Open PHACTS
Open Pharmacological Space

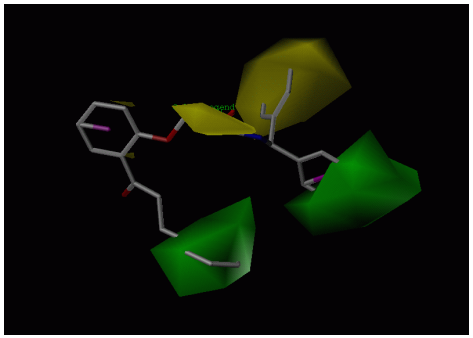
Open PHACTS – An Academic Researcher´s Perspective

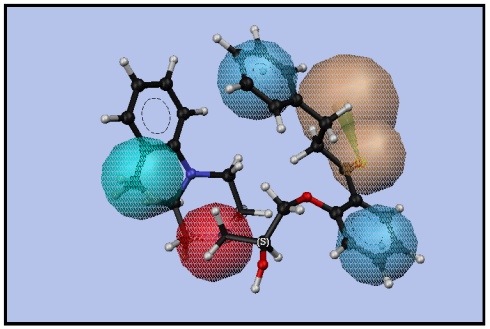
Gerhard F. Ecker

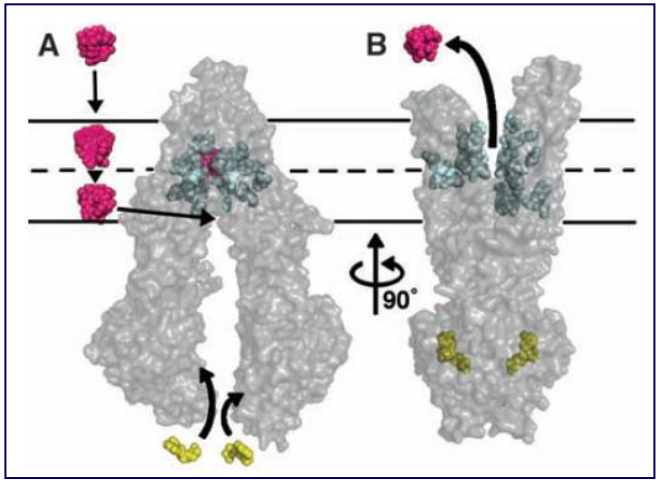
Univ. Vienna, Dept. Medicinal Chemistry

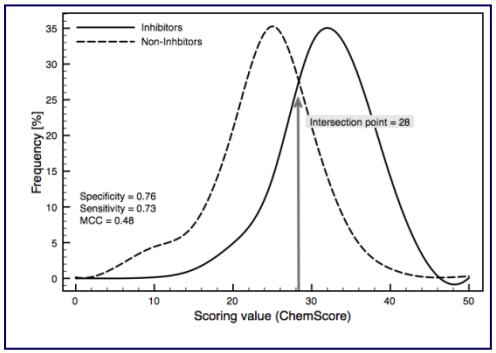
The Pharmacoinformatics Research Group

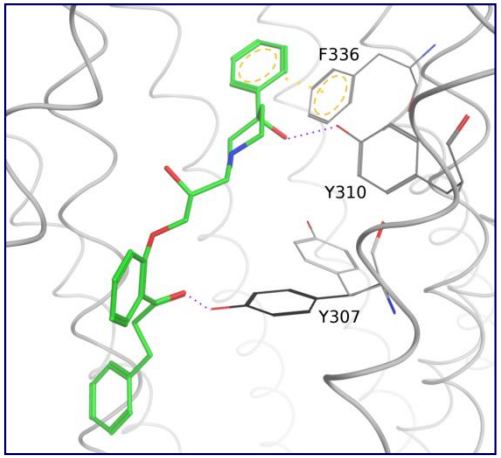
Transporter
Off-target predictions
Integrated approaches











Data, data, data, ...

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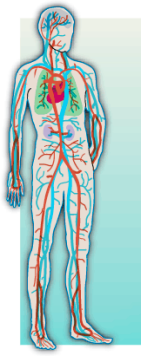

