

MedChemica

CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

**Explainable artificial intelligence systems that
deliver drug discovery results**



A suite of secure enterprise and online compound design tools to augment scientists' capabilities and deliver quality compounds in fewer cycles.

MedChemica

CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

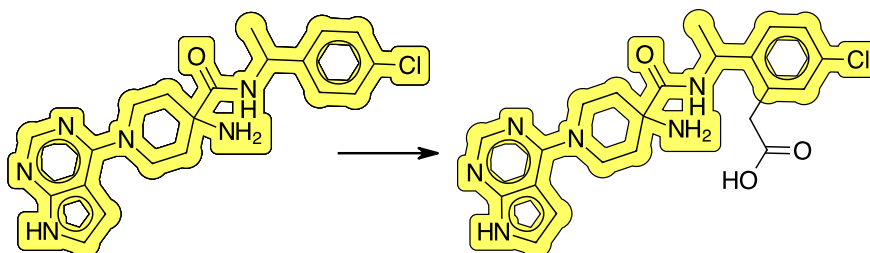
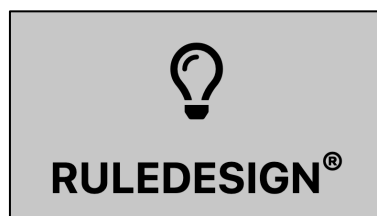
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MedChemica is a specialist software and scientific services company based in the UK. We develop and supply tools and services to help accelerate research in the life sciences sector.





A Design Tool for Fixing Compound Properties

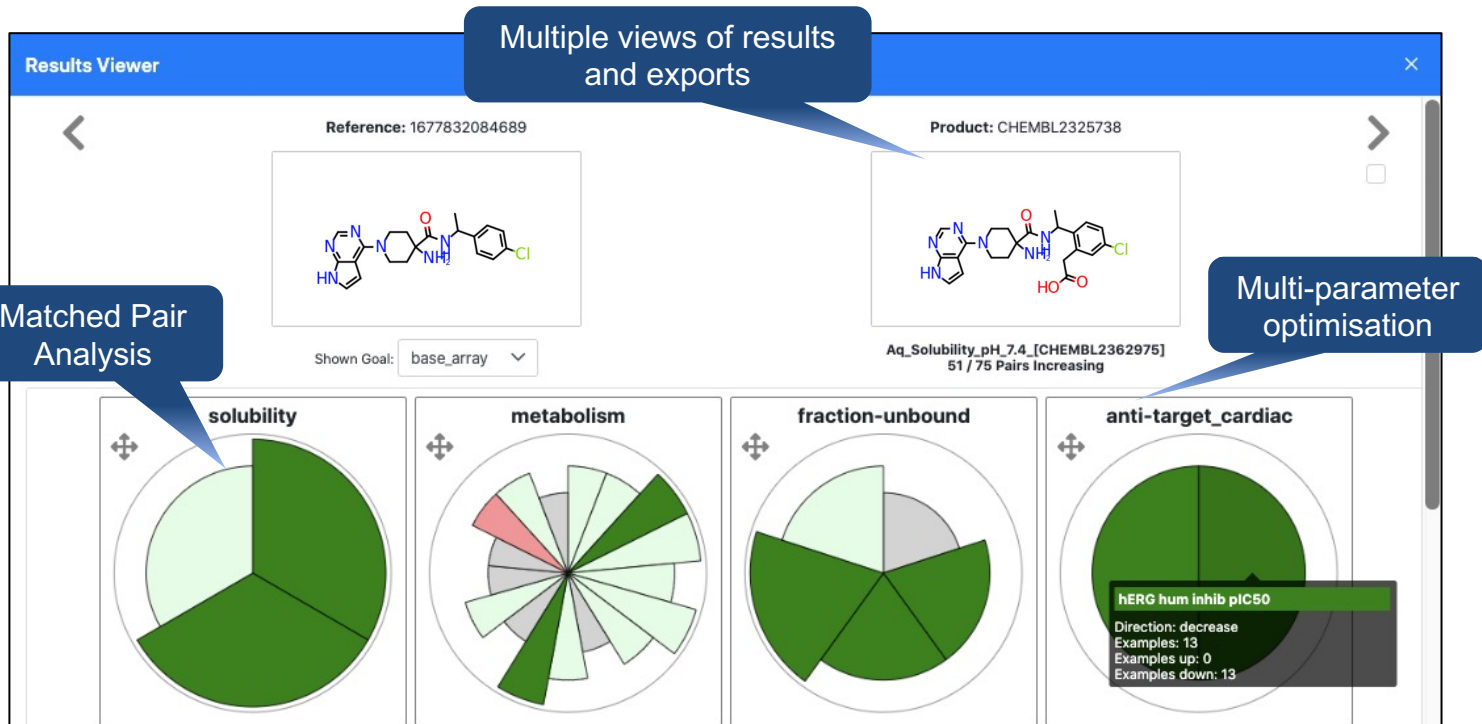


What is RuleDesign®?

- A robust ideas generator based on Medicinal Chemistry precedent

Why use RuleDesign®?

