The power of open data – linking transporter interaction profiles to in vivo toxicity

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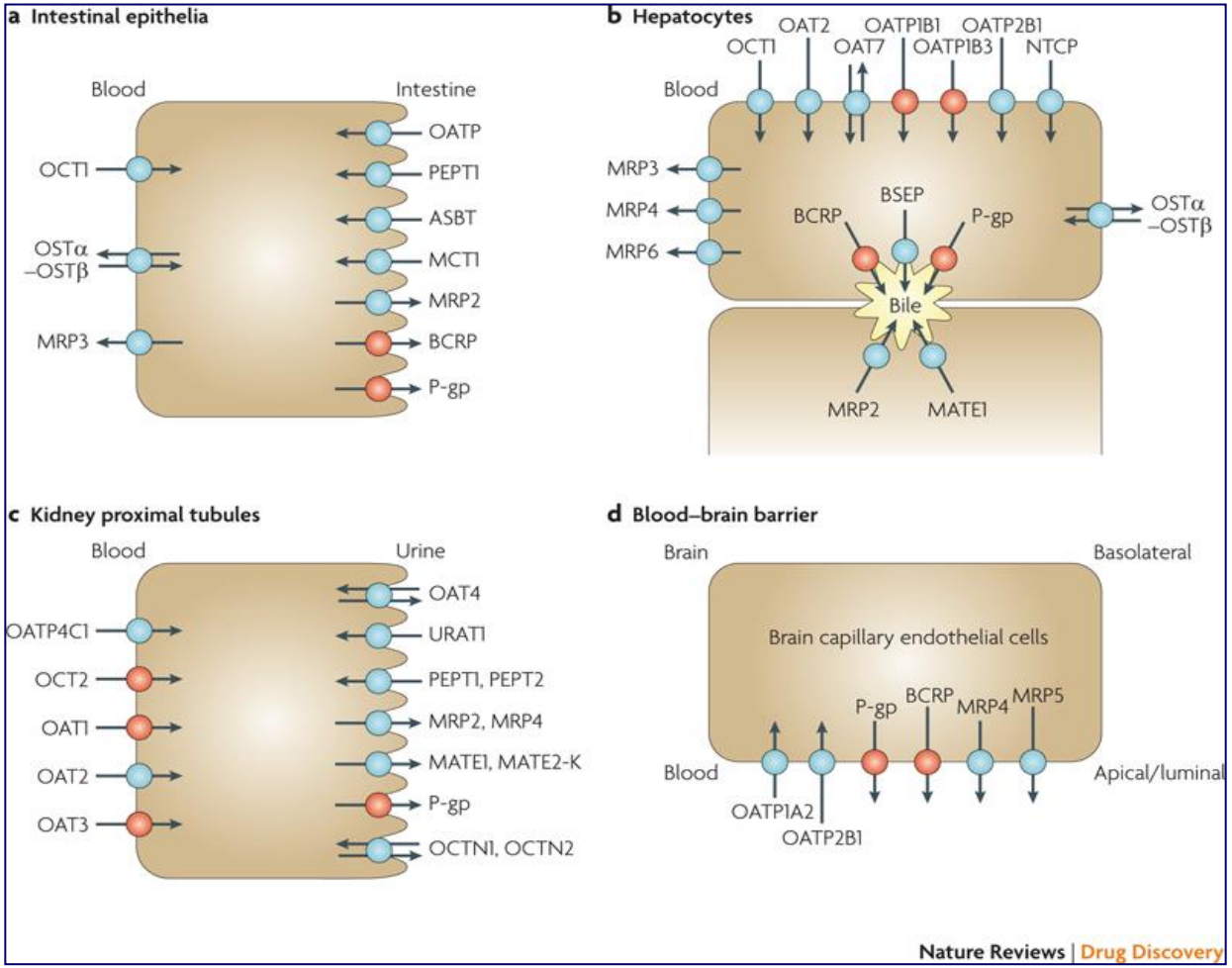
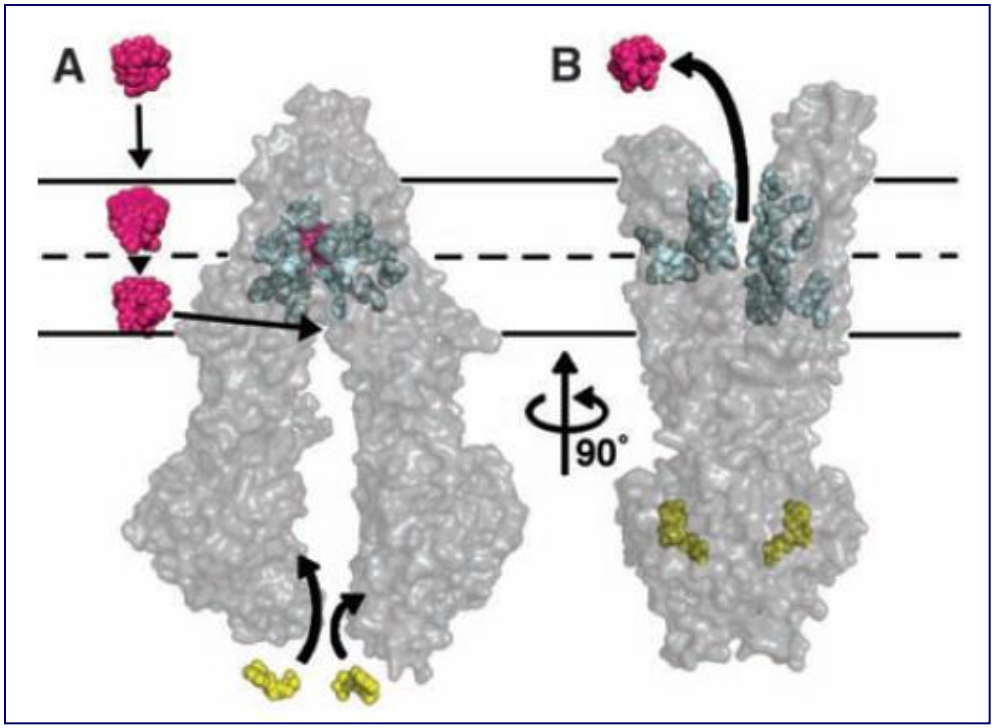
Transporters and ADMET

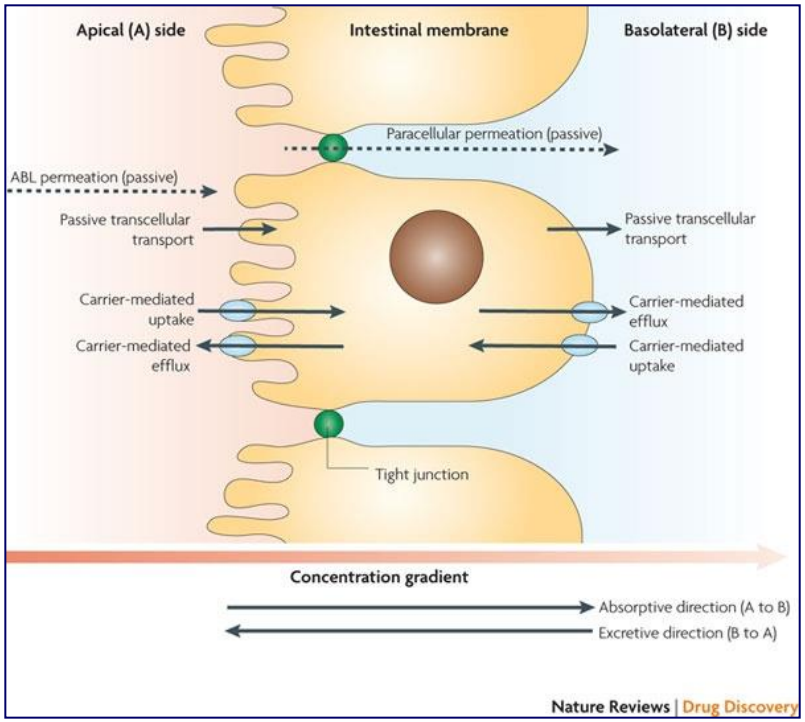


Nature Reviews Drug Discovery 9, 215-236 (March 2010)

Drug Transporter



Aller et al. Science 2009

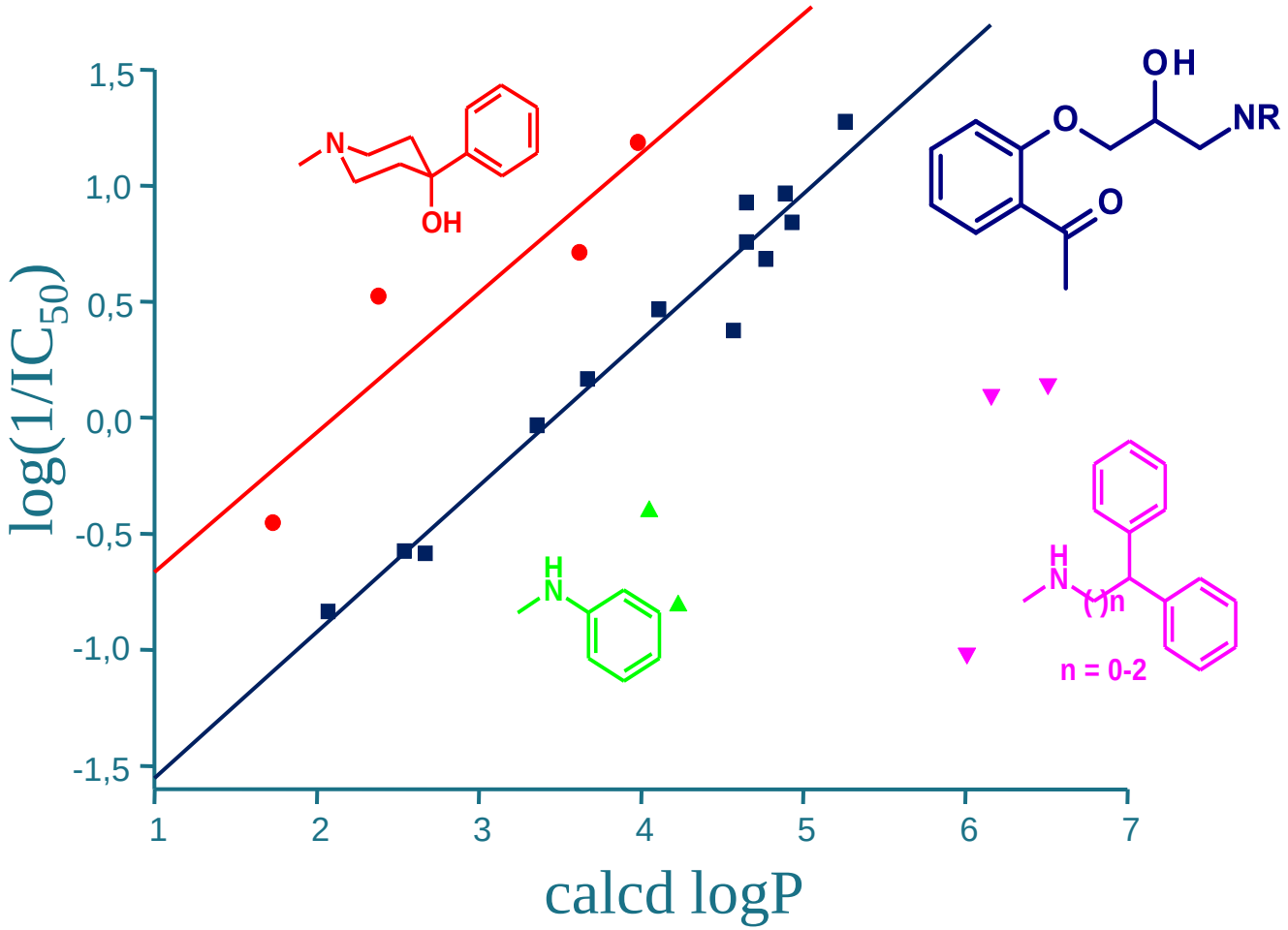


OPINION

Coexistence of passive and carrier-mediated processes in drug transport

Kiyohiko Sugano, Manfred Kansy, Per Artursson, Alex Avdeef, Stefanie Bendels, Li Di, Gerhard F. Ecker, Bernard Faller, Holger Fischer, Grégori Gerebtzoff, Hans Lennernaes and Frank Senner