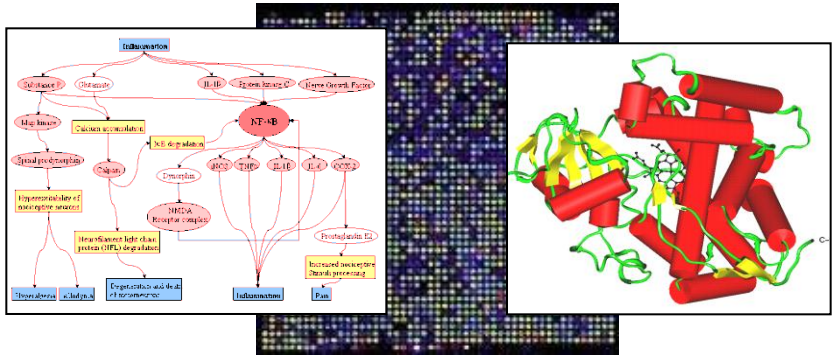

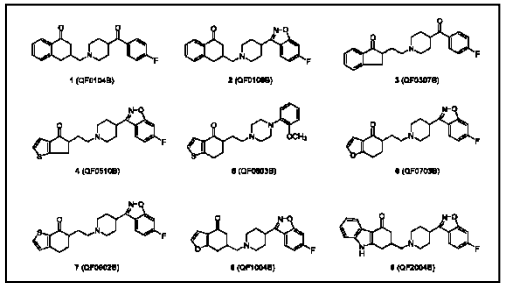

Disease ⟷ Pathway ⟷ Target ⟷ Ligand

Clinical information

"omics" information

Chemical/structural information

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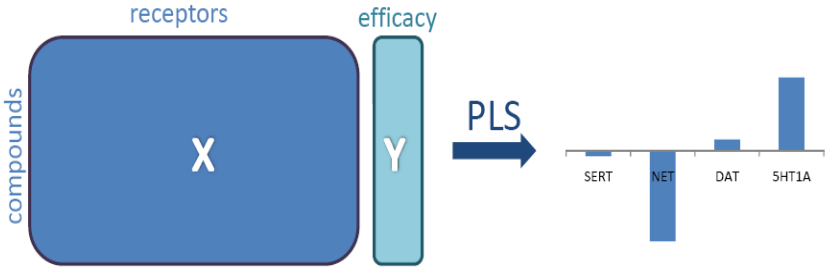
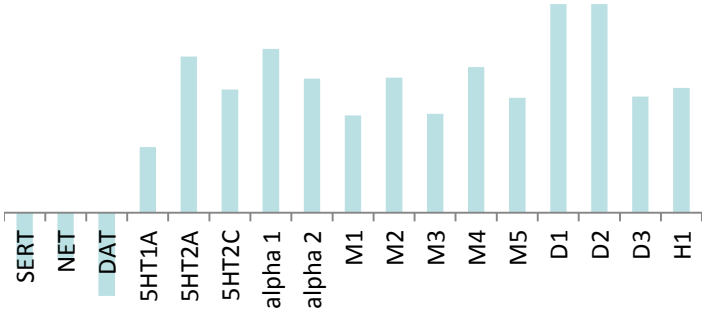
1.1 pKi Werte

	SERT	NET	DAT	5HT1A	5HT2A	5HT2C	alpha 1	alpha 2	M1	M2	M3	M4	M5	D1	D2	D3	H1
Citalopram	8.73	5.16	5.00	5.00	5.08	6.21	5.92	5.00	5.84	5.00	5.00	5.00	5.00	5.00	5.00	5.00	6.46
Escitalopram	8.96	5.11	5.00			5.60	5.41		5.91	5.00	5.00	5.00	5.00	5.00	5.00		5.70
Fluoxetin	8.61	6.18	5.39	5.00	6.71	6.59	5.56	5.07	6.06	5.57	5.96	5.54	5.57	5.00	5.00		5.49
Fluvoxamin	8.69	5.72	5.00	5.00	5.00	5.17	5.89	5.72	5.00	5.00	5.00	5.00	5.00	5.00	5.00		5.00
Paroxetine	10.00	7.25	6.42	5.00	5.00	5.00	5.56	5.00	6.73	6.47	7.10	6.49	6.19	5.00	5.00		5.00
Sertraline	9.64	5.88	7.59	5.00	5.27	5.64	6.70	5.64	6.06	5.68	5.89	5.85	5.72	5.20	5.97		7.62
Venlafaxin	8.09	5.56	5.09	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00		5.81
Desvenlafaxine	7.40	5.83	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Duloxetin	9.21	8.23	6.62	5.00	6.30	6.04	5.08	5.03	5.00	5.00	5.00	5.00	5.00	5.00	5.00		5.64
Milnacipran	8.08	7.66	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00		5.00
Trazodon	6.69	5.02	5.06	6.97	7.44	6.65	7.16	6.49	5.00	5.00	5.00	5.00	5.00	5.43	5.40		6.18
Nefazodon	6.48	6.31	6.44	7.10	8.15	7.14	7.57	6.44	5.00	5.00	5.00	5.00	5.00	5.82	6.04		5.00
Reboxetine	6.56	7.89	5.00	5.00	5.00	6.34	5.00	5.00	5.59	5.55	5.55	5.38	5.70		5.00	5.00	5.85
Atomoxetin	7.11	8.30	5.84	5.00	5.00	5.00	5.00	5.00	5.00	5.00				5.00	5.00		5.00
Bupropion	5.02	5.00	6.19	5.00	5.00	5.00	5.38	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00		5.00
Nomifensine	6.00	7.65	7.31	5.93	6.43	5.00	5.00	5.21	5.00	5.00	5.00	5.00	5.00	5.00	5.00		5.57
Mirtazapine	5.00	5.34	5.00	7.74	7.16	7.41	6.43	7.70	6.10					5.38	5.26	5.24	8.80
Mianserin	5.40	7.15	5.03	6.29	7.83	8.41	7.14	7.92	6.30					6.03	5.69	5.55	9.10
Maprotiline	5.24	7.95	6.00	5.00	7.29	6.91	7.17	5.51	6.46								9.10
Amitriptyline	8.46	7.65	5.54	6.35	7.64	8.37	7.85	6.40	7.89	7.93	7.59	8.14	7.70	7.09	5.84		9.15
Clomipramine	9.70	7.34	5.58	5.00	7.45	7.19	8.49	6.28						6.66	7.11	7.40	
Doxepin	7.17	7.53	5.00	6.56	7.59	8.06	7.63	5.90	7.42	6.80	7.28	7.09	7.12		6.44		9.70
Imipramin	8.89	7.29	5.03	5.10	6.93	6.92	7.49	5.51	7.38	7.36	7.22	6.95	7.08	5.00	6.17	6.41	7.58
Desipramin	7.70	8.46	5.11	5.09	7.02	6.61	7.21	5.46	6.96	6.27	6.68	6.80	6.84	5.26	5.60		7.12
Dothiepin	8.05	7.34	5.27	5.40	6.82		6.38	7.92	7.74	6.96	7.42	7.22	7.04				8.40
Lofepramine	7.15	8.27	5.00	5.34	5.92		7.00	5.57	7.17	6.48	6.89	6.47	6.34	6.30	5.70		6.44
Aripiprazol	5.97	5.68	5.49	8.25	8.06	7.65	7.60	7.13	5.17	5.45	5.33	5.82	5.63	6.41	9.02	8.01	7.54
Amisulpride	5.00		5.00	5.00	5.70	5.00	5.15	5.80						5.00	8.89	8.62	5.00
Chlorpromazine	5.89	5.61	5.00	5.51	8.46	8.21	9.55	6.12	7.60	6.67	7.17	7.40	7.38	7.36	8.10	8.52	8.52
Clozapine	5.79	5.50	5.00	6.85	8.19	7.44	8.17	7.82	8.85	7.32	8.15	8.22	8.30	6.71	6.89	6.55	8.92
Haloperidol	5.49	5.68	5.00	5.29	6.70	5.00	7.77	6.22	5.00	5.00	5.00	5.00	5.00	7.24	9.37	8.66	5.77
Methylphenidate	5.00	6.47	7.38	5.00	5.00	5.00	5.00	5.25	5.00	5.00	5.00	5.00	5.00	5.00	5.00		
Olanzapine	5.43	5.00	5.00	5.57	8.60	8.17	7.36	6.55	8.60	7.02	7.89	8.00	8.22	7.46	7.50	7.52	9.19
Perphenazine				6.38	8.25	6.88	8.00	6.29						7.52	9.04	8.96	8.10
Quetiapin	5.00	5.00	5.00	6.49	7.02	5.93	8.09	7.10	6.87	6.20	6.15	6.65	5.52	6.15	6.61	6.19	8.66
Risperidon	5.00	5.00	5.00	6.38	9.38	7.19	8.57	8.12	5.00	5.43	5.00	5.54	5.00	7.22	8.57	7.85	7.48
Ziprasidone	6.95	7.36	5.00	7.92	8.85	7.89	8.59	6.81	5.00	5.00	5.00	5.00	5.00	7.52	8.07	8.00	7.82



