MedChemica

CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

MCPairs Online AI tools to accelerate projects Generic training Course

Twitter @MedChemica

Twitter @covid_moonshot

Twitter #BucketListPapers

www.medchemica.com/bucket-list/

Last update – 21st June 2020

June 2020

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

For the training today:

- Going to present Powerpoint slides, then live demos with MCPairs Online in Google Chrome

- What MCPairs gives to the experienced medicinal chemist?
- From SAR to Matched Molecular Pair Analysis
- How MCPairs works?

- SAR analysis with Compound-To-Pairs
- Testing your ideas with SpotDesign™

- **Ideas and new directions with RuleDesign**

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

What does a project need?

Training will use a literature example

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

Journal of Medicinal Chemistry

Article

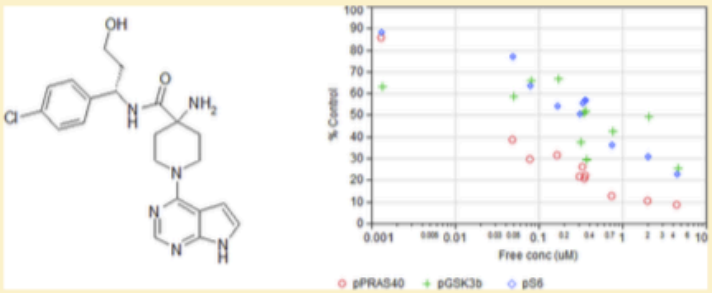
pubs.acs.org/jmc

Discovery of 4-Amino-*N*-[(1*S*)-1-(4-chlorophenyl)-3-hydroxypropyl]-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide (AZD5363), an Orally Bioavailable, Potent Inhibitor of Akt Kinases

Matt Addie, Peter Ballard, David Buttar, Claire Crafter, Gordon Currie, Barry R. Davies, Judit Debreczeni, Hannah Dry, Philippa Dudley, Ryan Greenwood, Paul D. Johnson, Jason G. Kettle,* Clare Lane, Gillian Lamont, Andrew Leach, Richard W. A. Luke, Jeff Morris, Donald Ogilvie,† Ken Page, Martin Pass, Stuart Pearson, and Linette Ruston

Oncology iMed, AstraZeneca, Alderley Park, Macclesfield SK10 4TG, United Kingdom

Supporting Information

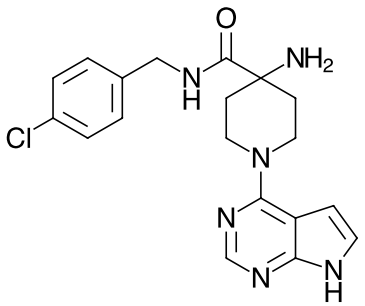


ABSTRACT: Wide-ranging exploration of analogues of an ATP-competitive pyrrolopyrimidine inhibitor of Akt led to the discovery of clinical candidate AZD5363, which showed increased potency, reduced hERG affinity, and higher selectivity against the closely related AGC kinase ROCK. This compound demonstrated good preclinical drug metabolism and pharmacokinetics (DMPK) properties and, after oral dosing, showed pharmacodynamic knockdown of phosphorylation of Akt and downstream biomarkers in vivo, and inhibition of tumor growth in a breast cancer xenograft model.

http://dx.doi.org/10.1021/jm301762v

Capivasertib (AZD5363) – AKT inhibitors

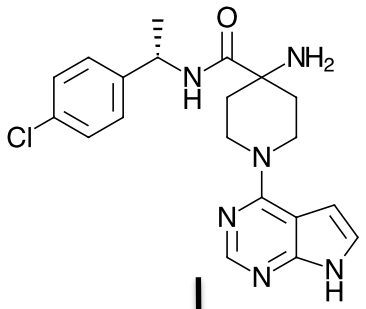
AKT pIC_{50} 7.89 (13nM)
LogD 2.9
Sol (pSol) -5.3 (5 – 150µM)
hERG pIC_{50} 5.2 (5.2 µM)
Potent enough
hERG and improved solubility



CHEMBL598194

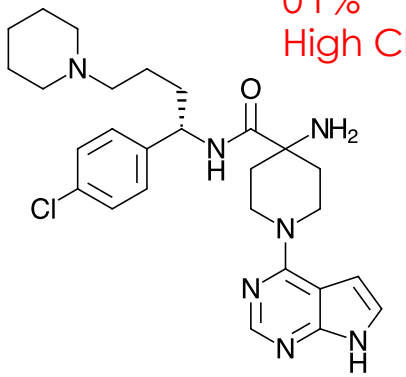
ΔpIC_{50} + 0.2
ΔLogD - 0.2 (?)
ΔpSol + 0.5
ΔhERG ~ 0.2

CHEMBL2325742

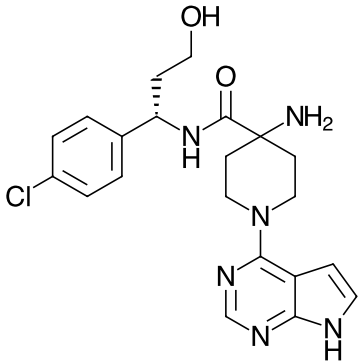


ΔpIC_{50} ~ 0.0
ΔLogD - 0.3
ΔpSol + 1.4
ΔhERG - 0.5

0 F%
High Cl



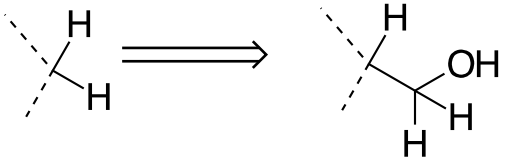
CHEMBL2325729



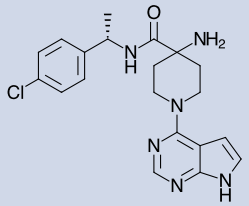
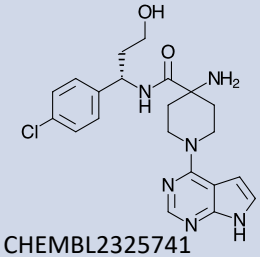
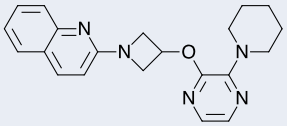
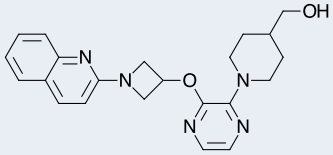
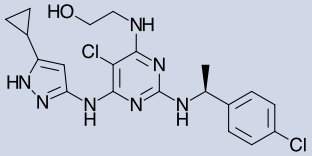
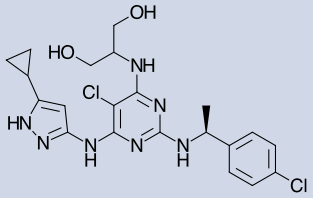
CHEMBL2325741

AKT pIC_{50} 8.4 (3nM)
LogD 2.5
Sol (pSol) -3.1 (780µM)
hERG pIC_{50} <4.0 (>100 µM)
Potent
No hERG and improved solubility

From SAR to MMPA.....



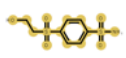
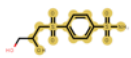
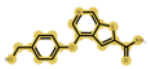
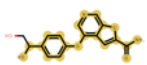
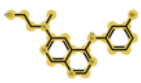
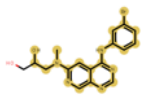
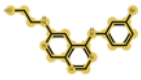
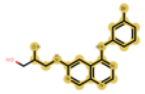
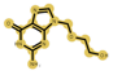
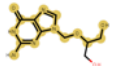
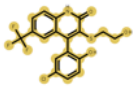
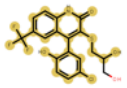
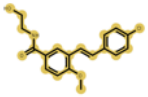
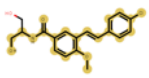
MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

A	B	pSol A (µM)	pSol B (µM)	ΔpSol
 CHEMBL2325742	 CHEMBL2325741	- 4.1 (77 µM)	- 3.1 (870 µM)	1.0
 CHEMBL3356658	 CHEMBL218767	- 6.0 (1.0 µM)	- 3.7 (178 µM)	2.3
 CHEMBL456802	 CHEMBL456322	-5.7 (2.0 µM)	- 4.1 (82 µM)	1.6
				3 pairs +ve Sol Median 1.6

MCPairs Rule finder required 6 matched pairs for 95% confidence

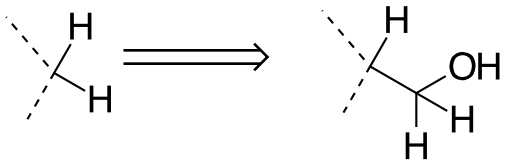
From SAR to MMPA.....

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

compound name A	compound name B	Depiction A	Depiction B	Aqueous Solubility at pH 7.4 solubility [CHEMBL2362975] unit	Aqueous Solubility at pH 7.4 solubility [CHEMBL2362975] qualifier A	Aqueous Solubility at pH 7.4 solubility [CHEMBL2362975] measurement A	Aqueous Solubility at pH 7.4 solubility [CHEMBL2362975] qualifier B	Aqueous Solubility at pH 7.4 solubility [CHEMBL2362975] measurement B	Aqueous Solubility at pH 7.4 solubility [CHEMBL2362975] measurement delta
CHEMBL104459	CHEMBL316800			log10(M)	=	-1.6042	=	-1.2971	0.3071
CHEMBL118022	CHEMBL115462			log10(M)	=	-4.63875	=	-4.3343	0.30445
CHEMBL161956	CHEMBL165547			log10(M)	=	-9.9586	=	-9.7447	0.2139
CHEMBL165864	CHEMBL166093			log10(M)	=	-10.699	=	-9.6778	1.0212
CHEMBL184	CHEMBL182			log10(M)	=	-5.2353	=	-4.7115	0.5238
CHEMBL184521	CHEMBL439660			log10(M)	=	-5.0168	=	-3.3704	1.6464
CHEMBL1949786	CHEMBL1949790			log10(M)	=	-4.31675	=	-3.1588	1.15795

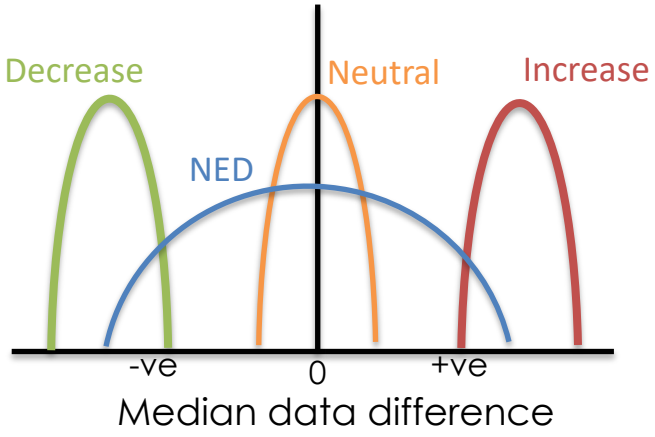
Actual Rule from MCPairs
Endpoint:
Aqueous Solubility at pH 7.4 [CHEMBL2362975]

n-qual	69
n-qual-up	47
n-qual-down	21
median ΔpSol	0.26
std dev +/-	0.636

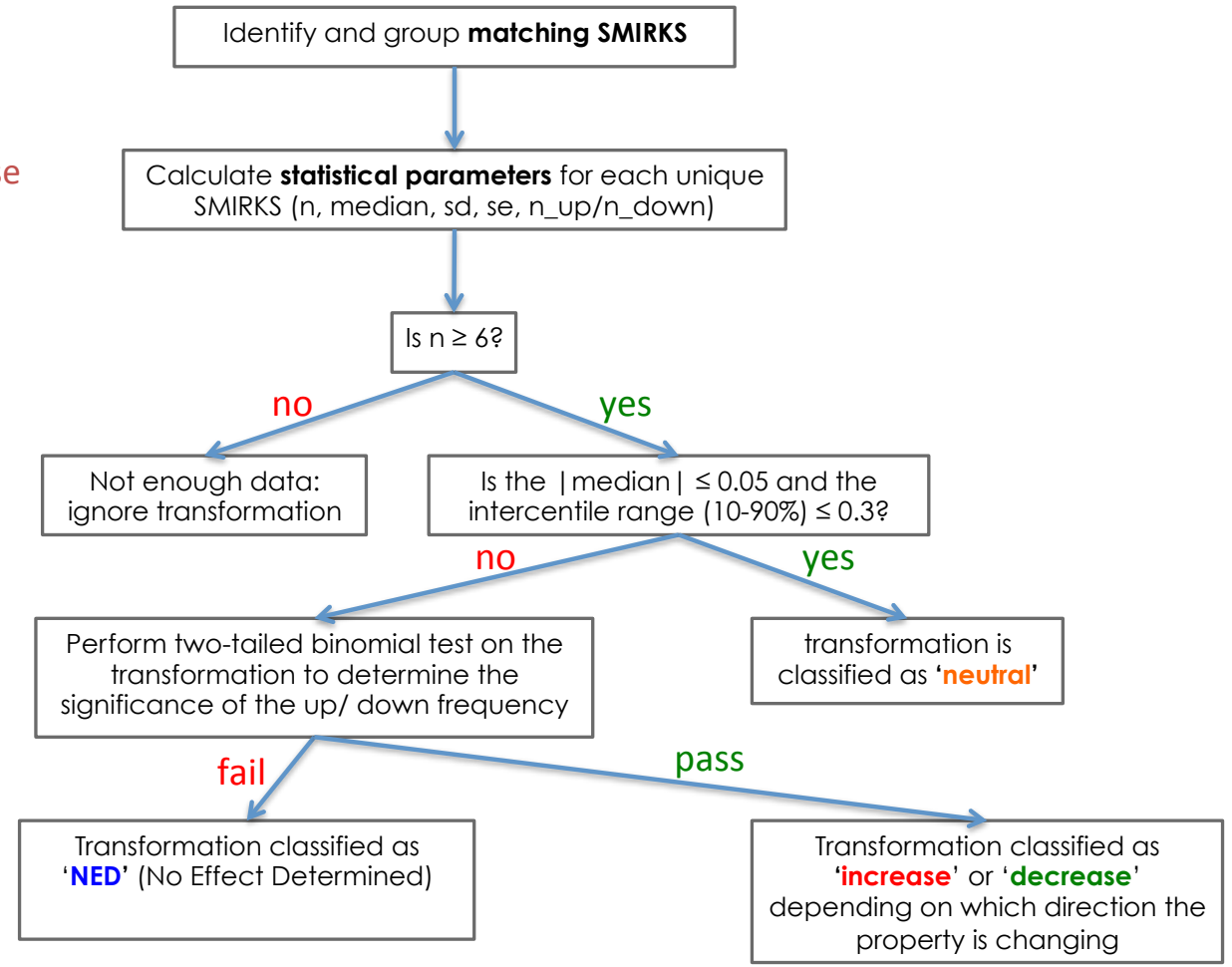


Rule selection

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY



- No assumption of normal distribution
- Manages 'censored' = qualified / out-of-range data