- ~ 870 000 Rules of medicinal chemists found by Matched Molecular Pair Analysis (MMPA)
- Complements CoreDesign®, by using robust Rules to generate the highest quality ideas
- **Links to the original pairs and data for key decision making**
- Part of MCPairs Online, a secure web app – **no software installation required**



"..it's like asking 150 of your peers for ideas in just a few seconds"
Principal Scientist (Large Pharma)

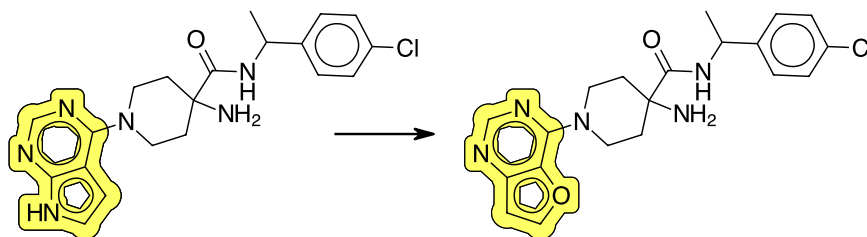
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A Design Tool for Scaffold Hops



What is a CoreDesign®?

- Either a Ring, Ring System or a Linking group between rings.

Why use CoreDesign®?

- Complements RuleDesign® by using diverse of Ring and Linker changes
- Over 1.3 million Ring and Linker transformations
- **Links to the literature and patent references for key decision making**
- User control of ring substitution and replacement linker length
- Part of MCPairs Online, a secure web app – **no software installation required**



Results viewer

Chemical structures shown: CHEMBL2325997 and chembl2325997_26

Product Properties

Matched Pair Analysis

Matched Pair Counts

Decrease	Neutral	Increase
30 / 62 (48%)	20 / 62 (32%)	12 / 62 (19%)

References

Compound A	Compound B	Source	Title	External Link
CHEMBL3715239	CHEMBL3718504	PATENT	Heterocyclic compounds for the inhibition of pask	WO2012149157A2
CHEMBL3715239	CHEMBL3718504	PATENT	Heterocyclic compounds for the inhibition of pask	US2012027724A1
CHEMBL3298430	CHEMBL3298688	Bioorg. Med.	Discovery of a 4-aryloxy-1H-pyrrolo[3,2-c]pyridine and a 1-aryloxyisoquinoline series of TRPA1 antagonists.	10.1016/j.bmc.2014.04.045

Physical properties calculations

Matched Pair Analysis

Literature and Patent References and links

Robust scaffold changes with good medicinal and synthetic chemistry precedent

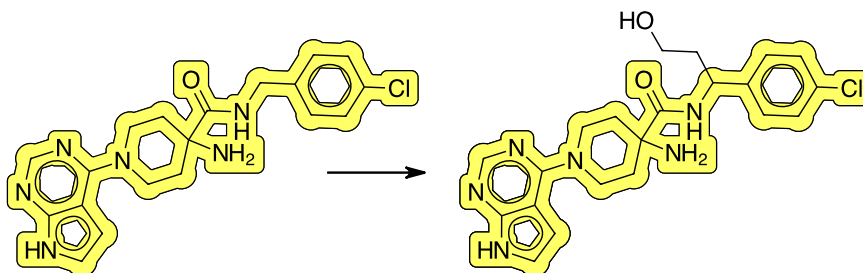
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A Design Tool for Testing Ideas before Synthesis