Decreased Libido



eTOX

imi
Innovative Medicines Initiative

FWF

SFB 35

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BCRP

Dataset

Acridone derivatives: Design, synthesis, and inhibition of breast cancer resistance protein ABCG2

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Available online 13 February 2007

Therapeutics

Reversal of Breast Cancer Resistance Protein-mediated Drug Resistance by Estrogen Antagonists and Agonists 1

MOL PHARM

Flavonoids Are Inhibitors of Breast Cancer Resistance Protein (ABCG2)-Mediated Transport

Shuzhong Zhang, Xinning Yang, and Marilyn E. Morris

Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, State University of New York, Amherst, New York

Received October 15, 2003; accepted January 30, 2004

This article is available online at http://molpharm.aspetjournals.org

Phytoestrogens/Flavonoids Rever Resistance Protein/ABCG2-Mediat

Yasuo Imai, Satomi Tsukahara, Sakiyo Asada, et al.

JPET

A Global Drug Inhibition Pattern for the Human ATP-Binding Cassette Transporter Breast Cancer Resistance Protein (ABCG2)[S]

Pär Matsson, Gunilla Englund, Gustav Ahlin, Christel A. S. Bergström, Ulf Norinder, and Per Artursson

Pharmaceutical Screening and Informatics, Department of Pharmacy, Uppsala University, Sweden (P.M., G.E., G.A., C.A.S.B., U.N., P.A.); and AstraZeneca R&D, Södertälje, Sweden (U.N.)

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journal homepage: www.elsevier.com/locate/bmcl

stituted-2-phenylquinazolines as inhibitors of BCRP

vale, Michael Wiese*

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

ELSEVIER

HERAPEUTICS

RESEARCH PAPER

The multidrug transporter ABCG2 inhibited by plant-derived cannabi

ML Holland[1], DTT Lau[2], JD Allen[2] and JC Arnold[1]

Investigation of chalcones and benzochalcones as inhibitors of breast cancer resistance protein

Kapil Juvale, Veronika F.S. Pape, Michael Wiese*

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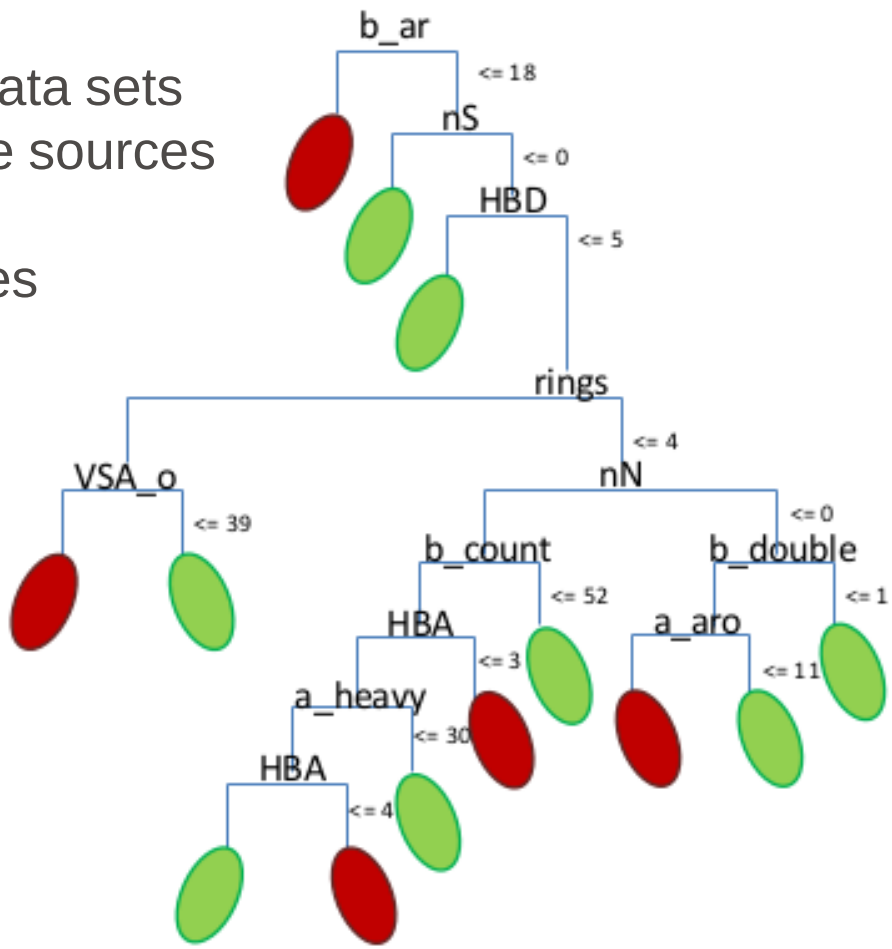
BCRP

