Notice the variety of safety-related parameters that are displayed.
- Filter the list by pX value. (The pX value is calculated from experimental data points. This allows you to compare data from different sources, different assays, or with different parameters. The Px value is hyperlinked to the real data). Use the filter on the left and slide the filter to about 4.5 to eliminate the least active compounds.
- Filter by **Biological Species** to view only **human** data using the filters on the left.
- Sort the ic50 column in descending order by clicking the arrow for the drop-down menu.
- View the active compounds by clicking the box next to **Structure View**. Enlarge a structure by single-clicking on the structure.
- Select the 7 active compounds by clicking in the grey area around a structure. This will highlight the row. Then click the **Limit to** button towards the top of the screen.

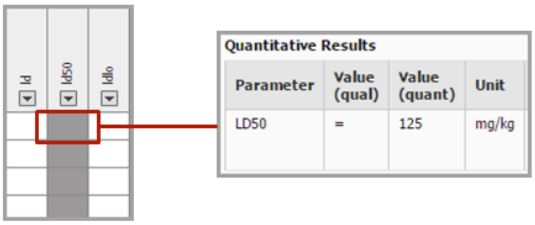
View Toxicity/Safety Pharmacology Results – (Heatmap)



Click a pX value in the Heatmap to view the data



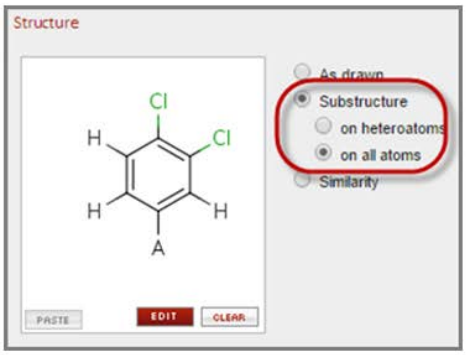
Return to the original heat map (before any filtering was done)



Select a parameter (for example: LD50, LC50, TD) and sort the column in descending order. Click to view a data point. Grey cells will also take you to data.

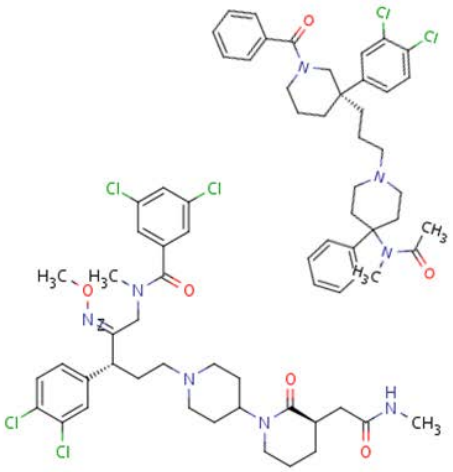
- Each pX value represents a data point. Click the px value to open the substance record and view the actual data.
- The Breadcrumbs will take you back to lists you have been creating. Click the first breadcrumb to return to the original result list (before any filtering was done).
- Select a parameter in the Heatmap (for example LD50, LC50, TD) and sort the list in descending order. (You could also filter to see only the parameters you want). Click a cell to view the data. Grey cells will also take you to data. In some cases, grey cells indicate that there is only *qualitative* data, not *quantitative* data.

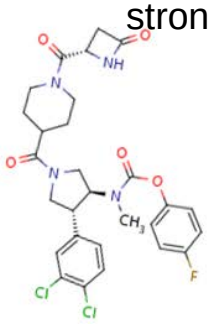
Exploration of a Lead Series of Compounds



Within NK_3 the 3,4-dichlorophenyl group appears to be important as structural feature

- Are there more target classes in which the dichlorophenyl- play an important role?
- Does the 3,4-dichlorophenyl cause a certain activity profile?
  - Are there other di-substitution patterns, other than 3,4- with a strong pharmacological response?
    - Are other 3,4-diX Phe structures known and what is their pharmacological profile?



