

A novel platform for integrated data-driven drug discovery

Gerhard F. Ecker

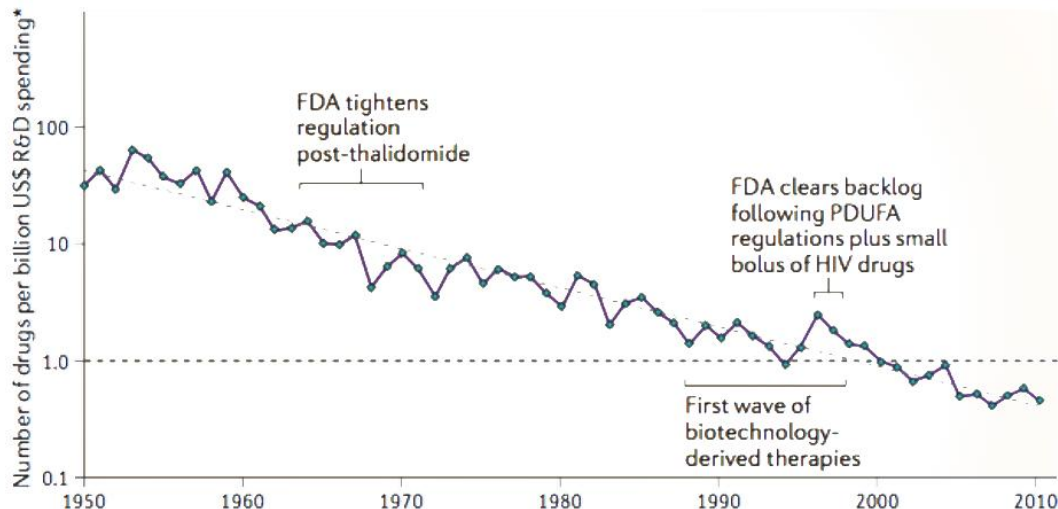
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Why do we need Open PHACTS?

Pharmaceutical companies currently expend significant effort integrating the vast amount of data publicly available into internal architectures.

Currently, pharmaceutical companies assemble their own in-house databases of pharmacological and physicochemical data.



Overall trend in R&D efficiency, inflation-adjusted (J. W. Scannel, A. Blanckley, H. Boldon and B. Warrington, *Nat. Rev. Drug Discov.*, 2012, **11**, 191-200, (doi:10.1038/nrd3681))

Drug discovery process is hindered by repetition of:

- Data extraction
- Transformation
- Loading stage

The Innovative Medicines Initiative

- EC funded public-private partnership for pharmaceutical research
- Focus on key problems
 - Efficacy, Safety, Education & Training, **Knowledge Management**



The Open PHACTS Project

- Create a *semantic integration hub* (“Open Pharmacological Space”)...
- Delivering services to support on-going drug discovery programs in pharma and public domain
- *Not just another project*, Leading academics in semantics, pharmacology and informatics, driven by solid industry business requirements
- 16 academic partners, 8 pharmaceutical companies, 4 biotechs
- Work split into clusters:
 - Tehnical Build (*focus here*)
 - Scientific Drive
 - Community & Sustainability