Manual compilation of data sets
Identification of literature sources
Redrawing structures
Manual addition of values

J48 Tree, MOE descriptors



inhibitor
inactive

Area under ROC: 0.8

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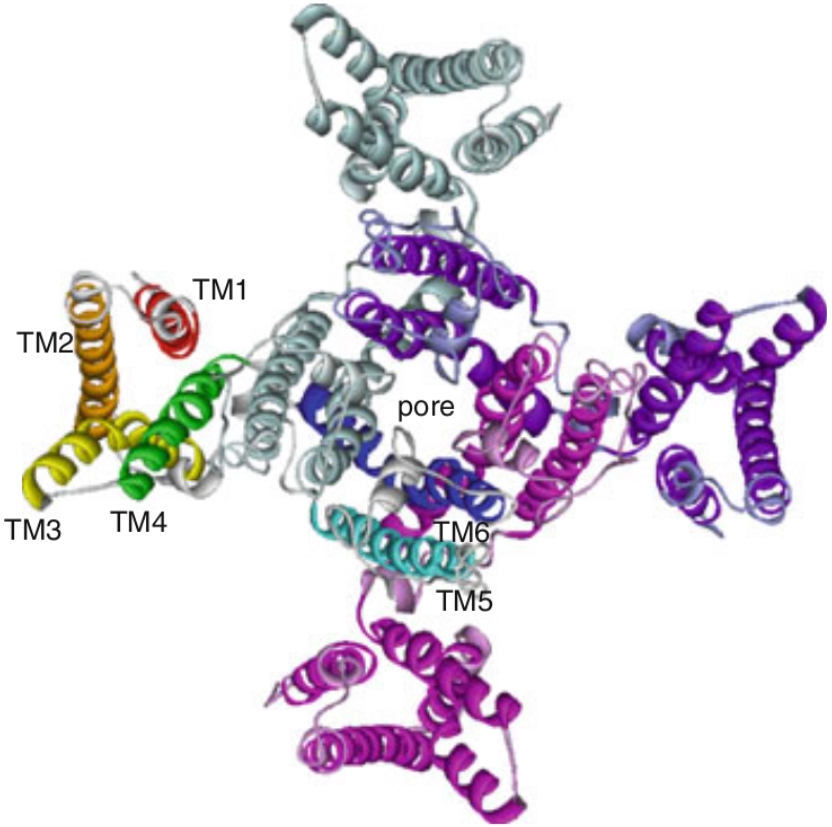
TRPV1

- Transmembrane receptor
- Tetramer
- Non-selective cation channel
- Peripheral nervous system
- Activation → influx of cations → depolarization of membrane → pain perception
- Prolonged activation – desensitization



Lee et al., J Comput Aided Mol Des (2011) 25: 317-37

Molecular Drug Targets

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TRPV1

Firefox | Louis Armstrong New Orleans Interna... | Google Kalender | Register for Open PHACTS Explorer | Open PHACTS

explorer.openphacts.org/#!p=PharmByTargetNameForm&u=http://www.conceptwiki.org/concept/f1c37c53-63c3-4107-a688-12d4dc082ef3

molecular informatics journal

Open PHACTS Explorer

Navigation

- Compound
- Target
- Pharmacology
  - Pharmacology by Enzyme family
  - Pharmacology by Compound
  - Pharmacology by Target

Help and Feedback

API Status

TSV Downloads

Pharmacology by Target Name

Hint: Type in protein name and species. E.g. "ADA protein human" and select a result

Protein name: Transient receptor potential cation channel subfamily V member 1 (Homo sapiens) Search...

Filter Provenance: On Off

Pharmacology by Target name search results - Total Records: 2328

Prepare tsv file

	Structure	Compound Name	Target Name	Target Organism	Assay Organism	Assay Description	Activity Type	Relation	Value	U
1		(3beta)-3-hydroxy-N-(4-hydroxy-3-methoxybenzyl)urs-12-en-28-amide	Transient receptor potential cation channel subfamily V member 1 (Homo sapiens)	Homo sapiens		Percent absolute effect obtained with ionomycin, measured by the entry of [Ca2+] into human embryonic kidney HEK293 cells overexpressing hVR1	Response	=	14.3	
2		(3beta)-3-hydroxy-N-(4-hydroxy-3-methoxybenzyl)urs-12-en-28-amide	Transient receptor potential cation channel subfamily V member 1 (Homo sapiens)	Homo sapiens	Homo sapiens	[Ca2+] influx into human embryonic kidney HEK293 cells overexpressing human VR1 (NM = non-measurable)				
3		(12R)-12-hydroxy-N-(4-hydroxy-3-methoxybenzyl)octadecanamide	Transient receptor potential cation channel subfamily V member 1 (Homo sapiens)	Homo sapiens		Percent absolute effect obtained with ionomycin, measured by the entry of [Ca2+] into human embryonic kidney HEK293 cells overexpressing hVR1	Response	=	69.7	