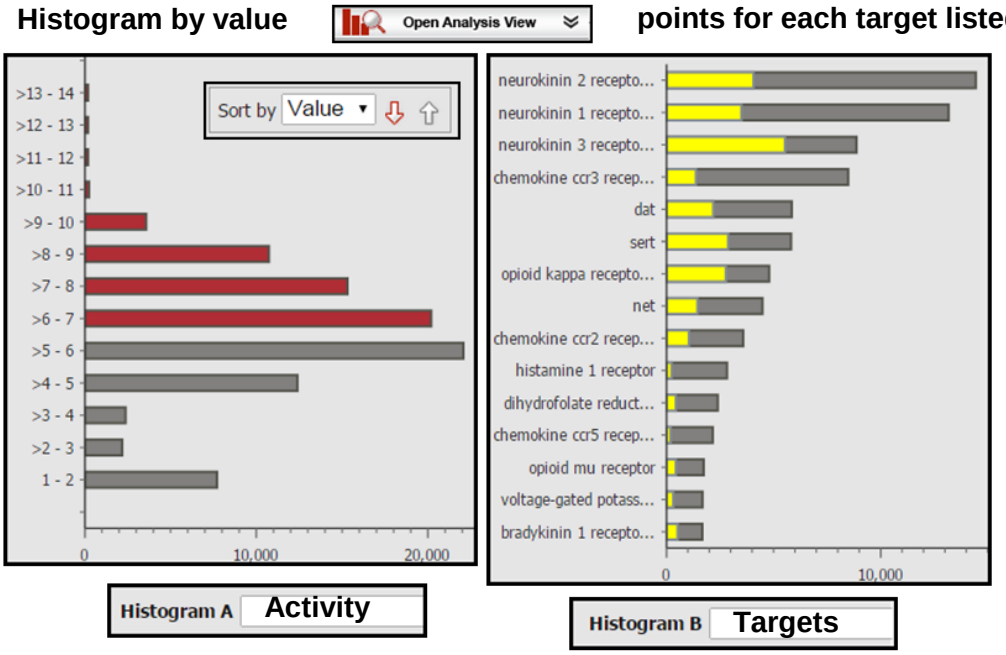


- There is a lot of information available regarding Tachykinin receptor 3 (NK3) (Neurokinin receptor 3) and substances that have the 2,3-dichlorophenyl group.
- Use Reaxys Medicinal Chemistry to find other targets associated with these compounds to determine their pharmacological profiles.
- Then determine if there is any information to support that making changes to the structure (different substitution patterns or different halogens) might impact the pharmacological response.
- Begin the workflow by performing a substructure search on the structure shown above.

Target-Activity Profile for Substances Containing the 3,4-dichlorophenyl Fragment

Sort the 'Actvities' Histogram by value

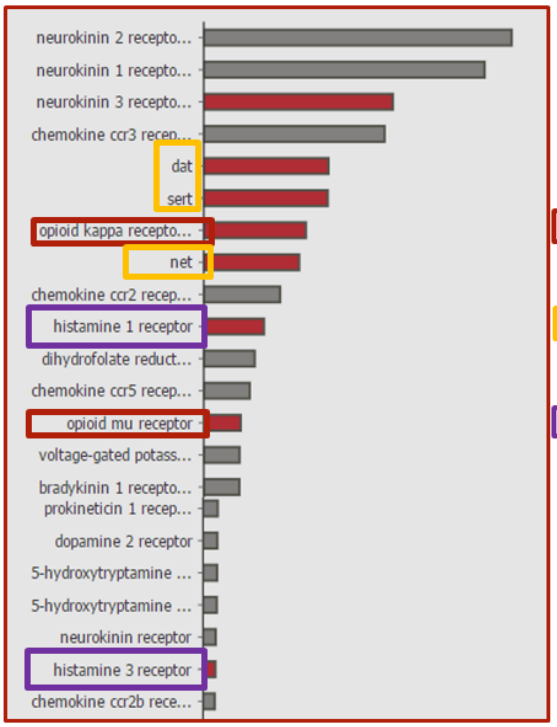
The grey bars indicate the number of bioactivity data points for each target listed



The yellow bars indicate the number of bioactivity data points with a pX value between 6-14 for each target listed

- Open the **Analysis View**.
- Set **Histogram A** to **Activity** and then **Sort** it **By Value**.
- Set **Histogram B** to **Targets**.
- In the image above, the higher activity values are selected (in red). You can see that they mostly correspond to the neurokinin receptors.
- However, there is also target data for the other roughly 30% of this list of compounds.