QSAR Studies of Propafenones



Target-based design

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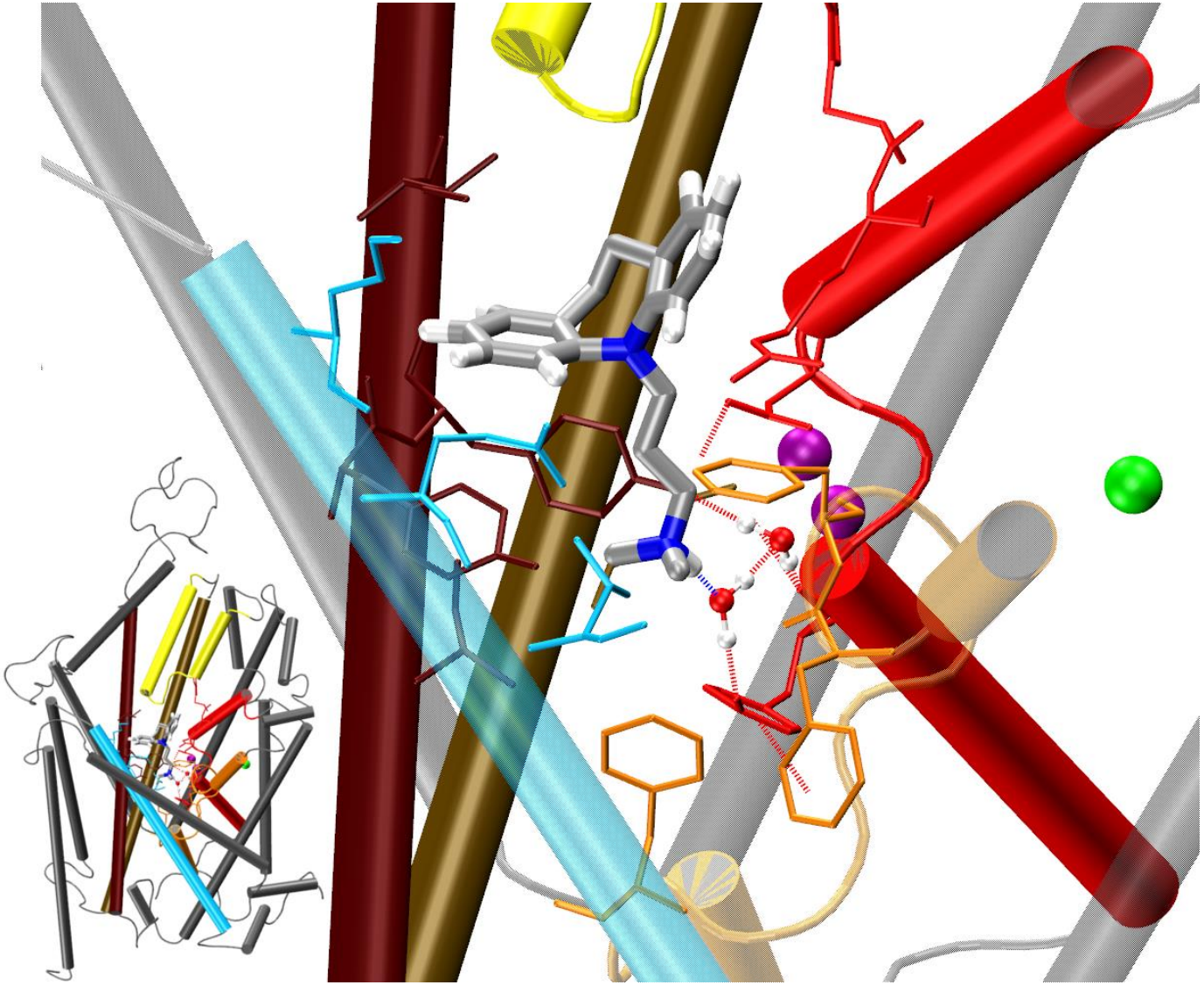

Target-based Design - Reality

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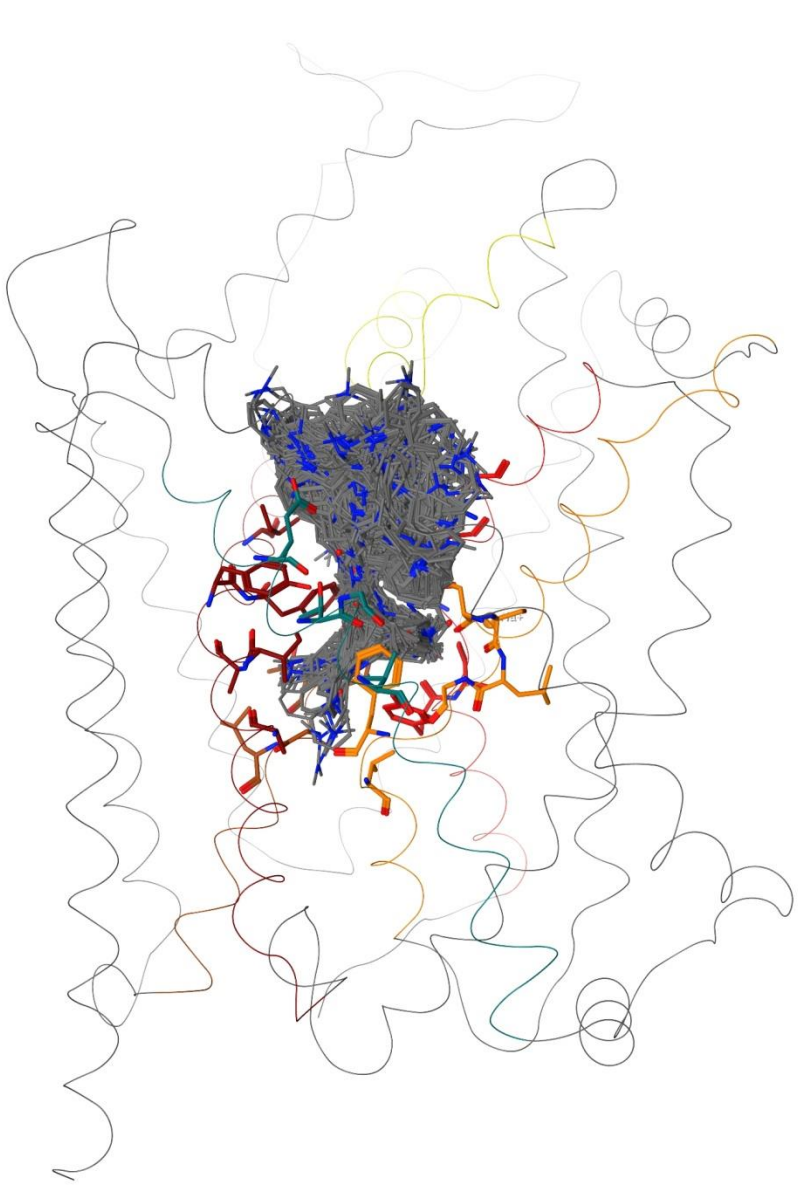
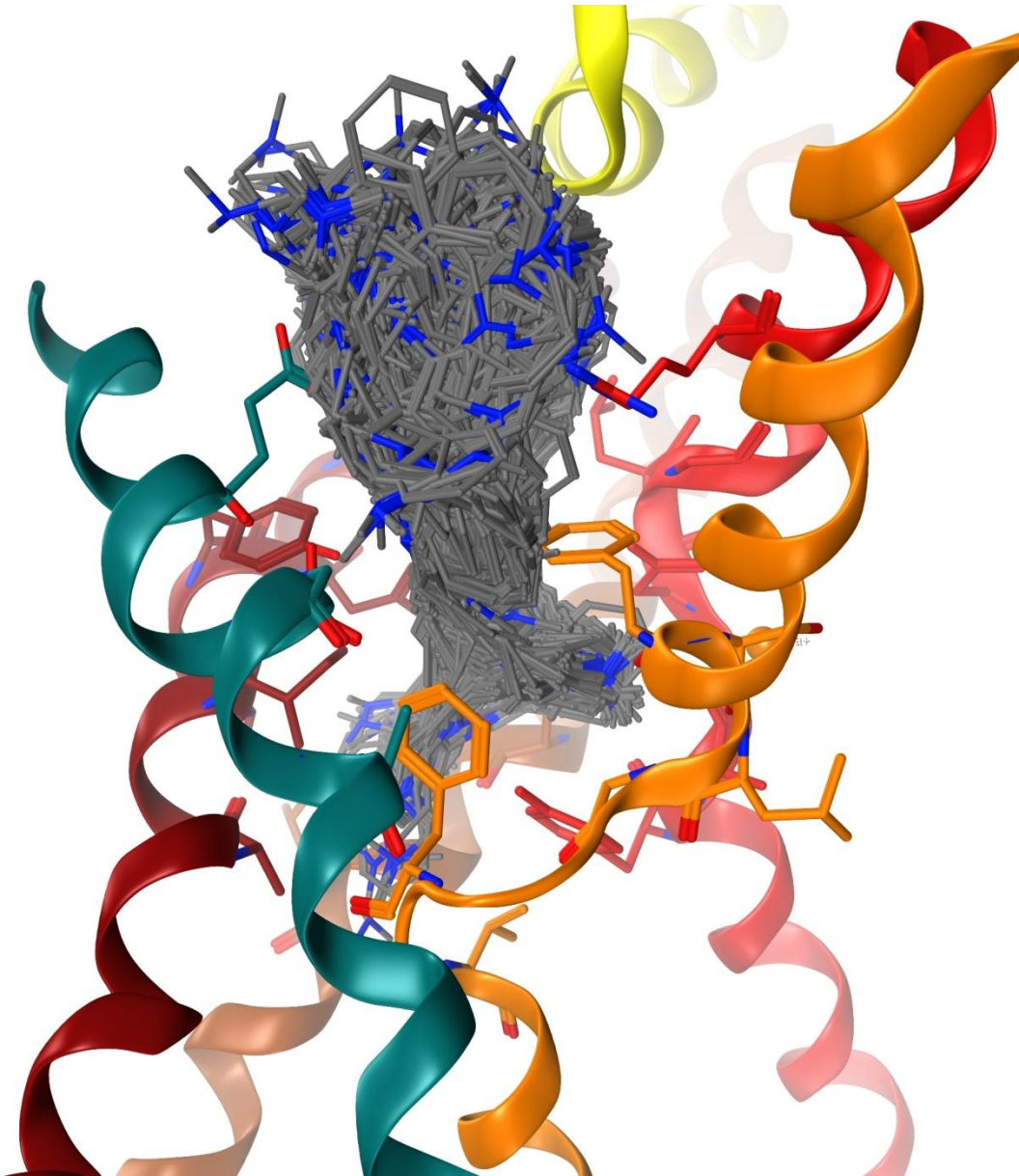
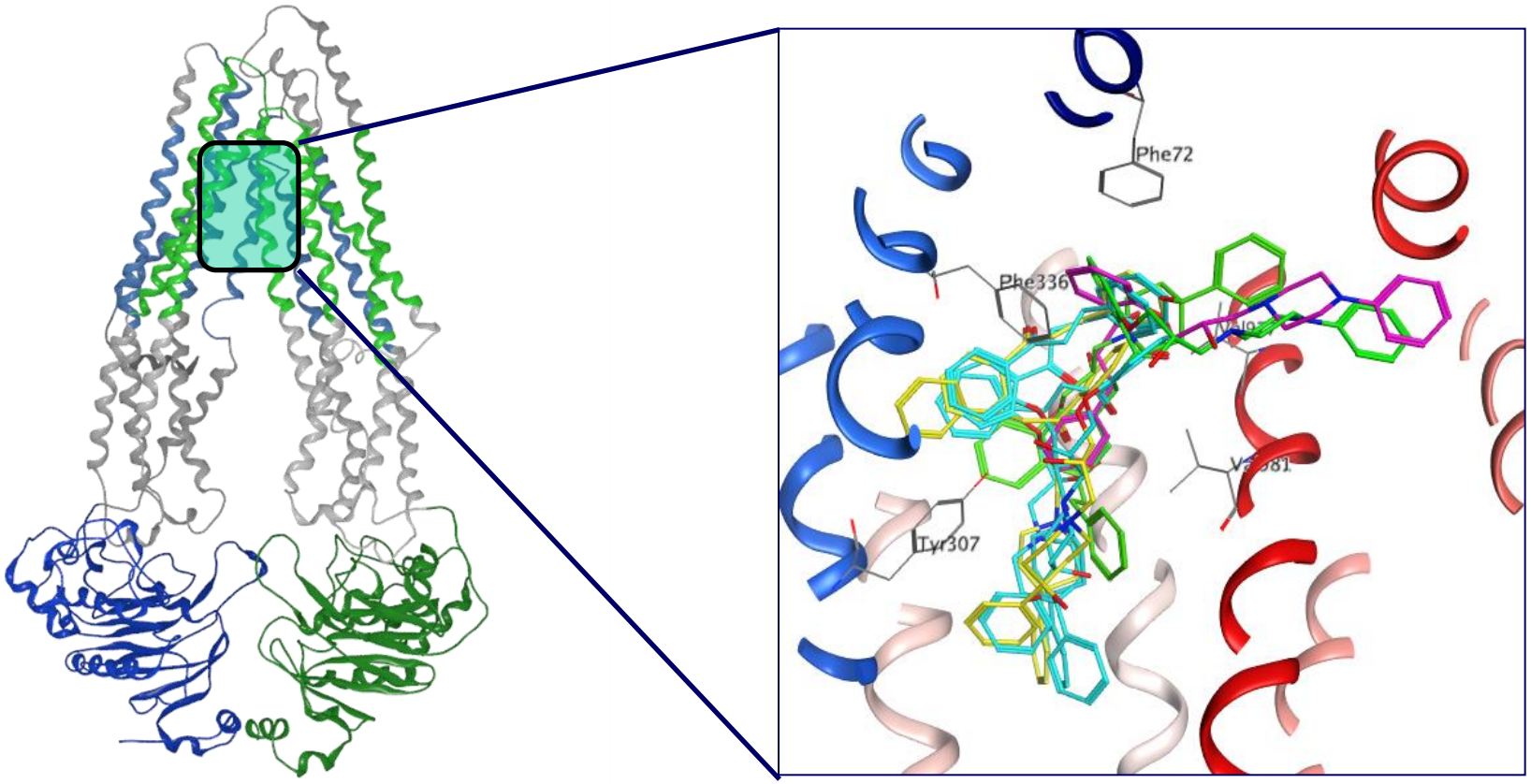
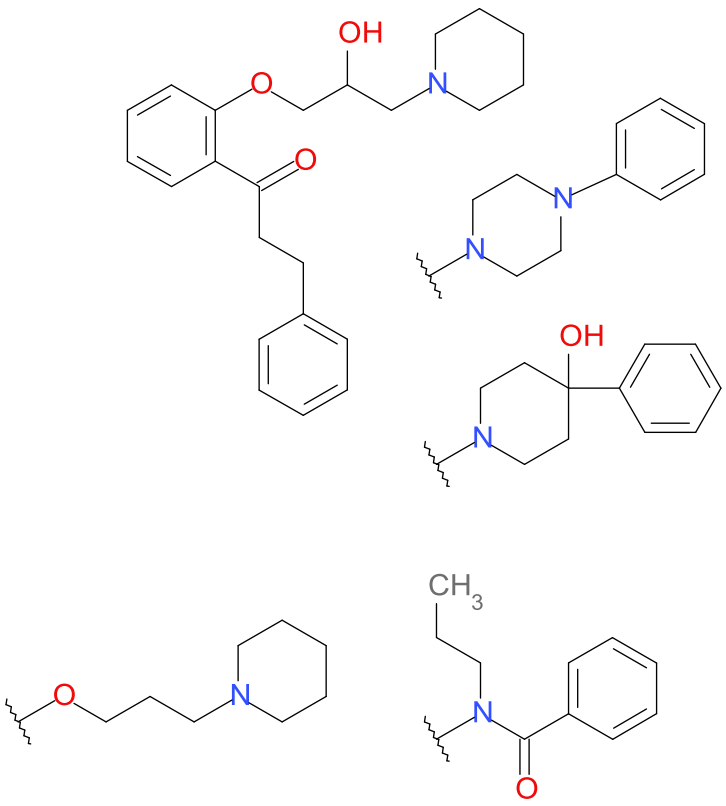