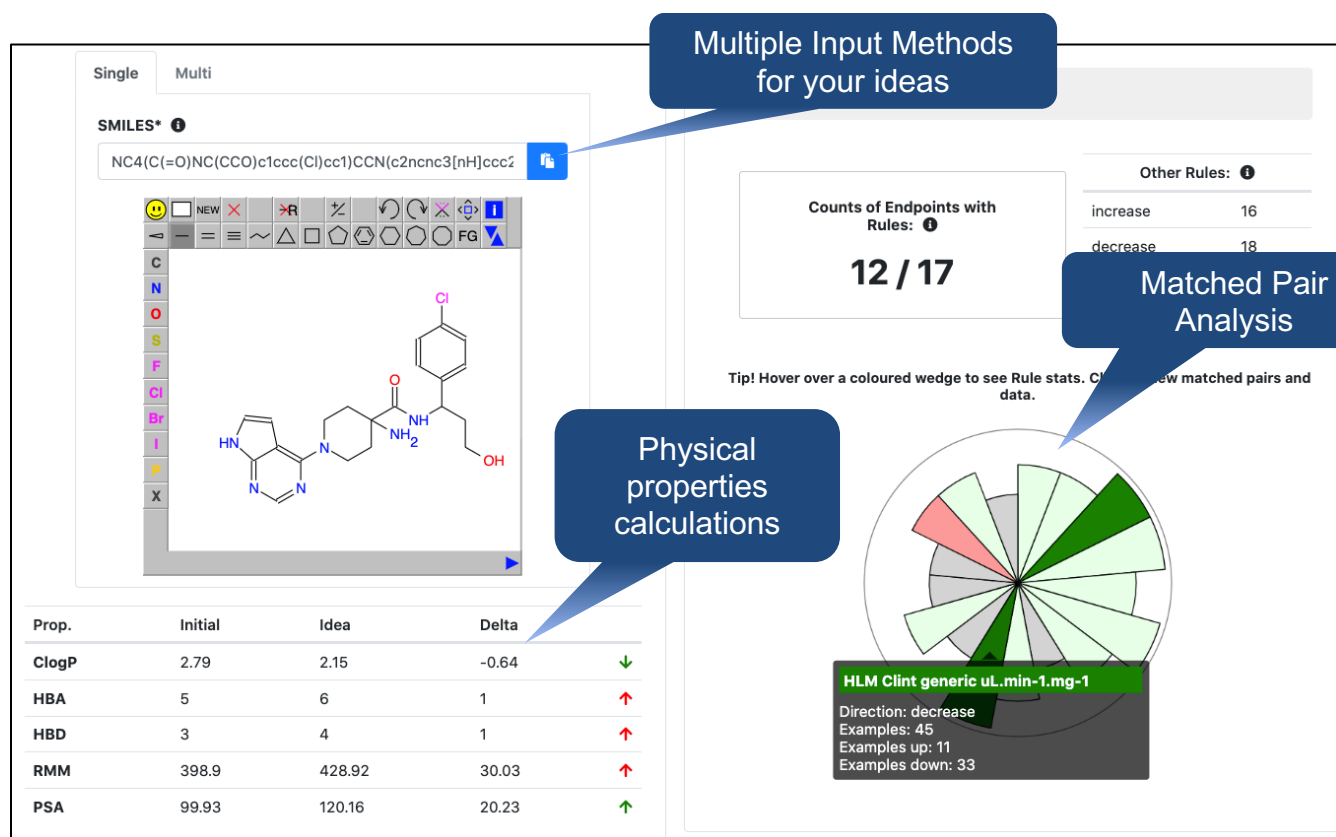


What is SpotDesign®?

- Sketch your ideas and test them against the Rules in the MCPairs database

Why use SpotDesign®?

- Approximately 870 000 Rules of medicinal chemists found by Matched Molecular Pair Analysis (MMPA)
- Explore the Rules to test your ideas and find matched pair data
- **Links to the original literature pairs and data for key decision making**
- Part of MCPairs Online, a secure web app – **no software installation required**



Use the knowledge of the past to prioritise your best ideas.

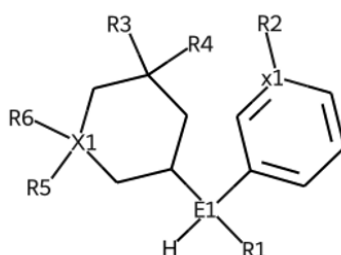
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Automated SAR Analysis via Markush like Structures



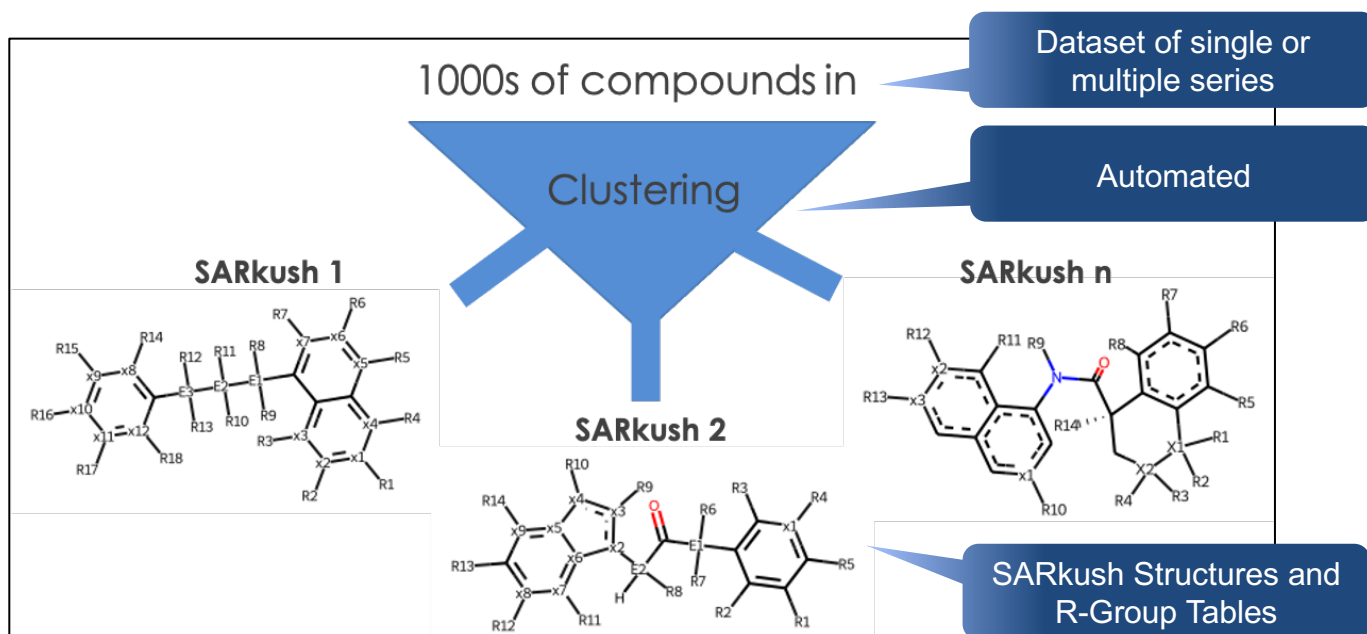
Variable atoms/ groups:

- x = aromatic atom
- X = aliphatic ring atom
- E = linker atom
- R = side chain

compound id	X1	E1	R1	...	data
1	C	N	None	...	measurement1
2	O	C	[H]	...	measurement2
...