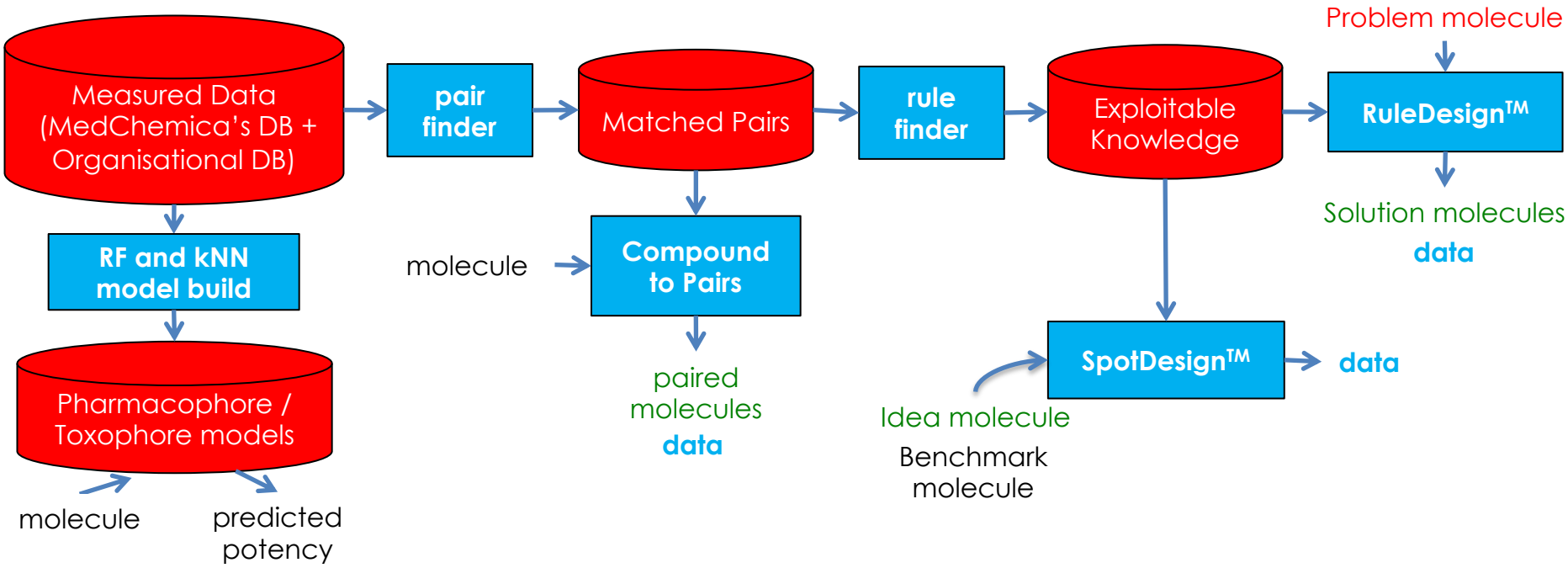


Leach et al. *J. Chem. Inf. Model.* **2017**, **57**, 2424 - 2436

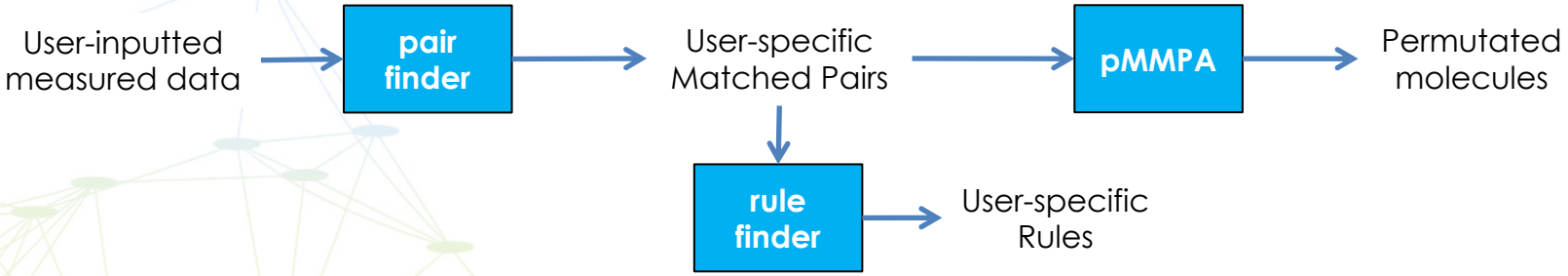
Exploiting data derived ADMET Knowledge

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

DATABASE TOOLS



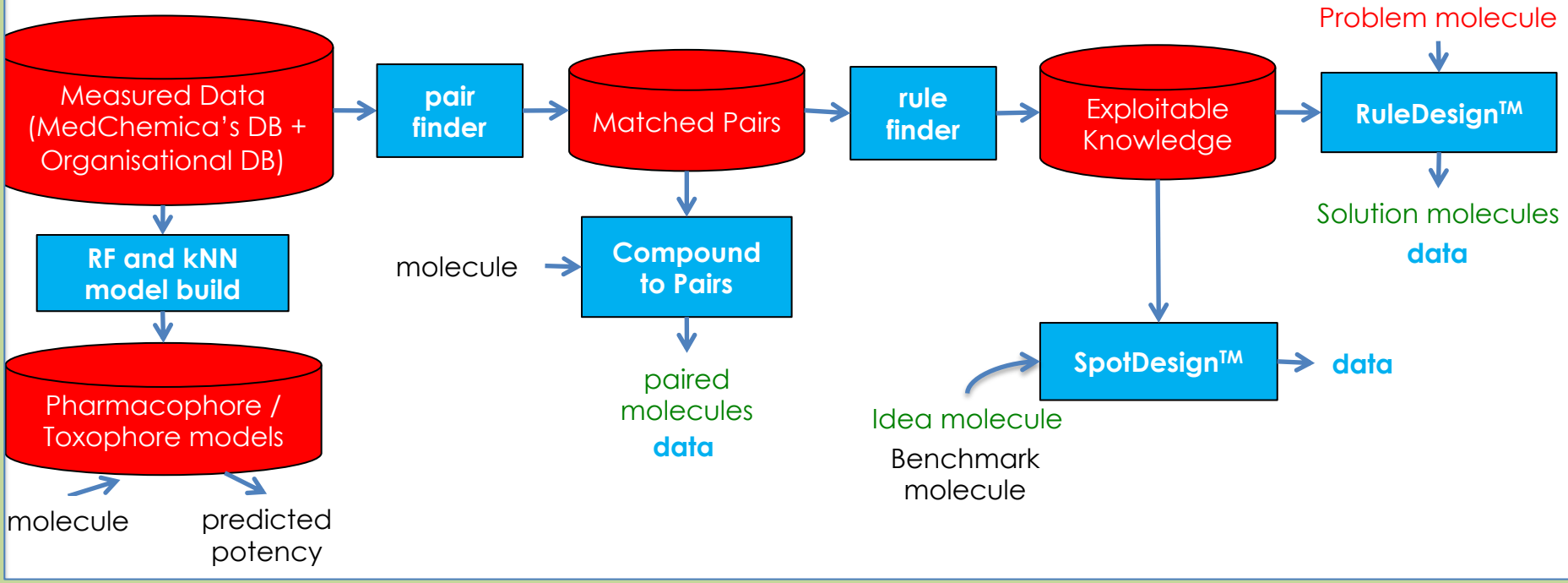
MyPAIRS



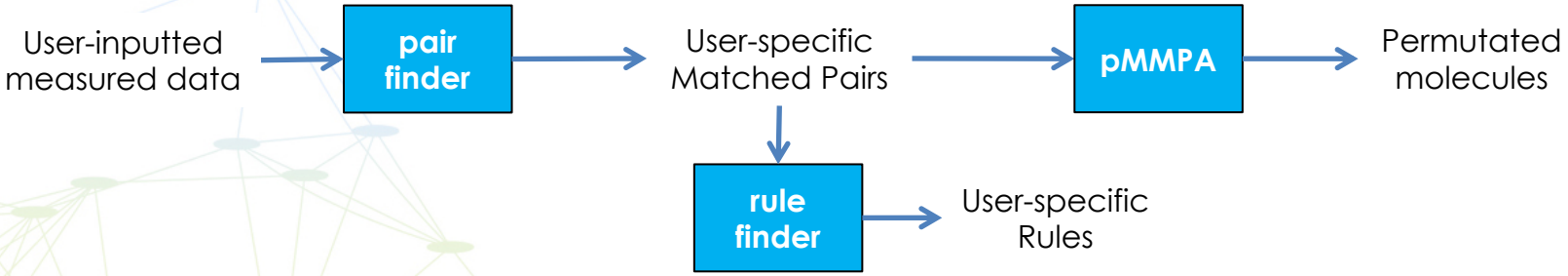
Exploiting data derived ADMET Knowledge

MedChemica

DATABASE TOOLS



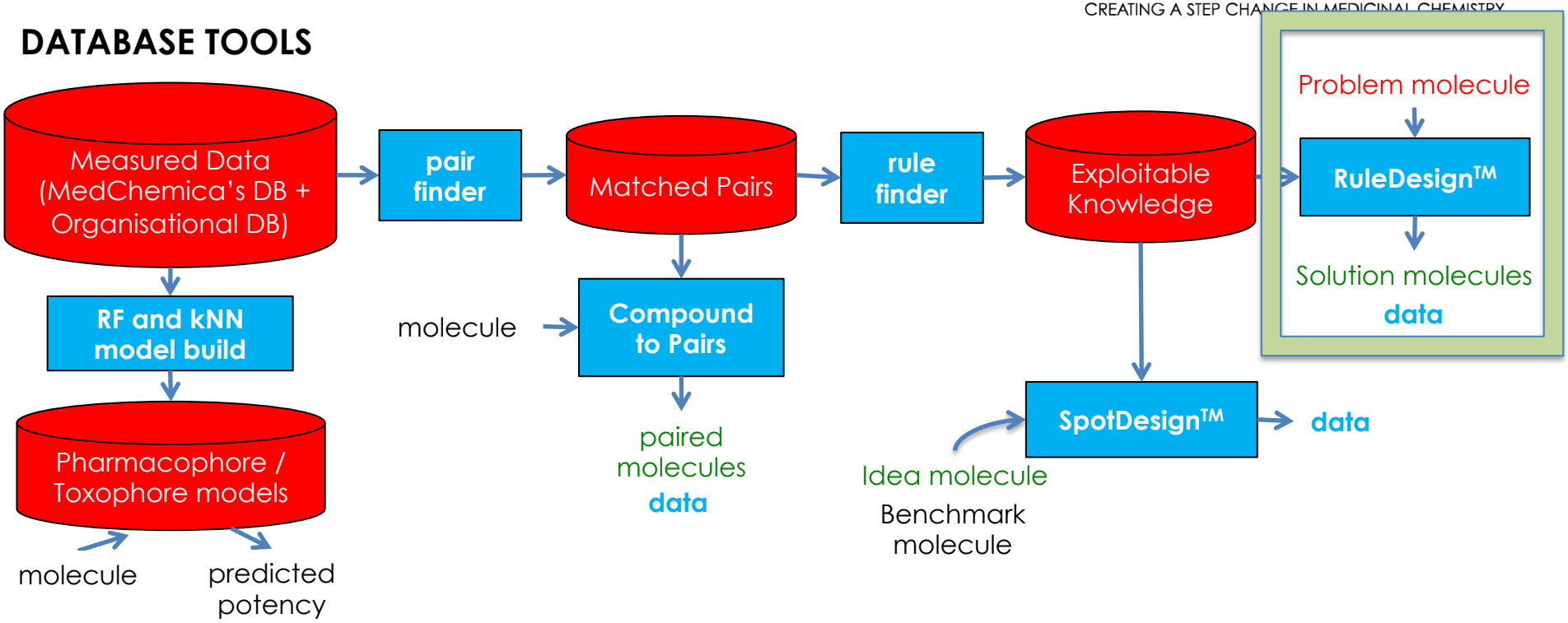
MyPAIRS



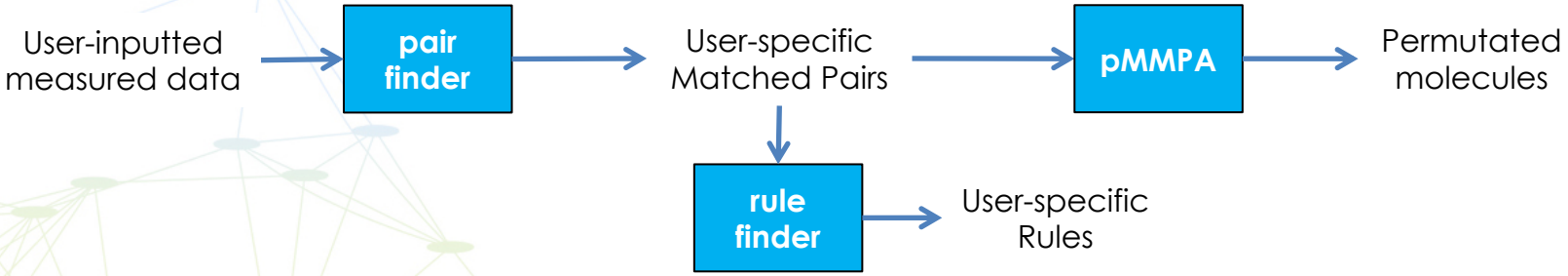
Exploiting data derived ADMET Knowledge

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

DATABASE TOOLS

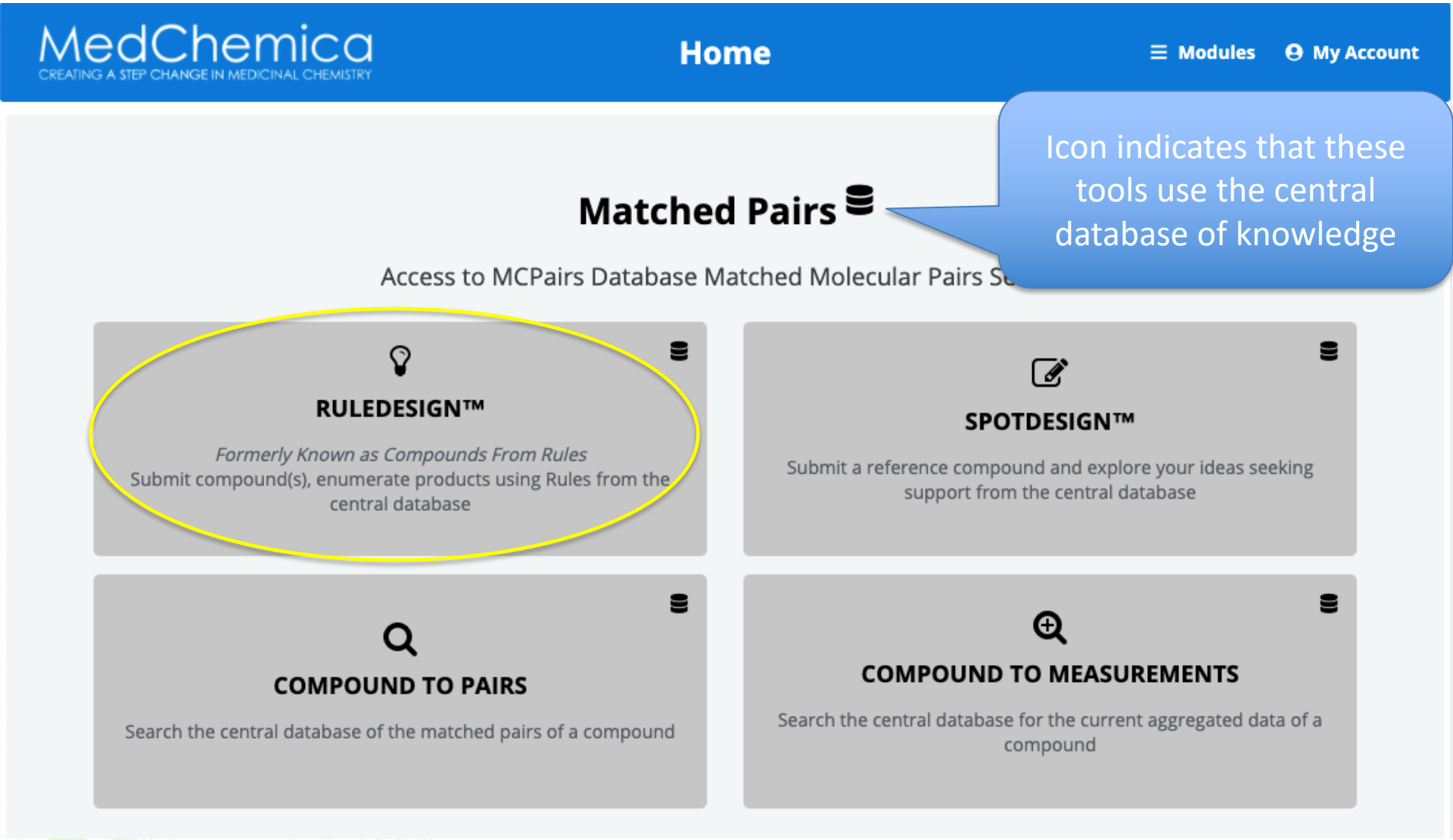


MyPAIRS



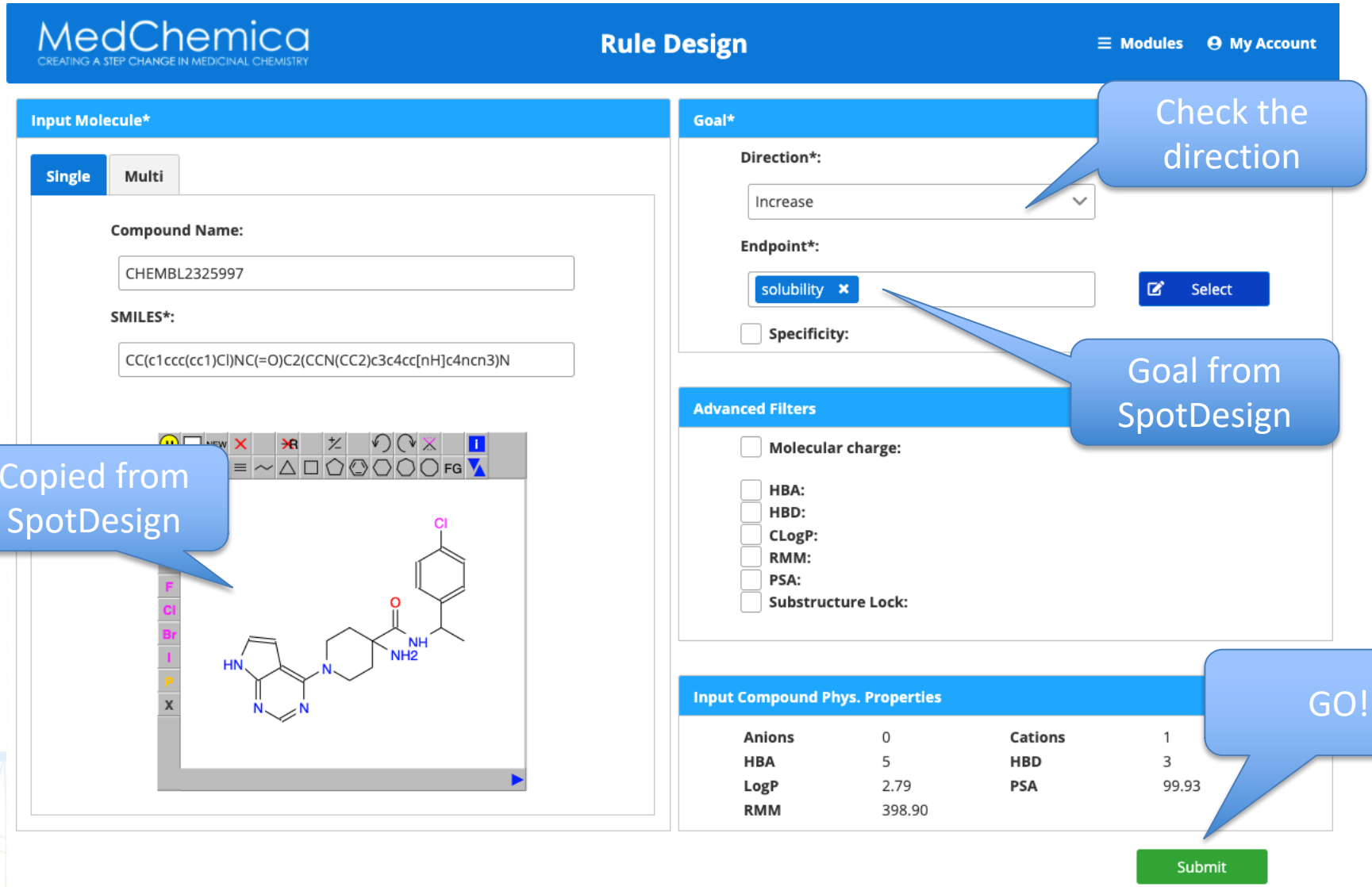
Exercise – New Idea based on rules (Show me the Gems'!)

- Input chemical name for lead molecule CHEMBL2325997
  - Choosing the property to improve (setting the Goal)
    - Find Phys_Prop -> Solubility (Broad Goal)
  - Filtering the results down by substructure and phys-props
  - Export the results – controlling the output
  - Exploring results in Excel
    - what do the numbers mean?
    - How do I use these to make a knowledge based decision?
  - Drilling back to the original source (looking at the matched pairs)



Rule Design

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY



Rule Design

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

Input Molecule*

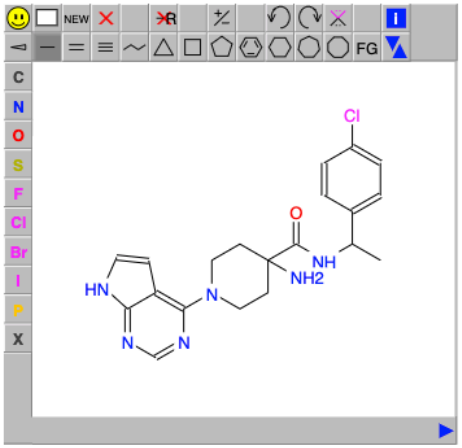
Single | Multi

Compound Name:

CHEMBL2325997

SMILES*:

CC(c1ccc(cc1)Cl)NC(=O)C2(CCN(CC2)c3c4cc[nH]c4ncn3)N



Goal*

Direction*:

Increase

Endpoint*:

solubility ×

Select

Specificity:

Advanced Filters

Molecular charge:

HBA:
HBD:
CLogP:
RMM:
PSA:
Substructure Lock:

Focus your design

Input Compound Phys. Properties

Anions	0	**Cations**	1
HBA	5	**HBD**	3
LogP	2.79	**PSA**	99.93
RMM	398.90		

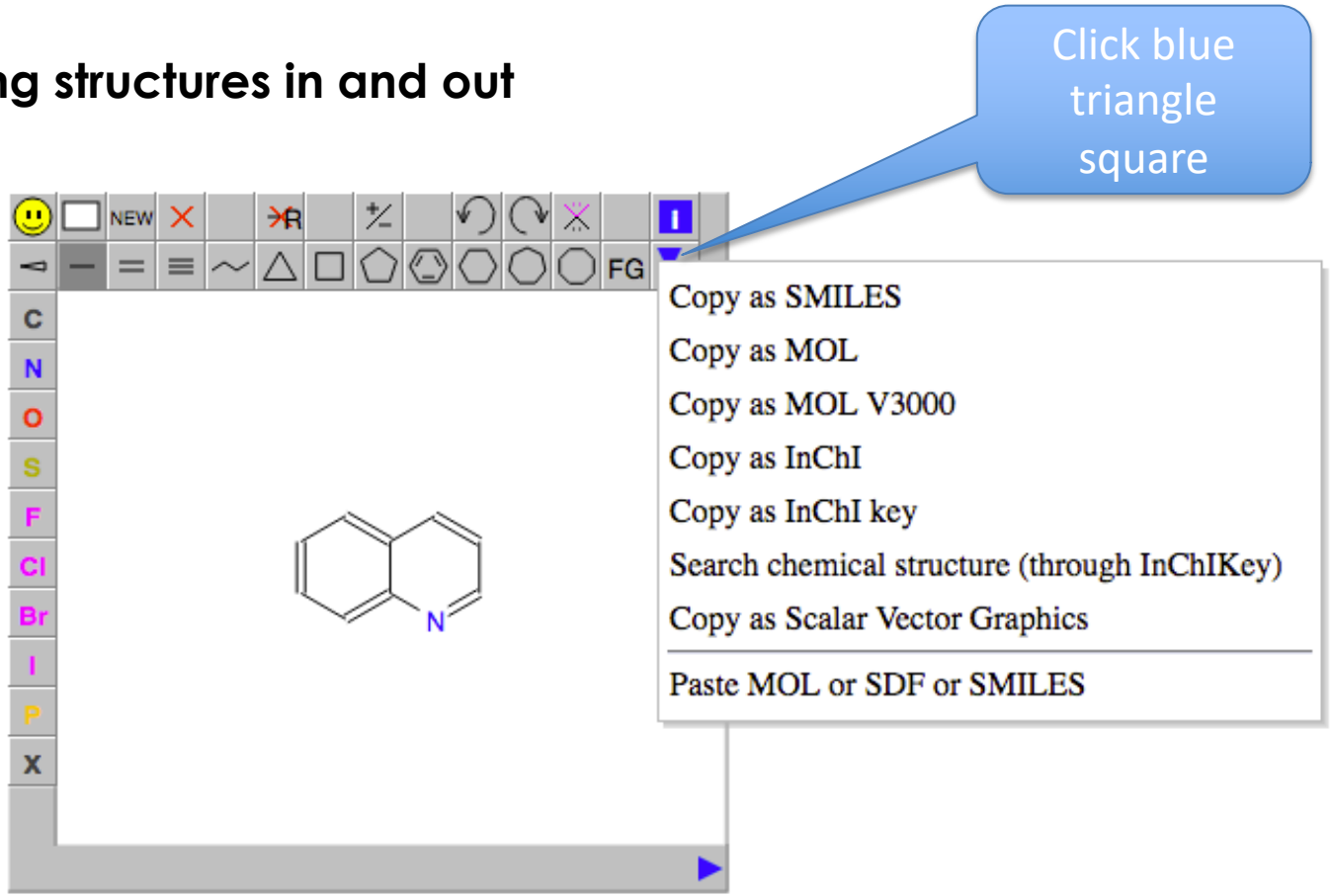
Save Your results

Submit

	#	Timestamp	Status	Number of Products	
◉	0	Feb 1, 2021, 11:46:13 AM	Complete	612	Save

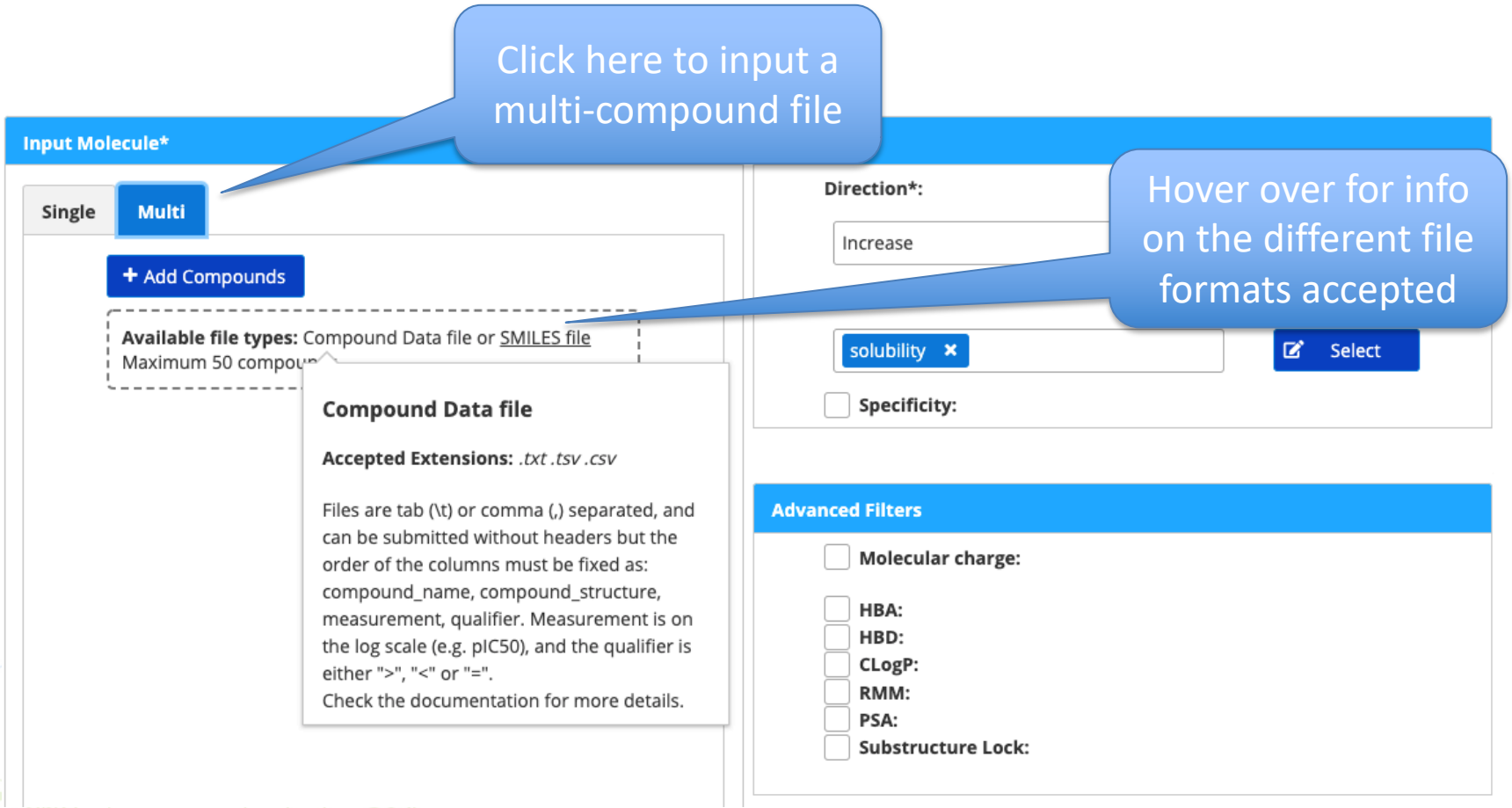
TopTip : Other methods to get a structure in

- **Pasting structures in and out**



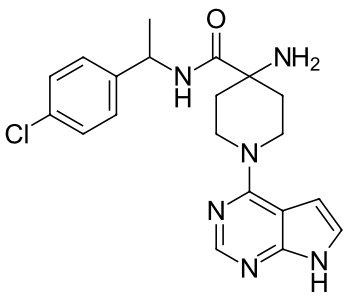
TopTip : Other methods to get a structure in

- **Upload a file of multiple compounds**
  - File can contain compounds + measurements or just compounds



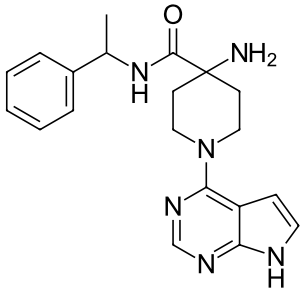
What molecule should I put in?

