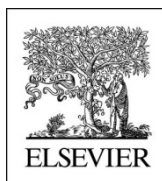





Reaxys Training

Reaxys Medicinal Chemistry

March 2015





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

Explore the pharmacological effect of selected compounds

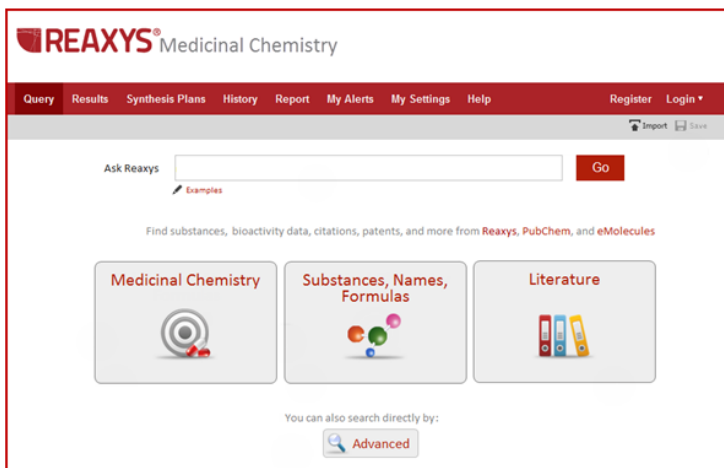
Investigate the targets with which the compound series interacts

This can be used for:

- the assessment of new drugs
- compound repurposing
- lead identification
- lead optimisation

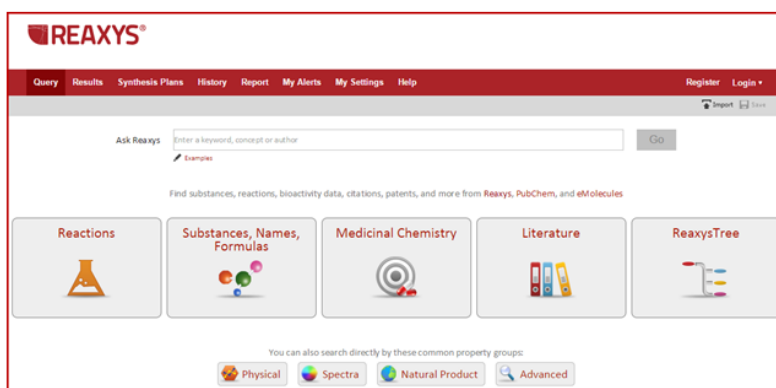
-
- **Reaxys Medicinal Chemistry** is all about connections between the bioactivity of compounds and their targets and helps you choose the right compound to develop during your preclinical work. We extract and index the following:
 - The **chemical structure**, name, code, synonym of a **compound**
 - **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

The image displays four overlapping search forms from the Ask Reaxys platform:

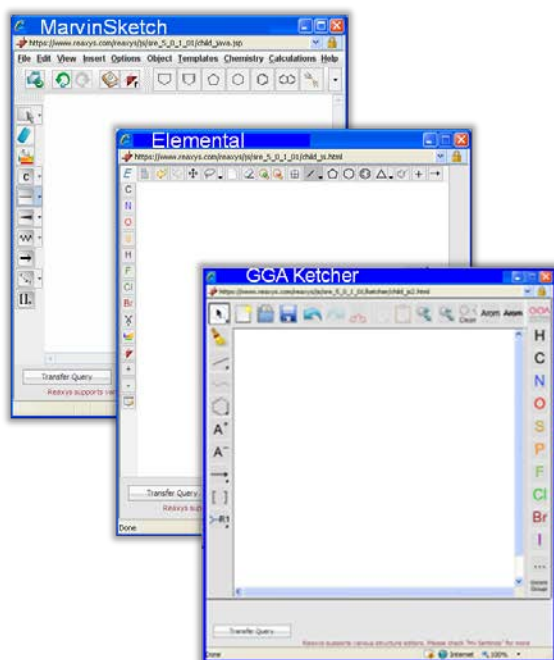
- Ask Reaxys:** A simple search box with a "Go" button and a link to "Examples".
- Bioactivities Form:** Includes fields for Target Name, Substance Highest Clin. Phase, Substance Action on Target, Bioassay Category, Bioassay Animal Model, Biological Species, Cells/Cell Lines, and Measurement pX.
- Literature Search Form:** Includes fields for Document Type, Authors, Journal Title, Publication Year, Title, Abstract, and Keywords.
- Substance Search Form:** Includes fields for Reaxys Registry Number, CAS Registry Number, Chemical Name, and Element Symbols.

Additional features include "Show AND Buttons" and "Add/Remove Fields..." links.

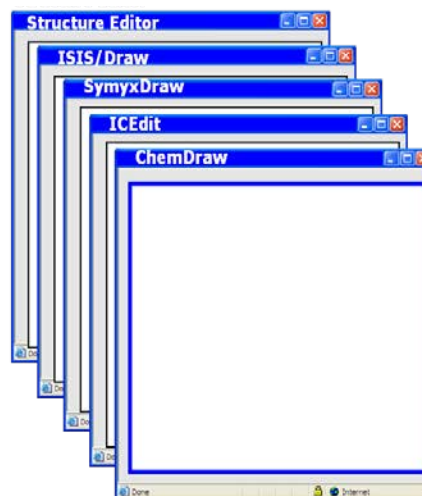
- **Ask Reaxys** allows you to type in terms and then interprets the query and performs either a substance or literature search*.
- Search forms can be customized with hundreds of different search fields by clicking the [Add/Remove Fields](#) link.
- Perform a structure search by drawing the structure 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