Why use SARkush®?

- Automatic curation of chemical cores and R-group tables for SAR analysis
- Automatically split very large datasets into structurally-similar groups for model building
- Correctly assigns R-groups in a symmetrical molecules
- Input for computational models (Free-Wilson, QSAR, etc)
- Aid for patent filing
- Part of MCPairs Online, a secure web app – **no software installation required**



Detailed and robust SAR analysis

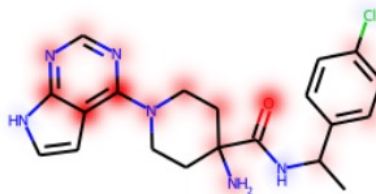
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Predicting Potential Toxic Liabilities



What is Toxophore?

- Predict binding to critical targets that are known to cause human toxicity

Why use Toxophore?

- Highlight potent pitfalls in Lead Identification / Lead optimisation
- Uses Machine Learning (ML) models that are **fully explainable**
- Output from two models provides higher confidence
- Part of MCPairs Online, a secure web app – **no software installation required**

Monoamine oxidase A Homo sapiens pIC50 [CHEMBL1951]

Hot spots of activity

< ?

Unit
To Rule Design

3 Pharmacophore(s)

Inactive
In Domain

pIC50: 4.448
Range: 3.878 - 5.017

HA_1atom_HA

median with [without]: 4.398[5]
n with / total: 916 / 3306

AR_directlink_AR

median with [without]: 5[4.395]
n with / total: 2660 / 3306

How each group contributes

7 Nearest Neighbour(s)

Weak Inactive
Out of Domain

pIC50: 4.823
Range: 4.725 - 4.921

CHEMBL4645906

pIC50: 5.4
Tan. Similarity: 0.733

BDBM159748

pIC50: 5.222
Tan. Similarity: 0.75

Nearest Neighbours in the dataset

Confident predictions that are fully explainable

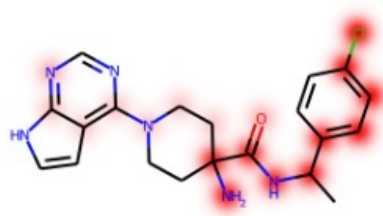
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Predicting Potential Binding



What is Pharmacophores?

- Predict binding to proteins in an explainable manner

Why use Pharmacophores?

- Compliments RuleDesign® by predicting potency of suggested molecules
- Uses Machine Learning (ML) models that are **fully explainable**
- Output from two models provides higher confidence
- Part of MCPairs Online, a secure web app – **no software installation required**

Fibroblast growth factor receptor 2 Homo sapiens pIC50 [CHEMBL4142]

Hot spots of activity

Unit
To Rule Design

3 Pharmacophore(s)

Active
In Domain

pIC50: 6.264
Range: 5.57 - 6.959

HA_8atom_HA
median with [without]: 8.14[6.854]
n with / total: 834 / 1092

HA_7atom_AR
median with [without]: 8.025[5]
n with / total: 1036 / 1092

How each group contributes

10 Nearest Neighbour(s)

Active
Out of Domain

pIC50: 6.842
Range: 6.792 - 6.892

CHEMBL4292020
pIC50: 6
Tan. Similarity: 0.744

CHEMBL4101681
pIC50: 6
Tan. Similarity: 0.783

Nearest Neighbours in the dataset

Confident predictions that are fully explainable

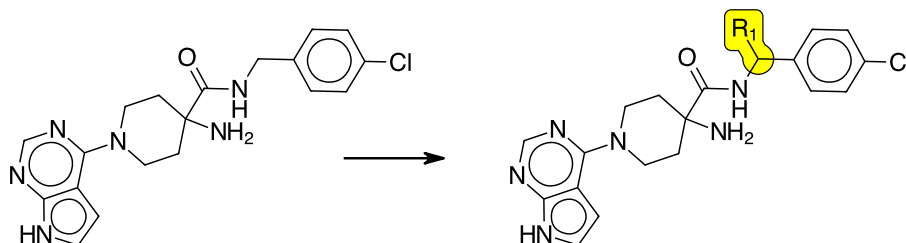
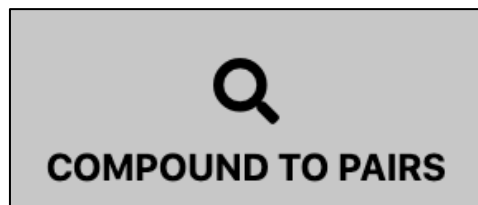
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Instant Structure Activity Relationship Analysis



What is Compound To Pairs?

- Rapid exploration of SAR from a single compound identifier

Why use Compound To Pairs?