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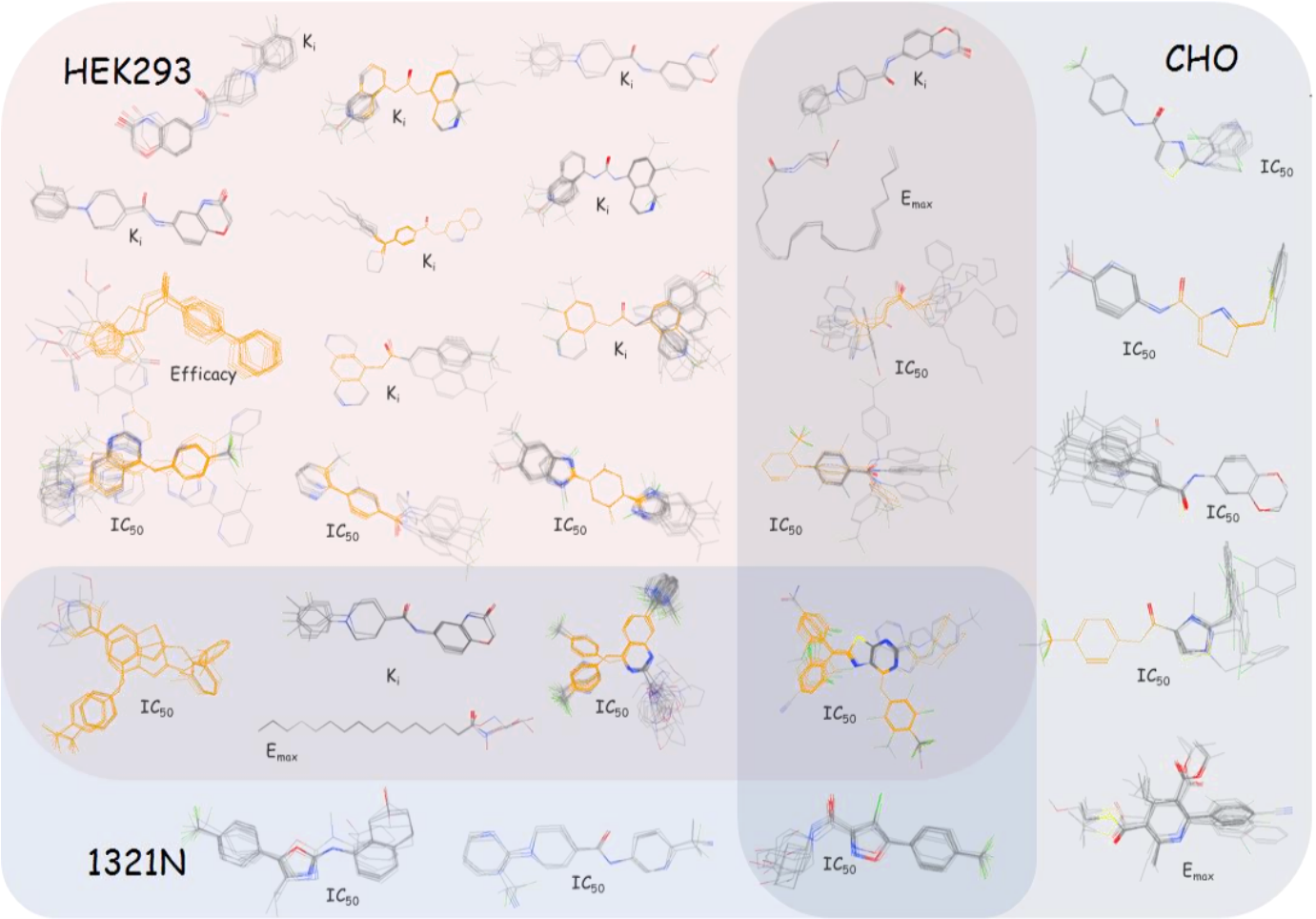
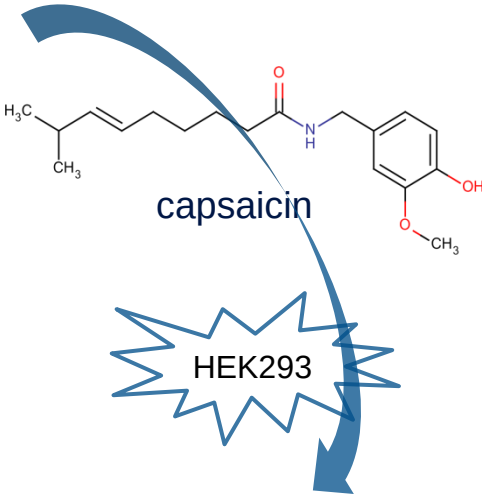
TRPV1