The more specific the 'seed' molecule, the fewer rules will apply to it

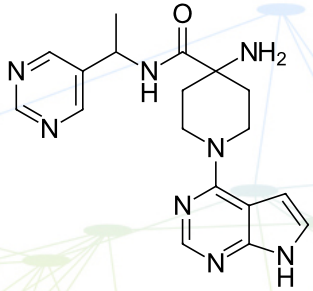


Suggestions to increase solubility

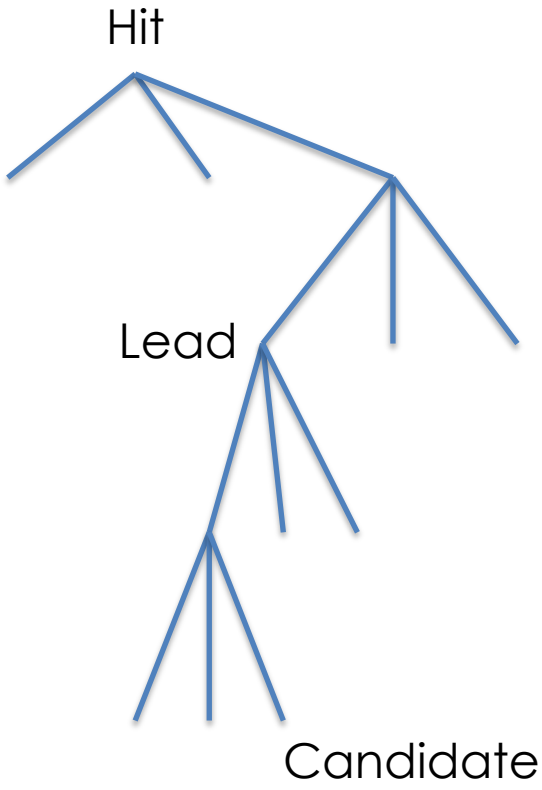
612



664



216



Filtering down the output

- Adding a locked structure (eg pharmacophore)
  - Highlighting the atoms to changes
  - Blocking H substitution
  - Variable atoms
  - 'Complete SMARTS patterns'
  - Also see Tips'n'Tricks document for a detailed work flow

- Charge control

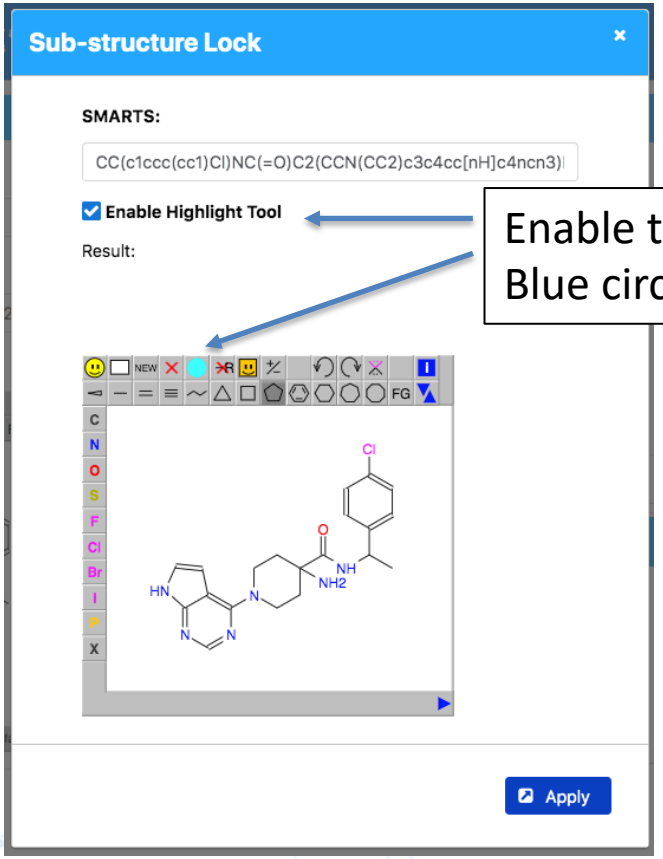
  Filtering by the charge of the final compounds (neutral, acidic, basic)

- Simple Lipinski property filters

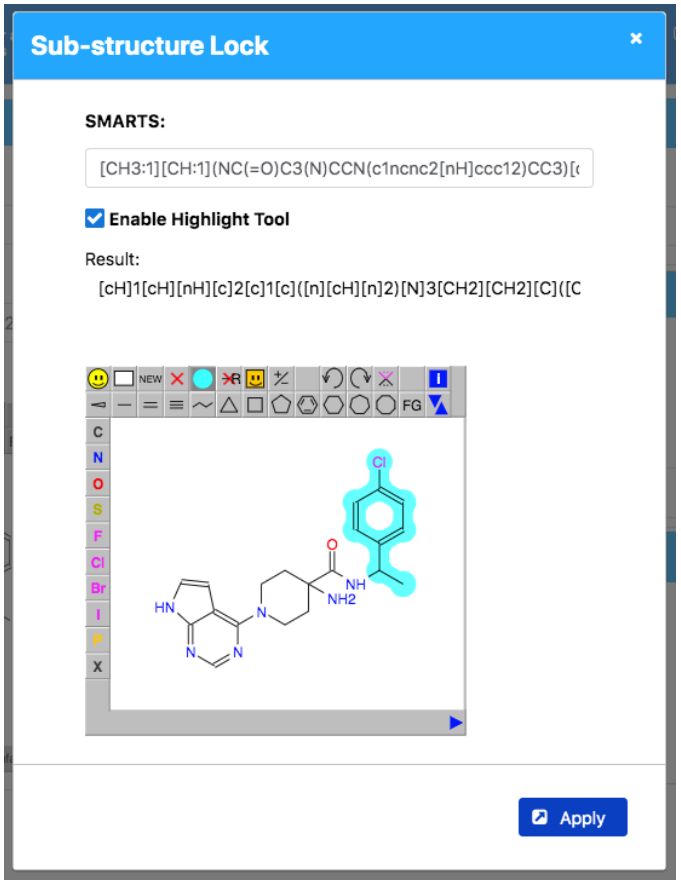
Highlight the part you want to change

Draw

- Add a locked structure with Substructure-Lock (eg pharmacophore)



Enable tool, click Blue circle

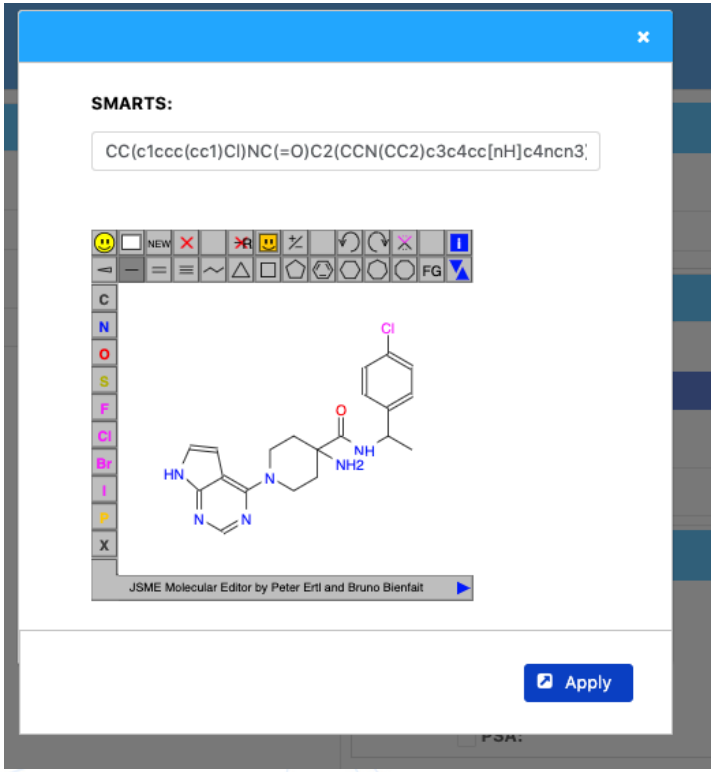


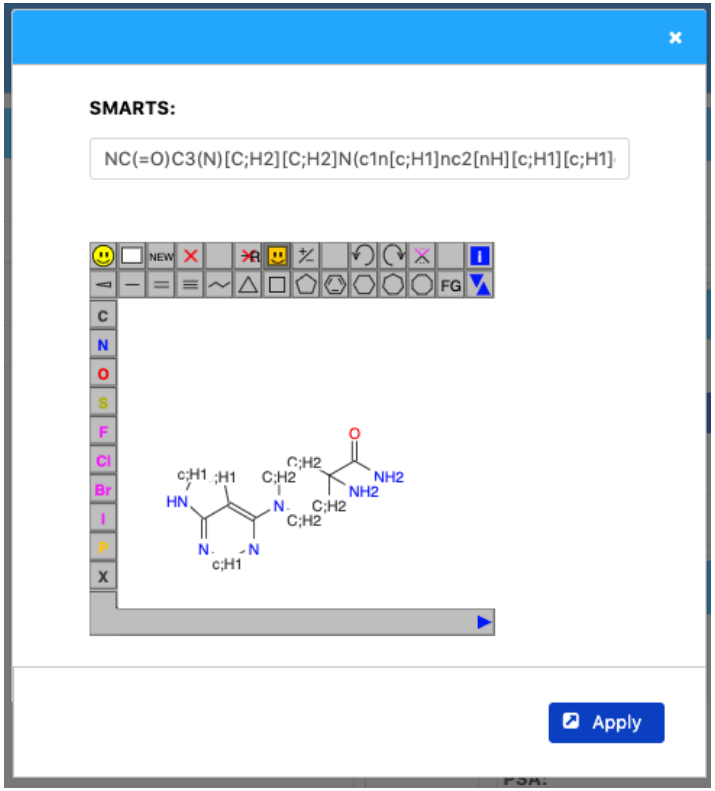
Click atoms with highlighter tool

Alternatively lock out specific hydrogens

Draw

- Add a locked structure with Substructure-Lock (eg pharmacophore)

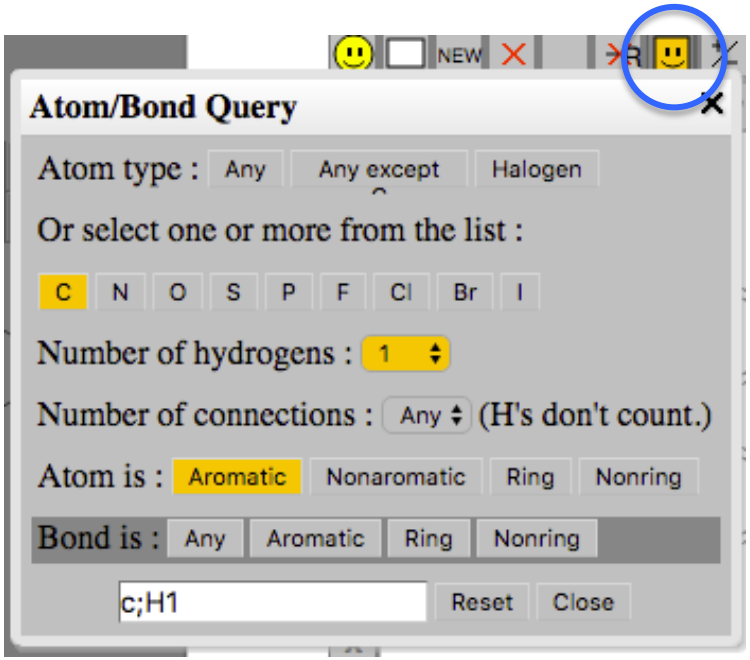




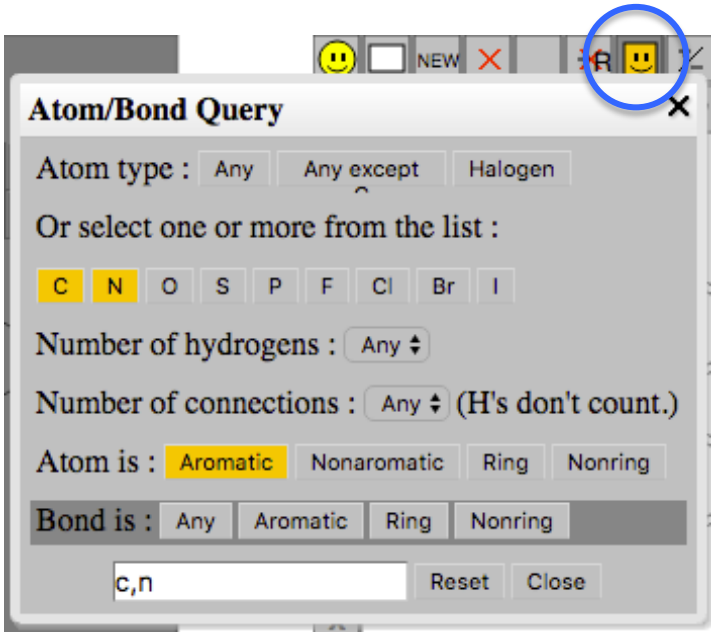
Delete to groups you want to change
Lock out hydrogens to stop substitution

Defining H-atoms to block out

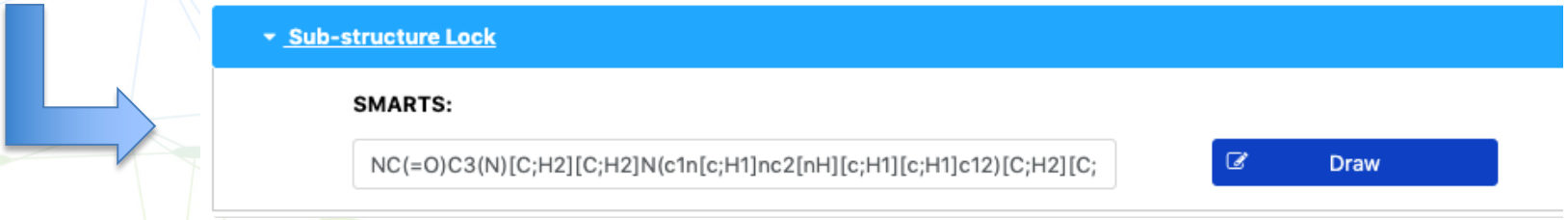
Blocking H



Variable atoms



Close the box, then click on atoms in the picture to change their filter types



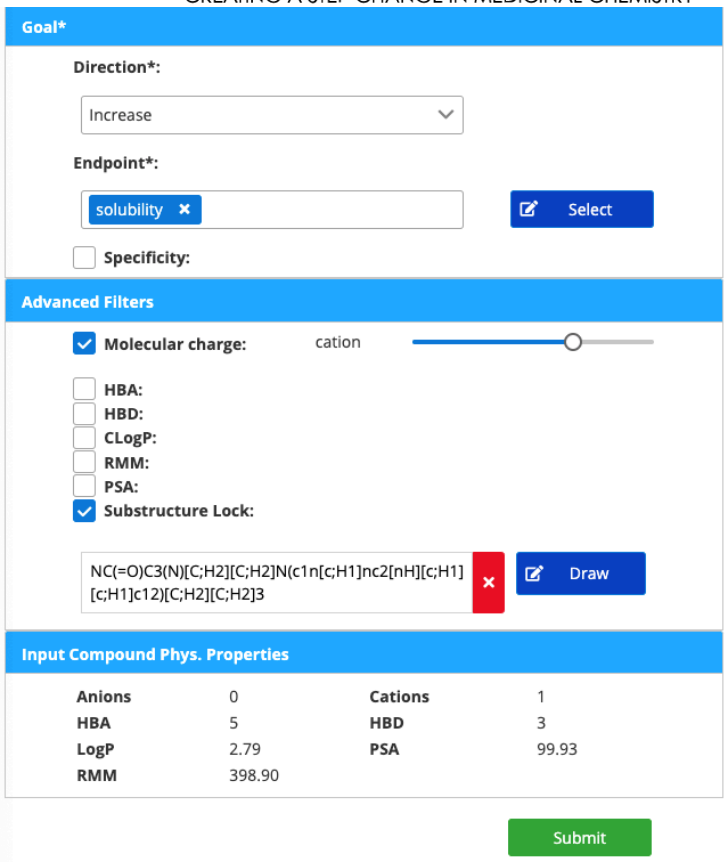
Combined Filters

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

Goal Selection

Charge and Calc Props

Sub-Structure Lock



History Box

1st run Solubility ideas	612
2nd run with Sub-Structure Lock	338
3rd Run no neutral molecules	1
4th with single cation	123

Common Goal Patterns

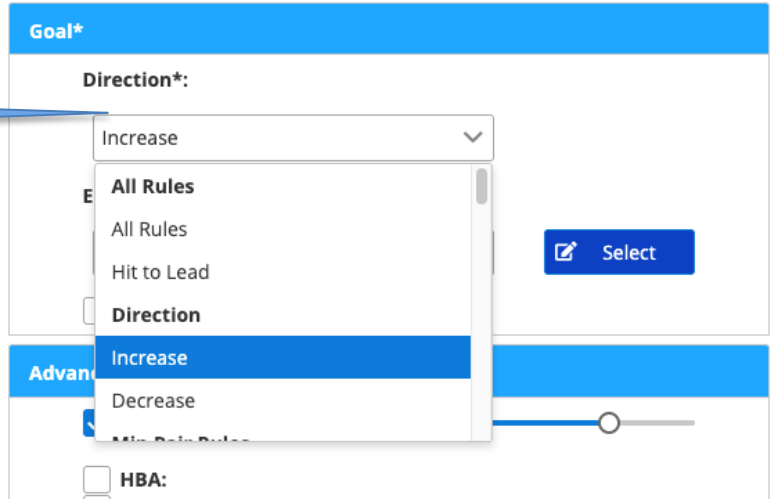
MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

Example	Goal	Directions
1	Solubility	increase
2	Metabolism	decrease
3	HLM_Clint_generic_uL.min-1.mg-1	decrease
4	Absorption	increase
5	Caco-2_A_to_B_perm_CHEMBL614058	increase
6	Transporter	decrease
7	MDCK-dog-perm-log(ER)-dog	decrease
8	Fraction unbound	increase
9	PPB_hum_log(proportion_Free)	increase
10	LogD_TM	decrease (usually)
11	Anti-target_cardiac	decrease
12	hERG_hum_inhib_pIC50	decrease
13	Anti-target_DDI	
14	CYP_inhibs_3A4_pIC50_hum	
15	CCR5_human_pIC50_CHEMBL274	decrease (reduce off target)

How many pairs? – deeper Goal setting

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

Specific Goal settings



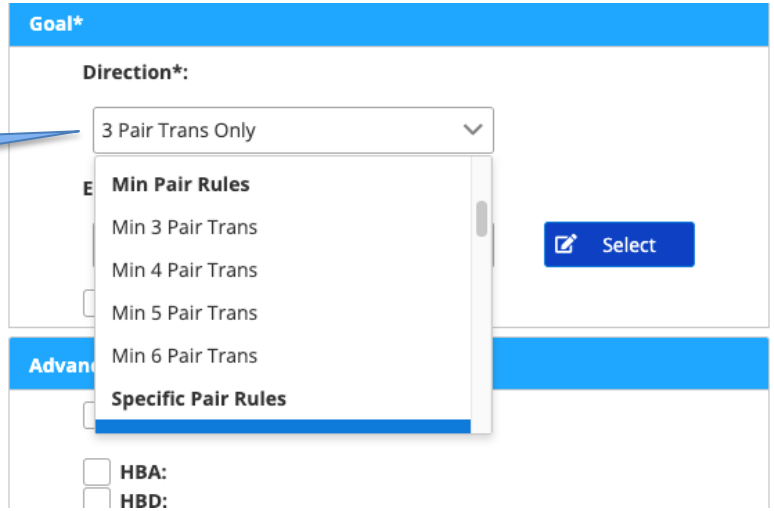
'All Rules'

- all of the Increase and Decrease Rules for all datasets
- warning output can be large
- not suitable for Excel spreadsheet

'Hit to Lead'

- most frequent transformations chemists perform

Non-rules transformations from pair counts



'Min 3 pair Trans'

- all transformations with 3 OR MORE matched pairs

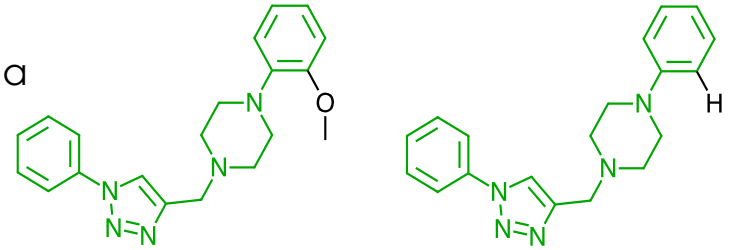
'Min 6 pair Trans'

- all transformations with 6 OR MORE matched pairs
- Actually Increase, Decrease, Neutral and NED

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

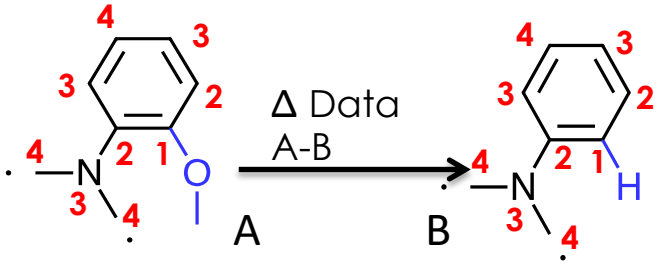
How much environment is captured?

- Matched Molecular Pairs – Molecules that differ only by a particular, well-defined structural transformation



- Capture the change and environment – MMPs can be recorded as transformations from A→ B

- Statistical analysis to define "medicinal chemistry rules"
  Defined transformations with high probability of improving properties of molecules



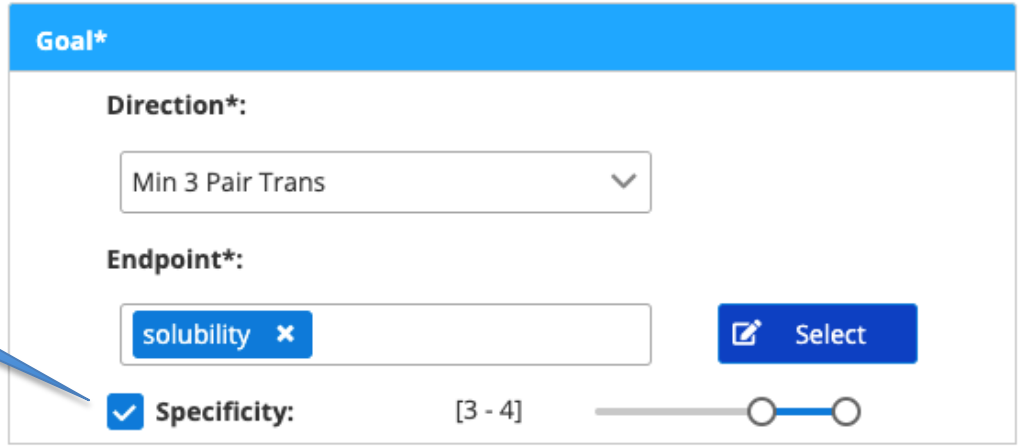
- High specificity are environment size 3 and 4, low is 1 and 2.

Griffen, E. *et al*. *J. Med. Chem.* **2011**, **54**(22), pp.7739-7750.

Specificity of Transformation

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

Specificity setting



'Specificity slider'

– Range 1 to 4
- 4 being the most specific
- setting 3-4 (or 3,4) only apply the most specific rules.

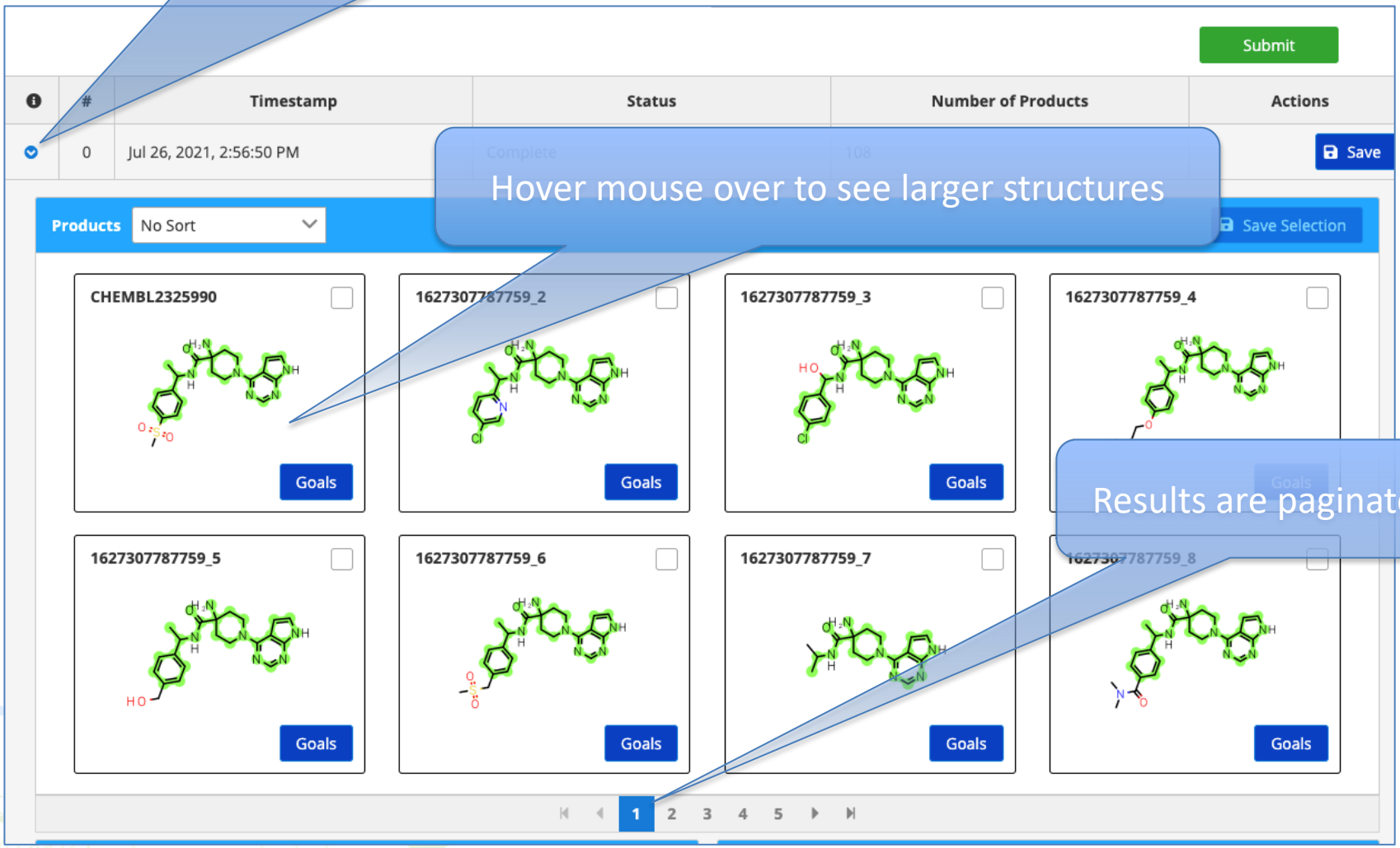
- The number refers to the amount of environment captured with the change in the group