The Project

Open PHACTS Project Partners

www.openphacts.org

Pfizer Limited – Coordinator

Universität Wien – Managing entity

Technical University of Denmark

University of Hamburg, Center for Bioinformatics

BioSolveIT GmbH

Consorti Mar Parc de Salut de Barcelona

Leiden University Medical Centre

Royal Society of Chemistry

Vrije Universiteit Amsterdam

Spanish National Cancer Research Centre

University of Manchester

Maastricht University

Aqnowledge

University of Santiago de Compostela

Rheinische Friedrich-Wilhelms-Universität Bonn

AstraZeneca

GlaxoSmithKline

Esteve

Novartis

Merck Serono

H. Lundbeck A/S

Eli Lilly

Netherlands Bioinformatics Centre

Swiss Institute of Bioinformatics

ConnectedDiscovery

EMBL-European Bioinformatics Institute

Janssen

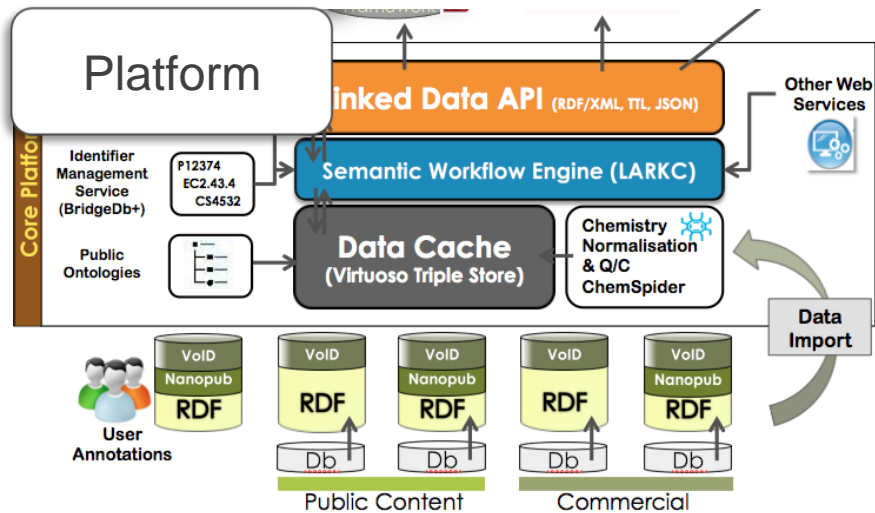
OpenLink



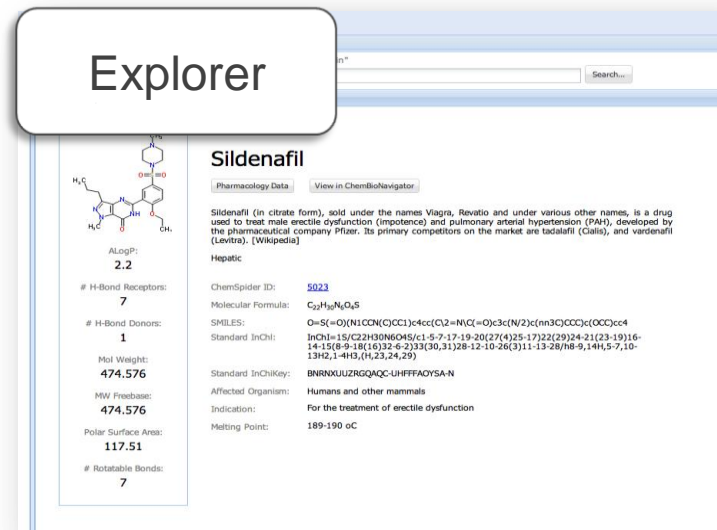
A user-friendly, full featured interface that allows scientists to explore and interrogate integrated biological and chemical data

What will users see?

Goals



Explorer



Sildenafil

Pharmacology Data | View in ChemBioNavigator


Sildenafil (in citrate form), sold under the names Viagra, Revatio and under various other names, is a drug used to treat male erectile dysfunction (impotence) and pulmonary arterial hypertension (PAH), developed by the pharmaceutical company Pfizer. Its primary competitors on the market are tadalafil (Cialis), and vardenafil (Levitra). [Wikipedia]

Hepatic:

ChemSpider ID:	5023
Molecular Formula:	C ₂₂ H ₂₆ N ₄ O ₅
SMILES:	O=C(=O)N1CCN(C)CC1c4c(C12=NC(=O)c3c(N12)c(n3)C)C(=O)C(=O)c4
Standard InChI:	InChI=1S/C22H30N6O4S/c1-5-7-17-19-20(27(4)25-17)22(29)24-21(23-19)16-14-15(8-9-18;16)32-6-2)33(30,31)28-12-10-26(3)11-13-28/h8-9,14H,5-7,10-13H2,1-4H3,(6,23,24,29)
Standard InChIKey:	BNRNULZRGQAQC-UHFFFAOYSA-N
Affected Organism:	Humans and other mammals
Indication:	For the treatment of erectile dysfunction
Melting Point:	189-190 °C

AllogP: 2.2
H-Bond Receptors: 7
H-Bond Donors: 1
Mol Weight: 474.576
MW Freebase: 474.576
Polar Surface Area: 117.51
Rotatable Bonds: 7

Apps




API

```
?ops_item skos:concept  
?ops_item skos:concept  
?cw_uri skos:preference  
void:inDataset  
?equiv_target domain  
ops:target  
ops:target  
void:inDataset  
ops:targetOfAssociation  
?equiv_assay chemical  
chembl:target  
?std_type ;
```




Standards


What do we need?



"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 $<1 \mu\text{M}$ "

ChEMBL

DrugBank

Gene
Ontology

Wikipathways

GeneGo

ChEBI

Uniprot

UMLS

GVKBio

ConceptWiki

ChemSpider

TrialTrove

TR Integrity

The Open PHACTS infrastructure can support many different domains & questions

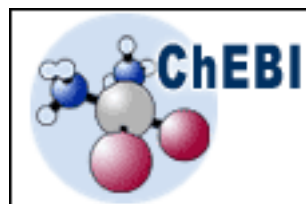
Research Questions

Number	sum	Nr of 1	Question
15	12	9	All oxido,reductase inhibitors active <100nM in both human and mouse
18	14	8	Given compound X, what is its predicted secondary pharmacology? What are the on and off,target safety concerns for a compound? What is the evidence and how reliable is that evidence (journal impact factor, KOL) for findings associated with a compound?
24	13	8	Given a target find me all actives against that target. Find/predict polypharmacology of actives. Determine ADMET profile of actives.
32	13	8	For a given interaction profile, give me compounds similar to it.
37	13	8	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.
38	13	8	Retrieve all experimental and clinical data for a given list of compounds defined by their chemical structure (with options to match stereochemistry or not).
41	13	8	A project is considering Protein Kinase C Alpha (PRKCA) as a target. What are all the compounds known to modulate the target directly? What are the compounds that may modulate the target directly? i.e. return all cmpds active in assays where the resolution is at least at the level of the target family (i.e. PKC) both from structured assay databases and the literature.
44	13	8	Give me all active compounds on a given target with the relevant assay data
46	13	8	Give me the compound(s) which hit most specifically the multiple targets in a given pathway (disease)
59	14	8	Identify all known protein-protein interaction inhibitors