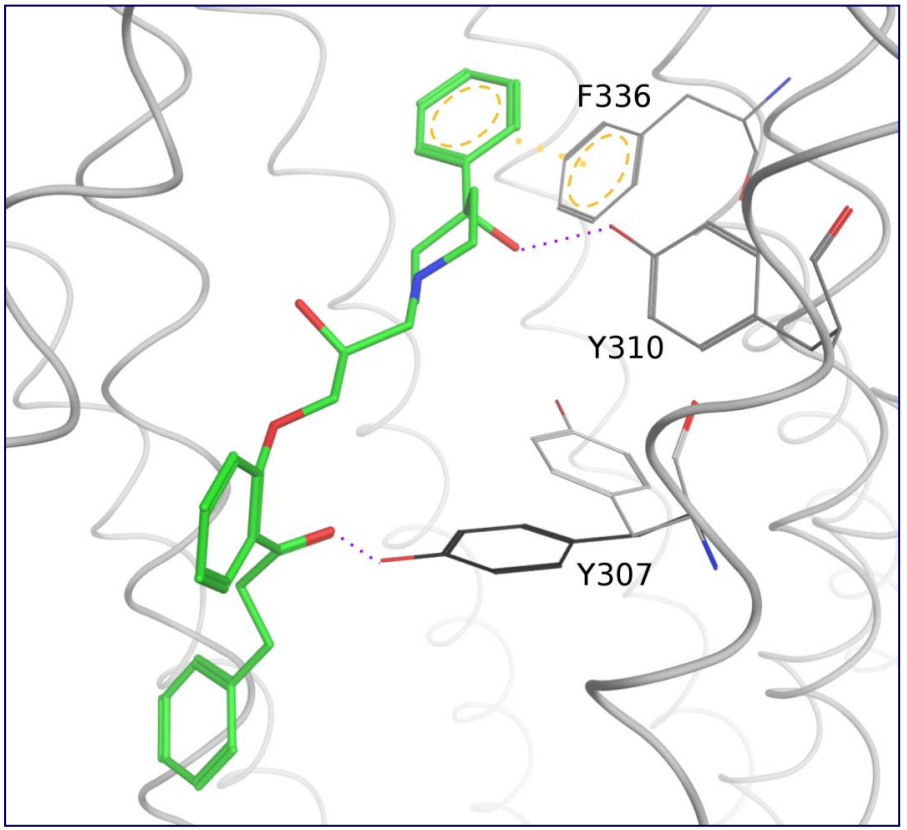


Docking into P-gp Model



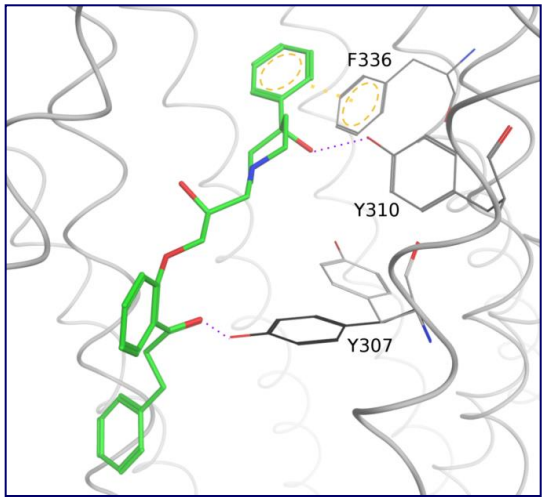
Experimental Data Guided Docking

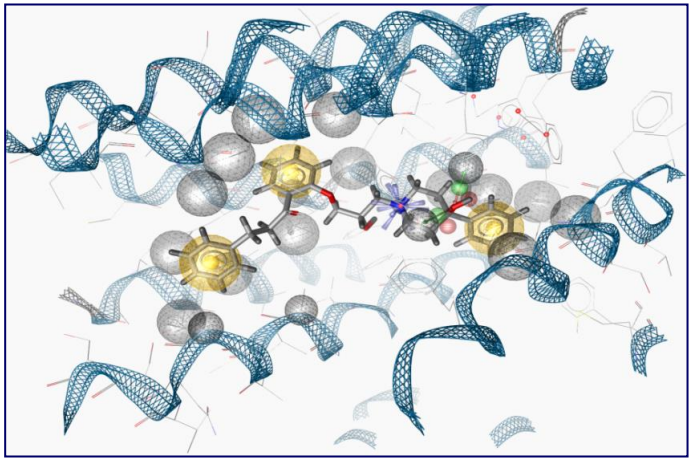


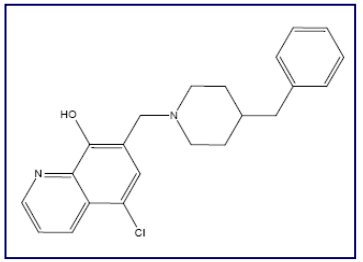


Sarker et al., *Mol Pharmacol* 2010
Klepsch et al., *PloS Comp Biol* 2011
Richter et al., *Nature Chem Biol* 2012