Useful combinations
- Min 3 pairs Trans with high specificity
  - with Kinase – best rules for kinase potency

- All Rules with high specificity
  - The most specific ADMET solutions

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

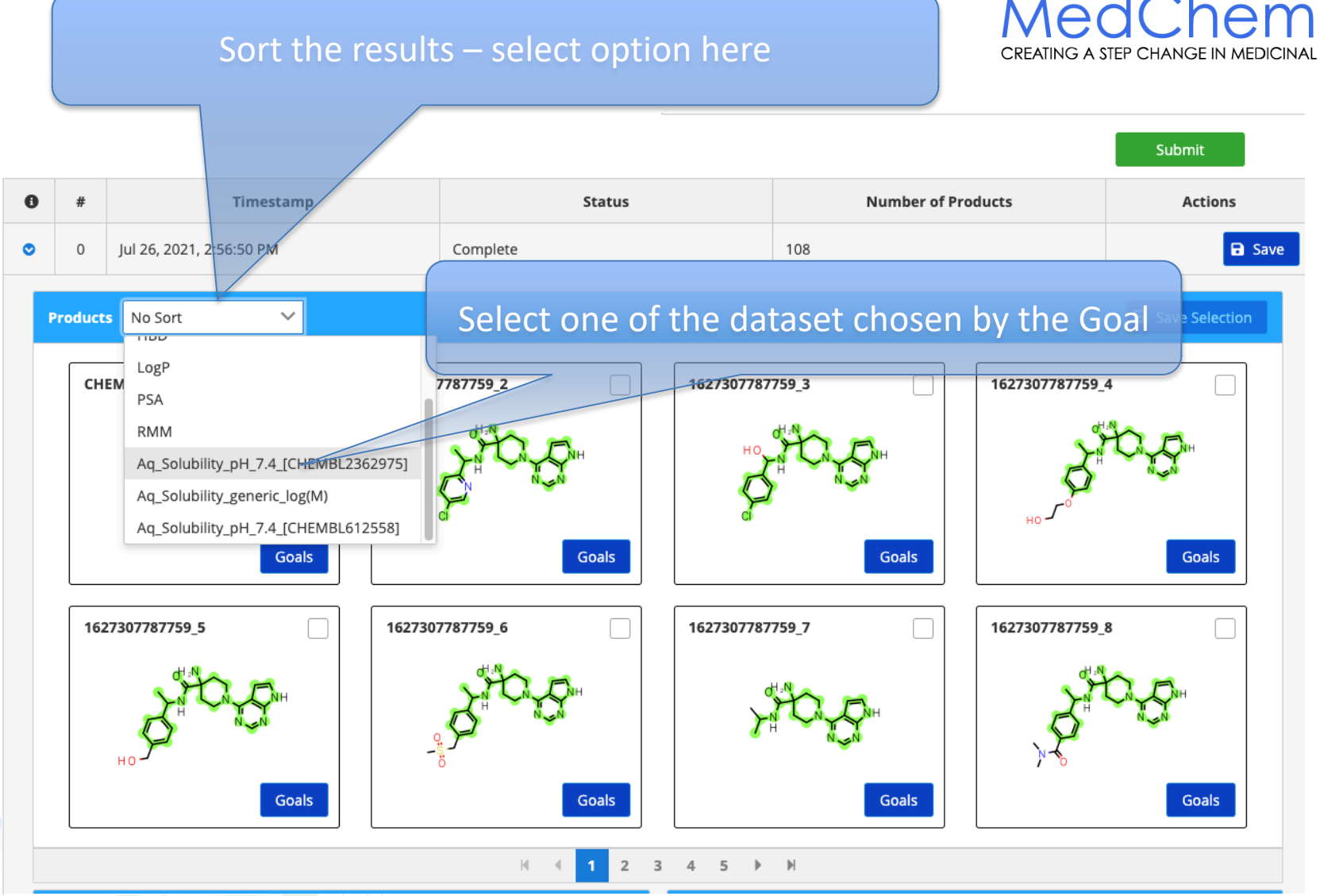
Click the Blue circle to see run results in Browser



MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

Sort the results – select option here

Select one of the dataset chosen by the Goal



MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

Selected Dataset / Goal

Select sort order – Median Change is the size of the change expected

#	Timestamp	Status	Number of Products	Actions
0	Jul 26, 2021, 2:56:50 PM	Complete	108	Save

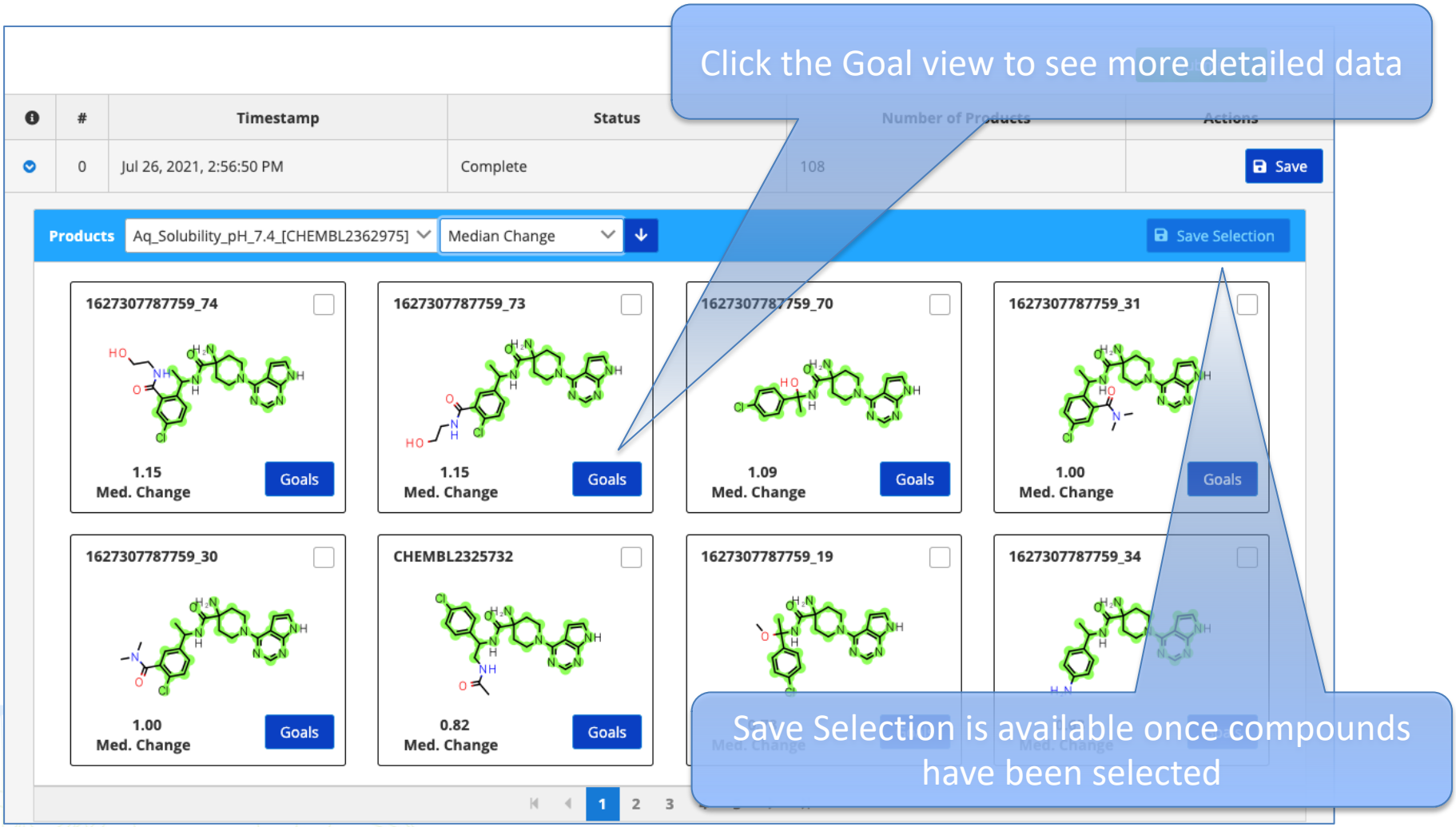
Products | Aq_Solubility_pH_7.4_[CHEMBL2362975] | Median Change | Save Selection

1627307787759_74	1627307787759_73	1627307787759_70	1627307787759_31
1.15 Med. Change	1.15 Med. Change	1.09 Med. Change	1.00 Med. Change
Goals	Goals	Goals	Goals
1627307787759_30	CHEMBL2325732	1627307787759_19	1627307787759_34
1.00 Med. Change	0.82 Med. Change	0.78 Med. Change	0.63 Med. Change
Goals	Goals	Goals	Goals

1 2 3

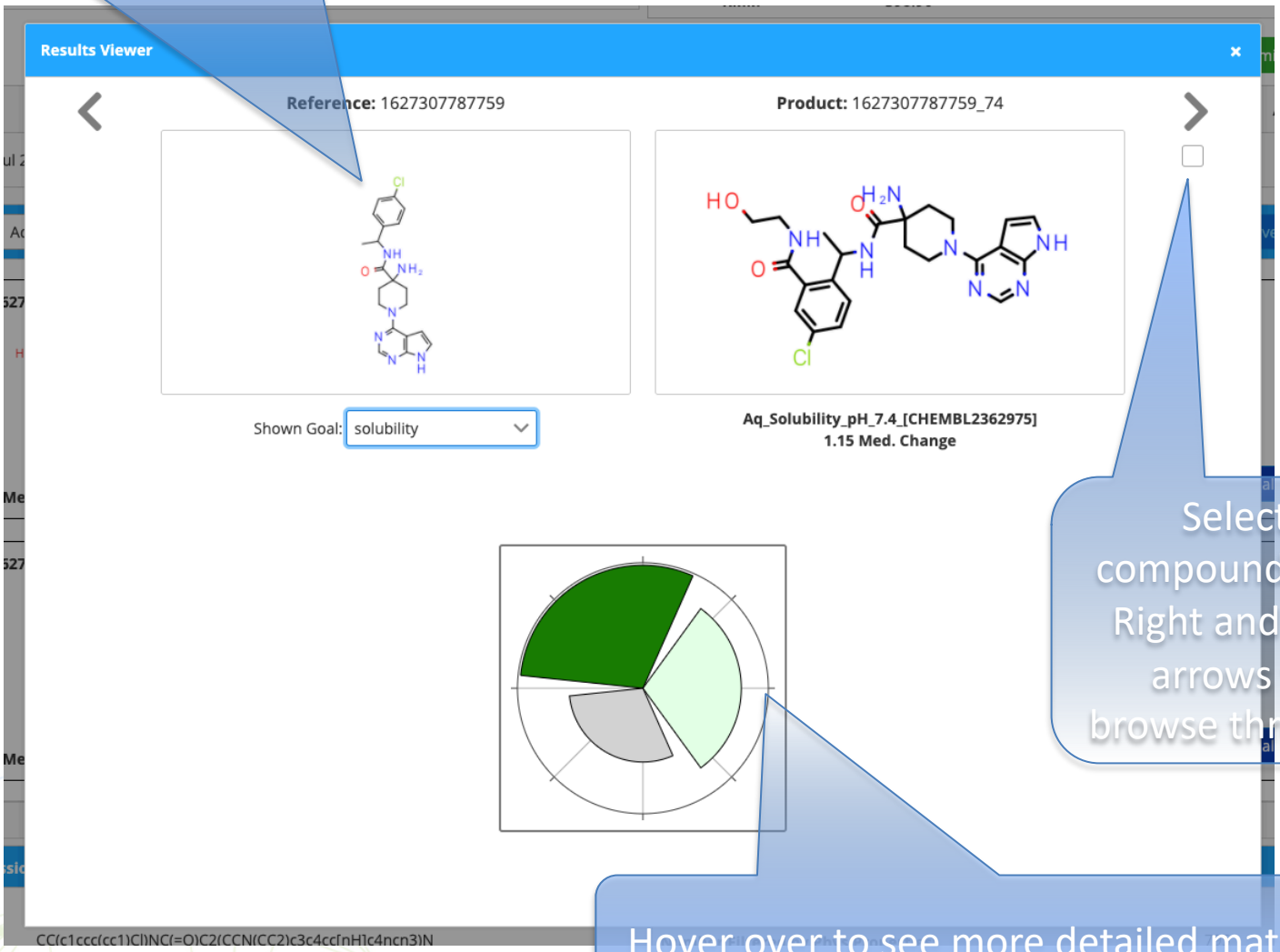
Select preferred example to export

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY



Input molecule and suggested molecule

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

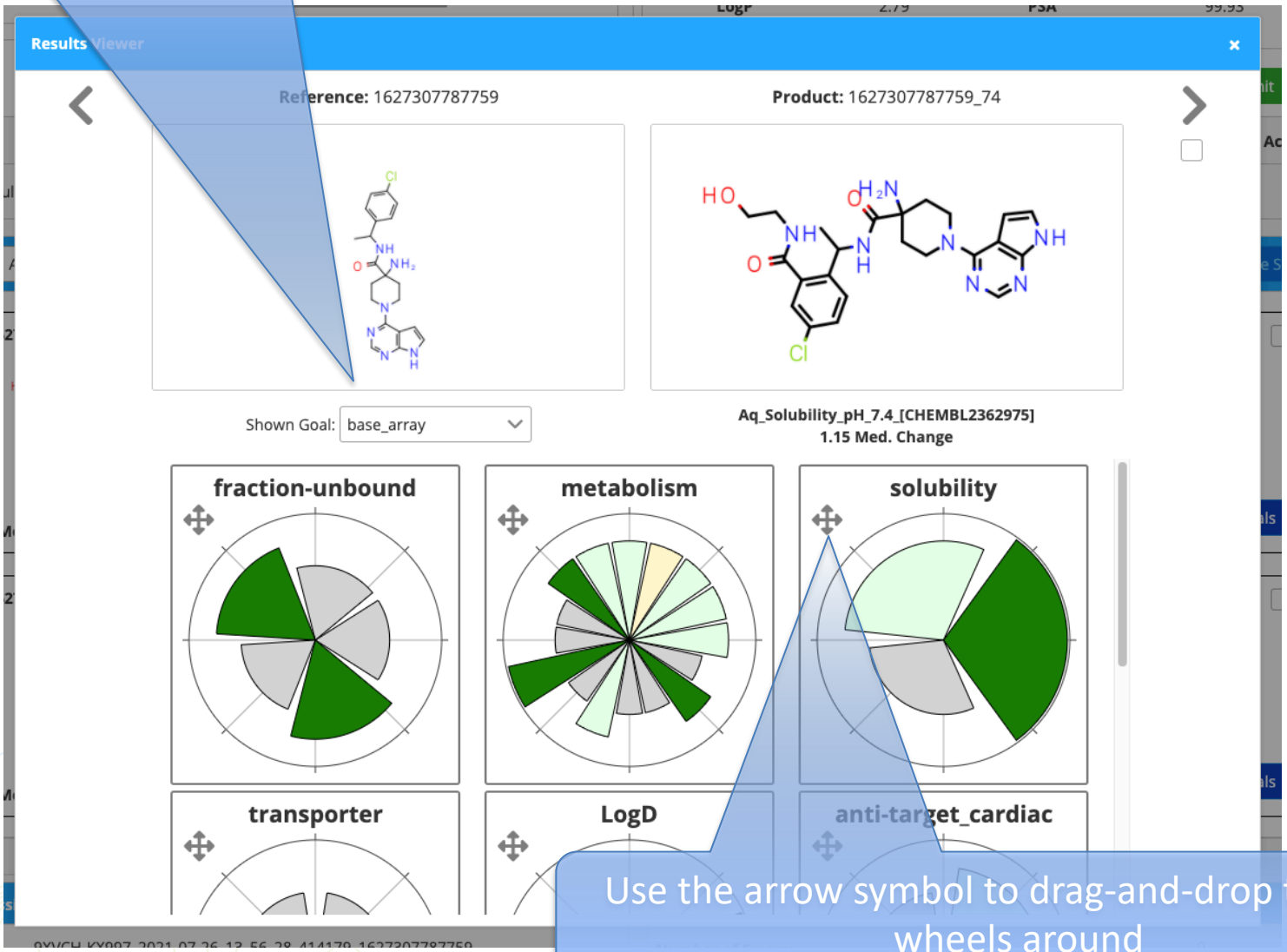


Select compound. Use Right and Left arrows to browse through.

Hover over to see more detailed matched pair data

Select base_array to get the basic ADMET properties

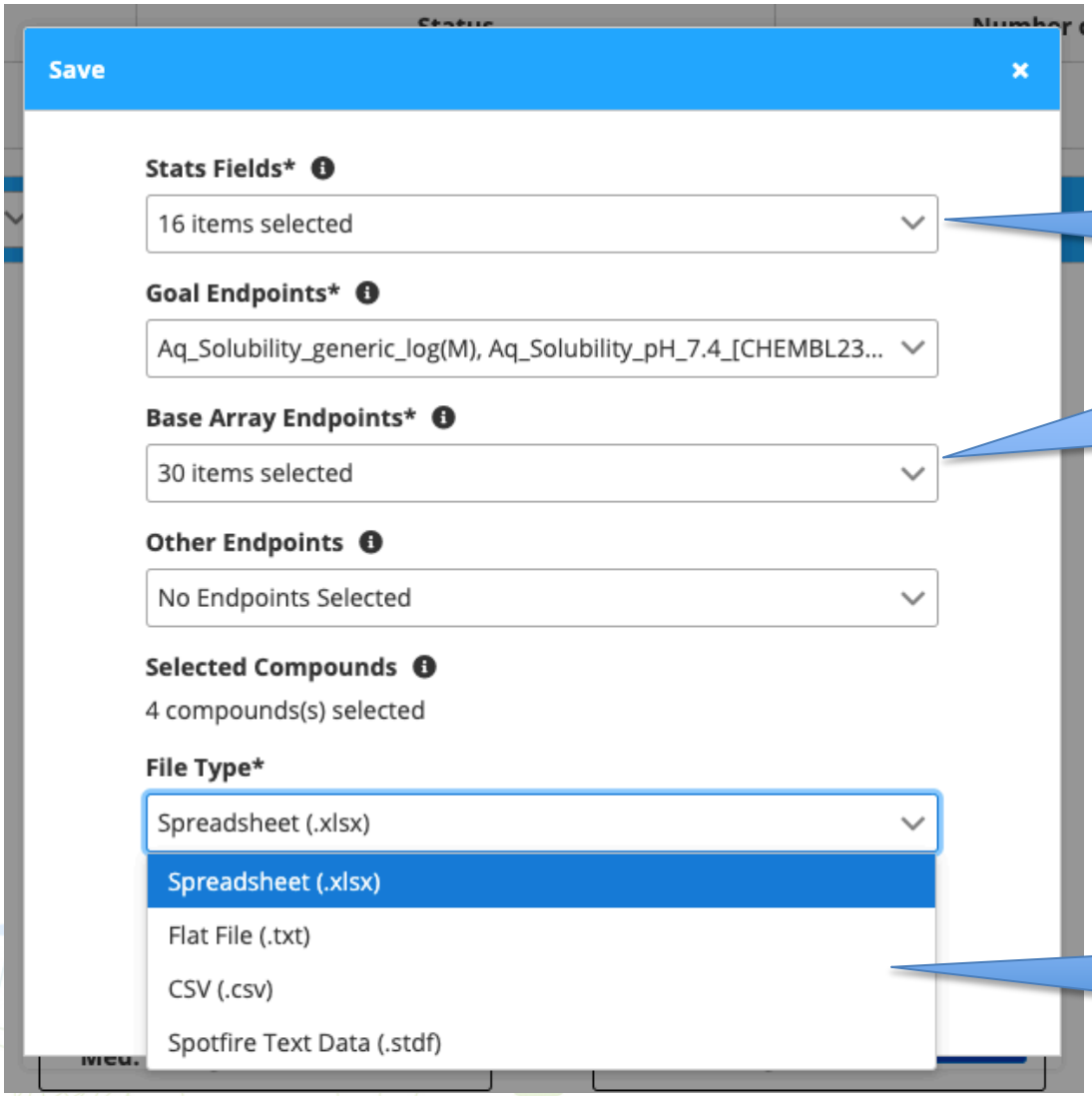
MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY



Use the arrow symbol to drag-and-drop the pizza wheels around

Export results

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY



Select preferred stats fields

Customise which datasets are exported. Default is your Goal and the Base Array

Select output file style

Using the results

- Download the Excel file
- Inspect the structures
  - Filtering and sorting is possible as structures locked to cells
- Look at the breadth of data
- Unhide columns for more data
- Or export csv and use Spotfire, Vortex, Datawarrior….

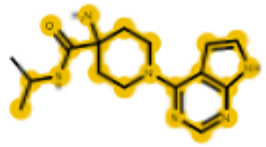
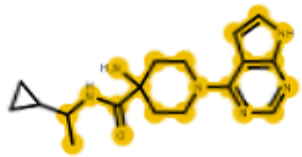
Looking at the results

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

Results sorted in increasing RMM (Mol Weight)

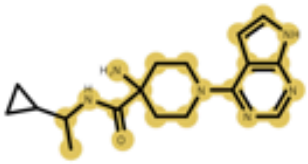
One column per assay
– colour and direction
- LogD decrease, Sol increase

Yellow highlight is the overlap with the input compound

	G	H	I	J	K	L			AD	AT
		pair data	CLogP	HBA	HBD	PSA	RMM	LogD TM direction	Aq Solubility pH 7.4 [CHEMBL2362975] direction	Aq Solubility pH 7.4 [CHEMBL612558] direction
		matched pair data	0.35	7	3	99.93	302.4	decrease	NED	.
		matched pair data	0.72	7	3	99.93	328.4	NED	.	.

Looking at the Stats

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

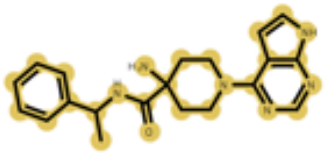
G	H	I	J	K	L	M	BJ	BQ	BR	BS	BT	BU	BV
Depiction	pair data	CLogP	HBA	HBD	PSA	RMM	Aq Solubility comb patent data log(M) direction	Aq Solubility comb patent data log(M) n quant	Aq Solubility comb patent data log(M) n qual	Aq Solubility comb patent data log(M) n qual up	Aq Solubility comb patent data log(M) n qual down	Aq Solubility comb patent data log(M) median change	Aq Solubility comb patent data log(M) std dev
													
C1(CCN(CC1)c2c3cc[nH]c3ncn2)N	matched pair	0.7	7	3	100	328.4	increase	9	9	9	0	1.701	0.586

Click the hyperlink to see the source data

n-qual – number of matched pairs used in analysis
n-qual-up – number of +ve delta measurements
n-qual-down – number of –ve delta measurements
n-median result – middle delta measurement
Std-dev – standard deviation – give an idea of the spread of data

Looking at the Stats

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

G	H	I	J	K	L	M	QD	QK	QL	QM	QN	QO	QP	QQ	QR
Depiction	pair data	CLogP	HBA	HBD	PSA	RMM	hERG hum inhib pIC50 direction	hERG hum inhib pIC50 n quant	hERG hum inhib pIC50 n qual	hERG hum inhib pIC50 n qual up	hERG hum inhib pIC50 n qual down	hERG hum inhib pIC50 median change	hERG hum inhib pIC50 std dev	hERG hum inhib pIC50 std err	hERG hum inhib pIC50 binom test	
																
)NC(=O)C2(CCN(CC2)c3c4cc[nH]c4ncn3)N	matched pair	1.6	7	3	100	364.4	decrease	133	133	19	114	-0.411	0.357	0	0	

Looking at this example – Cl to H to decrease hERG binding

- 133 matched pairs
- 114 pairs are –ve so pIC50 is lower for the phenyl
- 19 pairs are +ve so pIC50 is higher for the phenyl
- -0.411 – so half of the pairs are -0.411 or greater improvement
- 0.357 – std dev – small spread – very good chance of 3 fold improvement

Summary

- Choose a ‘reasonable’ start point
- Focus your results by iterative runs
- Use Substructure locking

Remember:

Always download your results – server stores nothing!