Are there more Target Classes where the 3,4-dichlorophenyl fragment plays an important role?



The 3,4-dichlorophenyl group is also involved in off-targets….mainly CNS-related

Off targets/CNS Adverse Effect: Addiction/psycho stimulent

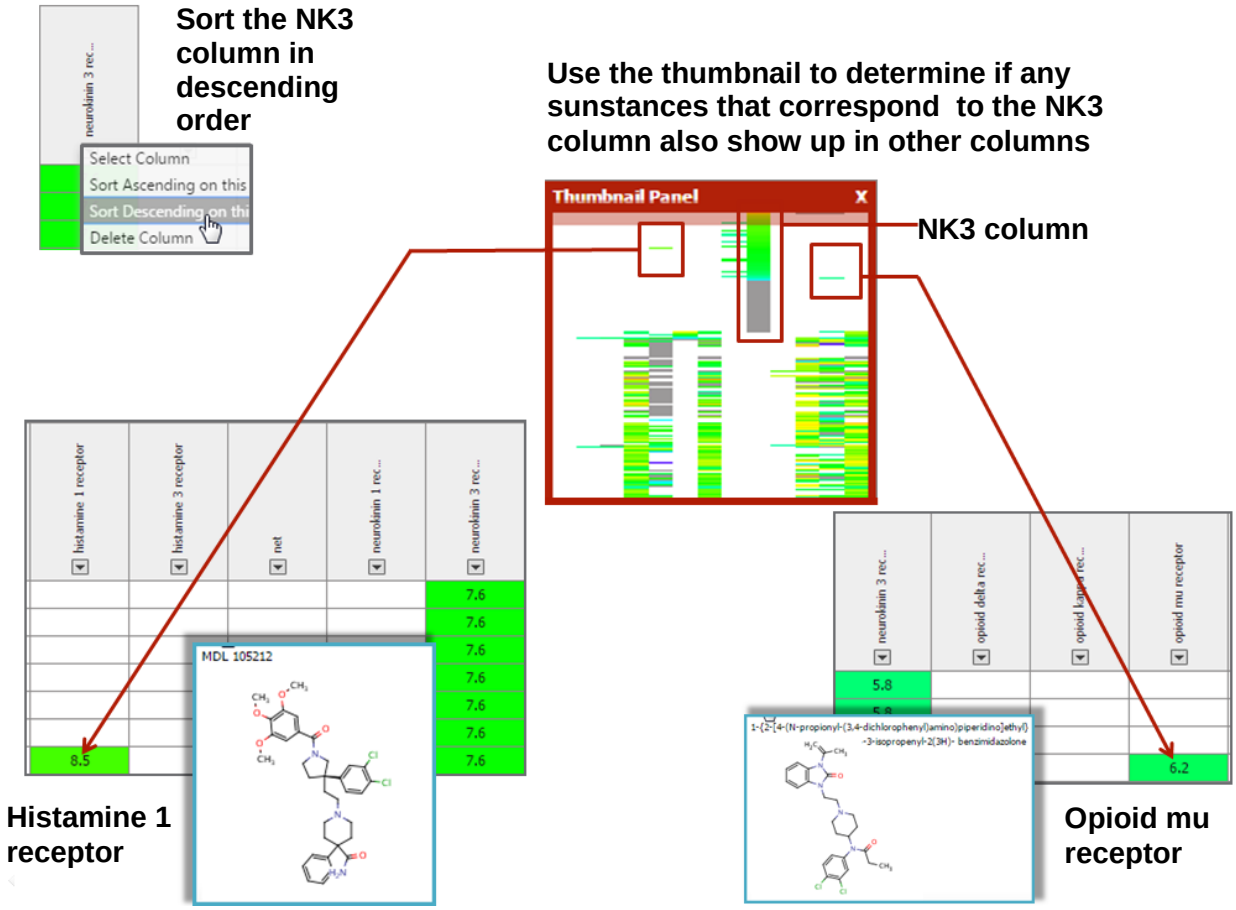
Off targets/CNS Adverse Effect: Attention/perception