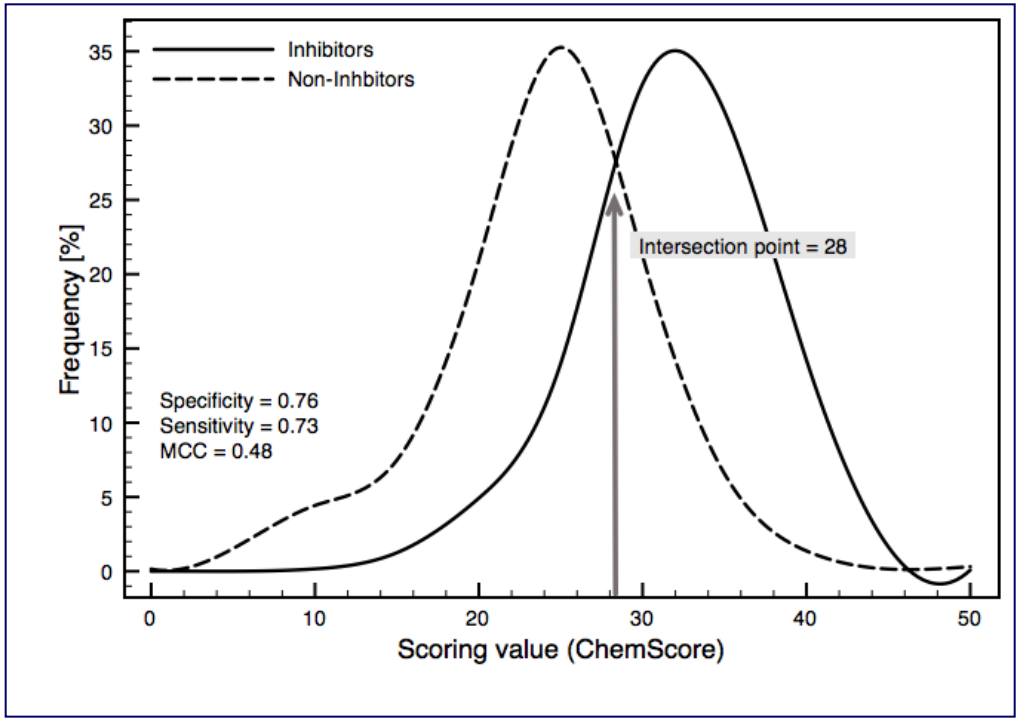
Validation *via* Pharmacophores







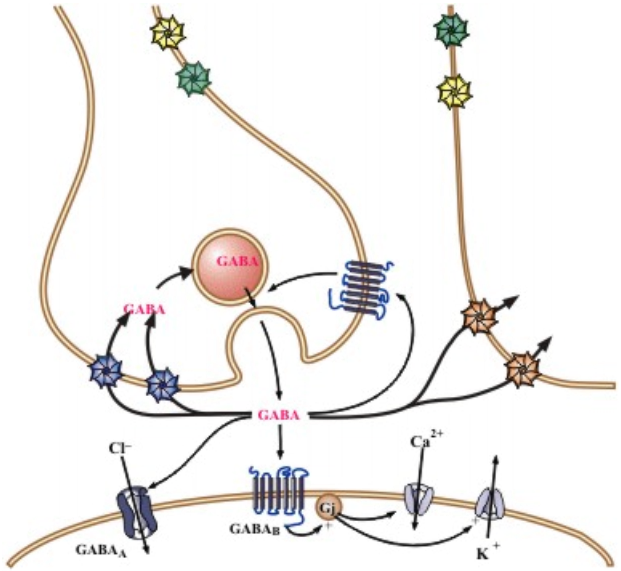
Docking-based classification



1935 compounds
dock, score
take top scored
run distribution
Accuracy 0,75

Klepsch, *J Chem Inf Mod* 2013

GABA transporters



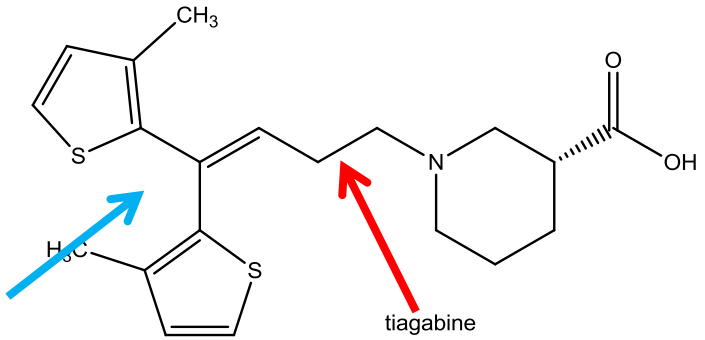
differences:
- localization
- expression rate
- kinetic parameters
- Cl^--dependence
- (sequence)

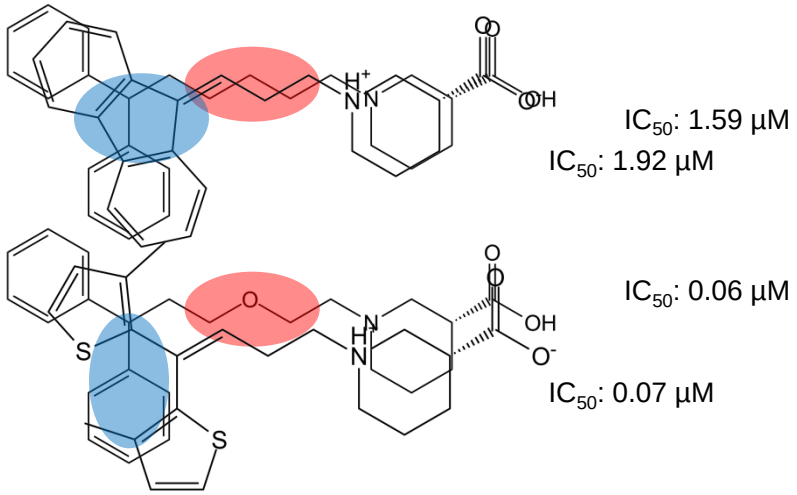
- GAT-1:
  - highest expression in CNS
  - mainly neuronal localization
  - established drug target
- BGT-1:
  - peripheral osmolyte transport
  - distal CNS localization
  - regulates spillover, crosstalk
- GAT-2:
  - least studied subtype
  - mainly peripheral localization
- GAT-3:
  - mainly CNS, synaptic localization
  - higher expression in astrocytes

Ligand derived information

- structure-activity relationship observations in literature:
  - ideal linker length
  - stereochemistry of GABA mimetic moiety
  - substitution of aromats
  - polarity of the linker

- QSAR analysis of 161 consistently tested compounds:
  - importance of rigidity, polarity distribution





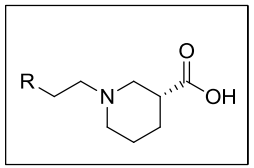
Jurik, *Mol Inform* 2013

Flexibility – ensemble docking

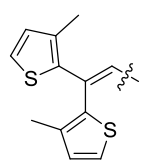
10 MD snapshots

100 poses / configuration

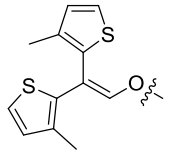
Σ=2000 poses / ligand



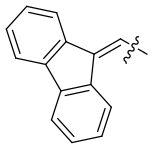
R=



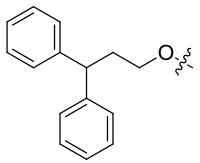
0.07 µM



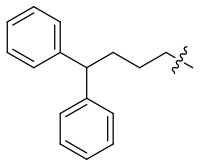
0.01 µM



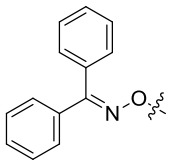
1.92 µM



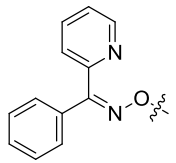
0.06 µM



1.59 µM

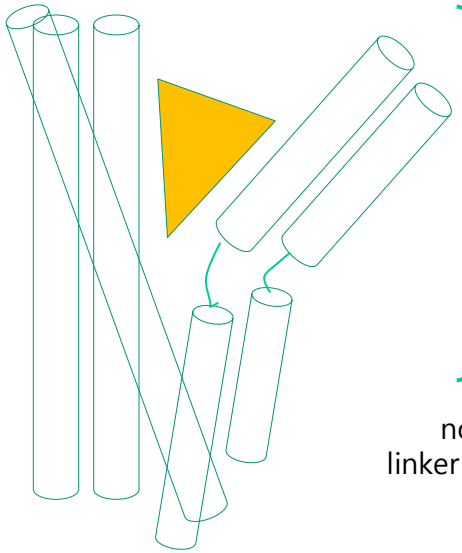


0.08 µM



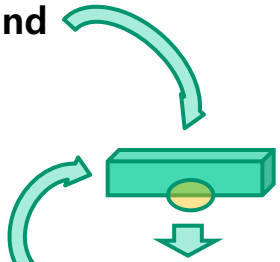
2.07 µM

Placement
ChemScore
Rescoring
GoldScore
ChemPLP
XScore
London dG
GBVI

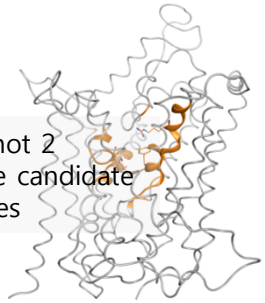


non-polar
linker compounds

consensus score:
10 top poses / ligand
visual analysis



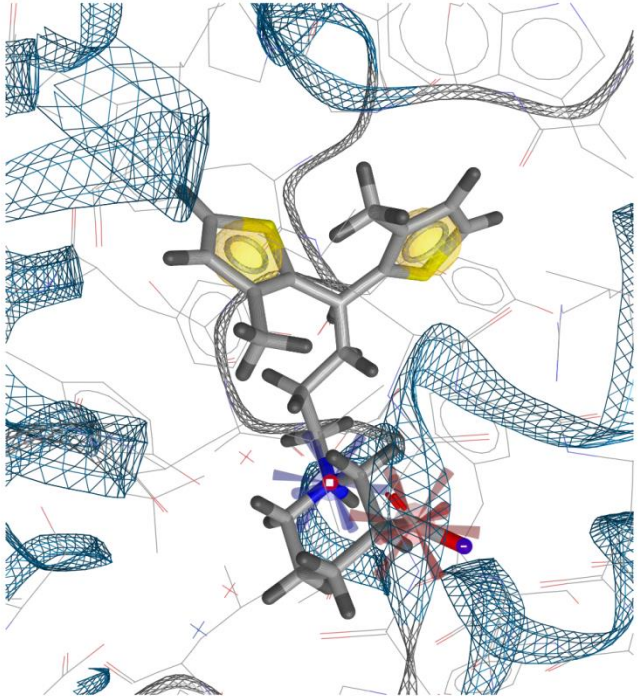
pose evaluation
literature cross-check



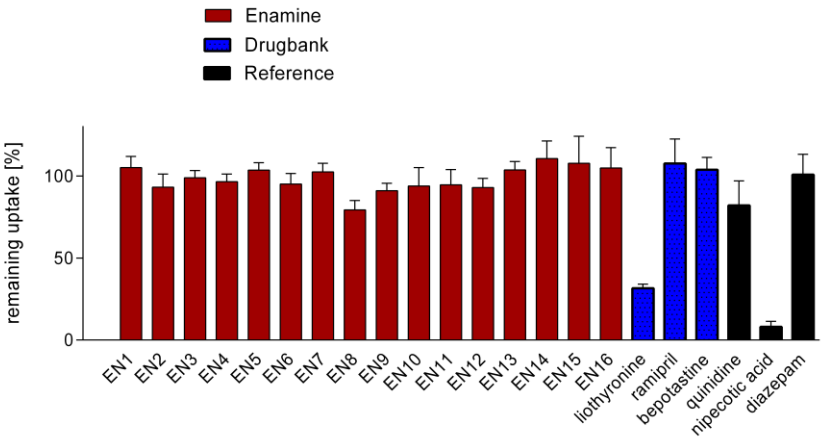
snapshot 2
flexible candidate
residues

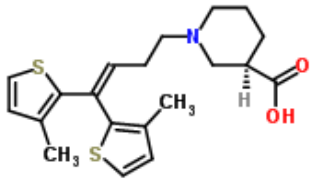
common binding mode

Validation

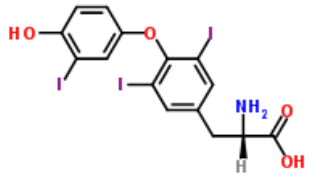


Jurik, *J Med Chem* 2015

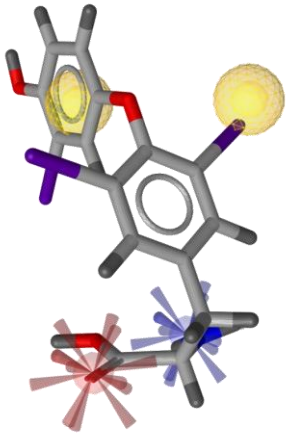




Tiagabine



Liothyronine



BCRP Inhibitors

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

Ahcene Boumendjel,[a,*] Sira Macalou,[b] Abdelhakim Ahmed-Belkacem,[b] Madeleine Blanc[a] and Attilio Di Pietro[b]

[a]*Département de Pharmacochimie Moléculaire, UMR 5063 CNRS/Université Jo*
5 avenue de Verdun BP 138, 38243 Meylan, France
[b]*Institut de Biologie et Chimie des Protéines, UMR 5086 CNRS/Université Lyon 1, IFR12*
7 passage du Vercors, 69367 Lyon Cedex 07, France

Received 20 September 2006; revised 1 February 2007; accepted 9 Febr
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.)