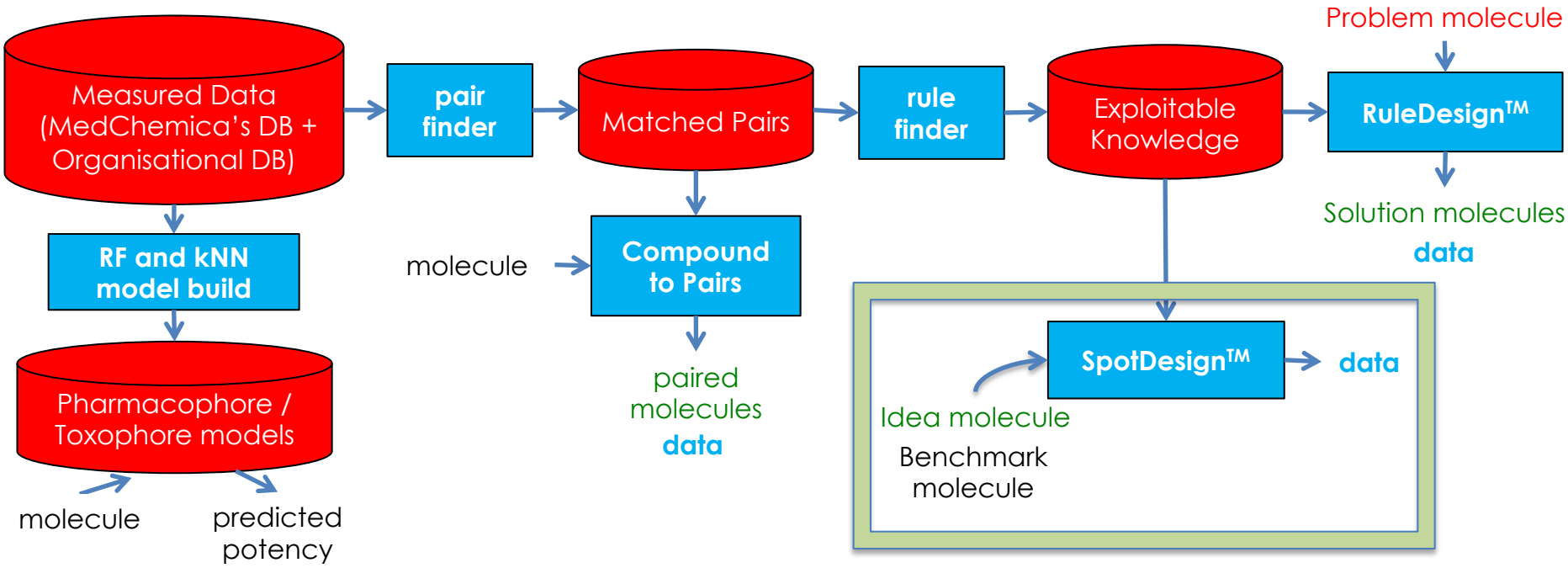
Questions on RuleDesign?

Please use Webinar tools if you are on-line

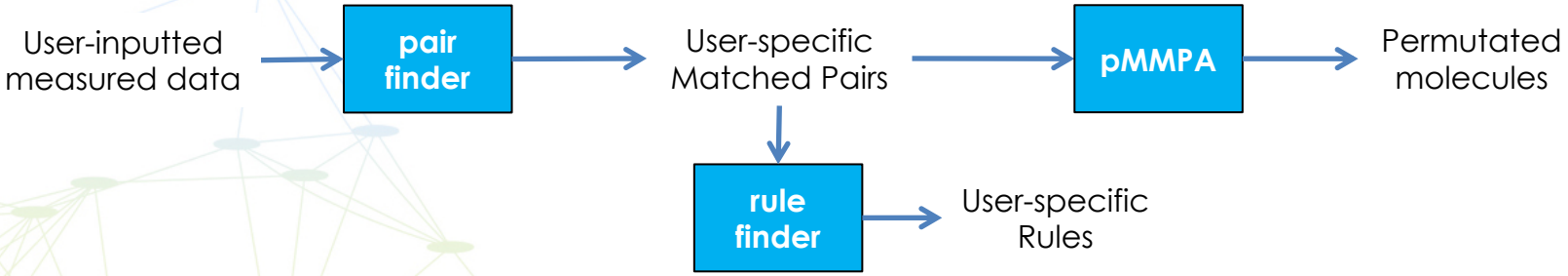
Exploiting data derived ADMET Knowledge

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

DATABASE TOOLS

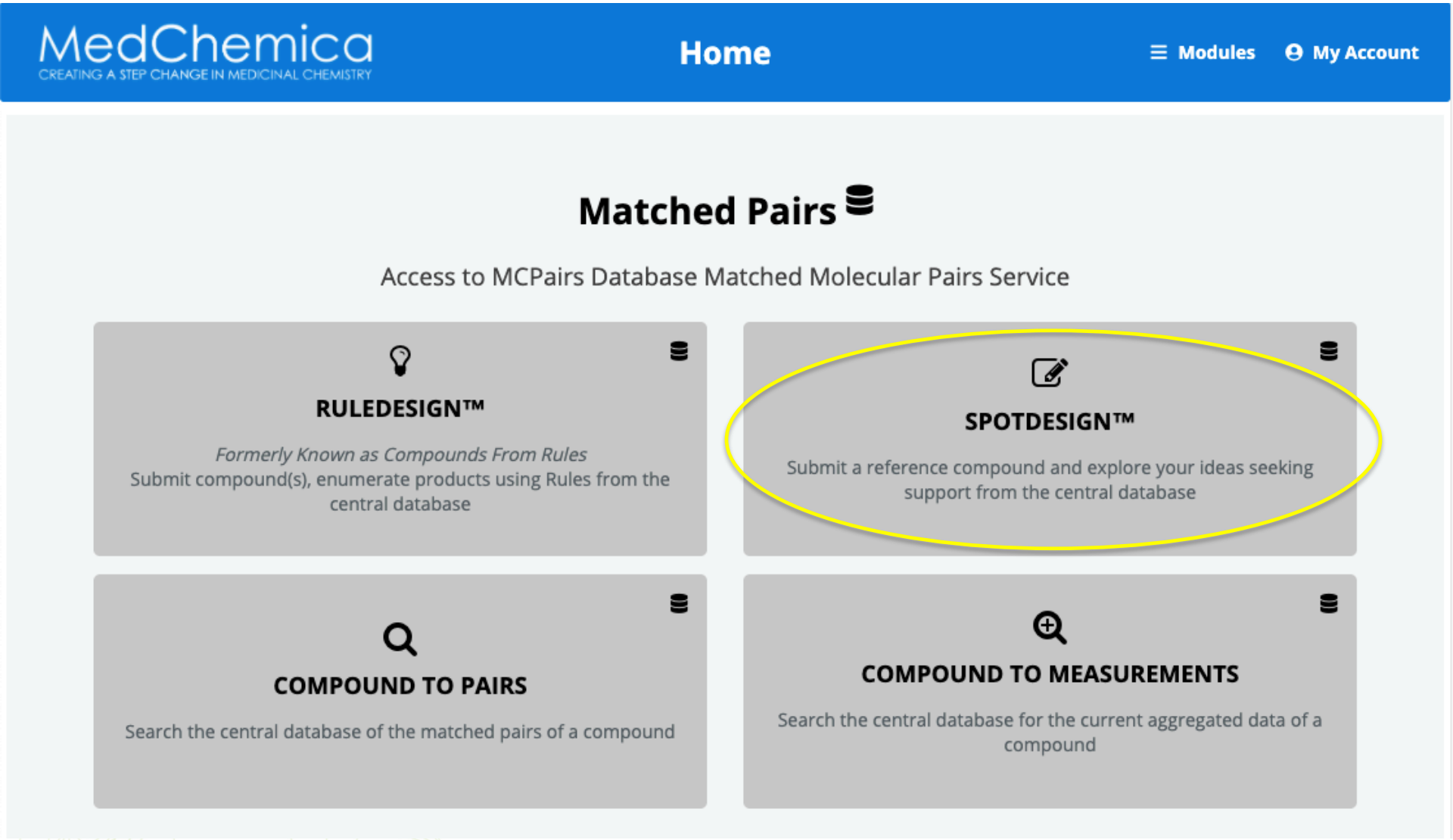


MyPAIRS



Exercise – Explore ideas to improve solubility

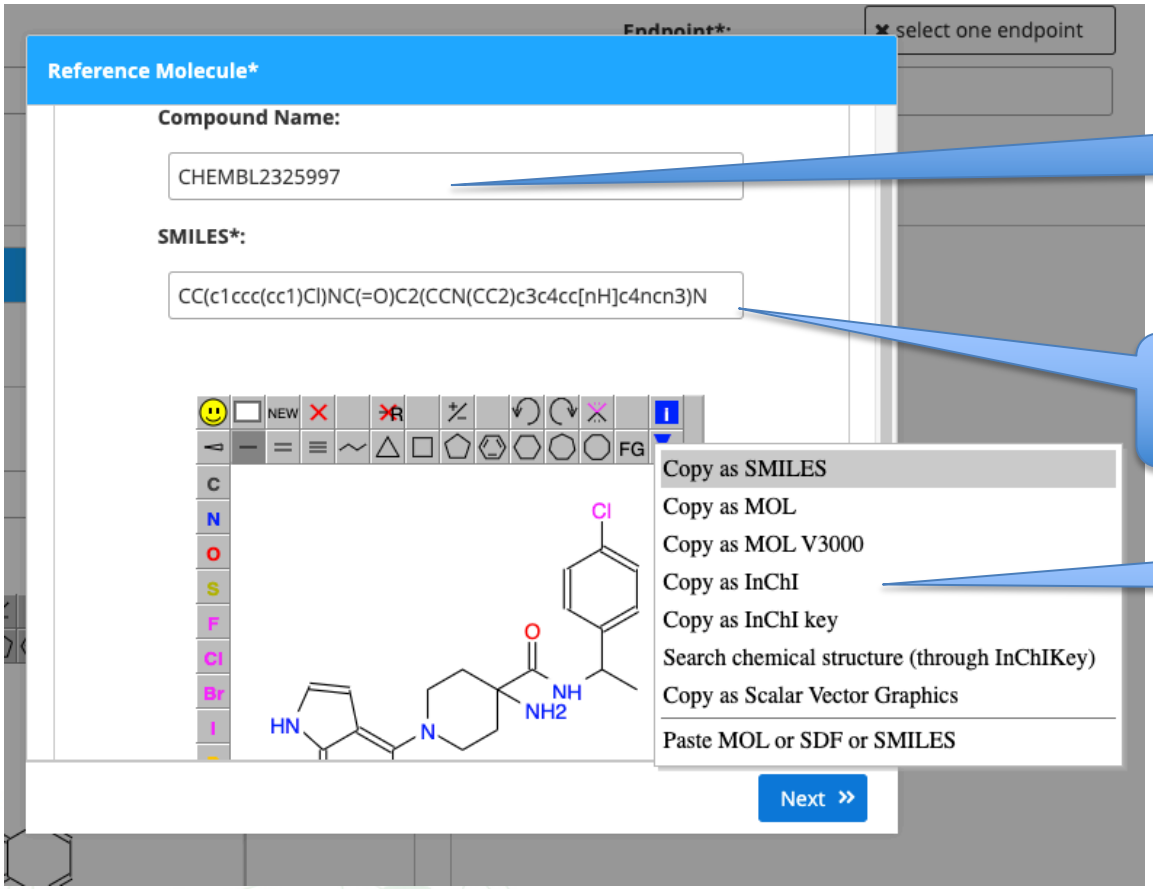
- Input chemical name for lead molecule CHEMBL2325997
  - Choosing the property to improve (setting the Goal)
    - Find Phys_Prop -> Solubility (Broad Goal)
  - Returning results, exploring results
    - what do the numbers mean?
  - Drilling back to the original source (looking at the matched pairs)
  - Running multiple ideas
- Search – Inspect – Export
  - Save with structures or as .csv for other applications
    - (Structures saved as SMILES)



SpotDesign : How good is my idea?

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

Entering a reference compound



Compound name?

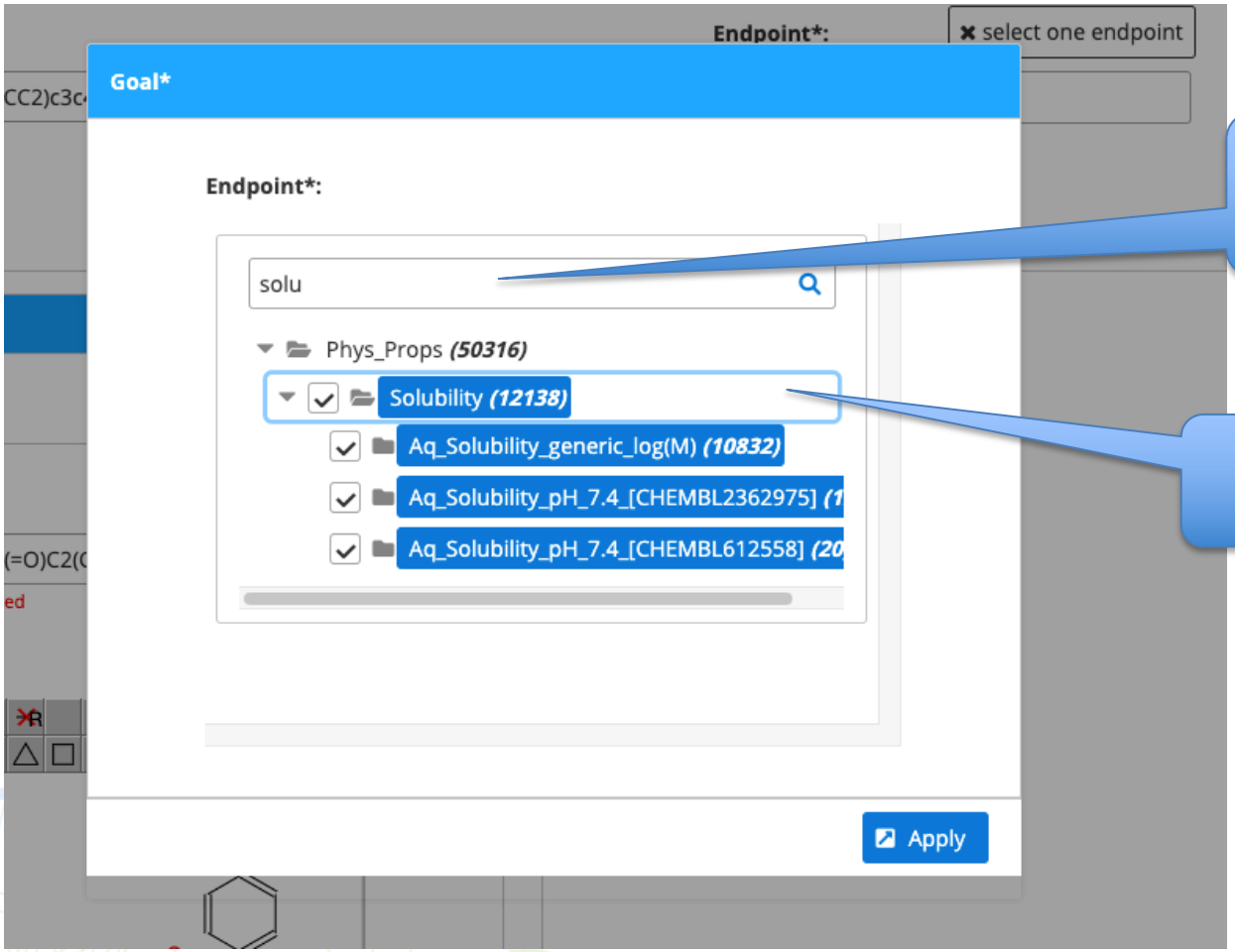
SMILES structure

Other methods

SpotDesign : How good is my idea?

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

Selecting a Goal



Text search

Select Goal

SpotDesign : How good is my idea?

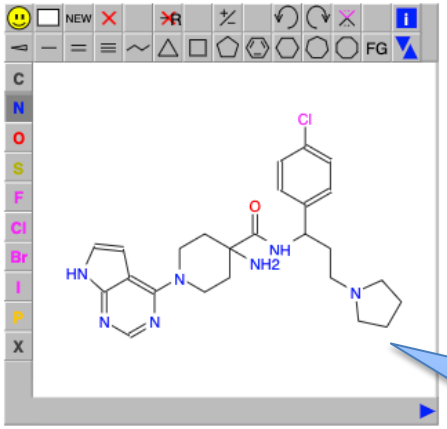
MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

Idea Molecule*

Single | Multi

SMILES*:

NC5(C(=O)NC(CCN1CCCC1)c2ccc(Cl)cc2)CCN(c3ncnc4[nH]ccc34)CC5



Draw your idea molecule

	Idea	Delta
ClogP	2.77	0.51 ↑
HBA	8.00	1.00 ↑
HBD	3.00	0.00 ●
PSA	103.17	3.24 ↑
RMM	482.02	83.13 ↑

Submit

GO!

Rules

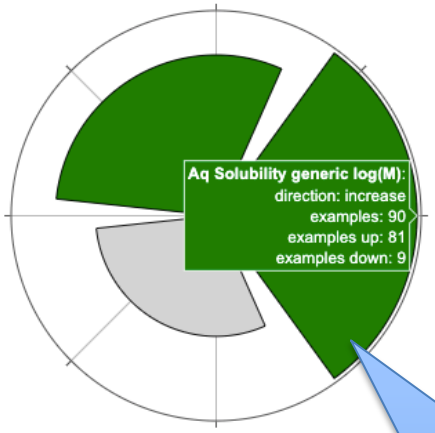
Phys_Props > Solubility

Endpoints with Rules:

2 / 3

Other Rules:

increase	2
decrease	2
remaining	37
total	41



Tip! Clicking an endpoin

Hover to explore results Click to drill deeper

Quick tip…

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

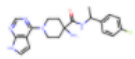
Spot Design

Modules | My Account

Reference Molecule* and Goal*

SMILES*:

CC(c1ccc(cc1)Cl)NC(=O)C2(CCN(CC2)c3c4cc[nH]c4ncn3)N



Endpoint*:

Solubility ×

Select

Copy to Rule Design

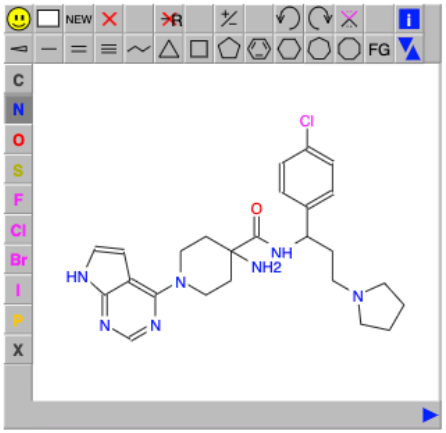
Shortcut to RuleDesign

Idea Molecule*

Single | Multi

SMILES*:

NC5(C(=O)NC(CCN1CCCC1)c2ccc(Cl)cc2)CCN(c3ncnc4[nH]ccc34)CC5

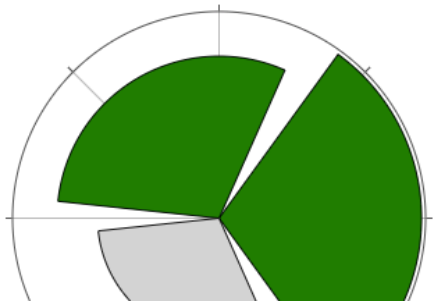


Rules

2 / 3

Other Rules:

increase	2
decrease	2
remaining	37
total	41



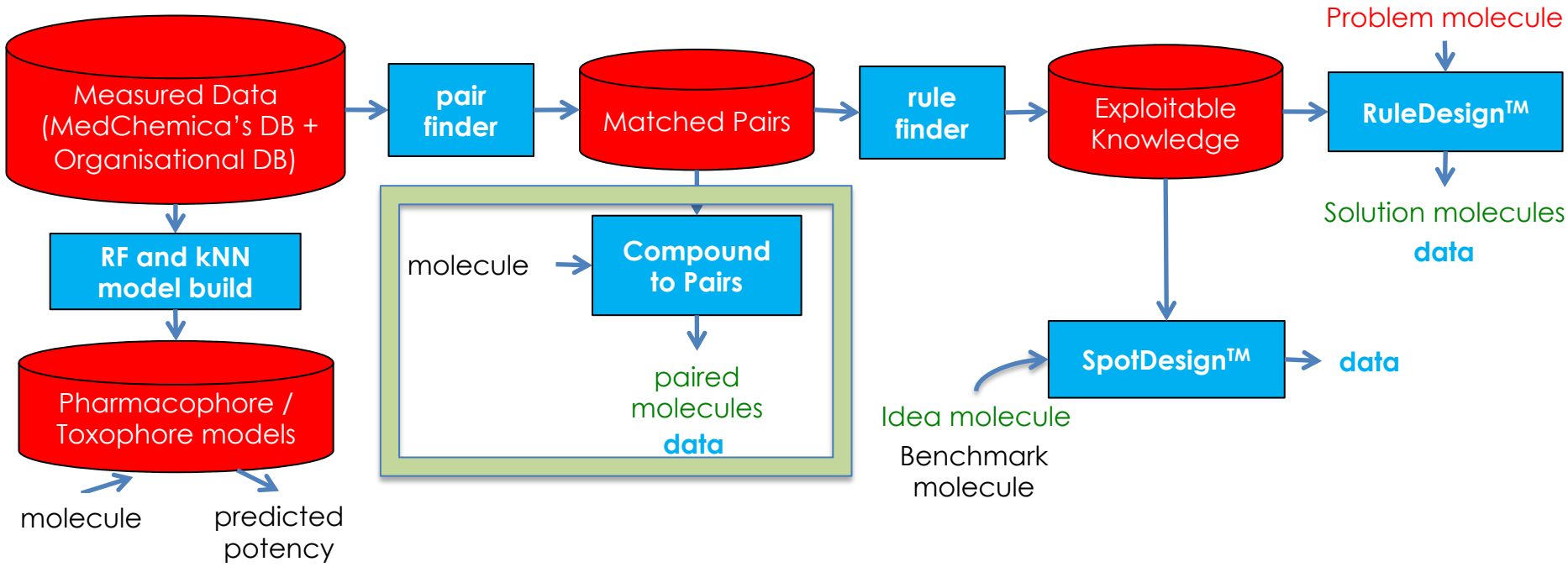
Questions on SpotDesign™?