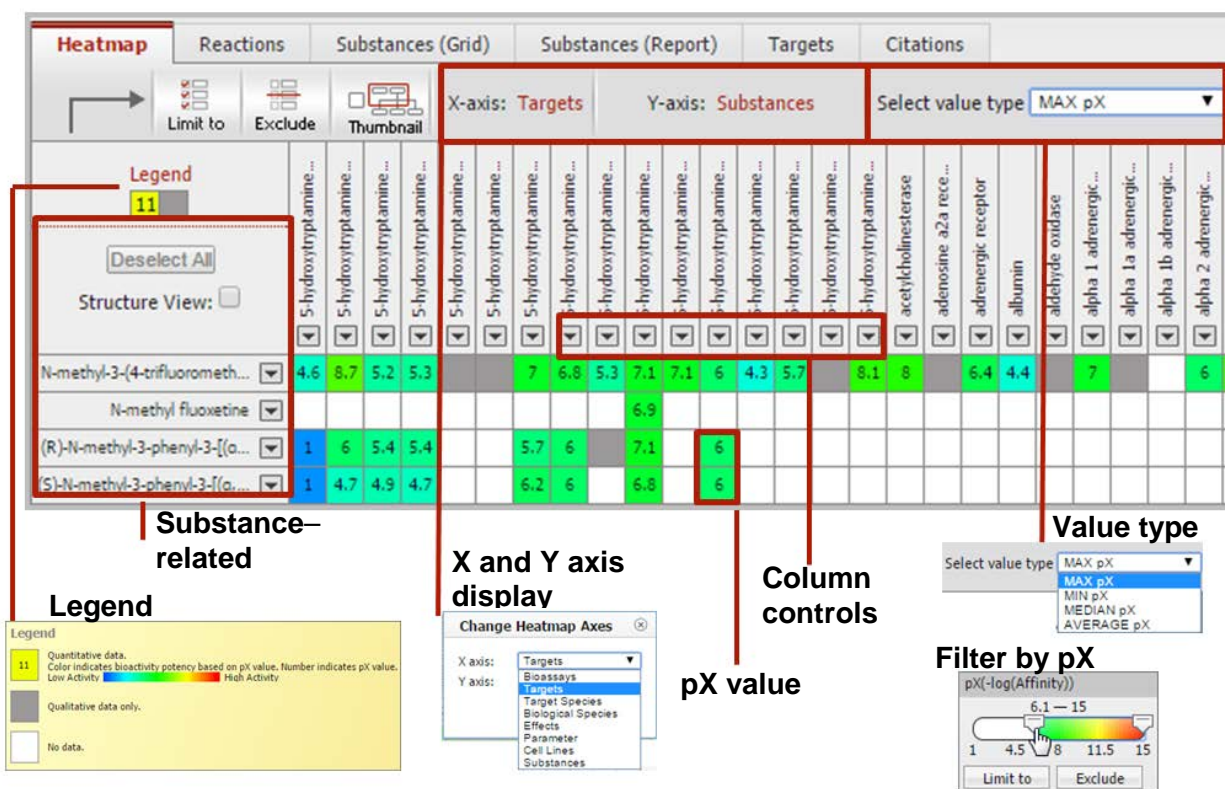


www.reaxys.com/info/support/downloads



- 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

The image displays three main sections of a software interface:

- Filter:** Two panels for filtering by 'Effect'. The left panel shows a list of effects with counts: 'antiviral' (12045), 'antineoplastic' (9372), and 'antibiotic' (8395). The right panel shows a search box for 'enter value/range' with 'vasodilator' entered.
- Sort:** Two dropdown menus for sorting. The first shows options like 'Reaxys-RN', 'No of Fragments', 'Molweight (g/mol)', 'Molecular Formula', 'Publication Year', 'No of References', and 'Similarity'. The second shows 'Relevance', 'Journal Title', 'Author', 'Document Type', and 'Publication Year'.
- Analysis View:** Two histograms. 'Histogram A' is for 'Targets' and shows bars for 'ak1', 'ak3', and 'ak2'. 'Histogram B' is for 'Effect' and shows bars for 'antineoplastic', 'inhibitory activity', 'residual activity', 'cytotoxic', and 'apoptotic'.





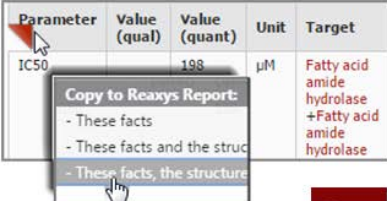


- **Filter - Filter by** categories are displayed on the left side of the results page. Some filters offer a **By Value** tab that allows you to type in a term. Some filters offer a **More** link that allows you to refine using more details.
- **Sort** – Click to view and select sorting options.
- **Analysis 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).

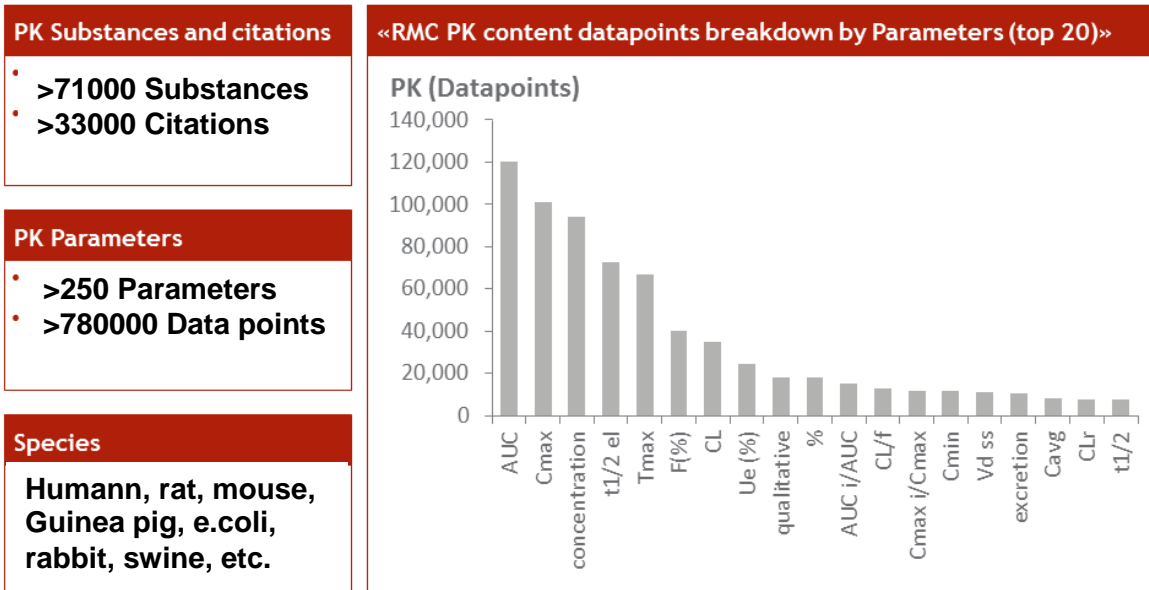
Step 3 - After analyzing various combinations, click **Limit to** (or **Exclude**).