Off targets/CNS Adverse Effect: Learning/memory

Select the targets shown here. Click 'Limit to'. Limit to

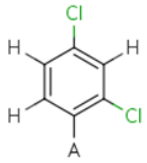
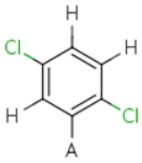
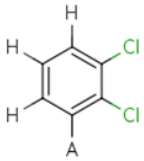
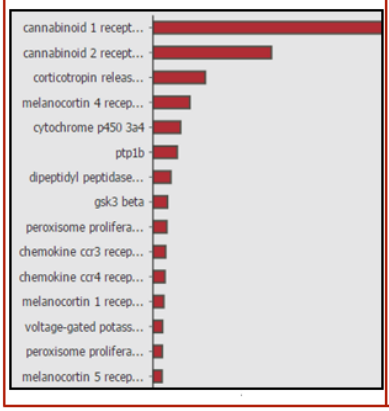
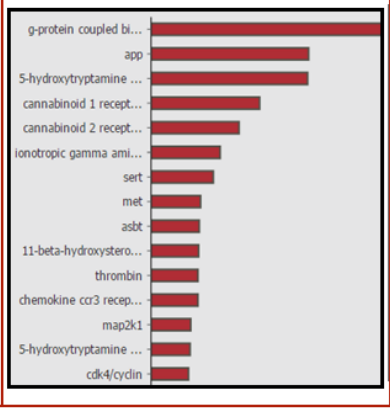
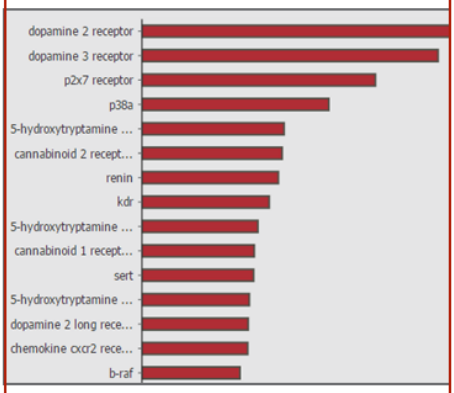
- The Targets Histogram contains many pages. Use the arrows at the bottom of the Histogram to view some of the other targets associated with these compounds.
- Some interesting ones are shown above. Select these targets and click the **Limit to** button.

Explore Other Targets



- Determine if the selected targets have any substances in common with the NK3 target.
- Use the **Thumbnail** to get an overview of the **Heatmap**. Find the sorted NK3 column and look for other targets.
- Only 2 were found here. This means that there are lots of compounds active on NK3 that haven't been tested on other targets.

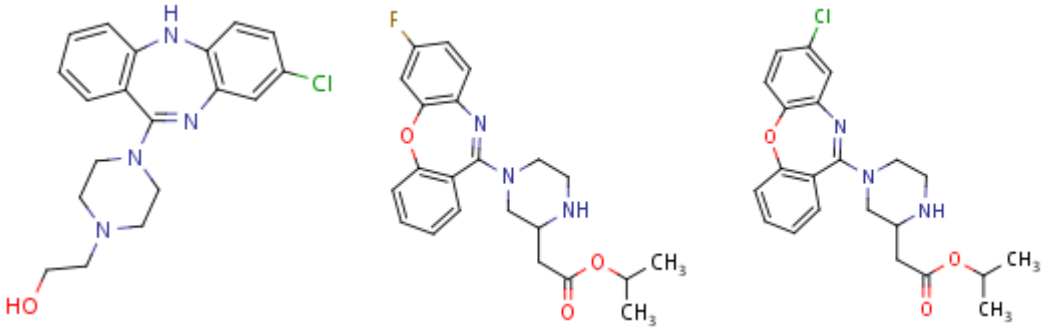
Are there other di-substitution Patterns with a Strong Pharmacological Response?

2,4-dichlorophenyl	2,5-dichlorophenyl	2,3-dichlorophenyl
		
Canabinoid receptor (1 and 2) Melanocortin 4	**5-HT 2C Amyloid precursor protein (App)**	**Dopamine receptor (2 and 3) p38a**
		

- Use the same ideas presented on the previous 3 slides to search for other dichlorophenyl substances……as well as di-*x*-phenyl compounds.