Please use Webinar tools if you are on-line

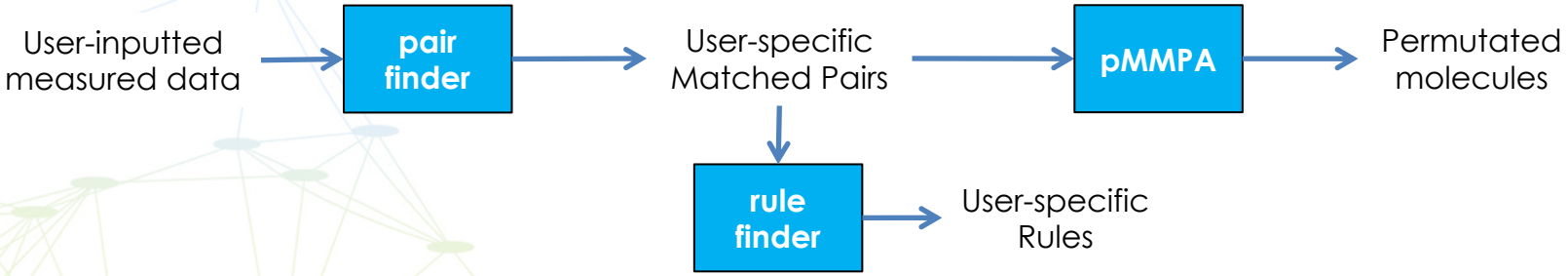
Exploiting data derived ADMET Knowledge

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

DATABASE TOOLS



MyPAIRS



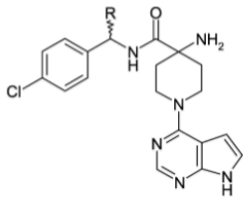
Fast SAR understanding via Matched pairs

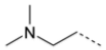
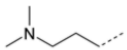
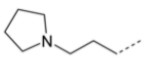
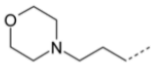
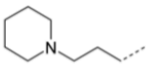
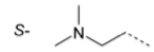
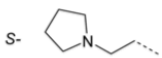
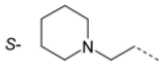
MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

Table 2. Akt Enzyme and Cell Potency, Selectivity, and hERG Activity for α-Alkyl-Substituted Benzylamide Analogues

Table 3. Akt Enzyme and Cell Potency, Selectivity, and hERG Activity for Selected Aryl-Substituted Benzylamide Analogues

Table 4. Akt Enzyme and Cell Potency, Selectivity, and hERG Activity for α-Substituted Benzylamide Analogues Carrying a Basic Side Chain

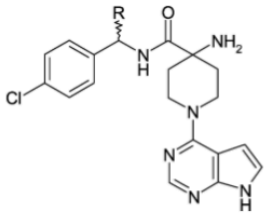


	R	IC_{50} (nM) Akt1[a]	Akt2[a]	Akt3[a]	Cell[b]	ROCK2[c]	hERG[d]	log *D*	solubility[e] (μM)
45		2	14	7	96	31 [16]	>100000		
46		3	15	4	126	71 [25]	>100000	1.4	> 1700
47		4	96	36	209	104 [29]	>100000	1.3	> 1500
48		5	42	15	156	134 [25]	74807	2.7	1400
49		5	30	10	81	112 [24]	>33300		
50		3			110	34 [12]	>33300		2320
51		4	31	18	43	39 [10]	21030		>2470
52		4	13	6	78	34 [10]	29367	2.4	>2090

SAR worked example: AKT inhibitors

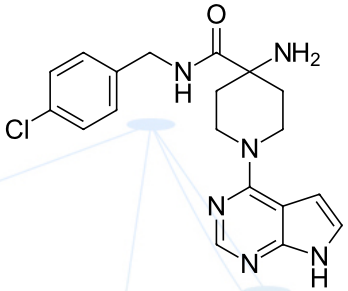
MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

Table 2. Akt Enzyme and Cell Potency, Selectivity, and hERG Activity for α-Alkyl-Substituted Benzylamide Analogues

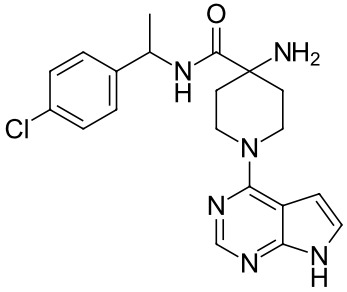


		IC_{50} (nM)							
	R	Akt1[a]	Akt2[a]	Akt3[a]	cell[b]	ROCK2[c]	hERG[d]	log *D*	solubility[e] (μM)
3	H	13	66	57	328	66 [5]	5235	2.9	150
32	Me	8	40	30	197	101 [13]	7200	2.7	180
33	*R*-Me	276	836	523	4594	1396 [5]	9092	3.3	77
34	*S*-Me	4	20	16	134	55 [15]	6747	2.7	110
35	Et	7	23	15	144	126 [19]	6495	3.5	13
36	c-Pr	5	30	24	208	261 [52]	2600	3.4	31
37	Ph	41	210	270	1620	576 [14]	1600	4.1	<1
38	Bn	31	190	150	1650	586 [19]	3500	4.1	<1

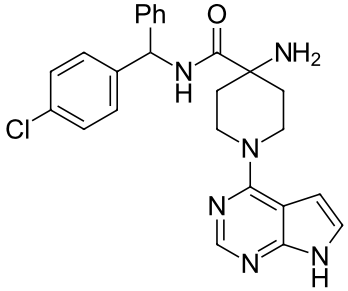
[a]All IC_{50} data are the mean of at least $n = 2$ independent measurements. Each has a standard error of measurement (SEM) ±0.2 log unit. [b]Inhibition of phosphorylation of GSK3β mediated by Akt in MDAMB468 cells. [c]Value in brackets indicates enzyme selectivity ratio to Akt1. [d]CHO cells, IonWorks assay. [e]Thermodynamic solubility in 0.1 M phosphate buffer at pH 7.4 (25 °C).



3
CHEMBL598194



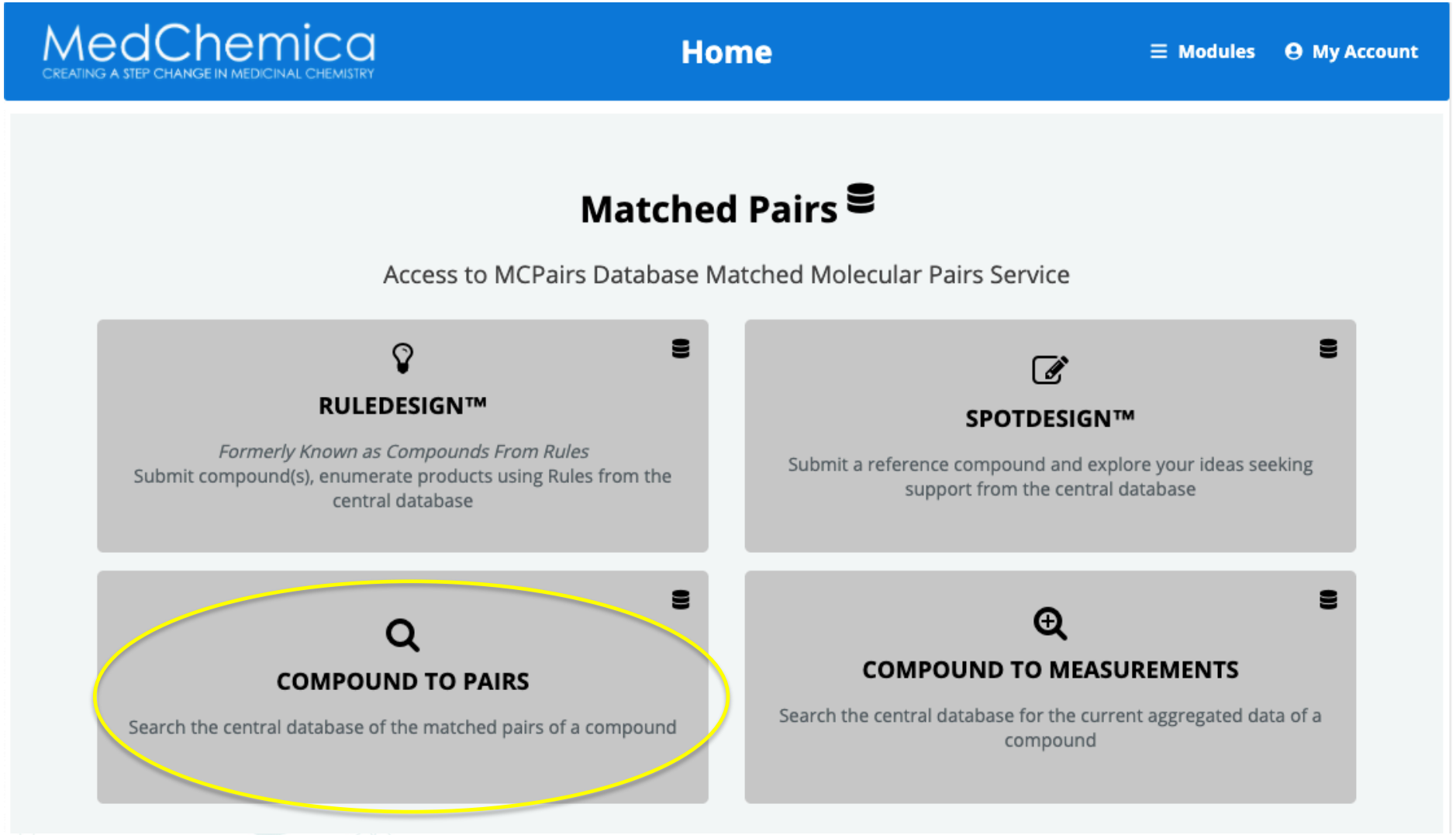
32
CHEMBL2325997



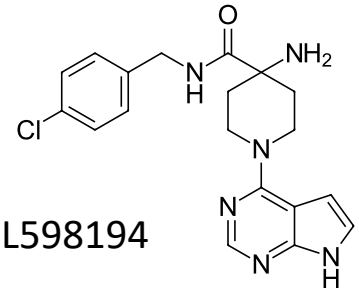
37
CHEMBL2325984

Exercise – Rapid exploration of SAR for literature compounds

- Input chemical name to return matched pairs (CHEMBL598194)
  - Add assay data and explore the SAR tables
  - Add structures, Add ALogp98
  - Change units and sort the data
  - Understand the "gaps" in data
- Search – Inspect – Export
  - Save with structures or as .csv for other applications
    - (Structures saved as SMILES)
- Extras:
  - Finding compounds in ChEMBL and patent literature

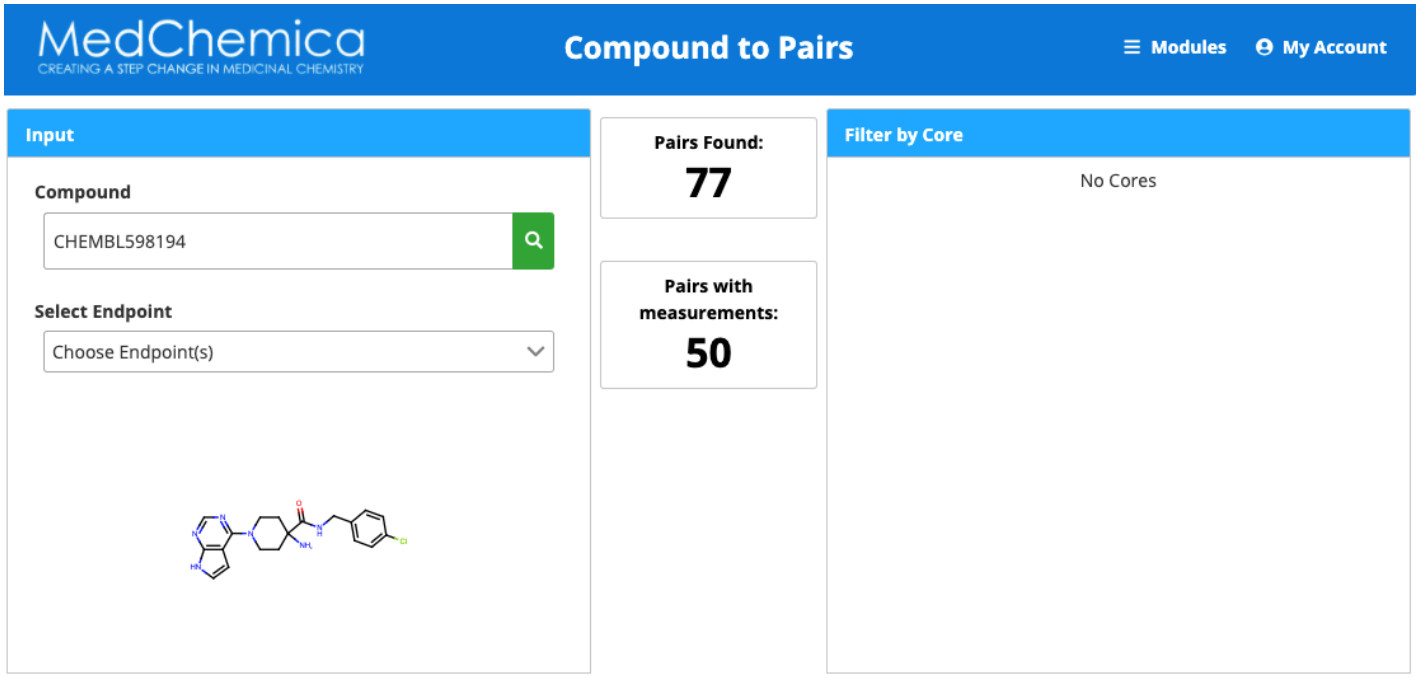


SAR worked example: AKT inhibitors

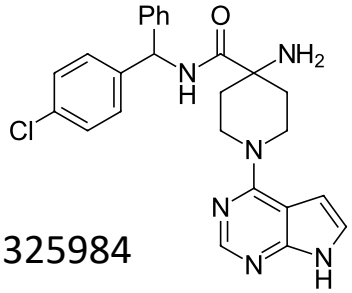


3
CHEMBL598194

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY



SAR worked example: AKT inhibitors



37
CHEMBL2325984

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

Compound to Pairs

Modules | My Account

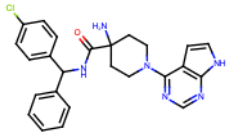
Input

Compound

CHEMBL2325984

Select Endpoint

Choose Endpoint(s)



Pairs Found: 55

Pairs with measurements: 55

Filter by Core

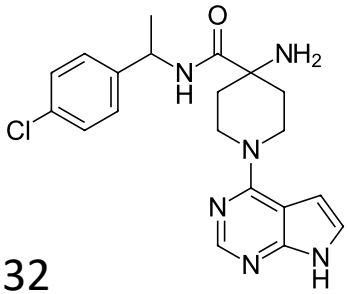
No Cores

Show ALogP98 | Show Structures

	A ?	B ↑↓	
◉	CHEMBL2325984	CHEMBL2325728	🔍

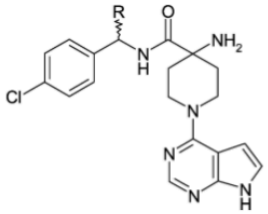
SAR worked example

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY



32
CHEMBL2325997

Table 2. Akt Enzyme and Cell Potency, Selectivity, and hERG Activity for α-Alkyl-Substituted Benzylamide Analogues



		IC$_{50}$ (nM)							
	R	Akt1[a]	Akt2[a]	Akt3[a]	cell[b]	ROCK2[c]	hERG[d]	log *D*	solubility[e] (μM)
3	H	13	66	57	328	66 [5]	5235	2.9	150
32	Me	8	40	30	197	101 [13]	7200	2.7	180
									77
									110
									13
									31
									<1
									<1

nit. [b]Inhibition
:1. [d]CHO cells,

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

Compound to Pairs ☰ Modules My Account

Input

Compound

CHEMBL2325997

Select Endpoint

Choose Endpoint(s)

- Serine/threonine-protein_kinase_AKT3_Homo_sapien
- Serine/threonine-protein_kinase_AKT2_Homo_sapien
- Rho-associated_protein_kinase_2_Homo_sapiens_pIC
- Serine/threonine-protein_kinase_AKT_Homo_sapiens
- HERG_Homo_sapiens_pIC50_[CHEMBL240]

Pairs Found: 68

Pairs with measurements: 68

Filter by Core

No Cores

Click to see data

AKT inhibitors

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

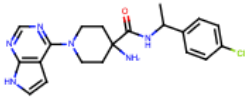
Input

Compound

CHEMBL2325997

Select Endpoint

3 Endpoint(s) Selected



Pairs Found: 68

Pairs with measurements: 32

Filter by Core

Click to show all structures

Or click to show just one pair

Show ALogP98 | Show Structures

	A ?	B		Serine/threonine-prote…ase_AKT… uM		HERG_Homo_sapiens_pIC50_[CHEMBL… uM	
				B	Fold Change	B	Fold Change
	CHEMBL2325997	CHEMBL2325988		4.260	~ 140 ↓	33.297	~ 4.6 ↓
	CHEMBL2325997	CHEMBL2325728		0.018	~ 1.7 ↑	21.028	~ 2.9 ↓

Instant SAR table

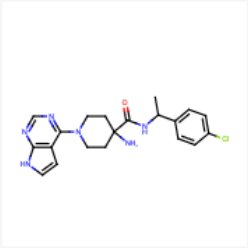
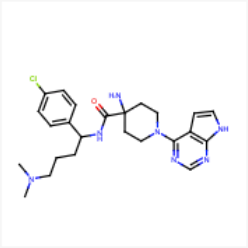
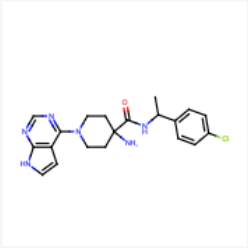
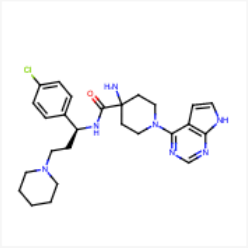
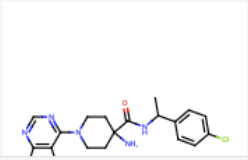
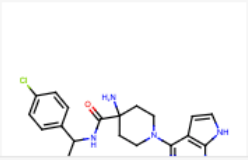
MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

Click to add lipophilicity data

Click to change units

Click to sort pair with large change to the top

Show ALogP98 | Hide Structures

	A ?	B		Serine/threonine-protein_kinas... uM		HERG_Homo_sapiens_pIC50_[CHEMBL... uM	
				B	Fold Change	B	Fold Change
				0.004	~ 7.5 ↑	100.000	~ 14
	CHEMBL2325997 	CHEMBL2325729 		0.006	~ 5 ↑	29.370	~ 4.1
	CHEMBL2325997 	CHEMBL2325992 		0.007	~ 4.3 ↑	100.000	~ 14

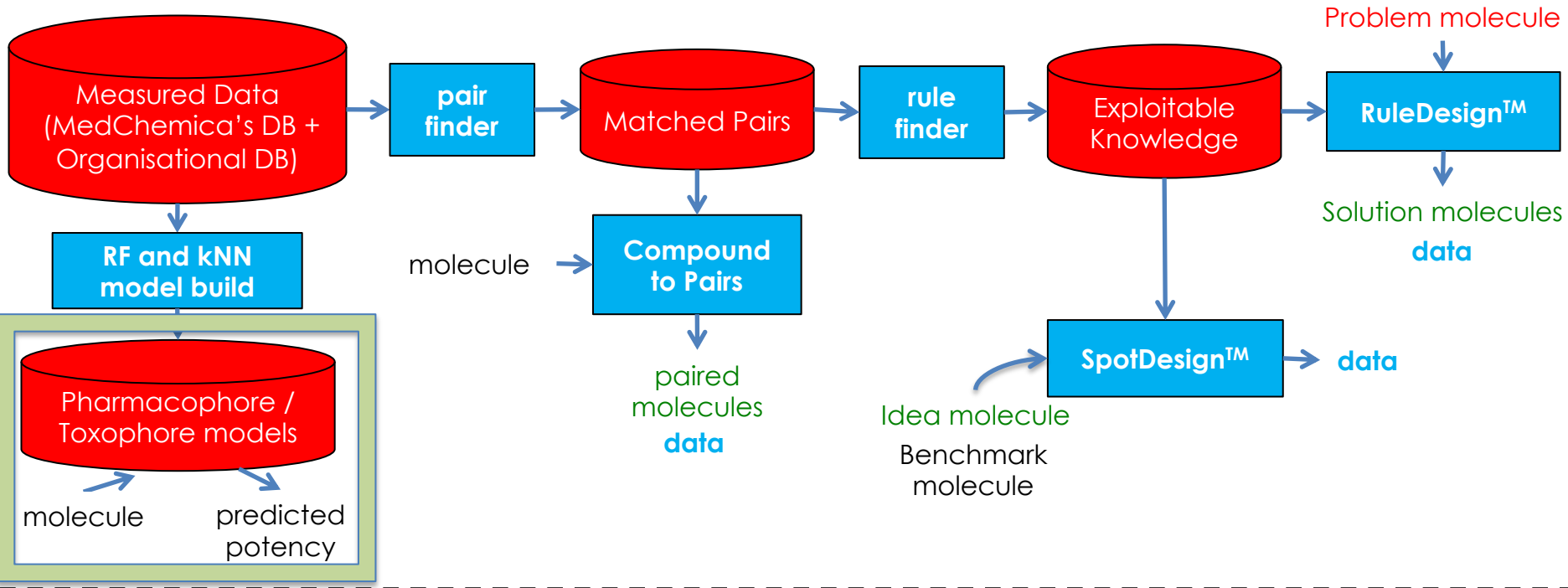
Questions on Compound-To-Pairs?

Please use Webinar tools if you are on-line

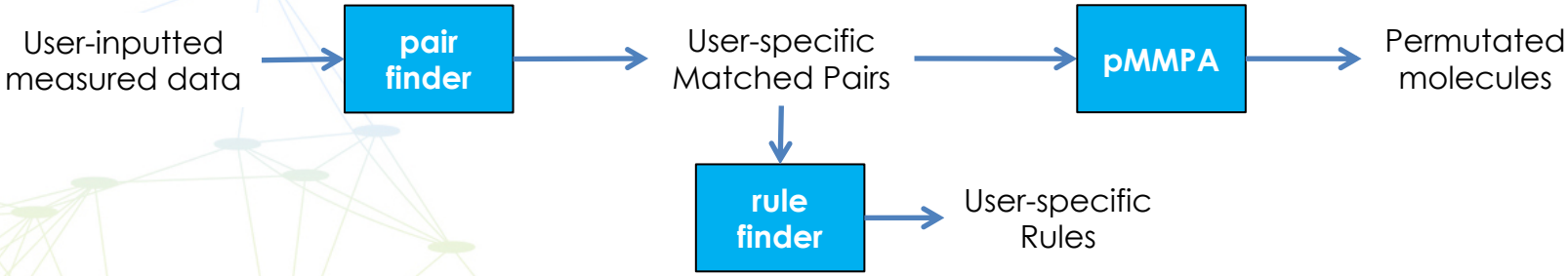
Exploiting data derived ADMET Knowledge

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

DATABASE TOOLS



MyPAIRS



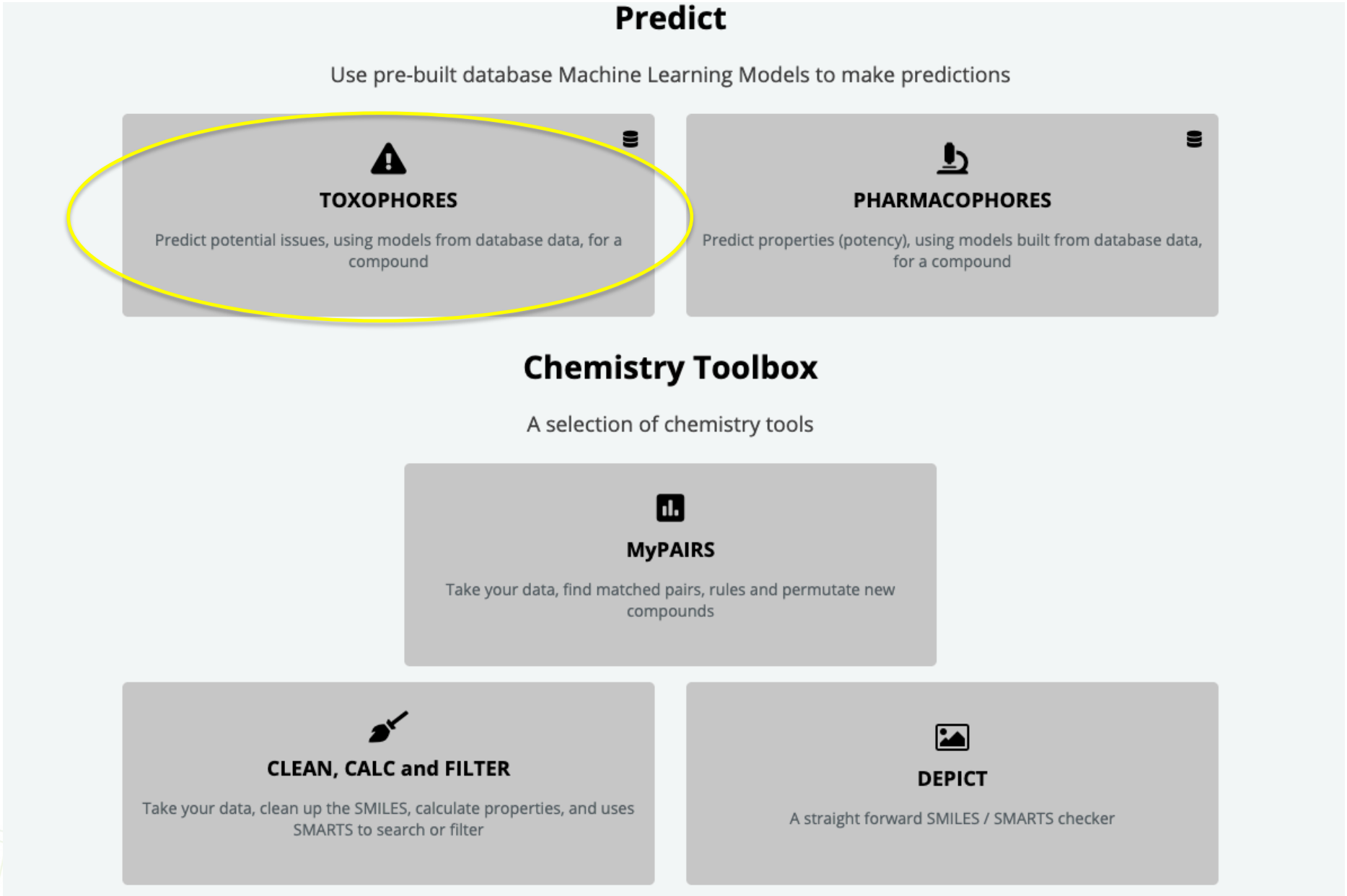
Toxophore and Pharmacophore prediction models

- Models that utilise knowledge from the central database to predict potency
  - Potency at a toxicologically-linked Endpoint = Toxophore
  - Potency at a target Endpoint = Pharmacophore
- 2 types of models are used:
  - Regression Forest (RF)
    - Decision trees trained on central database data
    - Descriptors = pairs of features connected by shortest bond path
  - k Nearest Neighbour (kNN)
    - Compares query molecule with central database molecules
    - Descriptor = Morgan fingerprint
    - Distance metric = Tanimoto distance

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

Exercise – Assess potential toxophore activity of CHEMBL2325997

- Input compound name: CHEMBL2325997
- Select Toxicologically-linked Endpoints
- Run Toxophore prediction
- View results
  - Take a minute to understand the predictions using the help information provided (click ?)
- Export as ready-to-use PowerPoint presentation



Toxicity predictions for CHEMBL2325997

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

Toxophores | Modules | My Account

Input Molecule*

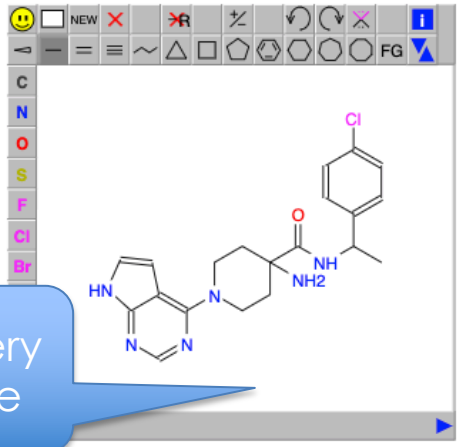
Single | Multi

Compound Name:

CHEMBL2325997

SMILES*:

CC(c1ccc(cc1)Cl)NC(=O)C2(CCN(CC2)c3c4cc[nH]c4ncn3)N



Input query molecule

Assay Selection

Toxophore Assays

	Assay	Labels
☑	Glutamate NMDA receptor; GRIN1/GRIN2B Homo sapiens pIC50 [CHEMBL1907603]	CNS
☑	Voltage-gated L-type calcium channel alpha-1C subunit Oryctolagus cuniculus pIC50 [CHEMBL2830]	CVS
☑	Neuronal acetylcholine receptor; alpha4/beta2 Homo sapiens pIC50 [CHEMBL1907589]	CNS
☑	Serotonin 1b (5-HT1b) receptor Homo sapiens pIC50 [CHEMBL1898]	CNS
☑	Phosphodiesterase 3A Homo sapiens pIC50 [CHEMBL241]	CVS
☑	Serotonin 1a (5-HT1a) receptor Homo sapiens pIC50 [CHEMBL214]	CNS
☑	Dopamine D1 receptor Homo sapiens pIC50 [CHEMBL2056]	CNS
☑	Muscarinic acetylcholine receptor M2 Homo sapiens pIC50 [CHEMBL211]	CNS
	Sodium channel protein type V alpha	

Select toxicity Endpoint(s)

Submit

Go!