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.
- 
- | Parameter | Value (qual) | Value (quant) | Unit | Target |
|-----------|--------------|---------------|------|---|
| IC50 | | 198 | µM | Fatty acid amide hydrolase
+Fatty acid amide hydrolase |
- Copy to Reaxys Report:
- These facts
 - These facts and the structure
 - These facts, the structure
- 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



- 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

The image shows a sequence of steps for creating a search query in the MedChemistry system:

- MedChemistry** logo is shown in the top left.
- An arrow points to the **Add to Query: Structure** button.
- The **Structure** box contains a chemical structure of 3-methylideneoxindole. To its right, the **Substructure** options are set to **on all atoms**.
- Below the structure box is the link **Create Structure Template from Name**.
- An arrow points to the **Add/Remove Fields...** button.
- The **Insert/Remove Properties** dialog is shown, with **bioassay** entered in the search field. The **Bioassay Category (DAT.CATEG)** field is highlighted.
- Two query examples are shown below:
 - Query #1**: Bioassay Category is pharmacokinetic
 - Query #2**: Measurement Parameter is cmax

- 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

1. The first search retrieves PK data with different parameters

Parameter	Value (qual)	Value (quant)	Unit	Species	Route of administration	Dose	Dosing regimen	Population	Reference
% Inhibition	NA			mouse	oral administration	100 mg/kg	Single		Blood Title
Cmax		23.3	ng/mL	human	oral administration	50 mg	Single	Healthy	Type Title
AUC		937	ng.h/mL	human	oral administration	50 mg	Single	Healthy	Type Title
Tmax		7.25	hour	human	oral administration	50 mg	Single	Healthy	Type Title

2. The second search retrieves only Cmax metabolism and PK data

Parameter	Value (qual)	Value (quant)	Unit	Species
Cmax		26.1		
Cmax		2.7		
Cmax		24.1		
Cmax		43.8	ng/mL	human
Cmax		11.9	ng/mL	human

Labels for the second table: Route of administration, Dose of the compound, Dosing regimen, Population group used in PK.

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	Parameters	Occurrence
>120000 Substances >29000 Citations	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

Parameters & data pts

>400 Parameters
609000 Data Points

Targets

>2200 Targets
Plus Target Species &
Cell Lines

Quantitative information

Metabolism (17)						
Quantitative Results						
Parameter	Value (qual)	Value (quant)	Unit	Target	Species	Tissue/Org
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

Qualitative Information

Metabolism (2)		
Qualitative Information		
1 of 2	Assay Description	Partition Coefficient of the compound was determined
	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 determined
	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

The image illustrates the steps to create a search query in the MedChemistry system. It shows a 'MedChemistry' logo, a 'Structure' box containing a chemical structure of 3-methylideneoxindole, and an 'Insert/Remove Properties' dialog box. Below these are two query examples: 'Query #1' using 'Bioassay Category' and 'Query #2' using 'Measurement Parameter'.

MedChemistry

Add a structure box to the form

Add to Query: **Structure**

Structure

As drawn
 Substructure
 on heteroatoms
 on all atoms
 Similarity

Create Structure Template from Name

Insert/Remove Properties
 Define the "MedChemistry" query layout

Find any property

Reaxys
 Bioactivities
 Medchem
 Bioassay Category (DAT.CATEG)
 Bioassay Subcategory (DAT.AFTYPE)
 Bioassay Name (DAT.ANAME)
 Bioassay Animal Model (DAT.MODEL)
 Bioassay Details (DAT.ADESC)
 Bioassay Population (DAT.BSTATE)

Add a field to the form

Add/Remove Fields...

Bioassay Category is metabolism/transport

Measurement Parameter is clint

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)

Parameter	Value (qual)	Value (quant)	Unit	Target	Species
t1/2					mouse
% Inhibition	<	10		Cytochrome P450 3A	human
Transport ratio		2.2		BCRP +MDR1	
Transport ratio		3.2		BCRP +MDR1	

1. The first search retrieves MET data with different parameters

Parameter	Value (qual)	Value (quant)	Unit	Target
Clint		3	μL/min/nmol target	Cytochrome P450 3A4
Clint		0.3	μL/min/nmol target	Cytochrome P450 3A5

2. The second search retrieves only Clint metabolism data

History – Display the results of the previous search

History

Two ways to filter by parameter

1.

Select a column. Then click 'Limit to'

2. Use the filters on the left

Value	Occurrence
ki	25
<input checked="" type="checkbox"/> clint	25
fu	20
vd	18
vmax	17

- 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 bioactivities (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

Quantitative information

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 supernat
	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 S

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

The image illustrates a multi-step search process in a software interface:

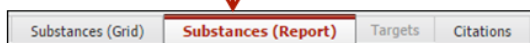
- Structure Panel:** Shows a chemical structure of a pyrazole scaffold. The search scope is set to **Substructure** and **on all atoms** (indicated by a red circle).
- Reaxys Search 1:** A search for "antineopl" returns results including "antineoplastic (421672)".
- Reaxys Search 2:** A search for "antiproliferative" returns results including "antiproliferative (324451)".
- Search Form:** The "Substance Effect" field is set to "is" and contains the query "'antineoplastic';'antiproliferative'". The "Bioassay Category" field is set to "is" and contains "'in vitro (efficacy)'".
- Final Results:** A search for the combined query returns results such as "in vitro (efficacy) (22120467)".

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



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

Parameter	Value (qual)	Value (quant)	Unit
%	=	4	%
TGI	>	0.0001	M
%	=	99	%

2. Select data points

Parameter	Value (qual)	Value (quant)	Unit
IC50	=	7.6	μ M
%	=	103	%

The screenshot shows the full software interface. At the top, there's a menu bar with 'File', 'Search', 'Substances', 'Targets', 'Reports', 'My Data', 'My Settings', and 'Help'. Below that, there's a search bar and a 'Report' button. The main area displays a table of substances with columns for 'Substance', 'IC50', 'TGI', 'IC50', 'TGI', 'IC50', 'TGI', 'IC50', 'TGI'. The 'Report' button is highlighted with a red box.