- Near instant look-up of matched pairs
- Automated R-Group analysis
- **Rapid SAR tables and export to PowerPoint**
- Part of MCPairs Enterprise – a platform for automated analysis – accessed securely, through a web application

Drag and Drop Columns

Export to Powerpoint

Switch to Pair View	Hide Pairs with no Data	Show Hidden Columns	Show Structures	Change Formatting	Export
	CHEMBL598194 - (Reference)	CHEMBL2325997	CHEMBL2325982	CHEMBL2325738	CHEMBL2325737
Structure	R1H	R1CH ₃	R1CH ₃	R1CH ₂ OH	R1CH ₂ OH
		Open as reference	Open as reference	Open as reference	Open as reference
AKT hum IC50 CHEMBL4282	0.01	0.01	0.01	0.00	0.01
AKT2 hum IC50 CHEMBL2431	0.01	0.04	0.02	0.02	0.05
ALogP98	2.23	2.79	3.18	2.15	1.76
Relative Molecular Mass (RMM)	384.87	398.9	412.93	428.92	414.9
HERG IC50 CHEMBL240	5.23	7.20	6.50	> 100.00	> 100.00
Aq Sol pH_7.4 CHEMBL2362975	27.33	181.01	13.00	20.70	46.90

Drag and Drop Rows

Fully Customisable colouring

The day-to-day go to tool for SAR analysis

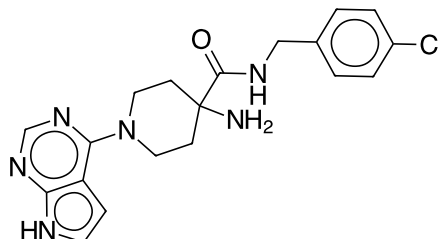
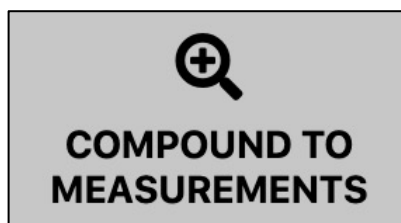
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Instant Compound Data Lookup



Assay	Result
AKT IC50	0.01 uM
AKT2 IC50	0.01 uM
hERG IC50	5.23 uM
Aq. Solubility	27.33 uM

What is Compound To Measurement?

- Find all the data for a compound in an instant

Why use Compound To Measurement?

- Near instant look-up of compounds and data
- Exported in multi-formats to aid communication**
- Part of MCPairs Enterprise – a platform for automated analysis – accessed securely, through a web application

Complete list of Assays

Sortable columns

Measurements					
Endpoint ↑↓	Compound Name ↑↓	Qualifier ↑↓	Measurement ↓↑	Unit ↑↓	Created Timestamp ↑↓
Serine/threonine-protein_kinase_AKT2_Homo_sapiens_pIC50_[CHEMBL2431]	CHEMBL598194	=	7.9191	pIC50	2017-05-01 00:00:00
Serine/threonine-protein_kinase_AKT_Homo_sapiens_pIC50_[CHEMBL4282]	CHEMBL598194	=	7.8861	pIC50	2017-05-01 00:00:00
Serine/threonine-protein_kinase_AKT3_Homo_sapiens_pIC50_[CHEMBL4816]	CHEMBL598194	=	7.2441	pIC50	2017-05-01 00:00:00
Rho-associated_protein_kinase_2_Homo_sapiens_pIC50_[CHEMBL2973]	CHEMBL598194	=	7.0126	pIC50	2017-05-01 00:00:00
Rho-associated_protein_kinase_2_Homo_sapiens_pIC50_[CHEMBL2973]	CHEMBL598194	=	6.9566	pIC50	2018-04-23 00:00:00
Rho-associated_protein_kinase_Homo_sapiens_pIC50_[6427.1]	BDBM50307942	=	6.8447	pIC50	2019-03-04 12:49:02
Cytochrome_P450_2C9_Homo_sapiens_pIC50_[CHEMBL3397]	CHEMBL598194	=	6	pIC50	2017-05-01 00:00:00
HERG_Homo_sapiens_pIC50_[CHEMBL240]	CHEMBL598194	=	5.2811	pIC50	2017-05-01 00:00:00
Cytochrome_P450_2C19_Homo_sapiens_pIC50_[CHEMBL3622]	CHEMBL598194	<	5	pIC50	2017-05-01 00:00:00
Cytochrome_P450_1A2_Homo_sapiens_pIC50_[CHEMBL3356]	CHEMBL598194	<	5	pIC50	2017-05-01 00:00:00

csvxlsx

Multi-format Exports

Day to day data exploration and sharing

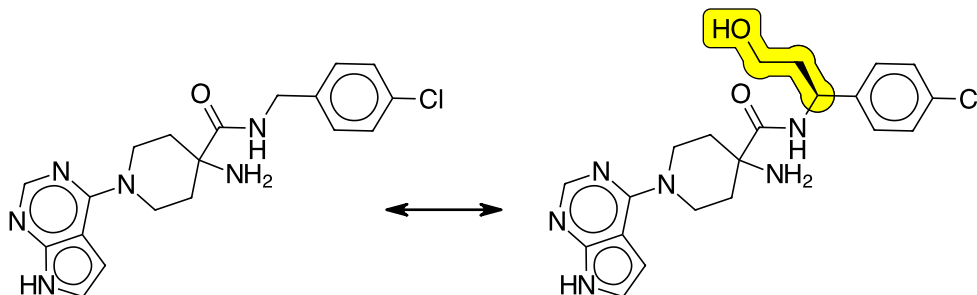
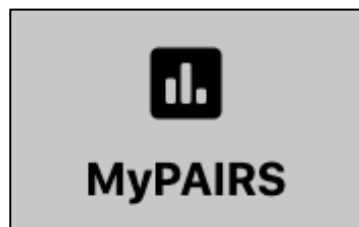
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Find Your Matched Pairs and Rules



What is MyPAIRS?