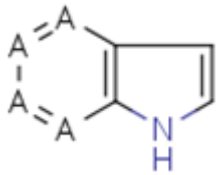
Practice Exercises

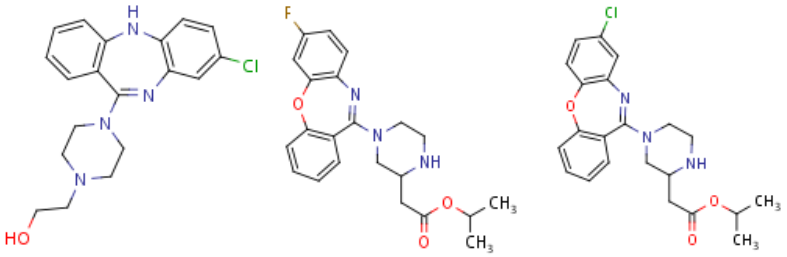
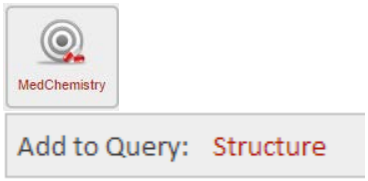
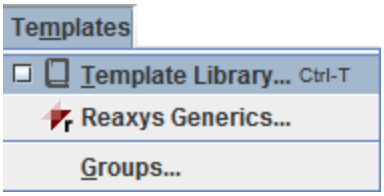
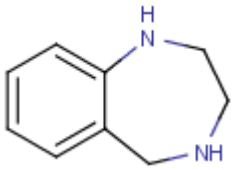
I. **Search for PK data.** Find substances like these with any kind of attachment on the 4 position of the piperazine ring and an N or O for the oxazepine (or diazepine). Search specifically for the following parameters: AUC, Cmax, t1/2, or Tmax.

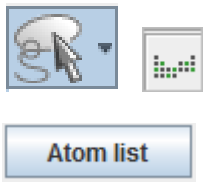


II. **AKT1 inhibitors.** Find substances that inhibit AKT1 and are less active on AKT2.

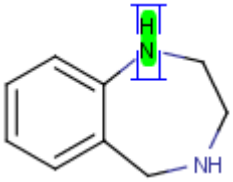
III. **Cytochrome P450 Inhibitors.** Find substances that contain the following substructure and have been tested and shown to have inhibitory activity on Cytochrome P450 targets.



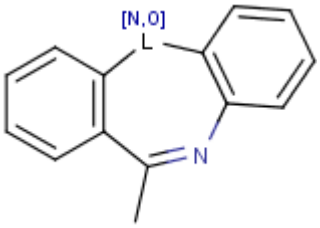
	Search for PK data
Exercise 1	Find substances like these with any kind of attachment on the 4 position of the piperazine ring and an N or O for the oxazepine (or diazepine). Search specifically for the following parameters: AUC, Cmax, t1/2, or Tmax. 
	1. Click the **Medicinal Chemistry** button. Click the Structure Box to open the Structure Editor. **MarvinSketch** is used in this example. *(If the Structure Box is not displayed, click the Structure link below the **Bioactivities** form to add a structure box.)*
	2. Use the **Template Library** and find an appropriate template in the **Heterocycle** section. 

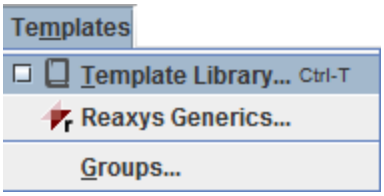


3. Use the **Lasso tool** to select the nitrogen (as shown). Then click the **Periodic Table** button, click the **Atom List** button, and then click the **N** and the **O**. Click **Close.**

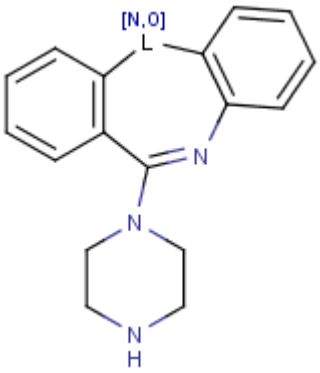


4. Use the **Benzene tool** to add a ring and the **Bond tool** to change the single bond to a double bond and to add a single bond.