Toxicity predictions for CHEMBL2325997

Red = predicted potency at toxic Endpoint

Scroll through results

Green = predicted inactivity at toxic Endpoint

Click on Endpoint for breakdown

Tip: click to design less toxic compounds

Tip: click ? for more info

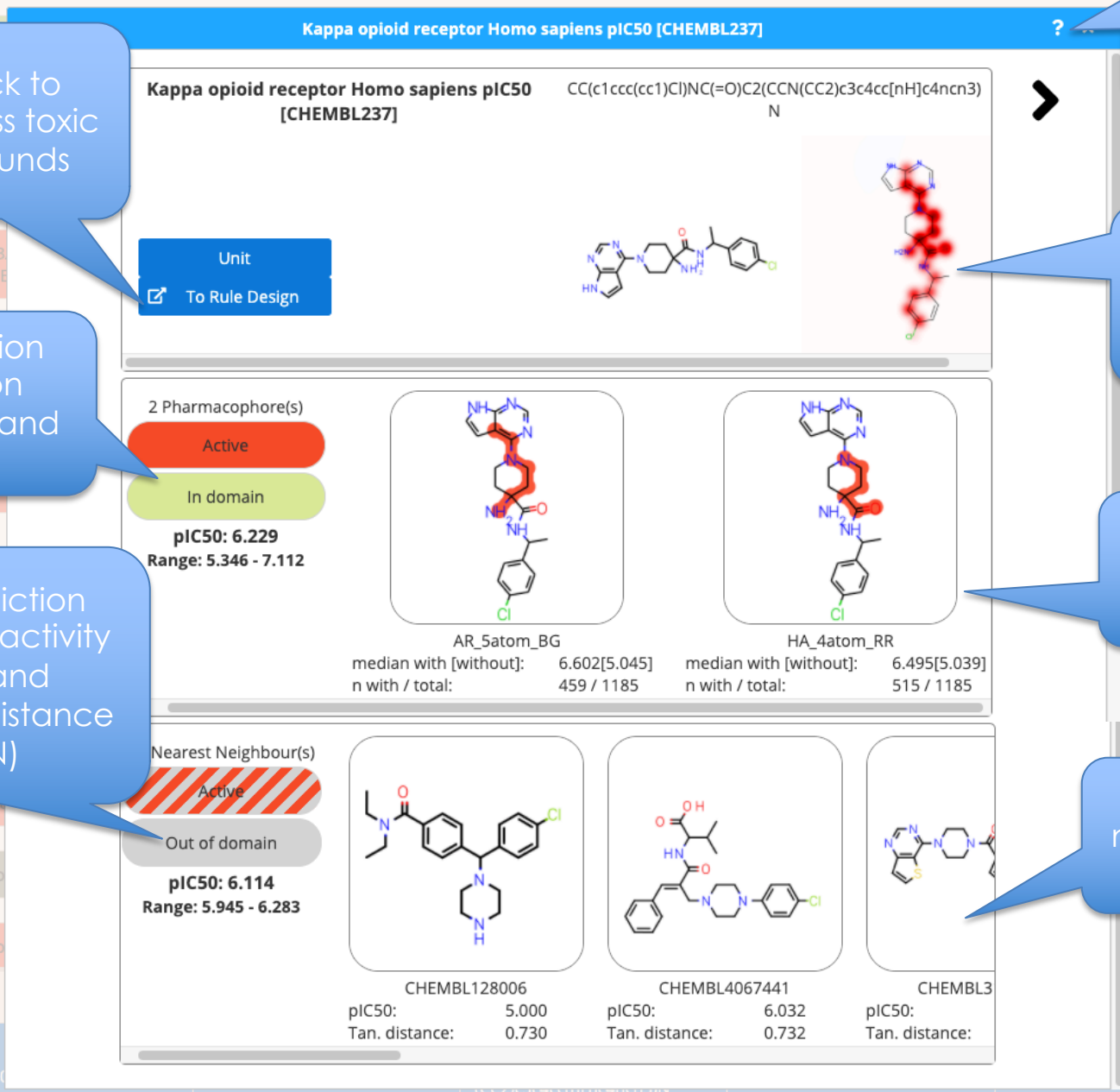
RF prediction (based on Cohen's d and R^2)

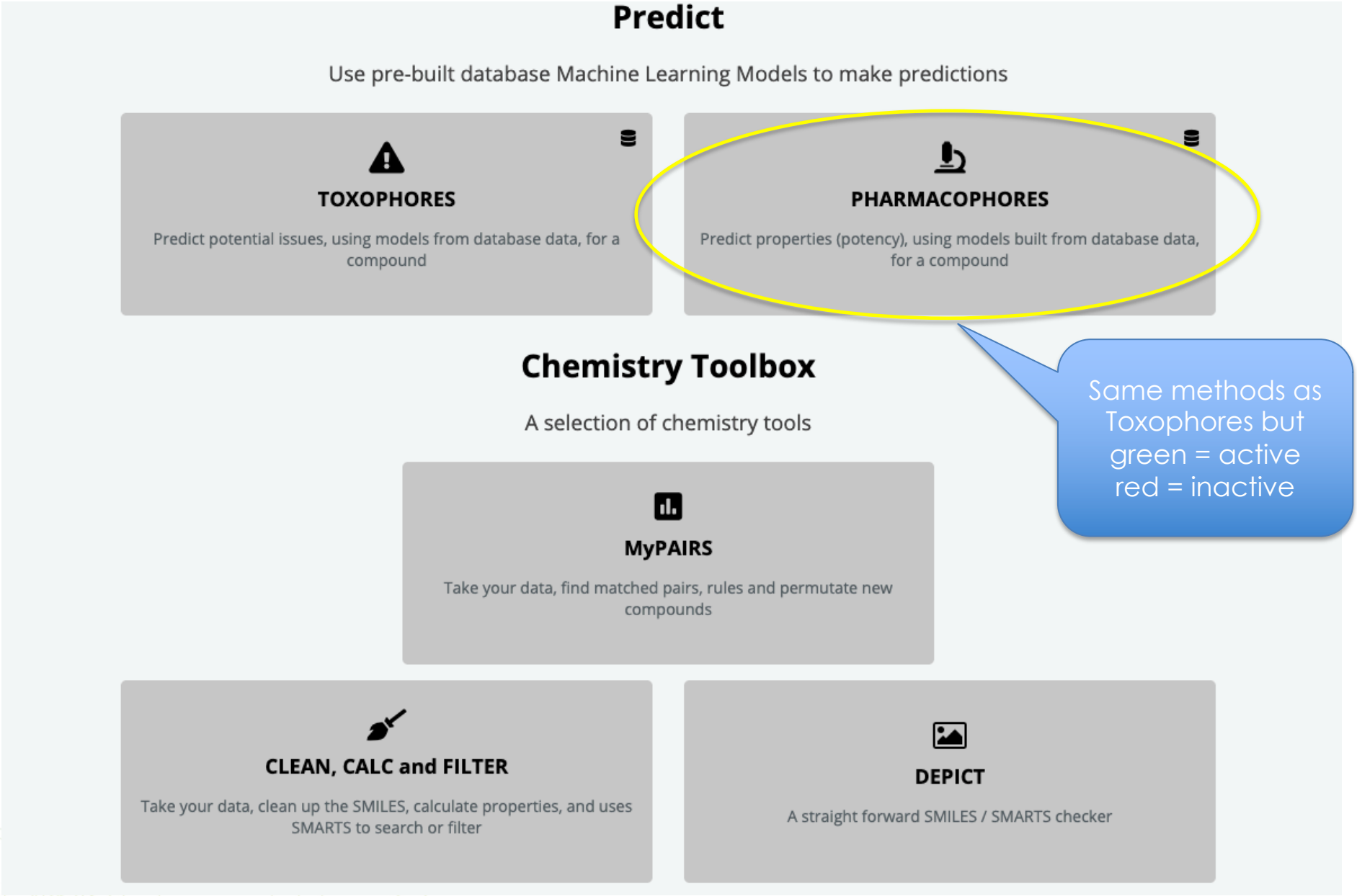
kNN prediction (based on activity of NN and Tanimoto distance to NN)

Overall heat map of atom contributions

Most important descriptors from RF

Nearest neighbours in database





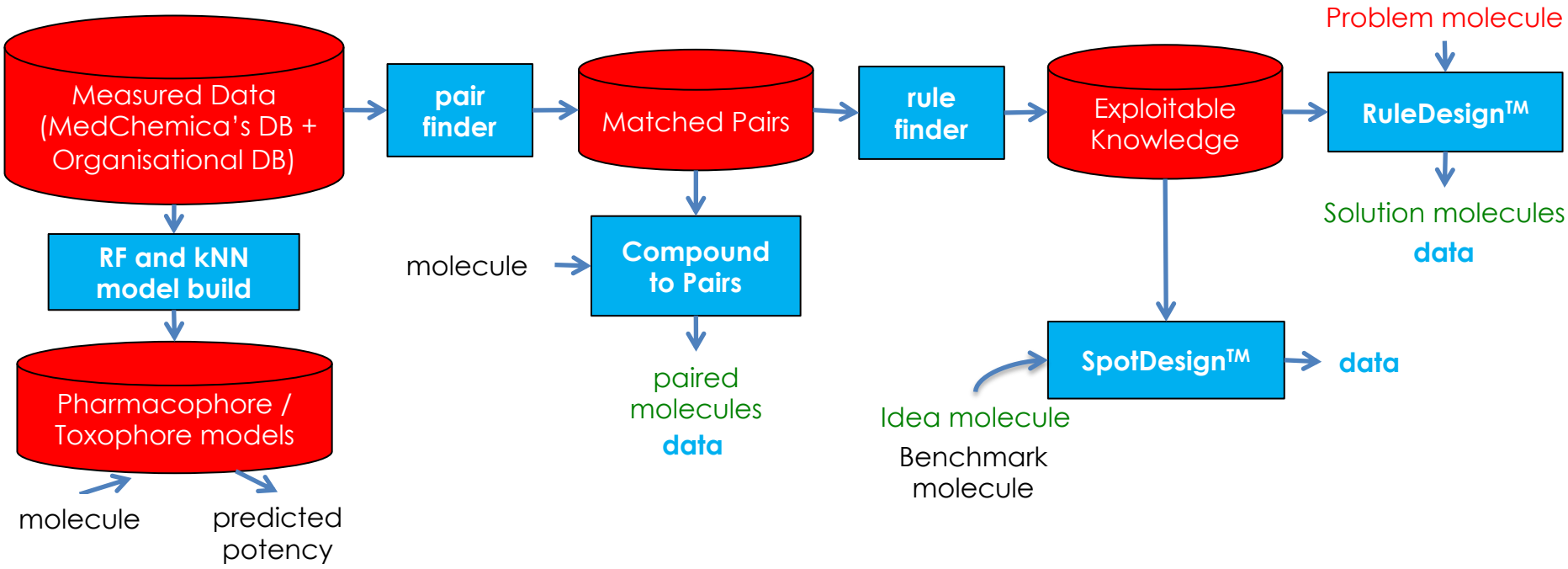
Questions on Toxophores / Pharmacophores?

Please use Webinar tools if you are on-line

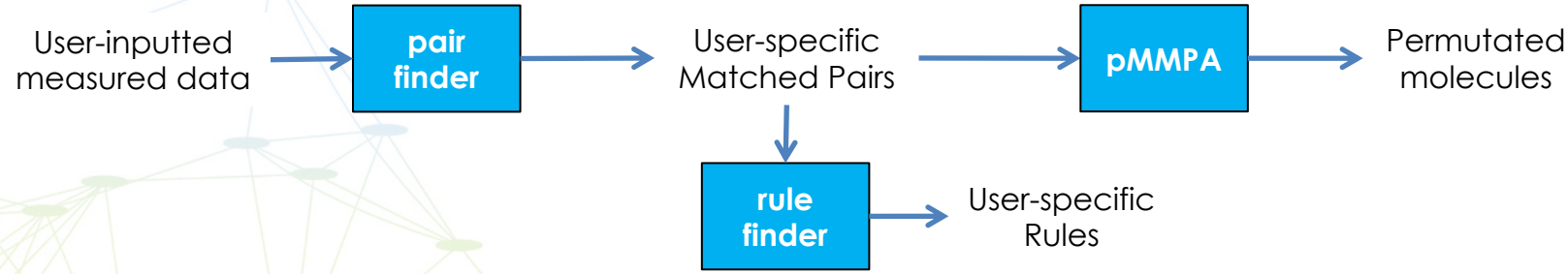
Exploiting data derived ADMET Knowledge

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

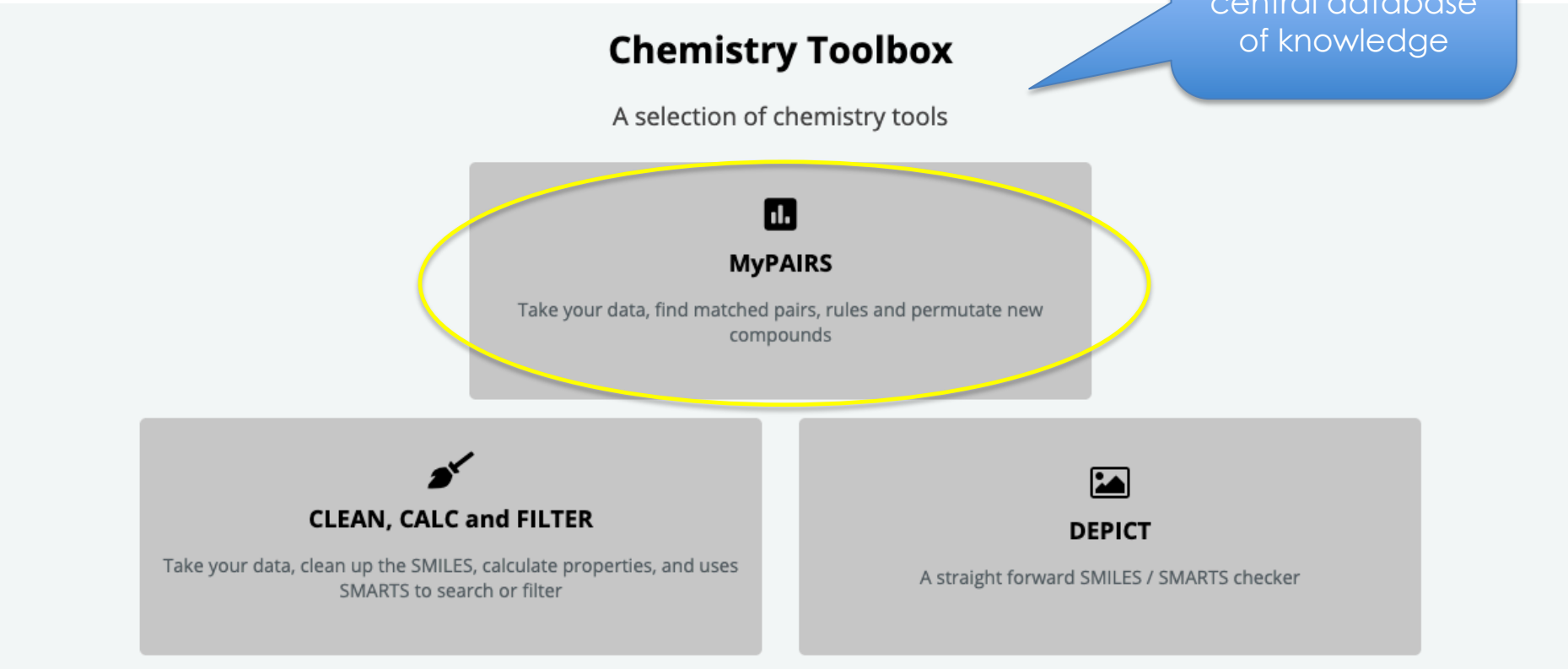
DATABASE TOOLS



MyPAIRS

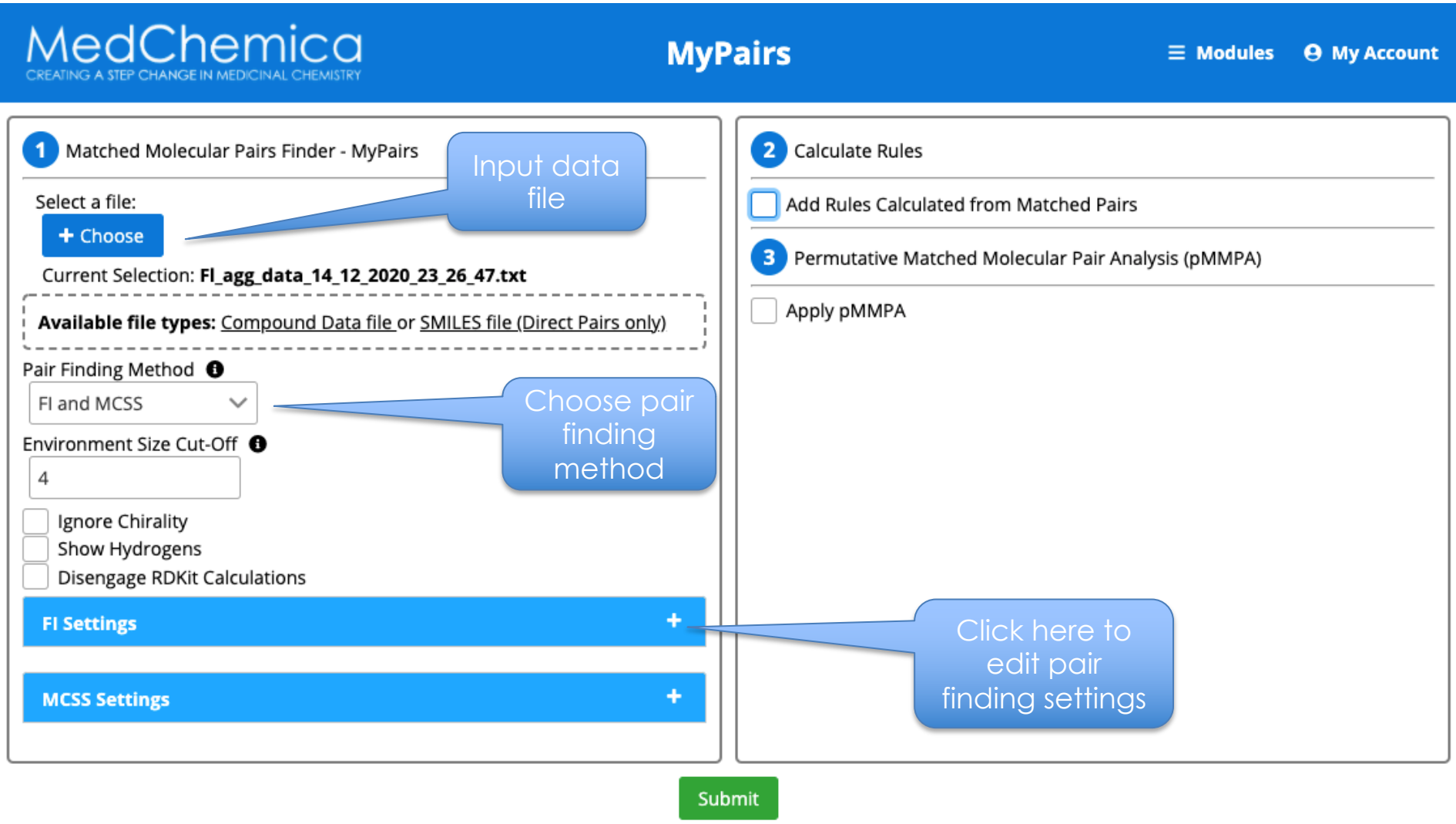


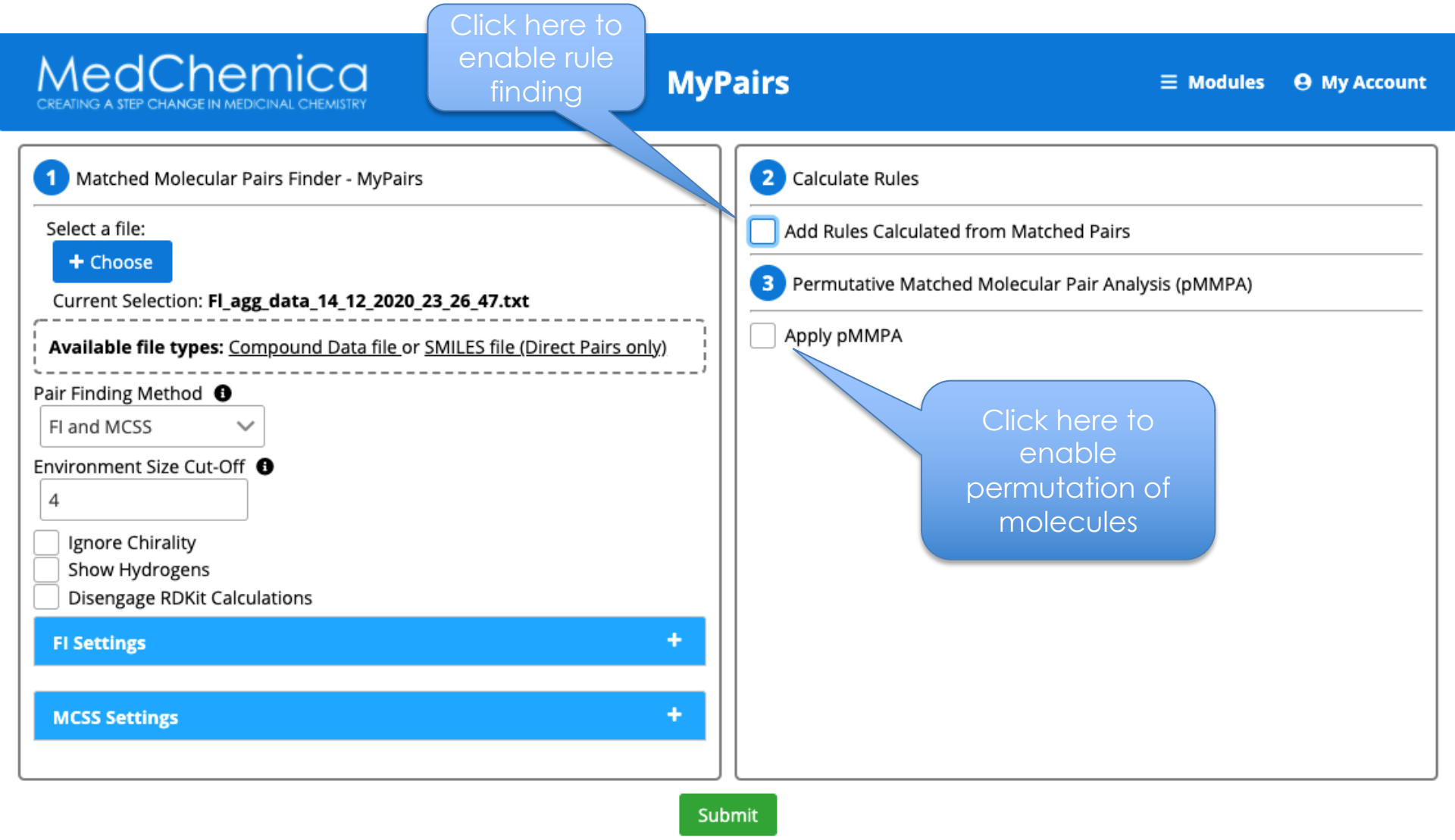
These tools do not interact with the central database of knowledge