hTRPV1 → 2328 ligands from Open PHACTS





http://www.openphacts.org

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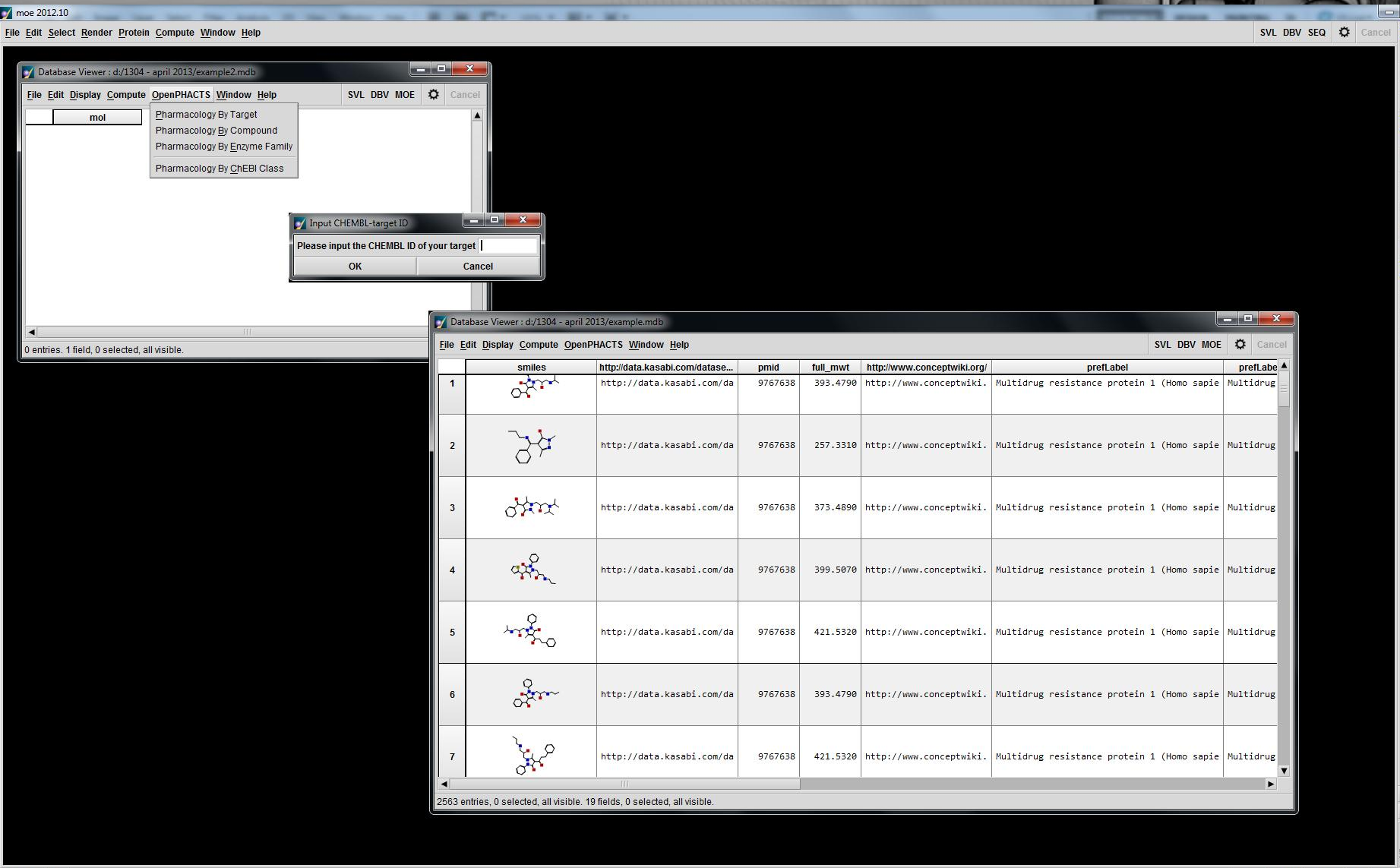
MOE



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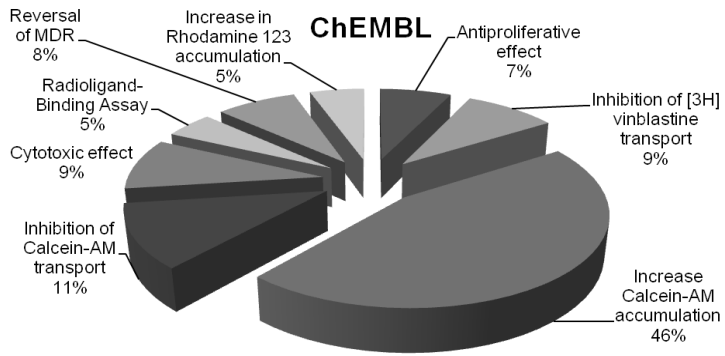
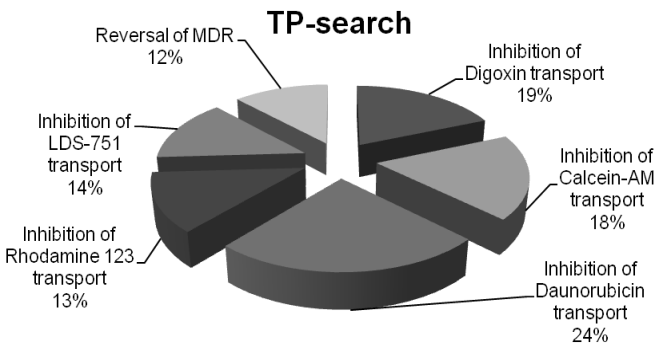
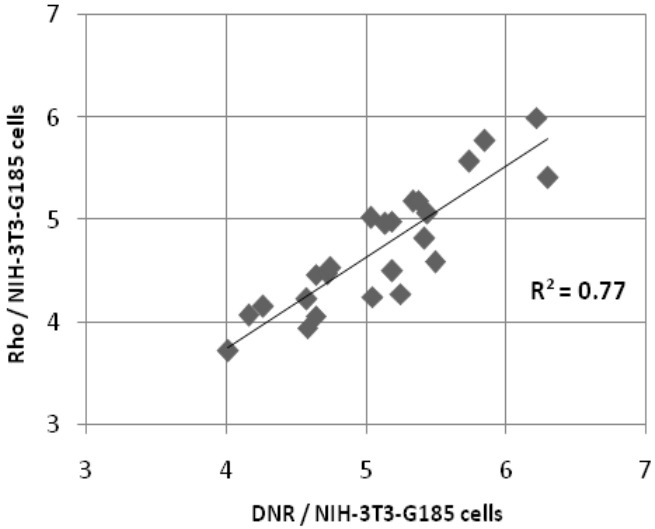
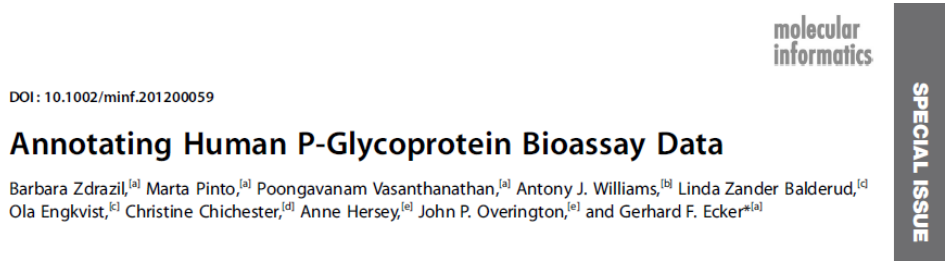
Assays








molecular informatics

SPECIAL ISSUE

DOI: 10.1002/minf.201200059

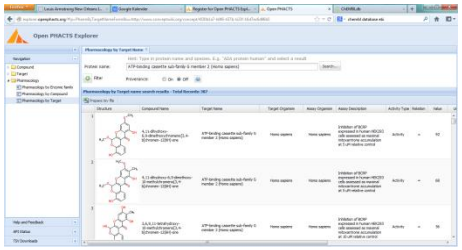
Annotating Human P-Glycoprotein Bioassay Data