- File-in / File-out access to Matched Pairs finding technology

Why use MyPAIRS?

- Two pair finding techniques provides wider chemical coverage
- **Fully configurable and comprehensive cheminformatics output**
- Robust statistical analysis techniques yielding unique medchem Rules
- Part of MCPairs Online, a secure web app – **no software installation required**

Matched Pairs

SMIRKS

compound A	compound B	methods	labelled_core	sidechain A	sidechain B	smirks
CHEMBL2325741	CHEMBL598194	both	[R1]C(c1ccc(cc1)Cl)NC(=O)C2(CCN(CC2)c3c4cc[nH]c4ncn3)N	[R1]CCO	[R1][H]	[C:1]([H])([C])([H])([H])([C])([H])([H])([O])([H])>>[C:1]([H])([H])
CHEMBL2325741	CHEMBL598194	both	[R1]C(c1ccc(cc1)Cl)NC(=O)C2(CCN(CC2)c3c4cc[nH]c4ncn3)N	[R1]CCO	[R1][H]	[c:1][C:2]([H])([C])([H])([H])([C])([H])([H])([O])([H])([N:3]([H])>>[c:1]([H])([H])([C])([H])([H])([C])([H])([H])([O])([H])
CHEMBL2325741	CHEMBL598194	both	[R1]C(c1ccc(cc1)Cl)NC(=O)C2(CCN(CC2)c3c4cc[nH]c4ncn3)N	[R1]CCO	[R1][H]	[c:1]([H])([C:2]([H])([H])([C])([H])([H])([C])([H])([H])([O])([H])
CHEMBL2325741	CHEMBL598194	both	[R1]C(c1ccc(cc1)Cl)NC(=O)C2(CCN(CC2)c3c4cc[nH]c4ncn3)N	[R1]CCO	[R1][H]	[c:1]([H])([C:2]([H])([H])([C])([H])([H])([C])([H])([H])([O])([H])
CHEMBL598194	CHEMBL2325741	both	[R1]C(c1ccc(cc1)Cl)NC(=O)C2(CCN(CC2)c3c4cc[nH]c4ncn3)N	[R1][H]	[R1]CCO	[c:1][C:2]([H])([H])([N:3]([H])>>[c:1][C:2]([H])([C])([H])([H])([C])([H])([H])([O])([H])
CHEMBL598194	CHEMBL2325741	both	[R1]C(c1ccc(cc1)Cl)NC(=O)C2(CCN(CC2)c3c4cc[nH]c4ncn3)N	[R1][H]	[R1]CCO	[c:1]([H])([C:2]([H])([H])([C])([H])([H])([N:5]([H])([C:6]([H])([H])([H])([H])>>[c:1]([H])([H])([C])([H])([H])([C])([H])([H])([O])([H])
CHEMBL598194	CHEMBL2325741	both	[R1]C(c1ccc(cc1)Cl)NC(=O)C2(CCN(CC2)c3c4cc[nH]c4ncn3)N	[R1][H]	[R1]CCO	[c:1]([H])([C:2]([H])([H])([C])([H])([H])([C])([H])([H])([O])([H])

Four levels of environment

Automatic R-Group Analysis

Robust Matched Molecular Pair Analysis

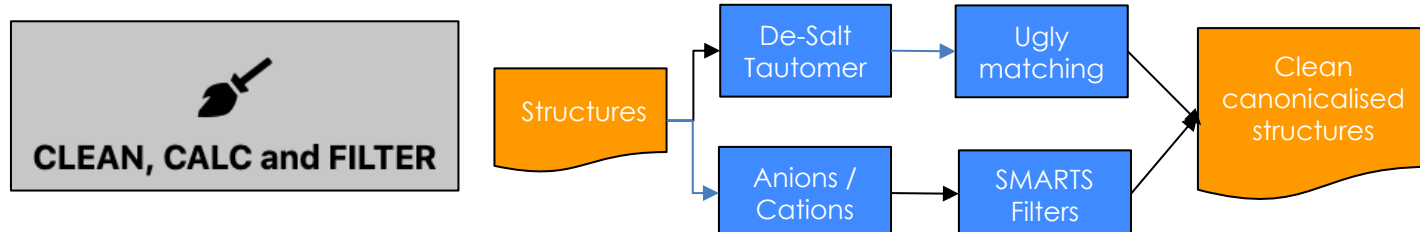
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Access to MedChemica's Cheminformatics Toolbox



What is Clean, Calc and Filter?

- Generate Canonical SMILES structures with consistent tautomer forms

Why use Clean, Calc and Filter?