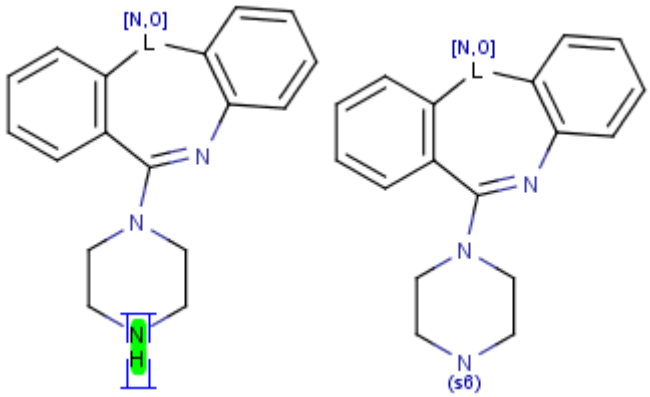


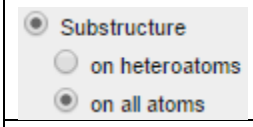


5. Use the **Template Library** and find an appropriate template in the **Heterocycle** section and add it to the end of the methyl.



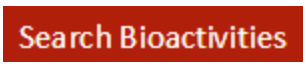
6. Allow attachments on the N (shown below) by selecting it with the **Lasso tool** and then typing the following 3 keys from the computer keyboard: [.] [S] [6]



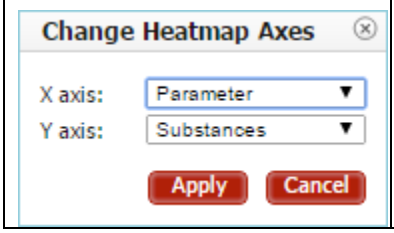


7. Click the **Transfer Query** button. Select **Substructure on all atoms**.

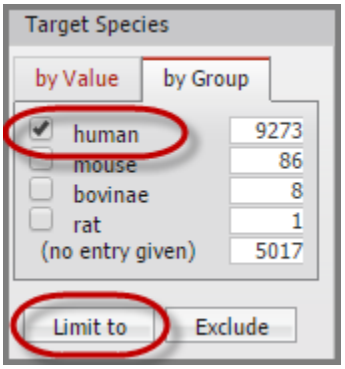
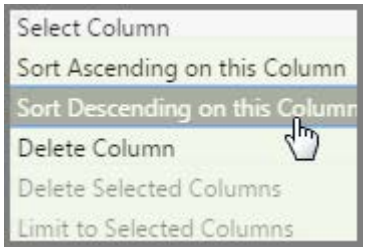
8. Use the **Measurement Parameter** field. Click the Lookup link. In the **Search for** box, type *auc*. Then select *auc.* Type *cmax*. Then hold down the **Control key** and select *cmax*. Type *t1/2.* Then hold down the **Control key** and select *t1/2*. Type *tmax*. Then hold down the **Control key** and select *tmax*.

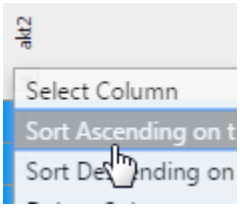


9. Click the **Search Bioactivities** button.

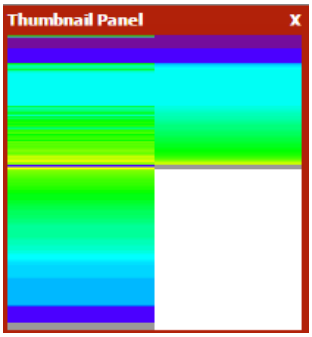


10. In the **Heatmap**, change the view to X=Parameter and Y=Substances. Click **Apply**. Click a grey box in the **Heatmap** to view the specific PK data for that substance.