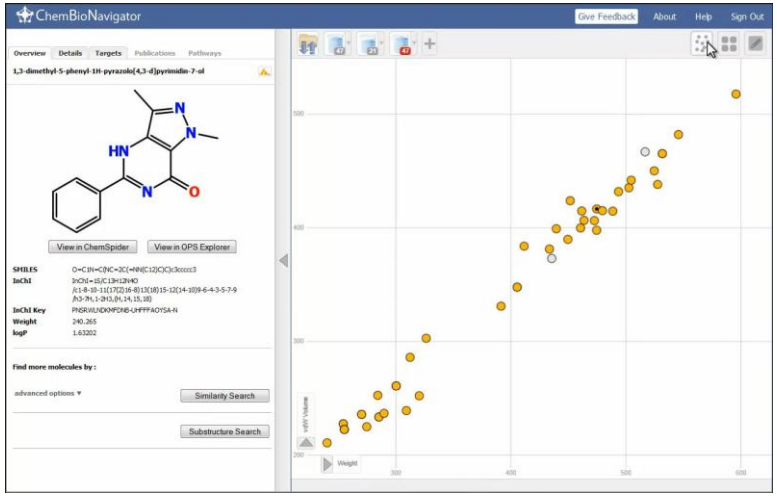
Barbara Zdrazil,[a] Marta Pinto,[a] Poongavanam Vasanthanathan,[a] Antony J. Williams,[b] Linda Zander Balderud,[c] Ola Engkvist,[c] Christine Chichester,[d] Anne Hersey,[e] John P. Overington,[e] and Gerhard F. Ecker*[a]

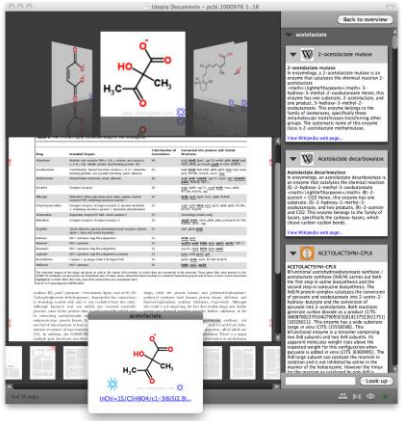
Develop assay ontology
Create tools for semiautomatic combination
Propose reference compounds

Data

- Workflow for enriching the chemical space







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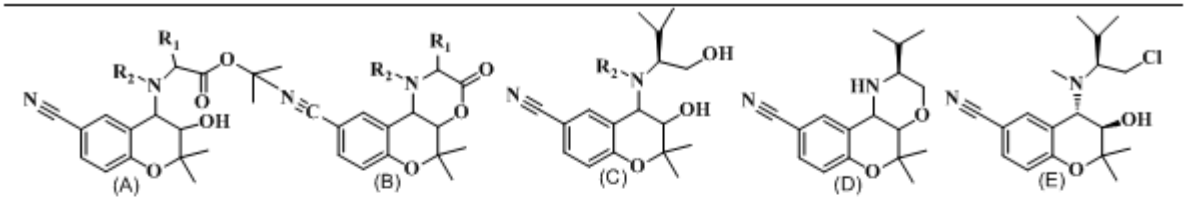
Data

Table 1 Enantiomerically pure benzopyrano [3,4b][1,4] oxazines (**5a-22b**) and their IC_{50} values.