- Options to de-salt, normalise and calculated physical properties
- Standardise tautomers and protonation states
- Access to MedChemica's charge models and proprietary Ugly filters
- Program multiple sub-structure searches to subset large sets
- Part of MCPairs Online, a secure web app – **no software installation required**

Canonicalised SMILES /
Standardised Tautomer model

Anions, Cations and Uglies

compound_name	compound_struct	compound_s	mol_wt	ALogP98	HA	HBA	HBD	Hetero_atoms	Rings	Rot_bonds	TPSA	count_anions	count_cations	is_ugly
CHEMBL117055	CCOc1ccc2c(c1)sc(n2)SCc3cc(cc(c3O)OC)/C=C\	CCOc1ccc2nc	441.5	4.09	30	8	2	9	3	8	118.5	0	0	0
CHEMBL116353	COc1cc2c(=O)cc(cc2c(c1N)c3ccc(cc3)N	COc1cc(N)c2	282.3	2.63	21	5	2	5	3	2	91.48	0	0	0
CHEMBL116051	c1cc(ccc1c2cc(=O)c3c(c2)ccc(c3O)N)N	Nc1ccc(cc1)(268.3	2.33	20	5	3	5	3	1	102.5	0	0	0
CHEMBL115601	c1cc(ccc1c2cc(=O)c3cc(c(c(c3o2)N)O)N)N	Nc1ccc(cc1)(283.3	1.91	21	6	4	6	3	1	128.5	0	0	0
CHEMBL115397	COc1ccc(c2c1c(=O)cc(o2)c3ccc(cc3)N)N	COc1ccc(N)c	282.3	2.63	21	5	2	5	3	2	91.48	0	0	0
CHEMBL115103	c1cc(cc(c1)N)c2cc(=O)c3cc(ccc3o2)N	Nc1cccc(c1)(252.3	2.62	19	4	2	4	3	1	82.25	0	0	0
CHEMBL115102	c1cc(cc(c1)N)c2cc(=O)c3cc(c(cc3o2)O)N	Nc1cccc(c1)(268.3	2.33	20	5	3	5	3	1	102.5	0	0	0
CHEMBL114814	c1cc(ccc1c2cc(=O)c3c(c2)cc(c(c3N)O)N)N	Nc1ccc(cc1)(283.3	1.91	21	6	4	6	3	1	128.5	0	0	0
CHEMBL114578	c1cc(ccc1c2cc(=O)c3cc(ccc3o2)N)O)N	Nc1ccc(cc1)(268.3	2.33	20	5	3	5	3	1	102.5	0	0	0
CHEMBL114568	c1cc(ccc1c2cc(=O)c3cc(c(c3o2)N)O)N	Nc1ccc(cc1)(268.3	2.33	20	5	3	5	3	1	102.5	0	0	0
CHEMBL114550	COc1cc2c(=O)cc(cc2c(c1)N)c3cccc(c3)N	COc1cc(N)c2	282.3	2.63	21	5	2	5	3	2	91.48	0	0	0
CHEMBL1159655	Cc1c(ccc1O)C(=O)N[C@H](Cc2ccccc2)[C@@H]	Nc1c(O)cccc1	567.8	4.75	40	6	4	8	4	9	101.9	0	1	0
CHEMBL1161236	COc1cc(cc(c1O)SCC(=O)O)C=C(C#N)C#N	COc1cc(C=C(290.3	2.01	20	6	2	7	1	5	114.3	1	0	0
CHEMBL1161234	COc1cc(cc(c1O)SCC(=O)O)C=C(C#N)/C(=O)	COc1cc(C=C	336.4	1.75	23	6	3	8	1	8	133.6	1	0	0
CHEMBL1171273	Cc1ncc(n1CCOC(=O)/C=C/c2cccc2OC)[N+](=O)	COc1cccc1\	331.3	2.36	24	7	0	8	2	7	96.49	0	0	0
CHEMBL1172419	CC(=O)N1C(Cc1=O)N1c2ccc(c(c2)Cl)Cl)c3cccc3	CC(=O)N1N=	333.2	4.69	22	2	0	5	3	2	32.67	0	0	0
CHEMBL1172877	Cc1ncc(n1CCOC(=O)/C=C/c2cccc2F)[N+](=O)[C	Cc1ncc([N+](319.3	2.50	23	6	0	8	2	6	87.26	0	0	0
CHEMBL1172602	CC(=O)N1C(Cc1=O)N1c2ccc(c(c2)Cl)Cl)c3ccc(cc3)	COc1cc(OC)c	393.3	4.71	26	4	0	7	3	4	51.13	0	0	0
CHEMBL1173789	Cc1ncc(n1CCOC(=O)/C=C/c2cccc2[N+](=O)[O-]	Cc1ncc([N+](346.3	2.26	25	8	0	10	2	7	130.4	0	0	0
CHEMBL1172947	Cc1ncc(n1CCOC(=O)/C=C/c2cccc2Br)[N+](=O)[C	Cc1ncc([N+](380.2	3.12	23	6	0	8	2	6	87.26	0	0	0
CHEMBL1172418	CC(=O)N1C(Cc1=O)N1c2ccc(c(c2)Cl)Cl)c3cccc3Cl	CC(=O)N1N=	367.7	5.34	23	2	0	6	3	2	32.67	0	0	0
CHEMBL115895	CC(=O)Nc1cccc1SCc2cc(cc(c2O)OC)/C=C/C#N	COc1cc(C=C	397.5	3.04	28	6	3	8	2	7	125.4	0	0	0