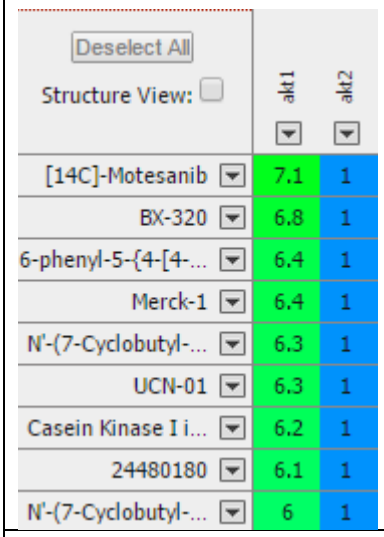
	AKT1 inhibitors
Exercise II	**AKT1 inhibitors.** Find AKT1 inhibitors that are less active on AKT2. You are only interested in human data.
	1. Click the Medicinal Chemistry button. Use the **Target Name** field and type the following: *akt1;akt2*. The semicolon represents the OR data operator.  **Results:** *About 8426 substances.*
	2. The results open to the **Heat map** showing 2 columns (AKT1 and AKT 2). Filter the results so that only *Human* **Target Species** is represented. **Results:** *About 5111 substances.*
	3. Sort the **AKT1** column to view the most active compounds at the top by clicking the down arrow and selecting ***Sort in Descending order*.**



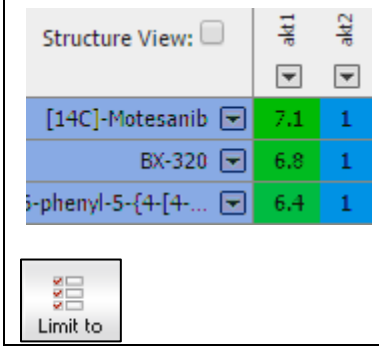
4. Sort the **AKT2** column to view the least active compounds at the top by clicking the down arrow and selecting ***Sort in Ascending order*.**



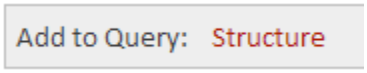
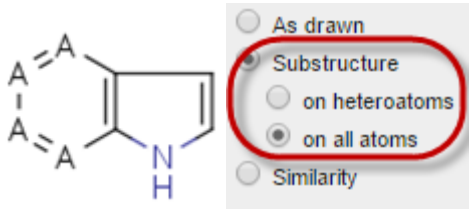
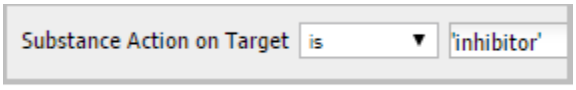
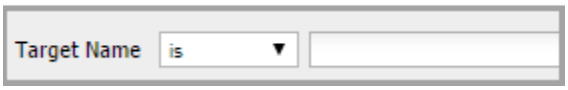
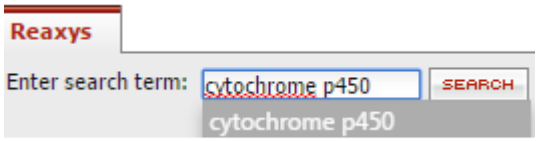
5. View the thumbnail to get an idea of the relative numbers of compounds and activities.



6. There are 24 compounds at the top of the list that show the greatest difference in pX values (active on AKT1 and less active on AKT2).



7. Select these 24 substances by clicking the substance name to select the row, and then clicking the **Limit to** button.

	Cytochrome P450 targets
Exercise III	**Mine RMC for Cytochrome P450 Targets.** Find substances that contain the following substructure and have been tested and shown to have inhibitory activity on Cytochrome P450 targets.
 	1. Click the **Medicinal Chemistry** button. Click the Structure Box to open the Structure Editor. **MarvinSketch** is used in this example. *(If the Structure Box is not displayed, click the Structure link below the **Bioactivities** form to add a structure box.)*
	2. Draw the structure shown here. “A” is a label for “Any atom” (except hydrogen). Use the settings for **Substructure on all atoms**.
	3. Use the **Substance Action on Target** field. Click the Lookup link and select **inhibitor**.
  	4. Use the **Target Name** field. Click Lookup. Type in *cytochrome p450* and click **Search**. Click **Transfer**. Click **Search Bioactivities**.

	5. Use the **Analysis View** to determine which Targets have the highest activity values. Set the Histograms to **Targets** and **Activity.** Click the bars for activity between 5-10. Click **Limit to**.

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