Received May 9, 2007; accepted July 5, 2007

HERAPEUTICS

Bioorganic & Medicinal Chemistry Letters

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

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*

Pharmaceutical Institute, University of Bonn, Pharmaceutical Chemistry II, An der Immenburg 4, 53121 Bonn, Germany

BCRP Inhibitors

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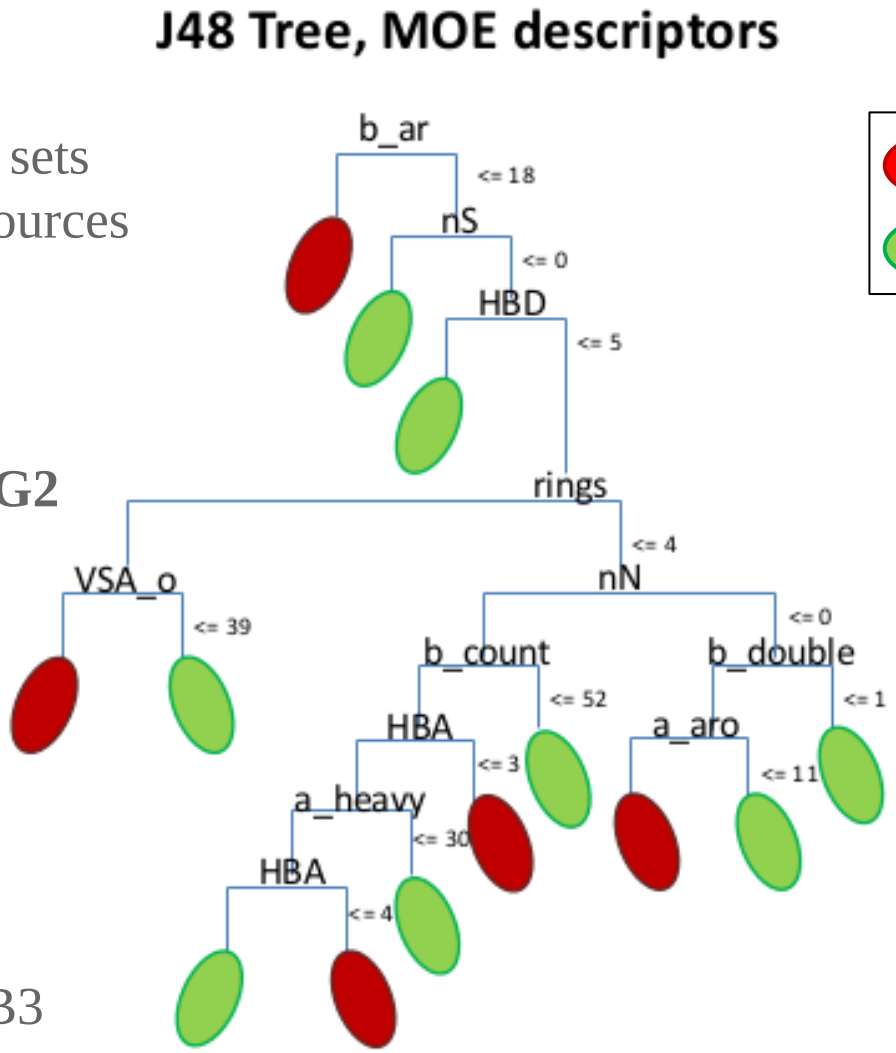
Manual compilation of data sets
Identification of literature sources
Redrawing structures
Manual addition of values

Prioritising ligands in B1/G2 selectivity profiling



Analogous approach for
BSEP, OATP1B1, OATP1B3

Area under ROC: 0.8

It‘s all about data

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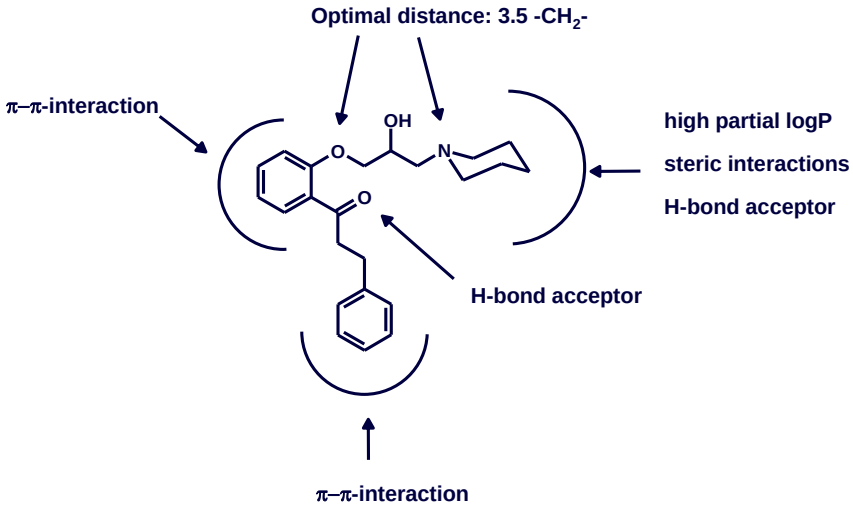

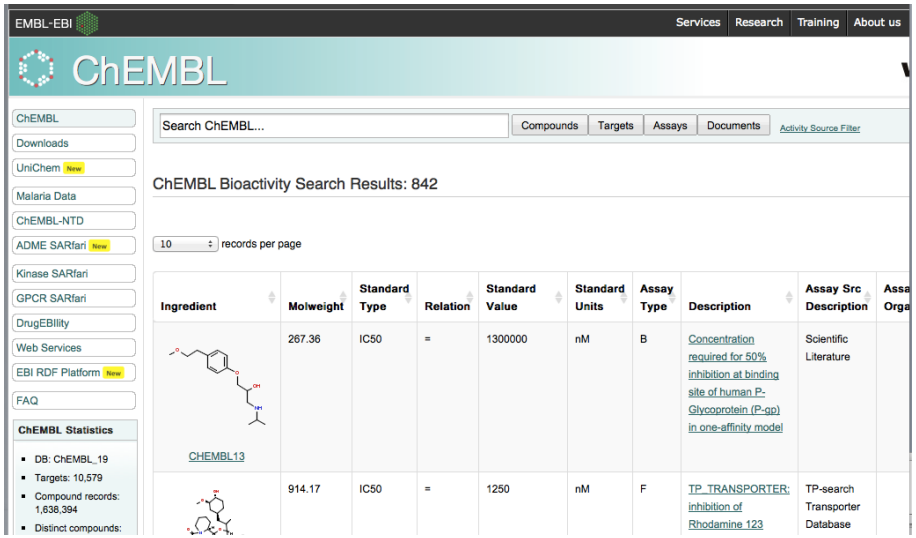

280 GPV compounds

AstraZeneca

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Open Pharmacological Space

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The **Open PHACTS Discovery Platform** has been developed to reduce barriers to drug discovery in industry, academia and for small businesses.

- It contains all the data sources you **already use**, **integrated** and **linked** together so that you can easily see the relationships between *compounds*, *targets*, *pathways*, *diseases* and *tissues*. Data sources include ChEBI, ChEMBL, ChemSpider, ConceptWiki, DisGeNET, DrugBank, Gene Ontology, neXtProt, UniProt and WikiPathways.

Open PHACTS
Open Pharmacological Space

"What is the selectivity profile of known p38 inhibitors?"

"Let me compare MW, logP and PSA for known oxidoreductase inhibitors"

"Find me compounds that inhibit targets in NFkB pathway assayed in only functional assays with a potency <1 μM"

ChEMBL | DrugBank | Gene Ontology | Wikipathways | GeneGo

ChEBI | Uniprot | UMLS | GVKBio

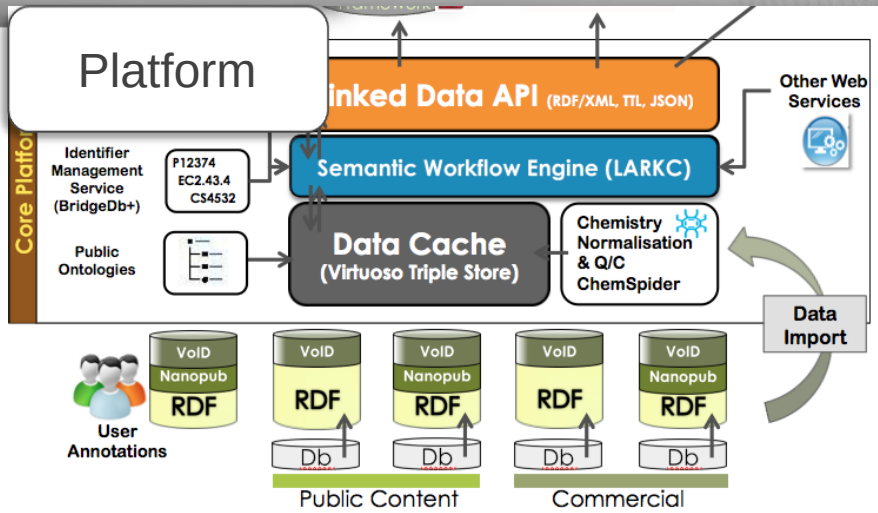
ConceptWiki | ChemSpider | TrialTrove | TR Integrity

Approaching complex research questions needs integration of data sources

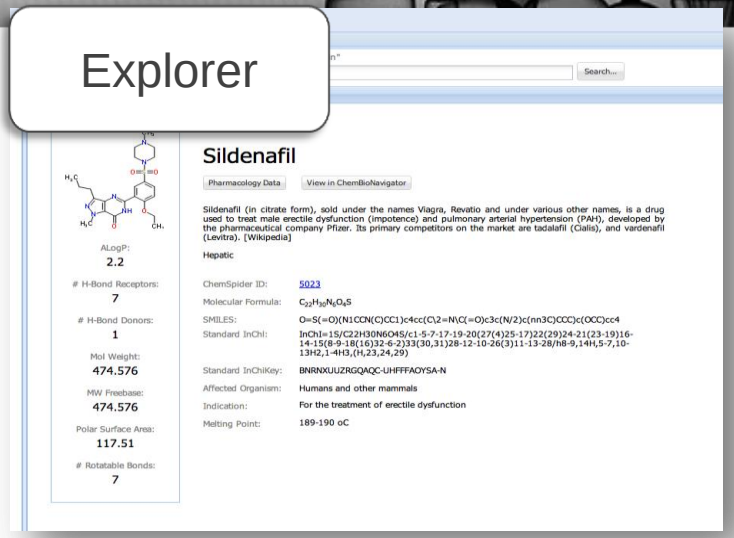
Open PHACTS

Open Pharmacological Space

Platform



Explorer



Apps

API

```
?ops_item skos:e
?ops_item skos:e
?cw_uri skos:pre
        void:inD
?equiv_target dc
        ops:targ
        ops:targ
        void:inD
ops:targetOfAssa
?equiv_assay che
        chembl:h
                                    ?std_type ;
```

Standards

explorer2.openphacts.org

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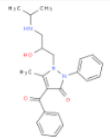
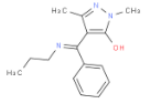
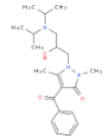
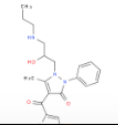
Open PHACTS Explorer | multidrug resistance prot | Search | Search for structure | Draw Molecule | Browse by Ontology | Help

Home / Multidrug resistance protein 1 (Homo sapiens) / Target Phamacology

Sorry, this image can't be found.