Prioritized Datasets



BETA
WIKIPATHWAYS
Pathways for the People



User Interfaces & Applications

Linked Data API

Linked Data Cache

Identity
Mapping
Service

Identity
Resolution
Service

Domain
Specific
Services

Data

Quantitative Data Challenges

STANDARD_TYPE	UNIT_COUNT
---------------	------------

AC50	7
Activity	421
EC50	39
IC50	46
ID50	42
Ki	23
Log IC50	4
Log Ki	7
Potency	11
log IC50	0

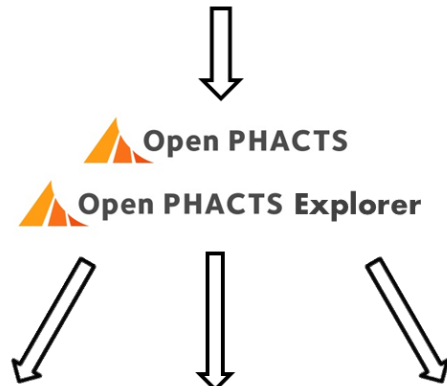
>5000 types

STANDARD_TYPE	STANDARD_UNITS	COUNT (*)
IC50	nM	829448
IC50	ug.mL-1	41000
IC50		38521
IC50	ug/ml	2038
IC50	ug ml-1	509
IC50	mg kg-1	295
IC50	molar ratio	178
IC50	ug	117
IC50	%	113
IC50	uM well-1	52
IC50	p.p.m.	51
IC50	ppm	36
IC50	uM-1	25
IC50	nM kg-1	25
IC50	milliequivalent	22
IC50	kJ m-2	20

Implemented using the Quantities, Dimension, Units, Types
Ontology (<http://www.qudt.org/>)

~ 100 units

What does Open PHACTS do?



Physicochemical data

Molecular weight & formula

H-Bond acceptors / donors

Polar surface area, AlogP

Melting point

Identifiers

Synonyms

SMILES

InChI / InChIkey

ChemSpider ID

Pharmacological data

Activity type, value and concentration

Assay description

Target organism

Target name

Currently integrated databases

Database	Number of triples (million)
ACD Labs / ChemSpider	161.34
ChEBI	0.91
ChEMBL_v13	146.08
ConceptWiki	3.74
DrugBank	0.52
Enzyme	0.07
Gene Ontology	0.85
SwissProt	156.57
WikiPathways	0.14
TOTAL	470.21

Open PHACTS draws together multiple sources of publicly-available pharmacological and chemical data, allowing public access to the information via the Open PHACTS Explorer, an intuitive interface.

Chemistry within Open PHACTS

The challenges associated with handling chemistry data require the support of a publicly accessible platform to **integrate, standardise and host the data**.

ChemSpider, an online database from the Royal Society of Chemistry hosts the chemical compound collection underpinning Open PHACTS and is responsible for standardising the chemical compounds and providing both regular updates and ongoing data curation.

To serve the Open PHACTS platform, a **structure validation and standardisation platform** (CVSP) has been developed to ensure chemical structures are normalised to rules derived from the FDA structure standardisation guidelines and modified based on input from the EFPIA members.



Advanced analytics

ChemBioNavigator

Navigating at the interface of chemical and biological data with sorting and plotting options

TargetDossier

Interconnecting Open PHACTS with multiple target centric services. Exploring target similarity using diverse criteria