Basic Calculated Properties

Clean and subset compound structures with confidence

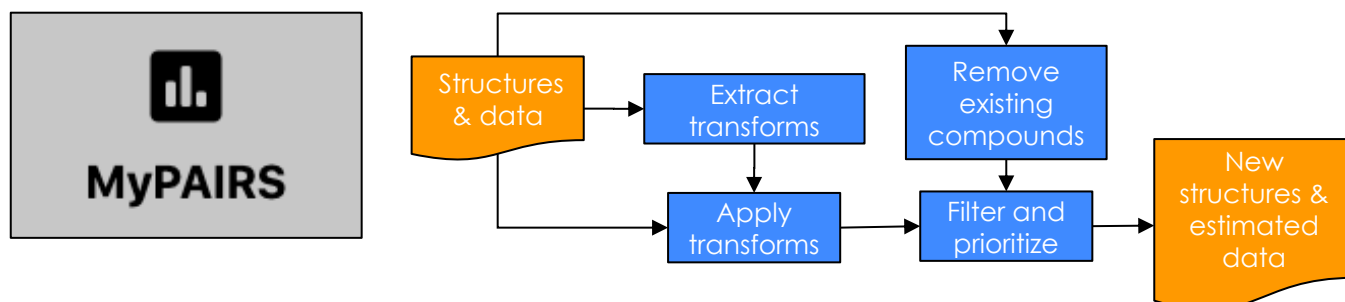
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Permute SAR across your series

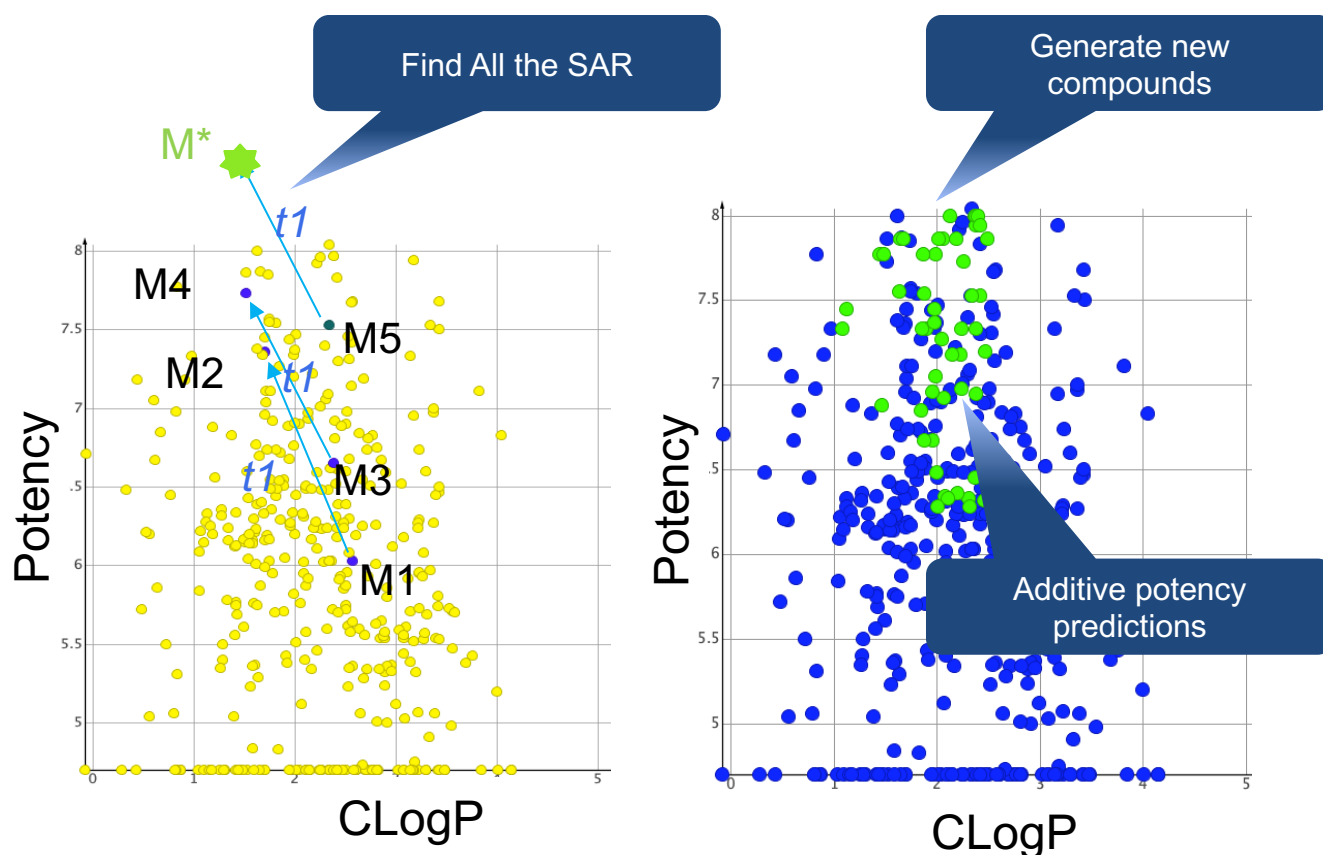


What is Permutative Matched Molecular Pair Analysis (pMMPA)?

- Use matched pairs to determine SAR, then generate all permutations

Why use pMMPA?

- Complements Free-Wilson approaches by using chemical transformations
- Check and verify SAR, spot transformations that would have been missed.
- Ideal for late LI and LO to 'make all the permutations'
- Part of MCPairs Online, a secure web app – **no software installation required**



Explore all the unrealised potential of your series

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