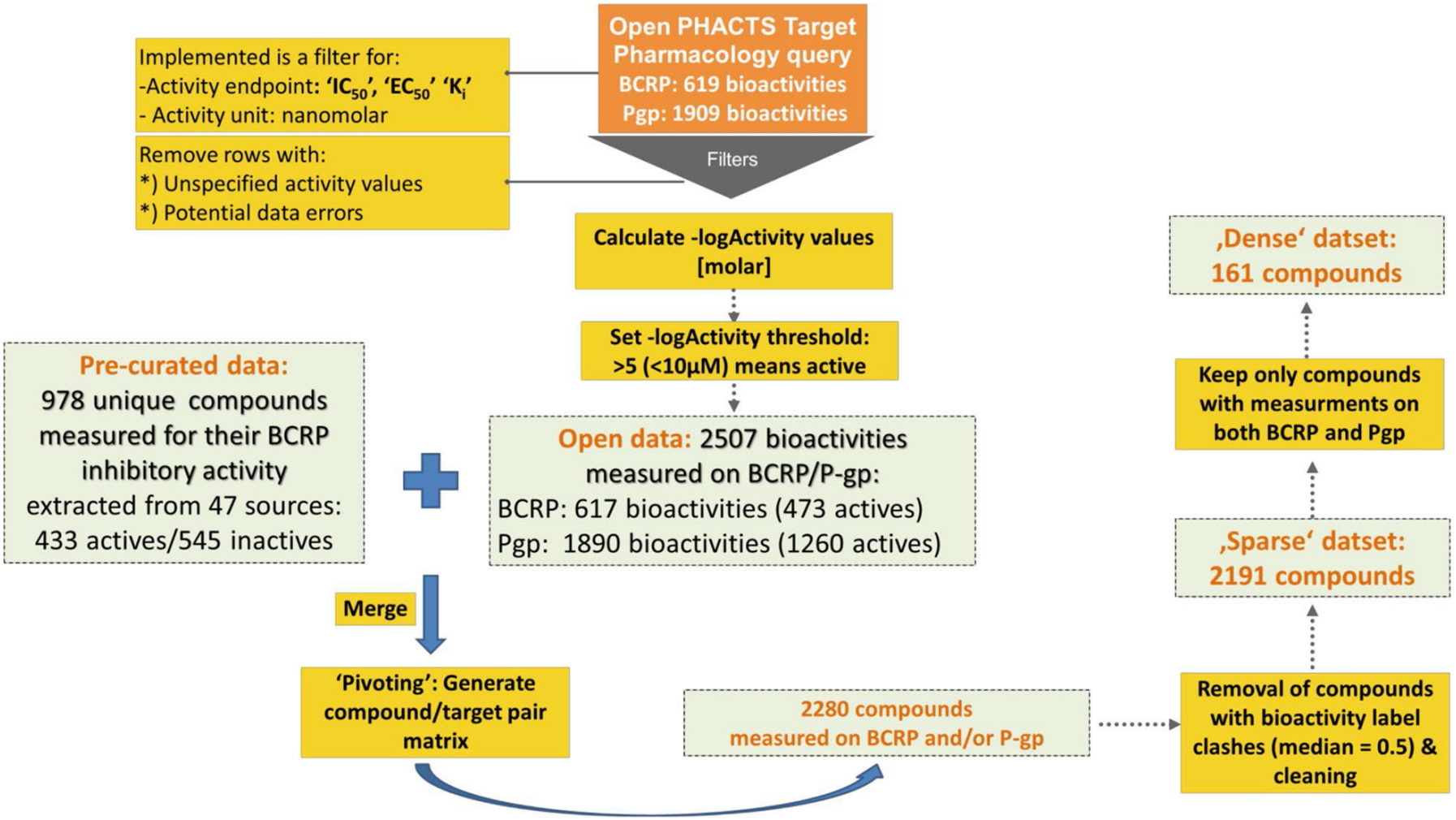
Multidrug resistance protein 1 (Homo sapiens) (100 of 5204 results loaded)

Filter Results | Create TSV | Show provenance | Hide provenance

Compound		Target	Assay		Activity					
Image	Name	Organism	Organism	Description	Type	Relation	Value	Units	Mol Weight	pChembl
	4-benzoyl-1-[2-hydroxy-3-(propan-2-ylamino)propyl]-5-methyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one	Homo sapiens		Compound was tested for inhibition of daunomycin efflux in the resistant human T-lymphoblast cell line CEM vcr1000.	EC50	=	83180	nM	393.479	4.08
	1,3-dimethyl-4-[(E)-phenyl(propylimino)methyl]-1H-pyrazol-5-ol	Homo sapiens		Compound was tested for inhibition of daunomycin efflux in the resistant human T-lymphoblast cell line CEM vcr1000.	EC50	=	272500	nM	257.331	
	4-benzoyl-1-[3-(dipropan-2-ylamino)-2-hydroxypropyl]-2,5-dimethyl-1,2-dihydro-3H-pyrazol-3-one	Homo sapiens		Compound was tested for inhibition of daunomycin efflux in the resistant human T-lymphoblast cell line CEM vcr1000.	EC50	=	24120	nM	373.489	4.62
	1-[2-Hydroxy-3-(propylamino)propyl]-5-methyl-2-phenyl-4-(2-thienylcarbonyl)-1,2-dihydro-3H-pyrazol-3-one	Homo sapiens		Compound was tested for inhibition of daunomycin efflux in the resistant human T-lymphoblast cell line CEM vcr1000.	EC50	=	72440	nM	399.	4

Go to top

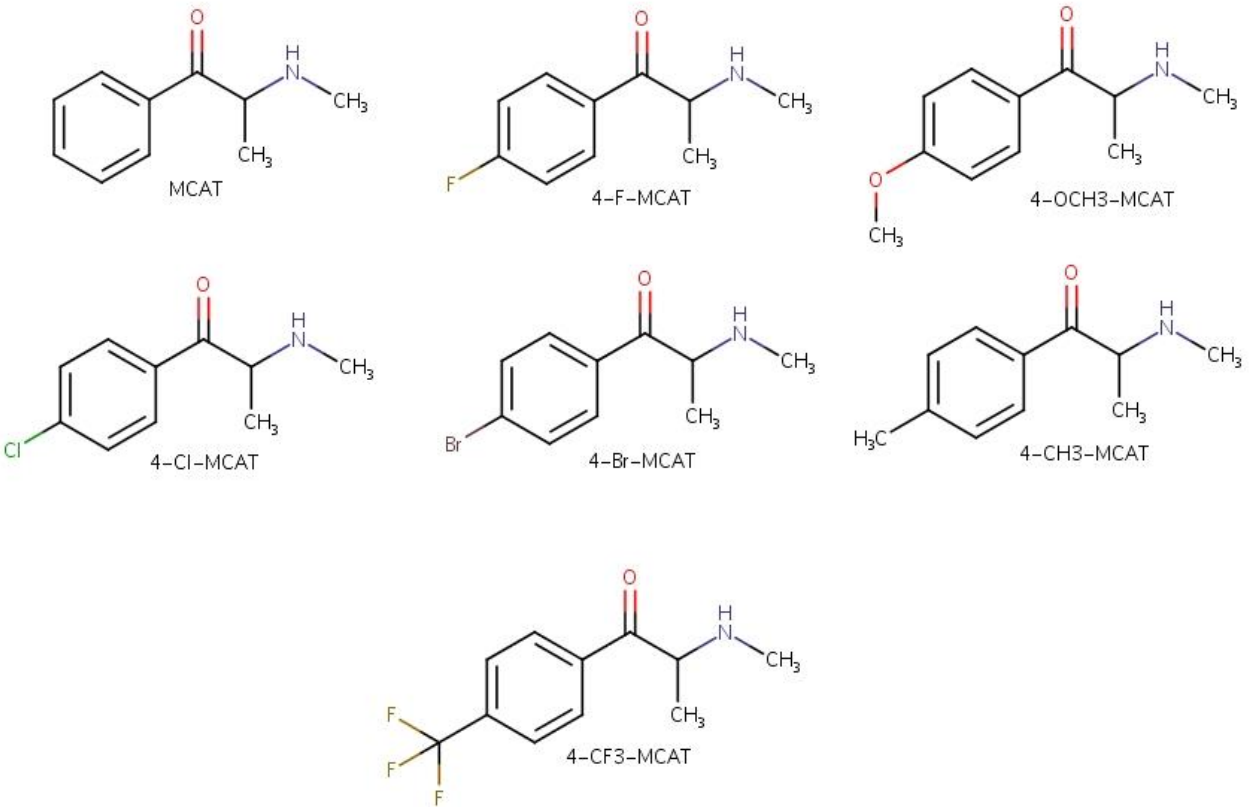
BCRP vs P-gp Profiling



Montanari et al., J Cheminform 2016

Cathinones and MATs

Bonano et.al, British Journal of Pharmacology (2015) 172 2433-2444 2433



Pred. SERT pIC50 = 6.089 (±0.217) + 5.030 (±0.374) p-mr

Workflow Scheme

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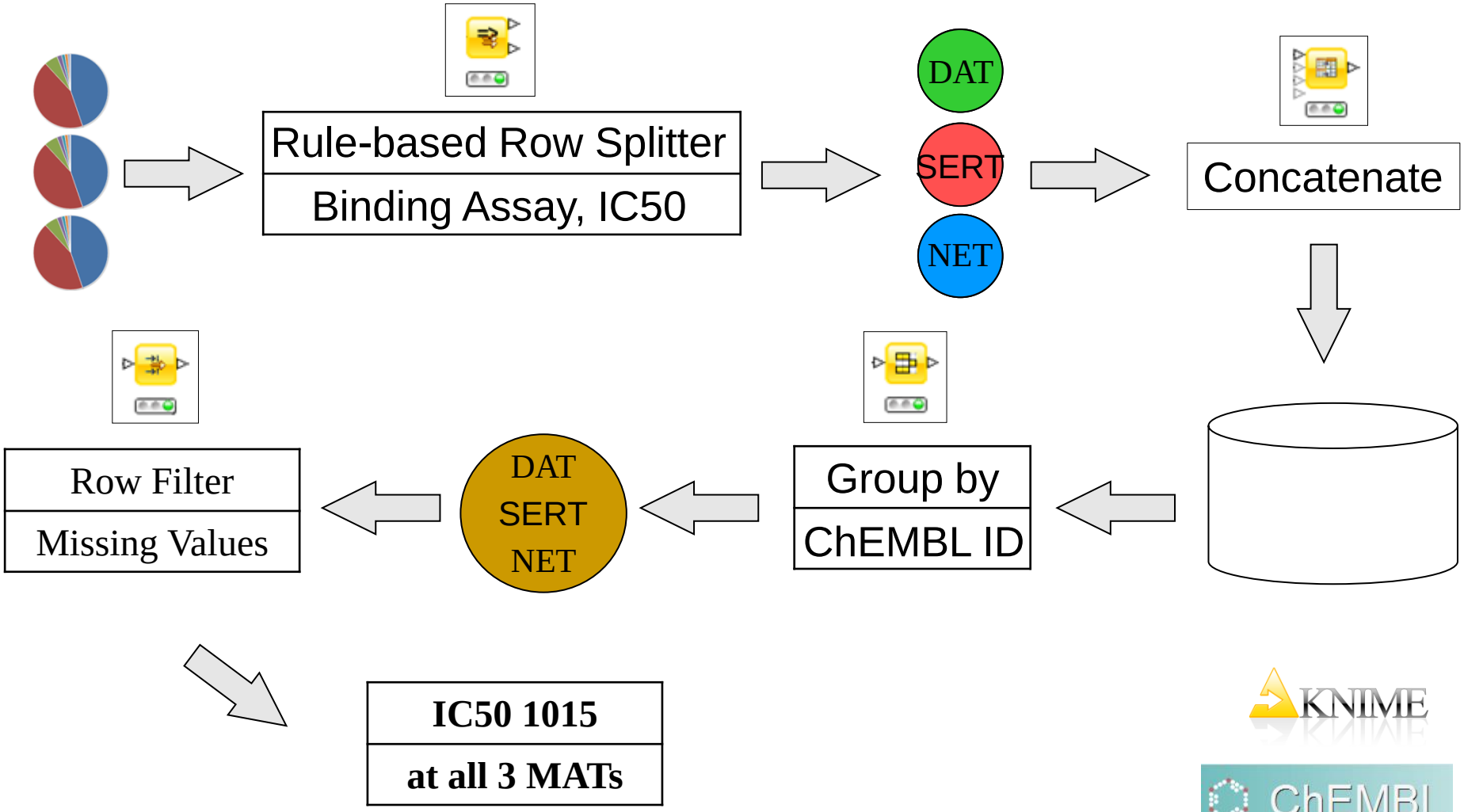