PharmaTrek

Interactive Polypharmacology space of experimental annotations

UTOPIA

Semantic enrichment of scientific PDFs

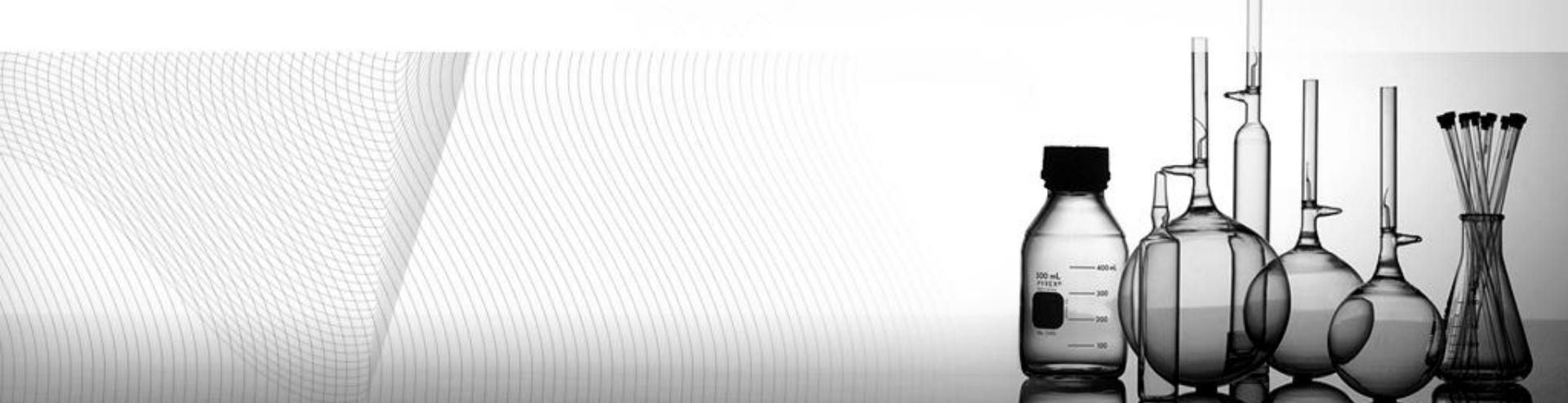
Predictions

GARFIELD

Prediction of target pharmacology based on the Similar Ensemble Approach

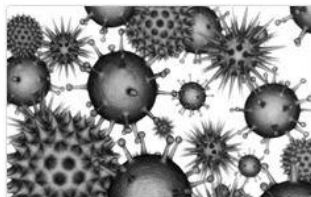
eTOX connector

Automatic extraction of data for building predictive toxicology models in eTOX project



Open PHACTS Explorer

Exploring the Open Pharmacological Space



Menu Explorer

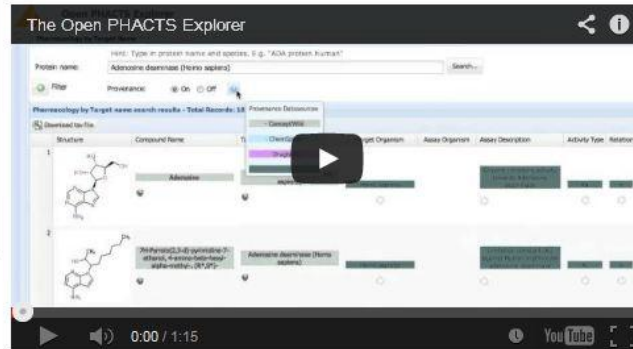
- ▶ [Welcome](#)
- ▶ [The Project](#)
- ▶ [Explorer Release Notes](#)
- ▶ [Tutorials](#)
- ▶ [The Data](#)
- ▶ [Terms and Conditions](#)
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 - ▶ [Take-down policy](#)

Welcome to the Open PHACTS Explorer

We are pleased to present the first public release of the beta Open PHACTS Explorer.

The Open PHACTS Explorer allows multiple sources of publicly-available pharmacological and physicochemical data to be intuitively queried, and makes data provenance accessible at every step. The Open PHACTS Explorer was built to answer **critical pharmacological questions** as defined by academic and pharmaceutical industry scientists.

To get started watch our tutorial introduction, visit the [tutorials page](#) or click on the [registration link](#) :



This is the first public **release** of the Open PHACTS Explorer, and we look forward to and value your **feedback and comments** .

Explorer

[Registration and access to the Open PHACTS Explorer](#)

[Known issues with beta Open PHACTS Explorer](#)

[Feedback](#)



Firefox | uni Universität Wien | Google Kalender | 03-Liveradio Player | Register for Open PHACTS Explorer | Open PHACTS

explorer.openphacts.org

Open PHACTS Explorer


Navigation

- Compound
- Target
- Pharmacology

Help and Feedback (+)

API Status (+)

TSV Downloads (+)


Open PHACTS Explorer

Compound by name

Hint: Type in compound name. E.g. "Aspirin"

Compound name: Provenance: On Off

Compound by Name search results

Navigation

- Compound
- Compound by name
- Compound by structure
- Target
- Target by name
- Pharmacology
- Pharmacology by Enzyme family
- Pharmacology by Compound
- Pharmacology by Target

Propafenone

Pharmacology Data
Structure Search
ChemSpider Info

An antiarrhythmia agent that is particularly effective in ventricular arrhythmias. It also has weak beta-blocking activity. The drug is generally well tolerated. [PubChem]

Metabolized primarily in the liver where it is rapidly and extensively metabolized to two active metabolites, 5-hydroxypropafenone and N-depropylpropafenone. These metabolites have antiarrhythmic activity comparable to propafenone but are present in concentrations less than 25% of propafenone concentrations.