- 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

Experimental Disease

- ⊕ experimental body function
- ⊕ experimental cardiovascular
- ⊕ experimental digestive syst
- ⊕ experimental disease by et
- ⊕ experimental ear nose throa
- ⊕ experimental endocrine dise
- ⊕ experimental eye disease
- ⊕ experimental mouth disease
- ⊕ experimental musculoskele
- ⊕ experimental neoplasm
- ⊕ experimental neurologic dis
- ⊕ experimental respiratory dis
- ⊕ experimental skin disease
- ⊕ experimental urogenital dise

**Unclassified
Experimental
Disease**

- Abortion
- active avoidance test
- Adhesion formation (tissue, organ)
- Analgesia
- Angiogenesis
- Anococcygeus muscle contraction
- antioxidant activity
- anxiety/defense test battery
- apomorphine test
- Apomorphine-induced climbing
- arachidonic acid-induced ear edema
- blood flow
- blood level
- blood pressure
- body temperature
- brain level

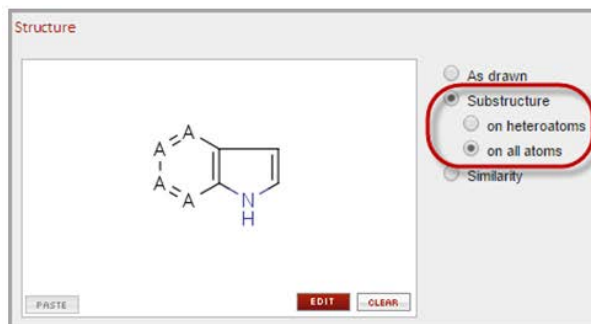
Results display the following categories:

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

Bioassay Animal Model is Lookup ✕

- 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



Find dosing information on substances containing this structure administered intraperitoneally and used with a specific animal model

Substance Route of Adm. is

- intraperitoneal administration
- intraperitoneal drug administration
- intraperitoneal infusion
- intraperitoneal injection
- intraplacental drug administration

Start typing directly into the 'Route of Administration' field and select the term from the drop-down

Type the model name and click the Search button

Reaxys

Enter search term: paw inflammation

Experimental Disease

experimental disease

Unclassified Experimental Dis

The name will be found within the hierarchy of terms

Reaxys

Enter search term: paw inflammation

Experimental Disease

Unclassified Experimental Disease

experimental paw inflammation

Bioassay Animal Model is

- 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	Effect
% Max		23		experimental paw inflammation	rat	intraperitoneal administration	30 µmol/kg	Single	
% Inhibition		83		experimental paw inflammation	rat	intraperitoneal administration	50 mg/kg		Antiinflammatory
E _{max} (%)		94		experimental paw inflammation	rat	intraperitoneal administration	11 mg/kg	Single	

Examples of in vivo results

Export to Excel

Choose format

- XML*
- Microsoft Word
- Microsoft Excel*
- RD File
- SD/Molfile*
- Smiles

Export contains

- Include structures
- All available data
- Identification data only
- Hit data only
- Select data

Select 'Hit Data Only'

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

	A	B	C	D	E	F	G
	Structure	Bioassay Name	Biological Species	Substance Dose	Substance Route of Adm.	Substance Dosing Regimen	Measurement Parameter
1	[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(C)=CC=C2N1	Hot plate	rat	30 mumol/kg	intraperitoneal administration	Single	% Max
4	CN1CCN(CC1)C(=O)C1=CC2=CC(C)=CC=C2N1	Hot plate	rat	100 mumol/kg	intraperitoneal administration	Single	% Max
5	CN1CCN(CC1)C(=O)C1=CC2=CC(C)=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
ad (x0025:)	11822

Parameters

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

Effects

- cryoprotective
- cytolytic
- cytopathic
- cytopathogenic
- cytoprotective
- cytostatic
- cytotoxic
- death
- dermatological
- developmental
- embryotoxic
- estrogen
- fetotoxicity
- fungistatic
- fungitoxic
- gametocytocid
- genotoxic
- germination ef
- hair growth
- abortifacient
- acaricidal
- adulticidal activity
- alkalosis
- allergenic
- anabolic
- anaesthetic
- analgesic
- angiogenic
- anorectic
- anti-adenovira
- anti-als
- anti-alzheim
- anti-arterioscl
- anti-bvdv
- anti-chagas
- anti-chikungu
- anti-dengue
- anti-dengue-2
- proliferative
- protective
- radioprotective
- reproductive effect
- resorptive
- scavenging
- sensitizing
- spermicidal
- sporadic
- teratogenic
- toxic
- toxic : acute
- toxic : chronic
- tuberculostatic
- tumorigenic
- ulcerogenic
- vascular disruptive
- vasoconstrictor
- vasodilator

Over 2 million bioactivities from over 40000 substances with over 3000 targets from almost 70000 citations

Search for Toxicity/Safety Pharmacology Data

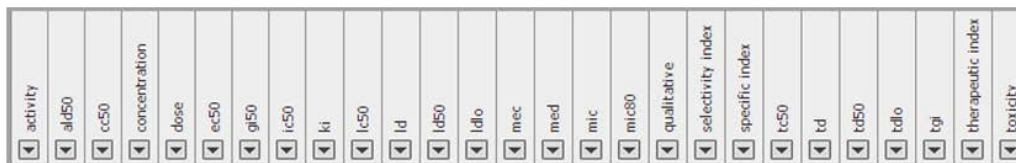
Search for tox/safety pharmacology information on this scaffold

The image shows a software interface for searching toxicity/safety pharmacology data. It consists of three main components:

- Structure Panel:** Displays a chemical structure of a scaffold (a benzene ring fused to a five-membered ring containing an NH group, which is further fused to a six-membered ring). The search options are: As drawn, Substructure, on heteroatoms, on all atoms, and Similarity. The 'Substructure' and 'on all atoms' options are circled in red.
- Reaxys Panel:** Shows search results for the scaffold. The results are: in vitro (efficacy) (22120467), in vivo (animal models) (1026535), metabolism/transport (608988), pharmacokinetic (787550), and toxicity/safety pharmacology (2040009). The 'toxicity/safety pharmacology (2040009)' result is highlighted in blue. A red arrow points from this result to the 'Lookup' button.
- Bioassay Category Panel:** Shows a dropdown menu set to 'is' and a 'Lookup' button with a red 'X' icon. The 'Lookup' button is highlighted with a red box.