KNIME

ChEMBL

Data Compilation - KNIME

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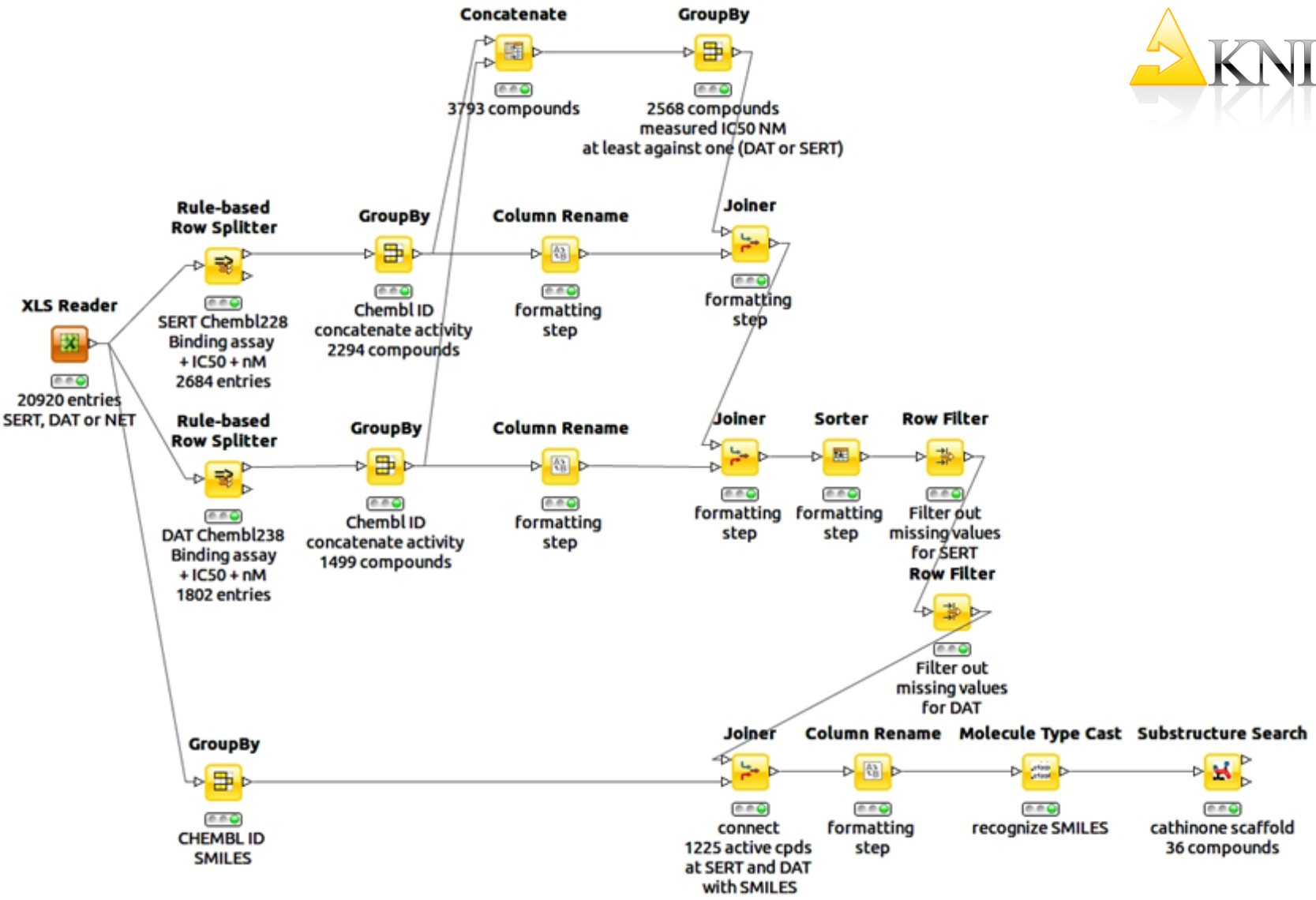

In vitro to *in vivo*

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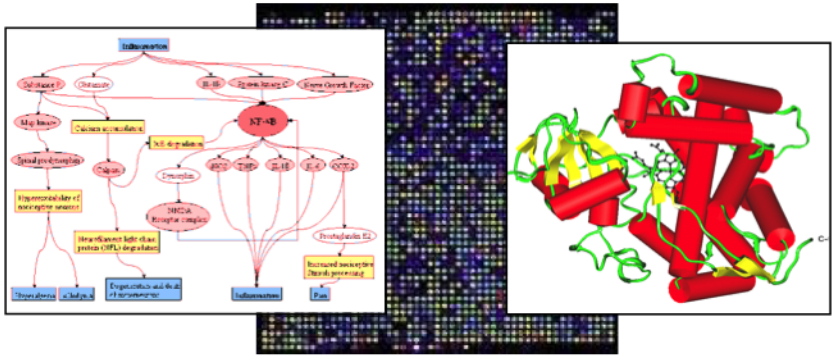

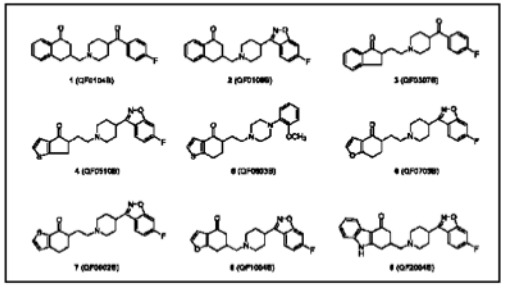

Disease ⟷ Pathway ⟷ Target ⟷ Ligand

Clinical information

"omics" information

Chemical/structural information

Transporter Profiling

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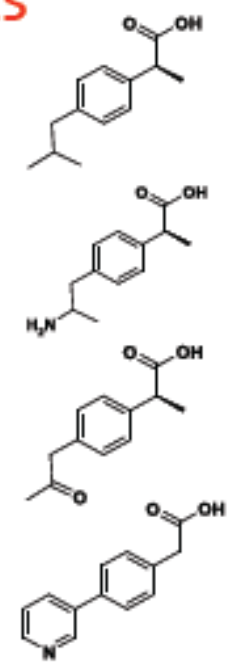
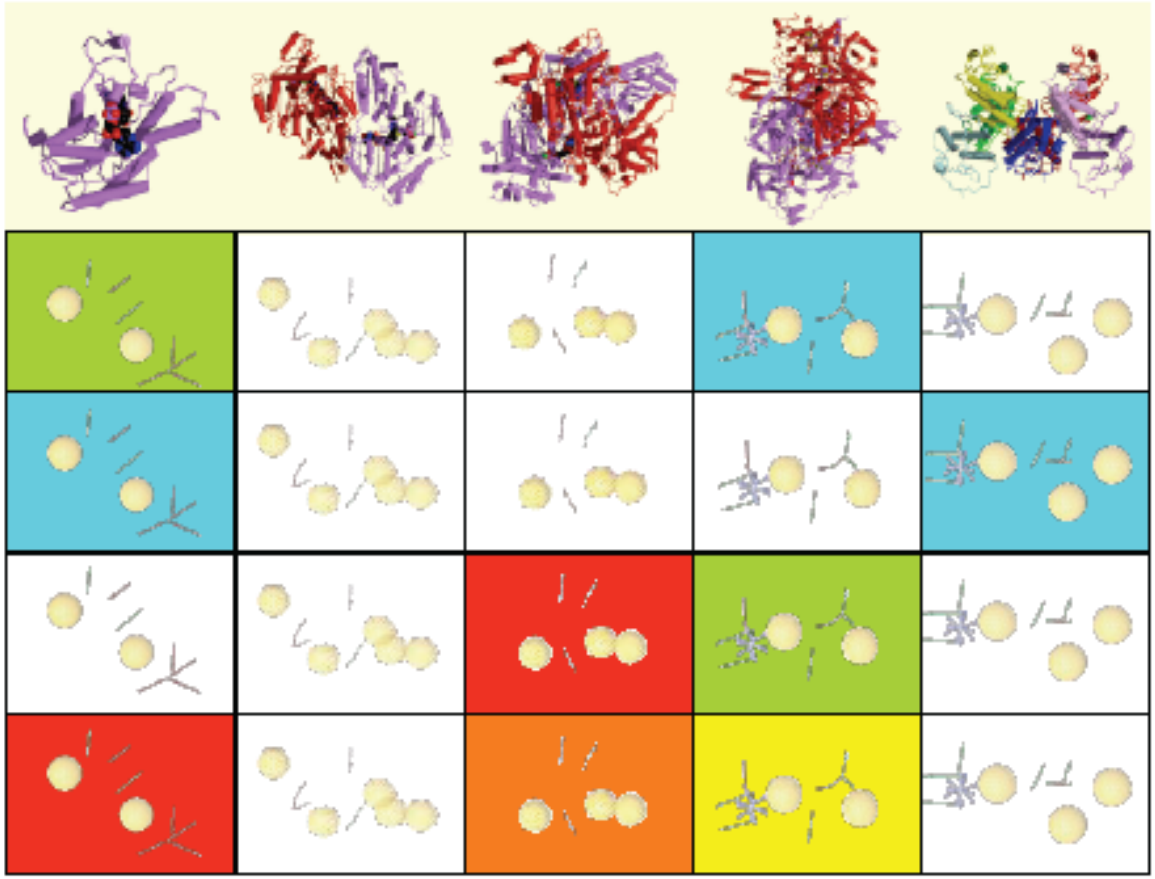
10^x molecules

against

10^x targets





... needs a large number of models !

Toxicity Profiling

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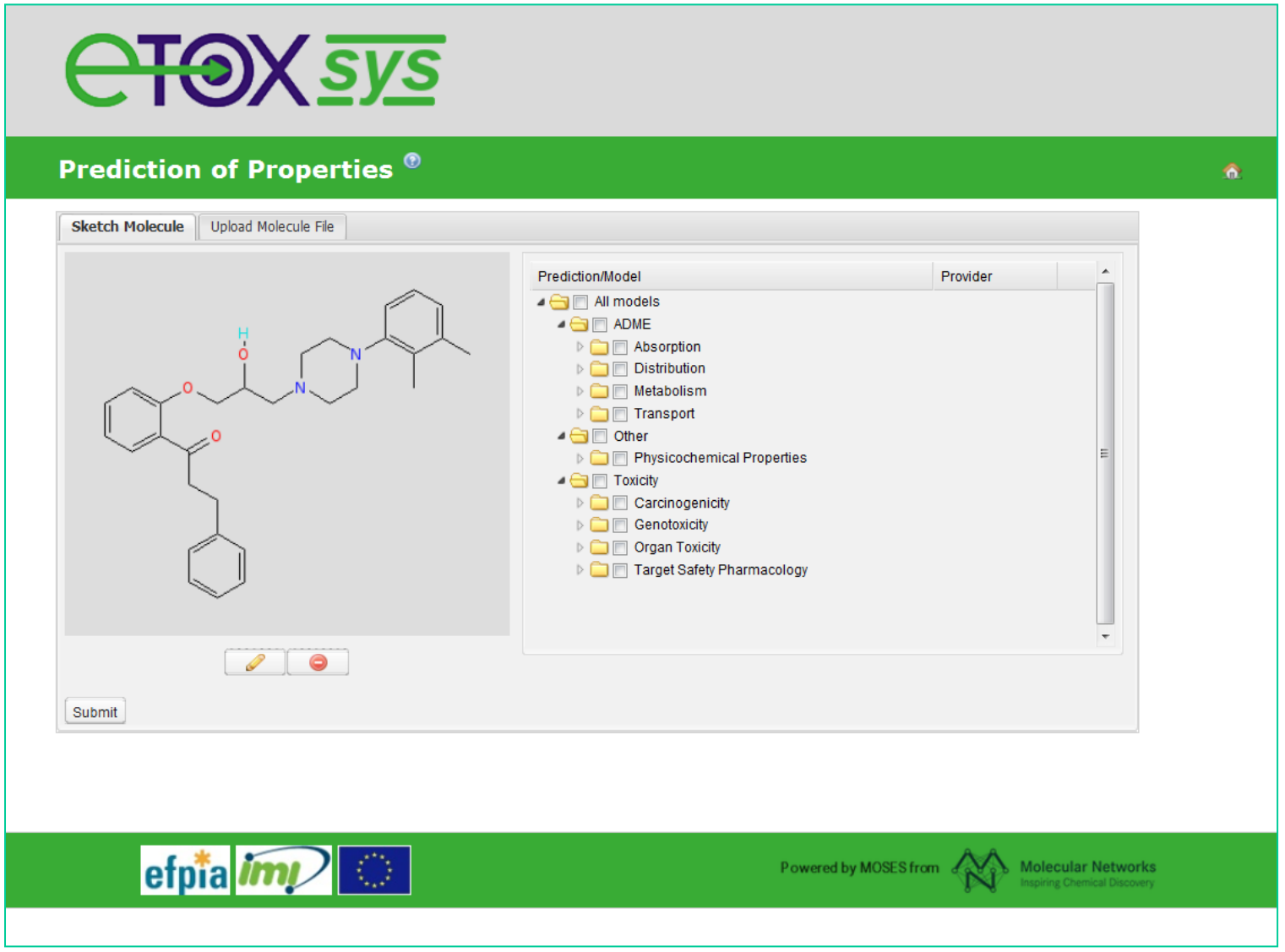