<p style="margin: 0;">ALogP: 3.4</p> <p style="margin: 0;"># H-Bond Acceptors: 4</p> <p style="margin: 0;"># H-Bond Donors: 2</p> <p style="margin: 0;">Mol Weight: 341.444</p> <p style="margin: 0;">MW Freebase: 341.444</p> <p style="margin: 0;">Polar Surface Area (Å²): 58.6</p> <p style="margin: 0;"># Rotatable Bonds: 11</p>	<p style="margin: 0;">ChemSpider ID: 4763</p> <p style="margin: 0;">Molecular Formula: C₂₁H₂₇NO₃</p> <p style="margin: 0;">SMILES: <chem>O=C(c1cccc1OCC(O)CNCCC)CCc2ccccc2</chem></p> <p style="margin: 0;">Standard InChI: InChI=1S/C21H27NO3/c1-2-14-22-15-18(23)16-25-21-11-7-6-10-19(21)20(24)13-12-17-8-4-3-5-9-17/h3-11,18,22-23H,2,12-16H2,1H3</p> <p style="margin: 0;">Standard InChIKey: JWH AUXFOSRPERK-UHFFFAOYSA-N</p> <p style="margin: 0;">Protein Binding: 97%</p> <p style="margin: 0;">Toxicity: Symptoms of propafenone overdose (usually most severe within the first 3 hours) may include convulsions (rarely), heartbeat irregularities, low blood pressure, and sleepiness.</p>
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Help and Feedback
API Status
TSV Downloads

Open PHACTS Explorer

Navigation


- Compound
 - Compound by name
 - Compound by structure
- Target
 - Target by name
- Pharmacology
 - Pharmacology by Enzyme family
 - Pharmacology by Compound
 - Pharmacology by Target

Compound by name Pharmacology by Compound name Compound Structure Search Target by name

Hint: Start typing in protein name and species. E.g. "Adenosine receptor A2a (Homo sapiens)"

Target name: Provenance: On Off

Target Data



Multidrug resistance protein 3 (Mus musculus)

Description: Multidrug resistance protein 3

Synonyms: ATP-binding cassette sub-family B member 1A, CHEMBL2573, MDR1A, Multidrug resistance protein 3, P-glycoprotein 3

Specific Function: Energy-dependent efflux pump responsible for decreased drug accumulation in multidrug-resistant cells.

Keywords: Hydrolase, Phosphoprotein, 3D-structure, ATP-binding, Cell membrane, Complete proteome, Direct protein sequencing, Glycoprotein, Membrane, Nucleotide-binding, Reference proteome, Repeat, Transmembrane, Transmembrane helix, Transport

PDB Entry: [3G61](#) [3GSU](#) [3G60](#)

Help and Feedback

API Status

TSV Downloads

Open PHACTS Explorer

Navigation:

- Compound
 - Compound by name
 - Compound by structure
- Target
 - Target by name
- Pharmacology
 - Pharmacology by Enzyme family
 - Pharmacology by Compound
 - Pharmacology by Target

Enzyme family class: No enzyme class selected - press button ->

Filter: Provenance: On Off

Start search...

Pharmacology by Enzyme Family search results

Prepare tsv file

Structure	Compound Name	Target Name

Select an enzyme family

EC number	Enzyme family name
1.-.-.-	Oxidoreductases
2.-.-.-	Transferases
2.1.-.-	Transferring one-carbon groups
2.10.-.-	Transferring molybdenum- or tungsten-containing groups
2.2.-.-	Transferring aldehyde or ketone residues
2.3.-.-	Acyltransferases
2.3.1.-	Transferring groups other than amino-acyl groups
2.3.2.-	Aminoacyltransferases
2.3.2.1	D-glutamyl transpeptidase,D-glutamyltransferase
2.3.2.10	UDP-N-acetylmuramoylpentapeptide-lysine N(6)-alanyltr...
2.3.2.11	Alanylphosphatidylglycerol synthase
2.3.2.12	Peptidyltransferase
2.3.2.13	Glutamylpeptide gamma-glutamyltransferase,Fibrinolg...
2.3.2.14	D-alanine gamma-glutamyltransferase
2.3.2.15	Glutathione gamma-glutamylcysteinyltransferase,Phyto...
2.3.2.16	Lipid II:glycine glycytransferase
2.3.2.17	N-acetylmuramoyl-L-alanyl-D-glutamyl-L-lysyl-(N(6)-glyc...
2.3.2.18	N-acetylmuramoyl-L-alanyl-D-glutamyl-L-lysyl-(N(6)-trigl...
2.3.2.2	Gamma-glutamyl transpeptidase,Gamma-glutamyltransf...
2.3.2.3	Lysyltransferase
2.3.2.4	Gamma-glutamylcyclotransferase
2.3.2.5	Glutaminy cyclase,Glutaminy-peptide cyclotransferase,...
2.3.2.6	Leucyl-tRNA--protein transferase,L/F transferase,Leuc...
2.3.2.7	Aspartyltransferase
2.3.2.8	Arginyltransferase,Arginyl-tRNA--protein transferase
2.3.2.9	Aqaritime gamma-qlutamyltransferase

Help and Feedback

API Status

TSV Downloads

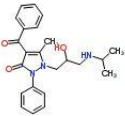

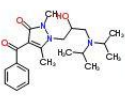
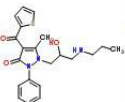
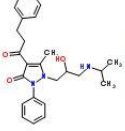

Compound by name
Pharmacology by Compound name
Compound Structure Search
Target by name
Compounds active against enzyme family
Pharmacology by Target Name

Protein name:

Filter: Provenance: On Off

Pharmacology by Target name search results - Total Records: 2563

[Prepare tsv file](#)

Structure	Compound Name	Target Name	Target Organism	Assay Organism	Assay Description	Activity Type	Relation	Value	Units	Mol Weight	SMILES	InChi	InChi Key
	4-benzoyl-1-[2-hydroxy-3-(propan-2-ylamino)propyl]-5-methyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one	Multidrug resistance protein 1 (Homo sapiens)	Homo sapiens		Compound was tested for inhibition of daunomycin efflux in the resistant human T-lymphoblast cell line CEM vcr 1000.	EC50	=	83180	nM	393.479	O=C2C(=C(N(...	InChI=1S/C23H...	VZPAOCHCLZMT...
	1,3-dimethyl-4-[(E)-phenyl(propylimino)methyl]pyrazol-5-ol	Multidrug resistance protein 1 (Homo sapiens)	Homo sapiens		Compound was tested for inhibition of daunomycin efflux in the resistant human T-lymphoblast cell line CEM vcr 1000.	EC50	=	272500	nM	257.331	CCC=N=C(\c1cc...	InChI=1S/C15H...	GJPFQWWTOPA...
	4-benzoyl-1-[3-(dipropan-2-ylamino)-2-hydroxypropyl]-2,5-dimethyl-1,2-dihydro-3H-pyrazol-3-one	Multidrug resistance protein 1 (Homo sapiens)	Homo sapiens		Compound was tested for inhibition of daunomycin efflux in the resistant human T-lymphoblast cell line CEM vcr 1000.	EC50	=	24120	nM	373.489	O=C1C(=C(N(...	InChI=1S/C21H...	UYZSJDVHQW...
	1-[2-Hydroxy-3-(propylamino)propyl]-5-methyl-2-phenyl-4-(2-thienylcarbonyl)-1,2-dihydro-3H-pyrazol-3-one	Multidrug resistance protein 1 (Homo sapiens)	Homo sapiens		Compound was tested for inhibition of daunomycin efflux in the resistant human T-lymphoblast cell line CEM vcr 1000.	EC50	=	72440	nM	399.507	O=C(C=2C(=O)...	InChI=1S/C21H...	JCKJIYACBBEC...
	1-[2-hydroxy-3-(propan-2-ylamino)propyl]-5-methyl-2-phenyl-4-(3-phenylpropanoyl)-1,2-dihydro-3H-pyrazol-3-one	Multidrug resistance protein 1 (Homo sapiens)	Homo sapiens		Compound was tested for inhibition of daunomycin efflux in the resistant human T-lymphoblast cell line CEM vcr 1000.	EC50	=	11750	nM	421.532	O=C2C(=C(N(...	InChI=1S/C25H...	DNSZEGKDVYSK...
													

Help and Feedback




API Status

TSV Downloads





TARGETS

p38 alpha homo X You have 1 targets selected




Mitogen-activated protein kinase 14 (Homo sapiens)
Amino Acid, Peptide, or Protein




  

Mitogen-activated protein kinase 14 (Homo sapiens)
Amino Acid, Peptide, or Protein

alpha thalassemia/mental retardation syndrome X-linked homolog (human) protein, mouse
Amino Acid, Peptide, or Protein


   connect

Interaction Map

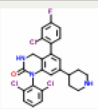





35 TARGETS
546 MOLECULES
Min annotation [8.00]
Max annotation [10.41]

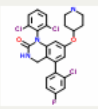
Expand target space




  