- 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

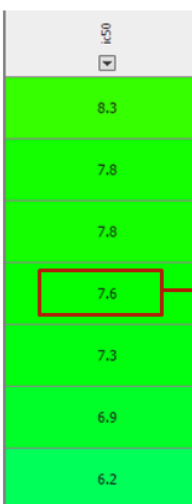
Filter to limit the list to human-related results

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

Click to view the active structures

- 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

▲ Toxicity/Safety Pharmacology (1)

Quantitative Results

Parameter	Value (qual)	Value (quant)	Unit	Target	Cell	Bioassay
IC50		25.3	nM	NPM-ALK	Karpas 299	Cell/tumor cell: proliferation/viability/growth

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



Id	LD50	Info

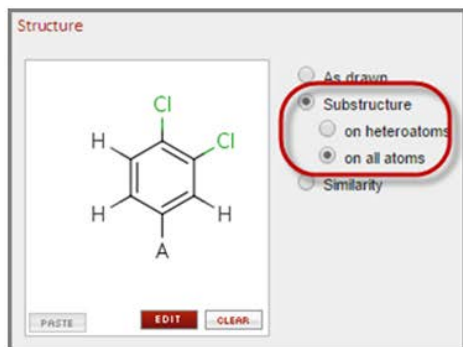
Quantitative Results

Parameter	Value (qual)	Value (quant)	Unit
LD50	=	125	mg/kg

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.

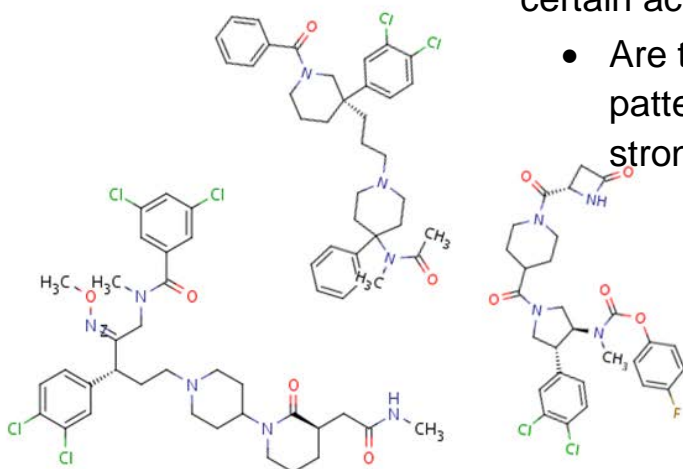
- Each pX value represents a data point. Click the px value to open the substance record and view the actual data.
- The Breadcrumbs will take you back to lists you have been creating. Click the first breadcrumb to return to the original result list (before any filtering was done).
- Select a parameter 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



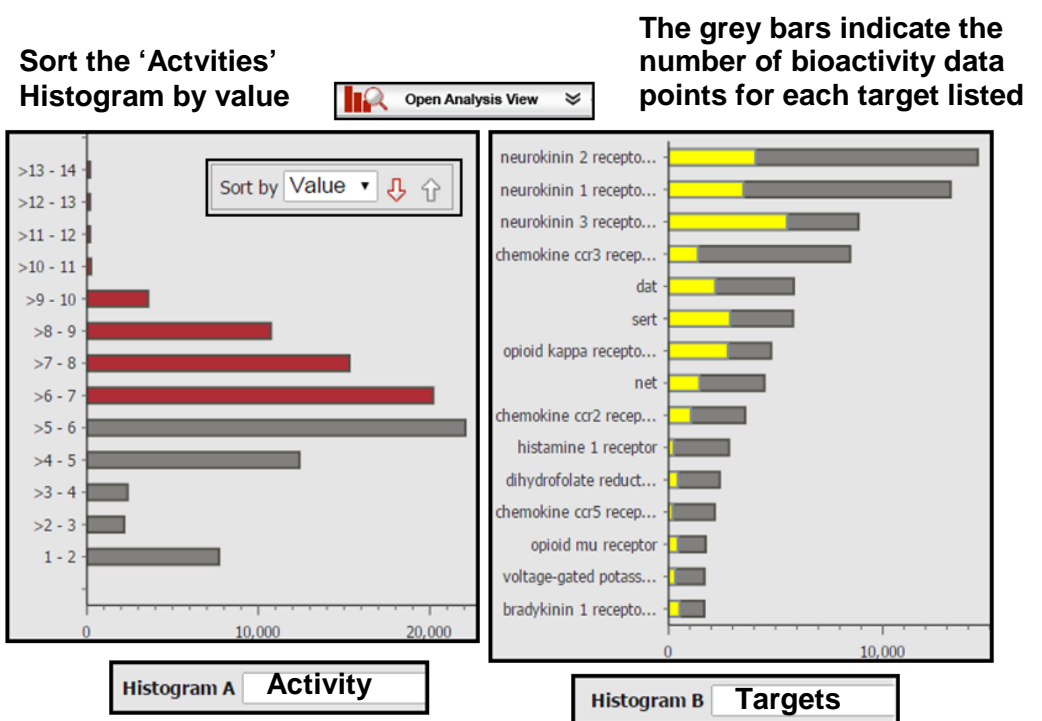
Within NK₃ the 3,4-dichlorophenyl group appears to be important as structural feature

- 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?