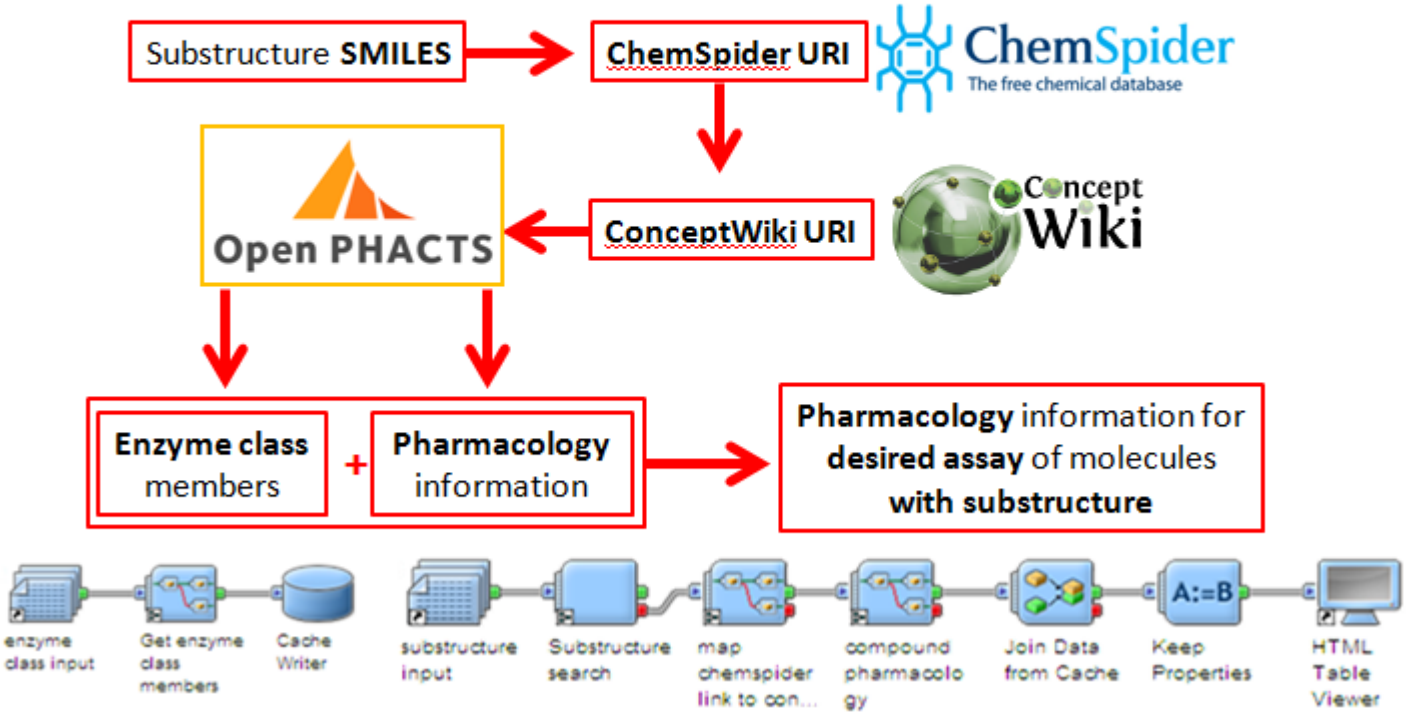
#	Scaffold	Stereochemistry	R1	R2	IC_{50}μM±SD	logP(o/w)
5a	(A)	(3S,4R)	(L) CH_3	H	29.85 ± 0.01	2.84
5b	(A)	(3R,4S)	(L) CH_3	H	14.55 ± 0.05	2.84
6a	(A)	(3S,4R)	(L) $CH(CH_3)_2$	H	2.40 ± 0.03	3.82
6b	(A)	(3R,4S)	(L) $CH(CH_3)_2$	H	2.70 ± 0.02	3.82
7a	(A)	(3S,4R)	(L) $CH_2(C_6H_5)$	H	0.55 ± 0.02	4.38
7b	(A)	(3R,4S)	(L) $CH_2(C_6H_5)$	H	0.77 ± 0.04	4.38
8a	(A)	(3S,4R)	(L) CH_3	CH_3	3.96 ± 0.06	3.11
8b	(A)	(3R,4S)	(L) CH_3	CH_3	3.72 ± 0.03	3.11
9a	(A)	(3S,4R)	(L) $CH(CH_3)_2$	CH_3	0.96 ± 0.06	4.08
9b	(A)	(3R,4S)	(L) $CH(CH_3)_2$	CH_3	1.35 ± 0.003	4.08
10a	(A)	(3S,4R)	(D) $CH(CH_3)_2$	H	4.62 ± 0.31	3.81
10b	(A)	(3R,4S)	(D) $CH(CH_3)_2$	H	1.34 ± 0.08	3.81
11a	(A)	(3S,4R)	(D) $CH(CH_3)_2$	CH_3	1.01 ± 0.02	4.08
11b	(A)	(3R,4S)	(D) $CH(CH_3)_2$	CH_3	1.00 ± 0.05	4.08
12a	(B)	(2S,4aS,10bR)	CH_3	H	1241.6 ± 0.04	1.98
12b	(B)	(2S,4aR,10bS)	CH_3	H	76.89 ± 0.06	1.98
13a	(B)	(2S,4aS,10bR)	$CH(CH_3)_2$	H	15.32 ± 0.32	2.94
13b	(B)	(2S,4aR,10bS)	$CH(CH_3)_2$	H	59.33 ± 0.60	2.94
14a	(B)	(2S,4aS,10bR)	$CH_2(C_6H_5)$	H	2.68 ± 0.18	3.51
14b	(B)	(2S,4aR,10bS)	$CH_2(C_6H_5)$	H	259.78 ± 0.06	3.51
15a	(B)	(2S,4aS,10bR)	CH_3	CH_3	47.83 ± 0.91	2.24

Data

- Establish Pipeline Pilot or KNIME workflow

Answer business question:

The current Factor Xa lead series is characterised by substructure X. Retrieve all bioactivity data in serine protease assays for molecules that contain substructure X



Data

- How to enrich the chemical space
  - Put your data into one of the sources

ChEMBL

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Document Report Card

Doc ID	CHEMBL2094195
Title	Structure-activity relationship data for a series of N-(phenylmethyl)-2-(1H-pyrazol-4-yl)acetamide and N-(phenylmethyl)2-(4-isoxazolyl) acetamide antagonists of the P2X7 receptor (Supplementary Bioactivity Data for publication CHEMBL1157144)
Authors	Senger S, Beswick PJ, Chambers LJ, Davies DJ, DK Demont EH, Roomann S, Walters DS
Abstract	Supplementary bioactivity data for the GlaxoSmithKline (GSK) publication Bioorg. Med. Chem. Lett. 2010, 20, 3161-3164 (ChEMBL Doc ID: CHEMBL1157144): pIC50 values for 54 compounds that have been tested in the ethidium bromide release assay (ChEMBL Assay ID: CHEMBL1103860) described in reference 24 of the aforementioned publication. All compounds have been tested at least four times and have been reported as being active in all test occasions.
DOI	http://dx.doi.org/10.6019/CHEMBL2094195

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ChEMBL supplementary bioactivity data depositions get assigned a DOI, i.e. they are citable.

Approaching new areas with increasing complexity

- BQ X1: Give me all pathways related to the regulation of P-glycoprotein, and all compounds hitting targets in these pathways.
- BQ 17: for a given disease, give me all targets in the pathway and for these targets all the active compounds
- Give me all compounds annotated with liver toxicity and their interaction profiles with all transporters expressed in the liver

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