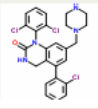
LIGANDS

 **2(1H)-quinazolinone, 5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-(4-piperidinyl)-**

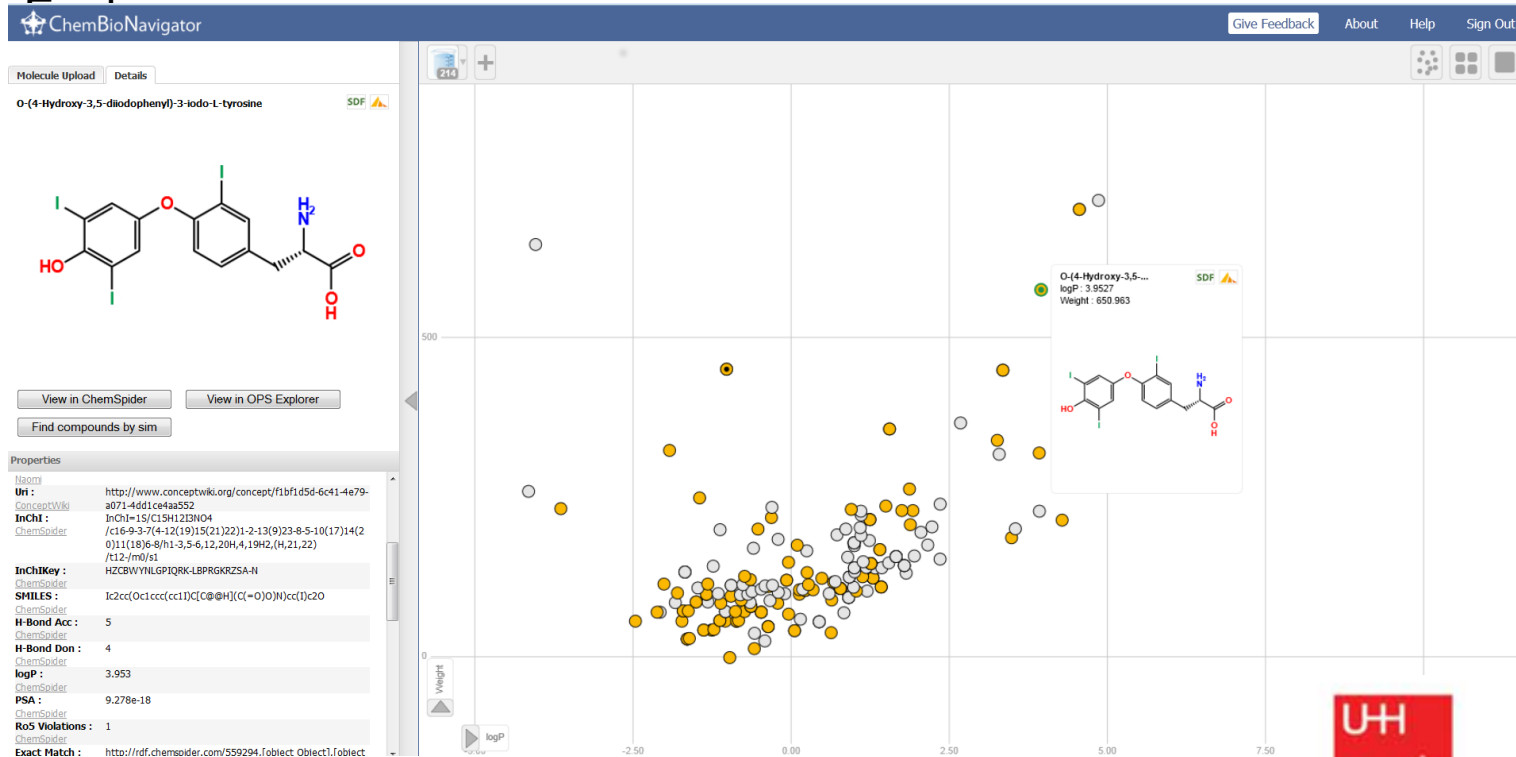
 **2(1H)-quinazolinone, 5-(2-chloro-4-fluorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-(4-piperidinyl)-**

 **2(1H)-quinazolinone, 5-(2-chlorophenyl)-1-(2,6-dichlorophenyl)-3,4-dihydro-7-(1-piperazinylmethyl)-**

Example Applications: ChemBioNavigator

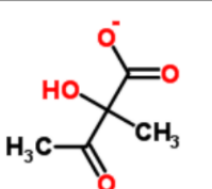
The ChemBioNavigator allows the user to **visualise the chemical and biological space of a molecule group** in a chemically-aware manner. Individual data points can be investigated further via direct links to ChemSpider and the Open PHACTS



Universität Hamburg

DER FORSCHUNG | DER LEHRE | DER BILDUNG

Utopia Documents – pcbi.1000976 1..16
Back to overview



CC(=O)C(O)C(=O)[O-]

TABLE 4. The 10 most highly connected drugs in the 19-organism.

Drug	Intended Targets	Total Number of Connections	Connected <i>MED</i> proteins with Solved Structures
Atazanavir	Retinoic acid receptor ROR- α , β & γ , retinoic acid receptor α , β & γ -1A2, cellular retinoic acid-binding protein 19.2	98	aroc1 , blebD , bpcC , cyp121 , embB , gblM , hnhA , lppX , mscA , pflE , pncA , pncD , pamB , Rv1264 , Rv3676
Levofloxacin	Tyrosyltransferase, thyroid hormone receptor β , β 1, thyroxine-binding globulin, mu-cystatin homolog, serum albumin	63	argH , blebD , hah , hnhB , gblM , gblN , hnhA , hnhC , pflA , Rv1264 , Rv3636 , sacA1 , tlyC
Methotrexate	Dihydrodipicolinate reductase, serum albumin	48	argH , arof , emaA2 , cyp121 , cyp51 , lppX , mmaA4 , pncC , Rv3636 , Rv3717
Estradiol	Estrogen receptor	38	argH , hnhD , cyp121 , cysM , hnhA , mscC , pflE , Rv1264 , Rv3636 , sfgC
Ritampin	DNA-directed RNA polymerase beta chain, eukaryotic nuclear receptor PXR, methylglucosyl transferase 1	34	hnhA , lppX , lppX , mscC , pflE , Rv3636
Hydroxytamoxifen	Estrogen receptor, estrogen receptor β , epoxide hydrolase 2, multidrug resistance protein 1, thymidine phosphorylase	33	argH , cysM , hnhA , hnhC , lppX , pflE , pflE , Rv1264 , Rv1941 , Rv3636
Anantradine	Dopamine receptor D1A2, matrix protein 2	32	(homology models only)
Rubrofline	Estrogen receptor, estrogen receptor β	28	blebD , hnhA , mscC , pflE , pflE , pncA , pncB , Rv1264 , Rv3636 , sacA1 , sfgC
Ropivacaine	Serum albumin, gamma-aminobutyric acid receptor subunit alpha-1, fatty acid amide hydrolase	24	clpF , gblN , hnhA
Indinavir	HIV-1 protease, Gag-Pol polyprotein	23	hnhA , lppX
Ritonavir	HIV-1 protease	22	accD5 , arof , fabM , lppX , pncC , serA1 , T831-7
Drimavirin	HIV-1 protease, Gag-Pol polyprotein	22	cyp24 , clpF , hnhA , lppX , pncC
Lopinavir	HIV-1 protease, Gag-Pol polyprotein, protease	22	lppX , mscB , pflE , sfgA
Pericollamine	Caspase-1, Iy kappa chain V-II region GOL	20	groEL , hnhA , mscA , Rv1264 , Rv3676
Nefazoline	HIV-1 protease	20	fabM , pncC , serA1