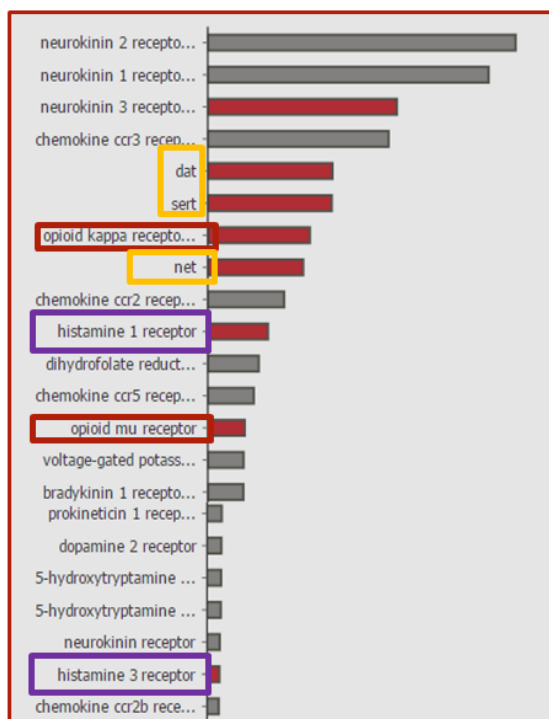
- There is a lot of information available regarding Tachykinin receptor 3 (NK3) (Neurokinin receptor 3) and substances that have the 2,3-dichlorophenyl group.
- Use Reaxys Medicinal Chemistry to find other targets associated with these compounds to determine their pharmacological profiles.
- Then determine 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



- 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

Sort the NK3 column in descending order

Select Column
Sort Ascending on this
Sort Descending on this
Delete Column

Use the thumbnail to determine if any substances that correspond to the NK3 column also show up in other columns

Thumbnail Panel

NK3 column

histamine 1 receptor	histamine 3 receptor	net	neurokinin 1 rec...	neurokinin 3 rec...
				7.6
				7.6
				7.6
				7.6
				7.6
				7.6
				7.6
				8.5

Histamine 1 receptor

MDL 105212

COC1=CC(OC)=C(C1)C(=O)N2C3=CC=C(C=C3)C4=CC=C(C=C4)N2

neurokinin 3 rec...	opioid delta rec...	opioid kappa rec...	opioid mu receptor
5.8			
			6.2

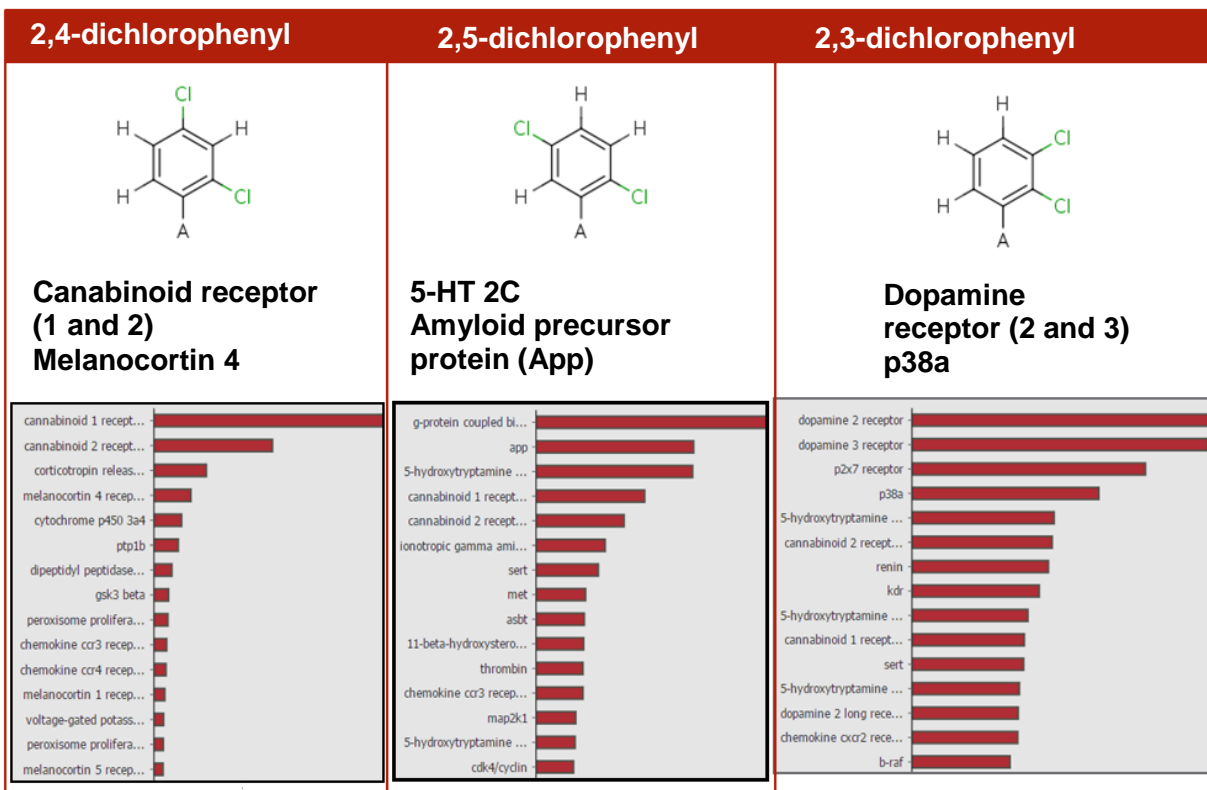
Opioid mu receptor

1-(2-[4-(N-propionyl-(3,4-dichlorophenyl)amino)piperidino]ethyl)-3-isopropenyl-2(3H)-benzimidazolone

CC(C)C(=O)N1CCN(C1)CC2=CC=C(C=C2)C3=CC=C(C=C3)N4C(=O)N(C)C=C4

- 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.

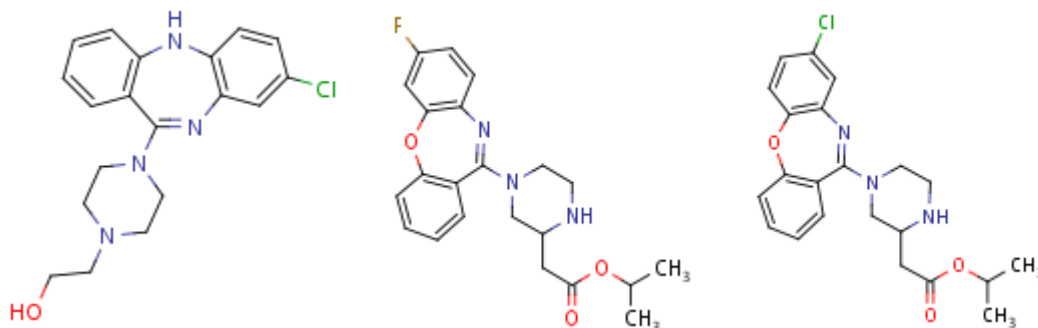
Are there other di-substitution Patterns with a Strong Pharmacological Response?