Interaction profiles and side effects

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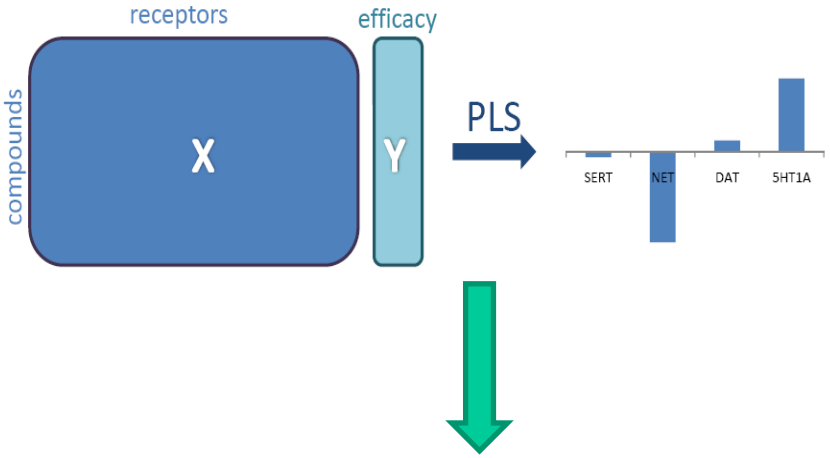
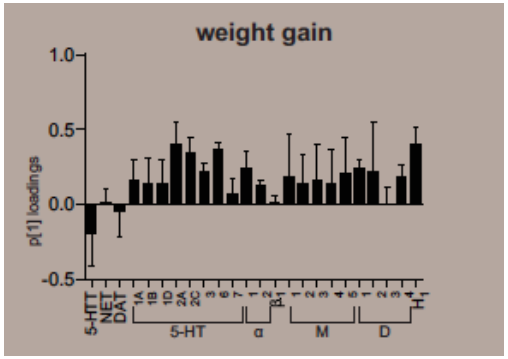
1.1 pKi Werte

	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
Mienserin	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





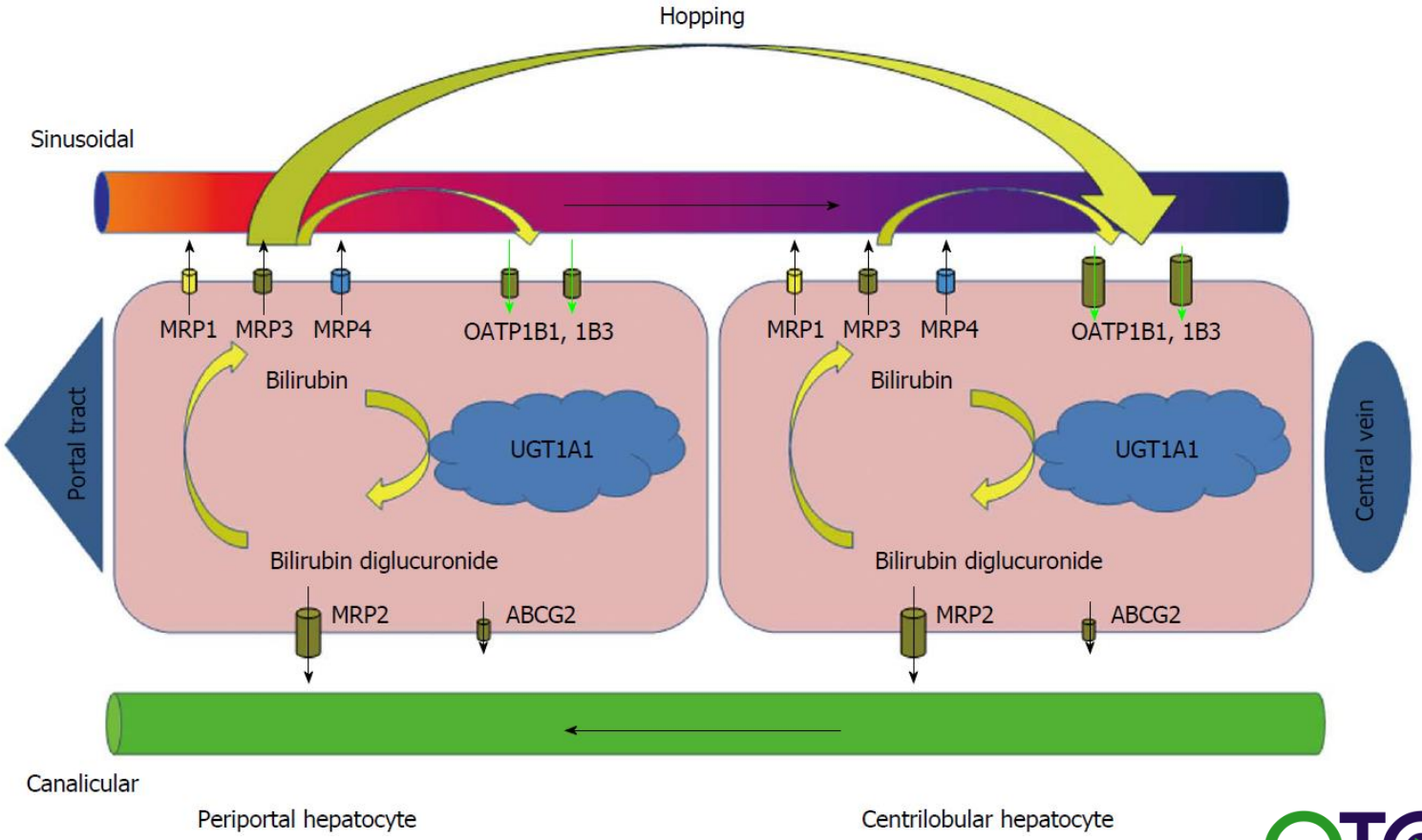
5-HT$_6$ and weigth gain

Michl, *Neuropsychpharmacology* 2014

Hyperbilirubinemia

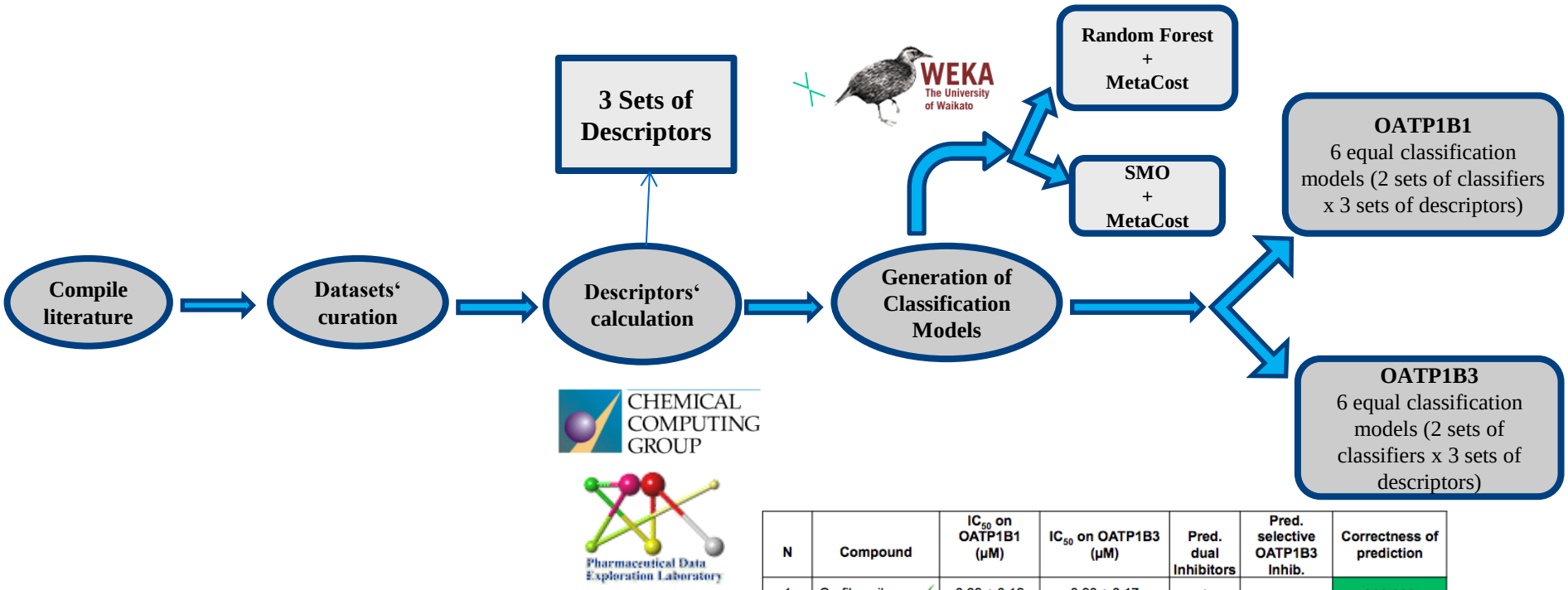
Hyperbilirubinemia- Background

Liver Transporters & Cycle of Bilirubin



Sticova and Jirsa, 2013, World J Gastroenterol, 6398-6407

Workflow – OATP Models



N	Compound	IC_{50} on OATP1B1 (µM)	IC_{50} on OATP1B3 (µM)	Pred. dual Inhibitors	Pred. selective OATP1B3 Inhib.	Correctness of prediction
1	Carfilzomib ✓	0.38 ± 0.12	0.90 ± 0.17	+		+++,+++
2	Dronedarone hydrochloride	0.32 ± 0.07	1.12 ± 0.20	+		+++,++
*3	Flavin adenine dinucleotide ✓	6.62 ± 1.15	10.02 ± 0.78		+	-,+
4	Fosinopril sodium	6.28 ± 1.13	5.19 ± 0.98	+		+,+
5	Gliquidone ✓	7.45 ± 1.64	1.17 ± 0.31	+		+,++
6	Lapatinib	0.37 ± 0.19	33.78 ± 2.45(s.i.)	+		+++,-
7	N,O-Didansyl-L-Tyrosine ?	6.07 ± 0.56	2.94 ± 0.75	+		+,++
8	Rapamycin (Sirolimus)	0.62 ± 0.19	0.40 ± 0.12	+		+++,+++
9	Trametinib	0.34 ± 0.09	30.82 ± 4.01(s.i.)	+		+++,-
10	Zafirlukast	7.84 ± 0.49	4.96 ± 0.92	+		+,++

References

1) De Bruyn et al., 2013, Mol Pharmacol, 1257-1267, Structure-Based Identification of OATP1B1/3 Inhibitors

2) Karlgren et al., 2012, J Med Chem, 4740-4763, Classification of Hepatic Organic Anion Transporting Polypeptides (OATPs): Influence of Protein Expression on Drug-Drug Interactions

Kotsampasakou, Mol Pharm 2015

Hyperbilirubinemia

Hyperbilirubinemia- Results

836 compounds for Hyperbilirubinemia:
86 positives
749 negatives

WEKA The University of Waikato

RDKit Open-Source Cheminformatics and Machine Learning

Model‘s Settings

ECFP6 + OATP Inhibition
MetaCost-
Attribute Selection-
SMO (RBF Kernel)

Valid. Method	Accuracy	Sensitivity (TPR)	Specificity (TNR)	MCC	ROC Area
10CV	0.675	0.651	0.678	0.209	0.687
5CV	0.690	0.581	0.702	0.184	0.679

- 1st model for Hyperbilirubinemia
- Suggestion for one more transporter for bilirubin (Lin et al., 2015, *Nature Reviews Drug Discovery)*

OATP Inhib → important dscr

The near Future

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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 hyperbilirubinemia, 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

Limitations are no longer in your computer, they are in your mind!

Be careful on the quality of the data!

Pharmacoinformatics Research Group

Department of Pharmaceutical Chemistry

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imi
Innovative Medicines Initiative

FWF

SFB 35

eTOX

Open PHACTS
Open Pharmacological Space

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