The intended targets of the drugs are given as well as the solved *MED* proteins to which they are connected in the network. Those genes that were present in the GSMN-TE metabolic reconstruction are underlined and, of these, those whose knock-out resulted in a maximal theoretical growth rate of zero or close to zero have been highlighted in bold. Note that only cross-fold connections are considered here. doi:10.1371/journal.pcbi.1000976.t004

synthase III], [pncC](#) (pantoate—beta-alanine lyase) and [serA1](#) (D-3-phosphoglycerate dehydrogenase). Anantradine has connections to homology models only and so was excluded from this study. Although ligand may not inhibit any essential metabolic proteins, some of the proteins that [pncC](#) and [serA1](#) inhibit are the interesting anti-tubercular [cyclooxigenase](#), protein kinase, for survival of mycobacteria in host or intrinsic resistance of mycobacteria [53]. In addition, the GSMN-TE multiple gene knockouts and their effects on drug response, while the protein kinases and poly(aryl)phosphate/poly(aryl)phosphate hyd human protein kinase inhibitors and farnesyl-diphosphate synthase inhibitors. Although this result is not surprising, the fact that similar drugs and similar targets are clustered together provides further validation of the [acetolactate](#) (acetolactate synthase), and [fabE13](#) (acyl-CoA dehydrogenase), all of which are inhibitors. There is a major role made in sub-Saharan

acetolactate

2-acetolactate mutase

2-acetolactate mutase
In enzymology, a 2-acetolactate mutase is an enzyme that catalyzes the chemical reaction 2-acetolactate + H₂O \rightleftharpoons 3-hydroxy-3-methyl-2-oxobutanoate. Hence, this enzyme has one substrate, 2-acetolactate, and one product, 3-hydroxy-3-methyl-2-oxobutanoate. This enzyme belongs to the family of isomerases, specifically the intramolecular transferases transferring other groups. The systematic name of this enzyme class is 2-acetolactate methylmutase.

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Acetolactate decarboxylase

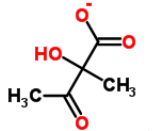
Acetolactate decarboxylase
In enzymology, an acetolactate decarboxylase is an enzyme that catalyzes the chemical reaction (S)-2-hydroxy-2-methyl-3-oxobutanoate \rightleftharpoons (R)-2-acetoin + CO₂. Hence, this enzyme has one substrate, (S)-2-hydroxy-2-methyl-3-oxobutanoate, and two products, (R)-2-acetoin and CO₂. This enzyme belongs to the family of lyases, specifically the carboxy-lyases, which cleave carbon-carbon bonds.

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ACETOLACTSYNI-CPLX

ACETOLACTSYNI-CPLX
Bifunctional aceto-hydroxybutanoate synthase / acetolactate synthase (IlvB/N) carries out both the first step in valine biosynthesis and the second step in isoleucine biosynthesis. The IlvB/N protein complex catalyzes the conversion of pyruvate and oxobutanoate into 2-aceto-2-hydroxy-butyrate and the conversion of pyruvate into 2-acetolactate. Both reactions generate carbon dioxide as a product [CITS: [4608700][370104][7009323][6181375][3011751][1632601]]. This enzyme has a wide substrate range *in vitro* [CITS: [15558598]]. This bifunctional enzyme is a tetramer comprising two IlvB subunits and two IlvN subunits. Its apparent molecular weight rises above the expected weight for this configuration when pyruvate is added *in vitro* [CITS: [6360995]]. The IlvB large subunit can catalyze the reaction in isolation and is not inhibited by valine in the manner of the holoenzyme. However the IlvN is for the reaction as catalyzed by only IlvB is

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- ✦ Launch of API at Community Workshop, April 22/23, London
- ✦ Open PHACTS Training Event, Sep 20, Vienna
- ✦ 2nd wave use cases (pathway, disease)
- ✦ Sustainability – Open PHACTS Foundation

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