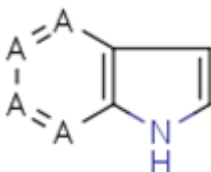
- Use the same ideas presented on the previous 3 slides to search for other dichlorophenyl substances.....as well as di-x-phenyl compounds.

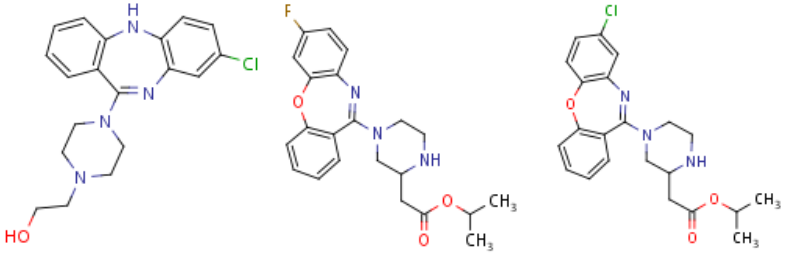

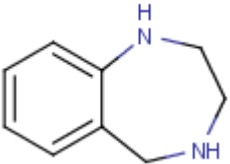
Practice Exercises


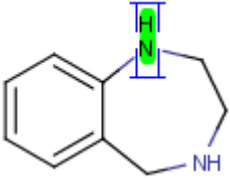

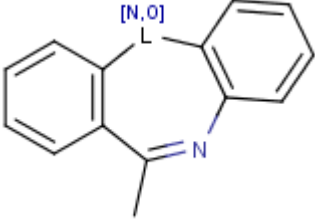
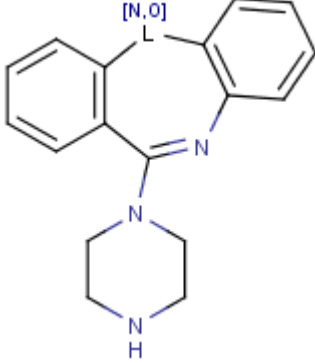
- I. **Search for PK data.** Find substances like these with any kind of attachment on the 4 position of the piperazine ring and an N or O for the oxazepine (or diazepine). Search specifically for the following parameters: AUC, Cmax, t1/2, or Tmax.


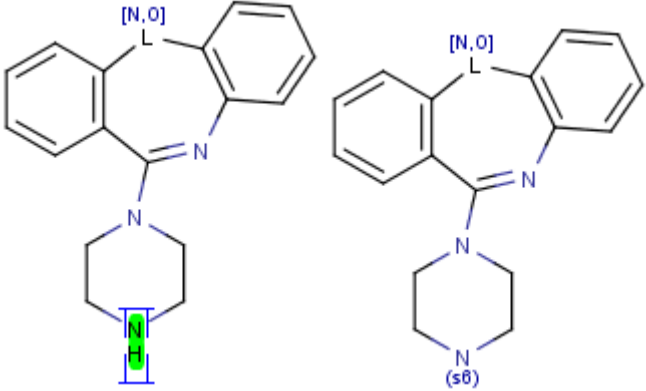
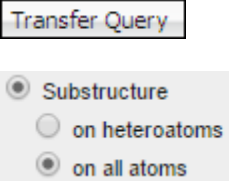
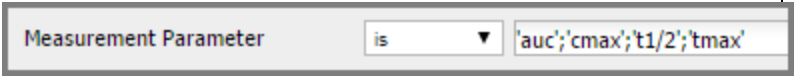
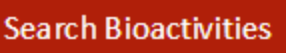




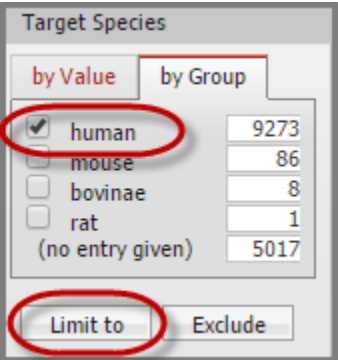
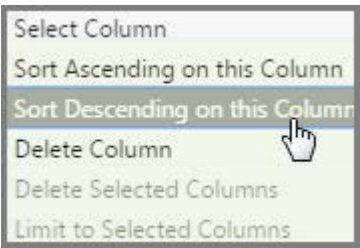
- II. **AKT1 inhibitors.** Find substances that inhibit AKT1 and are less active on AKT2.
- III. **Cytochrome P450 Inhibitors.** Find substances that contain the following substructure and have been tested and shown to have inhibitory activity on Cytochrome P450 targets.

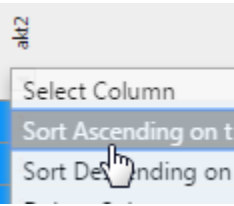
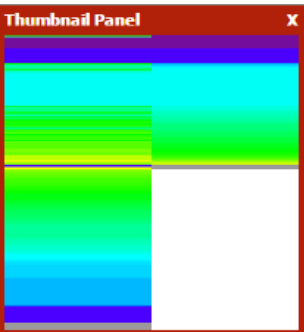
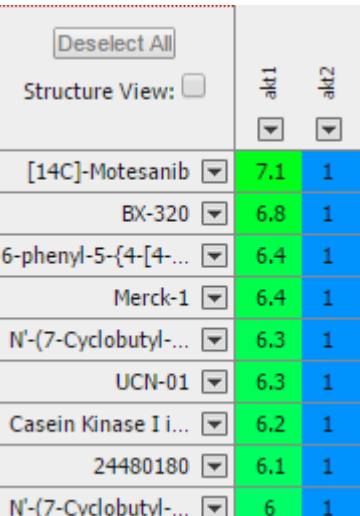
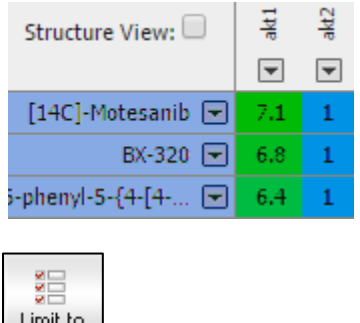



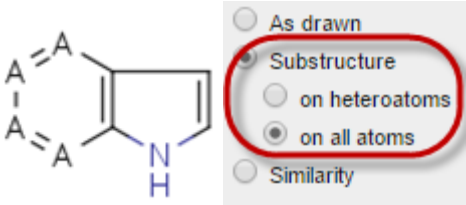
	Search for PK data
<p>Exercise 1</p>	<p>Find substances like these with any kind of attachment on the 4 position of the piperazine ring and an N or O for the oxazepine (or diazepine). Search specifically for the following parameters: AUC, Cmax, t1/2, or Tmax.</p> 
 <p>Add to Query: Structure</p>	<ol style="list-style-type: none"> 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.)
<p>Templates</p> <ul style="list-style-type: none"> <input type="checkbox"/> Template Library... Ctrl-T <input checked="" type="checkbox"/> Reaxys Generics... Groups... 	<ol style="list-style-type: none"> 2. Use the Template Library and find an appropriate template in the Heterocycle section. 