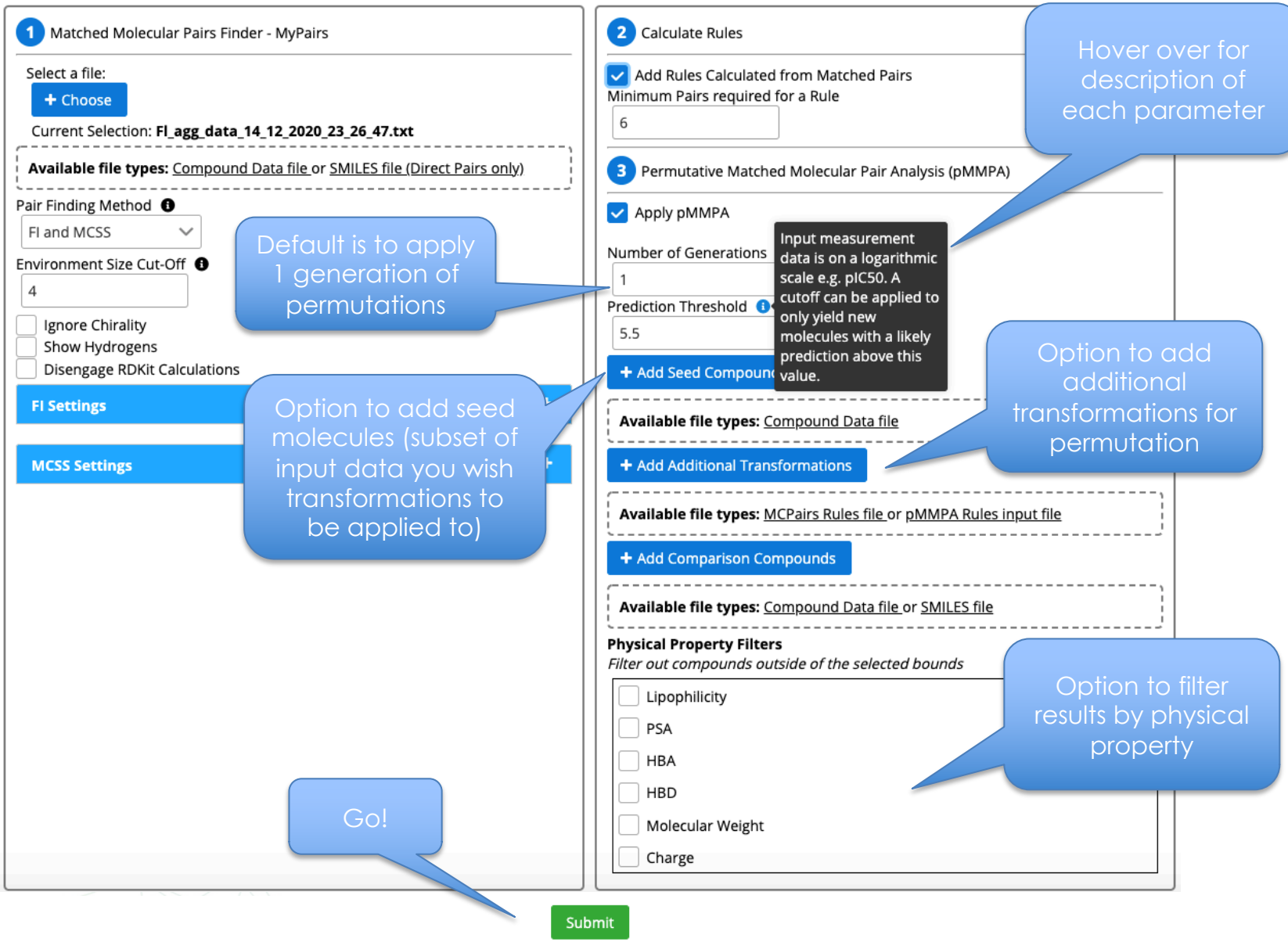


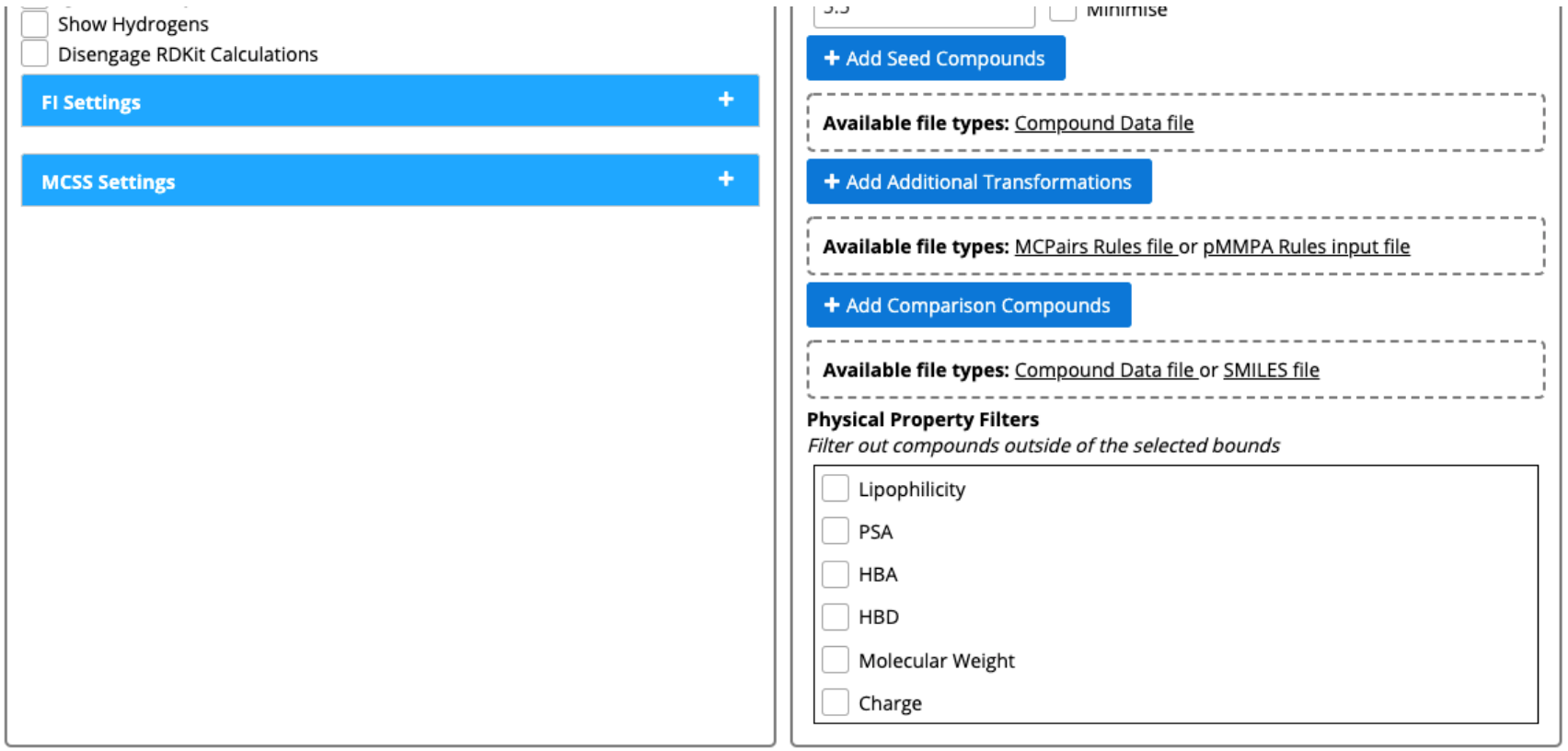
MyPairs

- Applies MCPairs methods to user-inputted data
  - Does not interact with central database
- Available methods:
  - Pair Finding
  - Rule Finding
  - Permutative MMPA (molecule suggestions based on application of transformations)
- Example use on a live project:
  - COVID moonshot
    - Open-source antiviral discovery project
    - Targeting SARS-COV-2 main protease
  - Input data = protease binding data dated 14-12-2020
  - Does pMMPA used on historical project data suggest our current lead compound (3-02-2021)?









#	Job ID	Timestamp	Progress	Save
0	BQZIA-U0FBK_2021-02-03_10_39_54_609375	Feb 3, 2021, 10:55:42 AM	Finished	Save

Export zip file of results

MyPairs – COVID results

- task_message.txt = breakdown of results
- pmmpa_results_gen_1.csv = suggested compounds

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
1	id	structure	generation	is_known	compound_name	is_match	match_id	precursor_id	precursor	precursor_mcss	pair_data	CLogP	PSA	RMM	HBA	HBD	measurement	qualifier
2	LON-WEI-b2874fec-27	CN(C)C(=O)C(CNC(=O)	0	FALSE		FALSE						3.48	69.72	441.52	6	1	4	<
3	LON-WEI-b2874fec-26	CNCC1CCCN(C1)C(=O)[	0	FALSE		FALSE						2.61	52.65	377.48	5	1	4	<
4	LON-WEI-b2874fec-25	c1ccc(cc1)[C@H](C(=O	0	FALSE		FALSE						2.46	62.3	343.38	5	1	4	<
5	LON-WEI-b2874fec-24	c1ccc(cc1)[C@H](C(=O	0	TRUE	CHEMBL2138941	FALSE						3.78	49.41	360.38	4	1	4	<
6	LON-WEI-b2874fec-23	c1ccc(cc1)[C@H](C(=O	0	FALSE		FALSE						3.41	73.2	367.4	5	1	4	<
7	LON-WEI-b2874fec-22	c1ccc	0	FALSE		FALSE						3.79	49.41	370.44	4	1	4	<

Generation 0 = seed compounds

Scroll down for generation 1 predictions

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
1	id	structure	generation	is_known	compound_name	is_match	match_id	precursor_id	precursor	precursor_mcss	pair_data	CLogP	PSA	RMM	HBA	HBD	measurement	qualifier
1393	prod_gen_1_236	[H][C@]1(Oc2c(cc(cc2	1	FALSE		FALSE		EDJ-MED-e4b030d8-3	C[C@H]1C[C	[H][C@@H]1C[C@H](c2cc(ccc2O1)Cl)C(=		3.74	51.22	352.81	4	1		~
1394	prod_gen_1_237	c1cc2c(cc1F)cncc2NC(=	1	FALSE		FALSE		MAT-POS-b3e365b9-1	c1ccc2c(c1)c	c1ccc2c(c1)cncc2NC(=O)[C@@H]3CCOc4		3.39	51.22	356.78	4	1		~
1395	prod_gen_1_238	c1ccc2c(c1)cncc2NC(=(	1	FALSE		FALSE		ALP-POS-477dc5b7-2	c1ccc2c(c1)c	c1ccc2c(c1)cncc2NC(=O)C3CCNc4c3cccc4		2.51	54.02	303.36	4	2		~
1396	prod_gen_1_239	[H][C@]1(C(Oc2c(cc(cc	1	FALSE		FALSE		MAT-POS-8a69d52e-7	C[C@@H]1C	[H][C@H]1COc2ccc(cc2[C@@H]1C(=O)N		3.79	51.22	352.81	4	1		~
1397	prod_gen_1_240	[H][C@]1(Oc2c(cc(cc2	1	FALSE		FALSE		MAT-POS-8a69d52e-2	C[C@@H]1C	[H][C@H]1C[C@@H](c2cc(ccc2O1)Cl)C(=		3.33	60.45	368.81	5	1		~
1398	prod_gen_1_241	COc1ccc2cncc(c2c1)N3	1	FALSE		FALSE		VLA-UCB-29506327-1	c1ccc2c(c1)c	c1ccc2c(c1)cncc2N3C(=O)C4(CCOc5c4cc(		2.46						

Scroll across for prediction statistics

	A	B	C	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y
1	id	structure	generation	CLogP	PSA	RMM	HBA	HBD	measurement	qualifier	combined_predicted_and_real_measurement	prediction_median	prediction_max	prediction_min	number_of_pairs	median_measurement_delta	environment_size
1393	prod_gen_1_236	[H][C@]1(Oc2c(cc(cc2	1	3.74	51.22	352.81	4	1		~	4.85	4.85	6.9	2.8	8	0.15	4
1394	prod_gen_1_237	c1cc2c(cc1F)cncc2NC(=	1	3.39	51.22	356.78	4	1		~	6.9	6.9	6.9	6.6	4	0	4
1395	prod_gen_1_238	c1ccc2c(c1)cncc2NC(=(	1	2.51	54.02	303.36	4	2		~	6.6	6.6	6.6	6.6	1	0	4
1396	prod_gen_1_239	[H][C@]1(C(Oc2c(cc(cc	1	3.79	51.22	352.81	4	1		~	6.15	6.15	8.4	3.3	16	0.35	4
1397	prod_gen_1_240	[H][C@]1(Oc2c(cc(cc2	1	3.33	60.45	368.81	5	1		~	4.75	4.75	5.9	3.6	4	-1.45	4
1398	prod_gen_1_241	COc1ccc2cncc(c2c1)N3	1	2.46	80.76	409.82	7	1		~	5.9	5.9	5.9	5.8000001	3	0	4

MyPairs – COVID results

- Use excel to apply project-relevant filters e.g:
  - Sort suggestions by predicted median binding measurement
  - Filter for CLogP < 4
  - And we find our current lead compound as a suggestion:

	A	B	C	I	J	K	L	M	N	O	P	Q	R	T
1	id	structure	generation	precursor	precursor_mcss	pair_dat	CLogP	PSA	RMM	HBA	HB	measureme	qualifier	prediction_median
1405	prod_gen_1_3930	Cc1ccncc1NC(=O)CN2CCN(CC2)C(=O)CCl	1	Cc1ccncc1NC(=O)CN2CCN(CC2)C(=O)C	Cc1ccncc1NC(=O)CN2CCN(CC2		-0.43	65.54	310.78	6	1		~	7.5
1409	prod_gen_1_284	[H][C@]1([C@H](c2c(ccc(c2C)Cl)OC1)C(=O)Nc3c4c(cnc3)cccc4)[H	1	C[C@H]1COc2ccc(cc2[C@@H]1C(=O)Nc3cncc4c3cccc4)Cl	[H][C@@H]1COc2ccc(cc2[C@(		3.55	51.22	352.81	4	1		~	7.3
1432	prod_gen_1_3667	Cc1ccccc1NC(=O)CC2C(=O)N(C(=O)S2)c3cccc(c3)C(F)(F)F	1	Cc1ccccc1NC(=O)CC2C(=O)N(C(=O)S2)c3cccc3	Cc1ccccc1NC(=O)CC2C(=O)N(C		3.89	66.48	408.39	5	1		~	7.2
1435	prod_gen_1_1755	c1ccc2c(c1)cncc2NC(=O)[C@@H]3CCNc4c3cc(cc4)Cl	1	c1ccc2c(c1)cncc2NC(=O)[C@@H]3CCOc4c3cc(cc4)Cl	CC[C@H](c1cccc(c1)Cl)C(=O)N		3.12	54.02	337.8	4	2		~	7.1
1436	prod_gen_1_1791	c1ccc2c(c1)cncc2NC(=O)C3CCNc4c3cc(cc4)Br	1	c1ccc2c(c1)cncc2NC(=O)C3CCOc4c3cc(cc4)Br	CCC(c1cccc(c1)Br)C(=O)Nc2cnc		3.31	54.02	382.25	4	2		~	7.1
1438	prod_gen_1_2384	c1cc(c2c(c1)c(c[nH]2)CCNC(=O)CCl)CN3CCN(CC3)C(=O)CCl	1	CC(=O)NCCc1c[nH]c2c1cccc2CN3CCN(CC3)C(=O)CCl	CC(=O)NCCc1c[nH]c2c1cccc2CN		1.34	68.44	411.33	6	2		~	7.1
1439	prod_gen_1_2717	c1ccc2c(c1)cncc2NC(=O)[C@@H]3CCS(=O)(=O)c4c3cccc4	1	c1ccc2c(c1)cncc2NC(=O)[C@@H]3CCOc4c3cc(cc4)Cl	CC[C@H](c1ccccc1)C(=O)Nc2cr		1.89	76.13	352.41	5	1		~	7.1

Lead Compound 14-12-2020
pIC50 = 6.7
Moderate antiviral cell activity
High microsomal clearance

Lead Compound 3-2-2021
pIC50 = 6.6
Good antiviral cell activity
Moderate microsomal clearance

  - Project benefit:
    - Alternative lead compound found with better antiviral and ADMET properties

MyPairs – COVID results

- pmmpa_evidence_gen_1.csv
  - Provides matched pair evidence for suggestions

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
1	product_id	product_structure	precursor_id	precursor_structure	idsmirks	smirks	environment	compound_name_A	compound_structure_A	measurement_A	qualifier_A	compound_name_B	compound_structure_B	measurement_B	qualifier_B
2	prod_gen_1_236	[H][C@]1(Oc2c(cc(c	EDJ-MED-e4b0	C[C@H]1C[C@H](c2c	MAT-POS	[H][C:1]1([	4	MAT-POS-8a69d52e-3	C[C@H]1C[C@@H](c2cc(	4.3	=	CHEMBL94657	C[C@@]1(CCOc2c1cc(cc	4.7	=
3	prod_gen_1_236	[H][C@]1(Oc2c(cc(c	EDJ-MED-e4b0	C[C@H]1C[C@H](c2c	MAT-POS	[H][C:1]1([	4	MAT-POS-8a69d52e-3	C[C@H]1C[C@@H](c2cc(	4.3	=	CHEMBL2182047	C[C@]1(CCOc2c1cc(cc2)	6.5	=
4	prod_gen_1_236	[H][C@]1(Oc2c(cc(c	EDJ-MED-e4b0	C[C@H]1C[C@H](c2c	MAT-POS	[H][C:1]1([	4	MAT-POS-8a69d52e-2	C[C@@H]1C[C@@H](c2	6.2	=	CHEMBL94657	C[C@@]1(CCOc2c1cc(cc	4.7	=
5	prod_gen_1_236	[H][C@]1(Oc2c(cc(c	EDJ-MED-e4b0	C[C@H]1C[C@H](c2c	MAT-POS	[H][C:1]1([	4	MAT-POS-8a69d52e-2	C[C@@H]1C[C@@H](c2	6.2	=	CHEMBL2182047	C[C@]1(CCOc2c1cc(cc2)	6.5	=
6	prod_gen_1_236	[H][C@]1(Oc2c(cc(c	EDJ-MED-e4b0	C[C@H]1C[C@H](c2c	MAT-POS	[H][C:1]1([	4	EDJ-MED-e4b030d8-3	C[C@H]1C[C@H](c2cc(cc	4.7	=	CHEMBL94657	C[C@@]1(CCOc2c1cc(cc	4.7	=
7	prod_gen_1_236	[H][C@]1(Oc2c(cc(c	EDJ-MED-e4b0	C[C@H]1C[C@H](c2c	MAT-POS	[H][C:1]1([	4	EDJ-MED-e4b030d8-3	C[C@H]1C[C@H](c2cc(cc	4.7	=	CHEMBL2182047	C[C@]1(CCOc2c1cc(cc2)	6.5	=
8	prod_gen_1_236	[H][C@]1(Oc2c(cc(c	EDJ-MED-e4b0	C[C@H]1C[C@H](c2c	MAT-POS	[H][C:1]1([	4	EDJ-MED-e4b030d8-2	C[C@@H]1C[C@H](c2cc(	6.6	=	CHEMBL94657	C[C@@]1(CCOc2c1cc(cc	4.7	=
9	prod_gen_1_236	[H][C@]1(Oc2c(cc(c	EDJ-MED-e4b0	C[C@H]1C[C@H](c2c	MAT-POS	[H][C:1]1([	4	EDJ-MED-e4b030d8-2	C[C@@H]1C[C@H](c2cc(	6.6	=	CHEMBL2182047	C[C@]1(CCOc2c1cc(cc2)	6.5	=
10	prod_gen_1_237	c1cc2c(cc1F)cncc2N	MAT-POS-b3e	c1ccc2c(c1)cncc2NC(	MAT-POS	[c:1][c:2]1[	4	MAT-POS-0c8fa4a7-3	c1ccc2c(c1)c(nn2C(=O)Cc	4	<	CHEMBL259181	c1cc(cc(c1)Cl)CC(=O)n2c	4	<
11	prod_gen_1_237	c1cc2c(cc1F)cncc2N	MAT-POS-b3e	c1ccc2c(c1)cncc2NC(	MAT-POS	[c:1][c:2]1[	4	EDJ-MED-c8e7a002-1	c1ccc2c(c1)c(n[nH]2)NC(	4	<	CHEMBL1667924	c1cc(cc(c1)Cl)CC(=O)Nc1	4	<
12	prod_gen_1_237	c1cc2c(cc1F)cncc2N	MAT-POS-b3e	c1ccc2c(c1)cncc2NC(	MAT-POS	[c:1][c:2]1[	4	VLA-UCB-1dbca3b4-15	c1ccc2c(c1)cncc2NC(=O)(	6.4	=	CHEMBL3407863	c1cc2cncc(c2cc1F)NC(=(	6.1	=
13	prod_gen_1_237	c1cc2c(cc1F)cncc2N	MAT-POS-b3e	c1ccc2c(c1)cncc2NC(	MAT-POS	[c:1][c:2]1[	4	BEN-DND-7e92b6ca-7	c1ccc(cc1)S(=O)(=O)N2C	4	<	CHEMBL48412	c1ccc(cc1)S(=O)(=O)N2(	4	<
14	prod_gen_1_238	c1ccc2c(c1)cncc2NC	ALP-POS-477d	c1ccc2c(c1)cncc2NC(	JAG-UCB-	[C:1]([H])[(	4	JAG-UCB-52b62a6f-11	Cc1ccn2cnnc2c1[	4	<	CHEMBL1667898	Cc1ccn2cnnc2c1NC(=O)(	4	<
15	prod_gen_1_239	[H][C@]1(C(Oc2c(cc	MAT-POS-8a6	C[C@@H]1COc2ccc(c	MAT-POS	[H][C:1]1([	4	MAT-POS-8a69d52e-5	C[C@H]1COc2ccc[	4	<	CHEMBL133016	C[C@@H]1C[C@H](c2cc	6.6	=

Matched pair structures and data listed for each suggestion

Questions on MyPairs?

Please use Webinar tools if you are on-line

And Finally…

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

- Problems, suggestions, ideas for interface / calculation engine
  - contact@medchemica.com