 <p>Atom list</p>	<p>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.</p> 
	<p>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.</p> 
<p>Templates</p> <ul style="list-style-type: none"><input type="checkbox"/> Template Library... Ctrl-T<input checked="" type="checkbox"/> Reaxys Generics...Groups...	<p>5. Use the Template Library and find an appropriate template in the Heterocycle section and add it to the end of the methyl.</p> 

	<p>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]</p> 
	<p>7. Click the Transfer Query button. Select Substructure on all atoms.</p>
	<p>8. Use the Measurement Parameter field. Click the Lookup link. In the Search for box, type <i>auc</i>. Then select <i>auc</i>. Type <i>cmax</i>. Then hold down the Control key and select <i>cmax</i>. Type <i>t1/2</i>. Then hold down the Control key and select <i>t1/2</i>. Type <i>tmax</i>. Then hold down the Control key and select <i>tmax</i>.</p> 
	<p>9. Click the Search Bioactivities button.</p>
	<p>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.</p>

	AKT1 inhibitors
Exercise II	<p>AKT1 inhibitors. Find AKT1 inhibitors that are less active on AKT2. You are only interested in human data.</p>
	<p>1. Click the Medicinal Chemistry button. Use the Target Name field and type the following: <i>akt1;akt2</i>. The semicolon represents the OR data operator.</p> <div data-bbox="750 577 1263 655" style="border: 1px solid gray; padding: 5px; margin: 10px 0;"> Target Name is <input type="text" value="akt1;akt2"/> </div> <p>Results: <i>About 8426 substances.</i></p>
	<p>2. The results open to the Heat map showing 2 columns (AKT1 and AKT 2). Filter the results so that only <i>Human Target Species</i> is represented.</p> <p>Results: <i>About 5111 substances.</i></p>
	<p>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.</p>

	<p>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.</p>																														
	<p>5. View the thumbnail to get an idea of the relative numbers of compounds and activities.</p>																														
 <table border="1"> <thead> <tr> <th></th> <th>akt1</th> <th>akt2</th> </tr> </thead> <tbody> <tr><td>[14C]-Motesanib</td><td>7.1</td><td>1</td></tr> <tr><td>BX-320</td><td>6.8</td><td>1</td></tr> <tr><td>6-phenyl-5-{4-[4-...</td><td>6.4</td><td>1</td></tr> <tr><td>Merck-1</td><td>6.4</td><td>1</td></tr> <tr><td>N'-(7-Cyclobutyl-...</td><td>6.3</td><td>1</td></tr> <tr><td>UCN-01</td><td>6.3</td><td>1</td></tr> <tr><td>Casein Kinase I i...</td><td>6.2</td><td>1</td></tr> <tr><td>24480180</td><td>6.1</td><td>1</td></tr> <tr><td>N'-(7-Cyclobutyl-...</td><td>6</td><td>1</td></tr> </tbody> </table>		akt1	akt2	[14C]-Motesanib	7.1	1	BX-320	6.8	1	6-phenyl-5-{4-[4-...	6.4	1	Merck-1	6.4	1	N'-(7-Cyclobutyl-...	6.3	1	UCN-01	6.3	1	Casein Kinase I i...	6.2	1	24480180	6.1	1	N'-(7-Cyclobutyl-...	6	1	<p>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).</p>
	akt1	akt2																													
[14C]-Motesanib	7.1	1																													
BX-320	6.8	1																													
6-phenyl-5-{4-[4-...	6.4	1																													
Merck-1	6.4	1																													
N'-(7-Cyclobutyl-...	6.3	1																													
UCN-01	6.3	1																													
Casein Kinase I i...	6.2	1																													
24480180	6.1	1																													
N'-(7-Cyclobutyl-...	6	1																													
	<p>7. Select these 24 substances by clicking the substance name to select the row, and then clicking the Limit to button.</p>																														

	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.
 <div style="border: 1px solid gray; padding: 5px; width: fit-content; margin-top: 10px;"> Add to Query: Structure </div>	<ol style="list-style-type: none"> Click the Medicinal Chemistry button. Click the Structure Box to open the Structure Editor. MarvinSketch is used in this example. <i>(If the Structure Box is not displayed, click the Structure link below the Bioactivities form to add a structure box.)</i>
	<ol style="list-style-type: none"> Draw the structure shown here. "A" is a label for "Any atom" (except hydrogen). Use the settings for Substructure on all atoms.
<div style="border: 1px solid gray; padding: 5px; width: fit-content;"> Substance Action on Target is inhibitor' </div>	<ol style="list-style-type: none"> Use the Substance Action on Target field. Click the Lookup link and select inhibitor.
<div style="border: 1px solid gray; padding: 5px; width: fit-content; margin-bottom: 10px;"> Target Name is </div> <div style="border: 1px solid gray; padding: 5px; width: fit-content;"> <p>Reaxys</p> Enter search term: cytochrome p450 SEARCH cytochrome p450 </div> <div style="background-color: red; color: white; padding: 5px; width: fit-content; margin-top: 10px;"> Search Bioactivities </div>	<ol style="list-style-type: none"> Use the Target Name field. Click Lookup. Type in <i>cytochrome p450</i> and click Search. Click Transfer. Click Search Bioactivities.

 The image shows a button with a magnifying glass icon over a bar chart, the text "Open Analysis View", and a downward-pointing chevron icon.	<p>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.</p>

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