Cheminformatics at geneXplain GmbH

Introducing PASS and PharmaExpert

geneXplain GmbH

Products

- bioinformatics and systems biology: geneXplain platform
- bioinformatics and NGS: IMC and GenomeTraveler
- **cheminformatics: PASS, PharmaExpert,** GUSAR

Bioinformatics, Systems Biology, NGS

- geneXplain platform
  - collection, storage and analysis of experimental data
  - network clustering and search for master regulators
  - features: graphical programming of workflows and the possibility to write new scripts and add-ons
- IMC
  - handling whole genome data
  - supports: feature mapping and annotation
  - PCR primer calculation
- GenomeTraveler
  - handling of next generation sequencing (NGS) data
  - genome analysis
  - all functions of IMC

Contents

PASS

- Prediction of Activity Spectra for Substances

General Information

- PASS…
  - does computational predictions of biological activity spectra for drug-like compounds.
  - uses 2D chemical structures from SD or MOL files.
  - predicts activities qualitatively.
  - gives probability estimates for every prediction.
  - has an average prediction accuracy of 95%.

Key Data

- included SAR base constructed from a training set with 250,407 substances and 69,950 MNA descriptors
  - drugs
  - drug-candidates
  - pharmacological substances

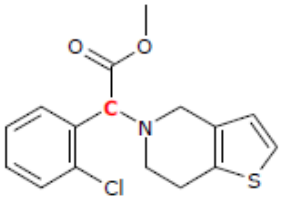
- 4,444 biological activities can be predicted
  - 498 pharmacotherapeutic effects
  - 3,378 biochemical mechanisms
  - 351 possible toxic and side effects
  - 116 possible antitargets/offtargets
  - about 300 terms related to metabolism, transport and gene expression

- mathematical algorithm based on Bayesian estimates of probabilities

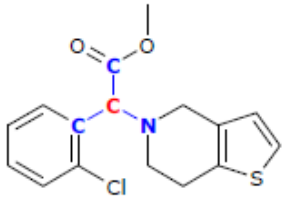
Filimonov D.A., Poroikov V.V. In: Chemoinformatics Approaches to Virtual Screening. RSC Publ., 2008, p.182-216.

MNA Descriptors

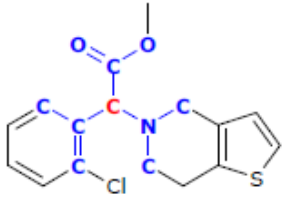
Multilevel Neighborhood of Atoms



MNA/0: -C



MNA/1: -C(CN-H-C)

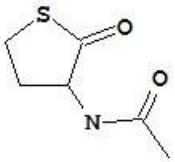


MNA/2: -C(C(CC-C)N(CC-C)-H(-C)-C(-C-O-O))

Filimonov D.A. et al. J. Chem. Inform. Computer Sci., 1999, 39, 666.
Filimonov D.A., Poroikov V.V. In: Chemoinformatics Approaches to Virtual Screening. RSC Publ., 2008, p.182-216.

Biological Activity Prediction

structure



The predicted activity spectrum is displayed with probability values for each activity:

- Pa, the probability to be active, and
- Pi, the probability for the structure to be inactive.

MNA/1

HC
HN
CHHHC
CHHCC
CHHCS
CHCCN
CCNO
CCOS
NHCC
OC
SCC

MNA/2

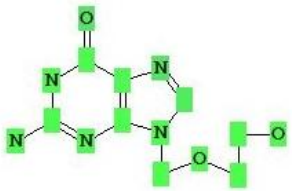
C(C(CC-H-H)C(CS-O)-H(C)-N(C-H-C))
C(C(CC-H-H)S(CC)-H(C)-H(C))
C(C(CC-H-N)C(CS-H-H)-H(C)-H(C))
C(C(CC-H-N)S(CC)-O(C))
S(C(CS-H-H)C(CS-O))
-H(C(CC-H-H))
-H(C(CC-H-N))
-H(C(CS-H-H))
-H(-C(-H-H-H-C))
-H(-N(C-H-C))
-C(-H(-C)-H(-C)-H(-C)-C(-C-N-O))
-C(-C(-H-H-H-C)-N(C-H-C)-O(-C))
-N(C(CC-H-N)-H(-N)-C(-C-N-O))
-O(C(CS-O))
-O(-C(-C-N-O))

predicted activity spectrum

53 of 4130 Possible Activities at Pa > 0.500

0.982	0.002	Hepatic disorders treatment
0.811	0.003	Lipotropic
0.790	0.002	Gastrointestinal motility stimulant
0.785	0.002	Antiemphysemic
0.787	0.004	Chronic obstructive pulmonary disease treatment
0.780	0.002	Free radical scavenger
0.766	0.002	Expectorant
0.724	0.002	Mucolytic
0.735	0.015	Muramoyltetrapeptide carboxypeptidase inhibitor
0.728	0.013	Proteasome ATPase inhibitor
0.686	0.011	Radioprotector
0.662	0.004	Thiopurine S-methyltransferase inhibitor

Substructures and Activity Spectra

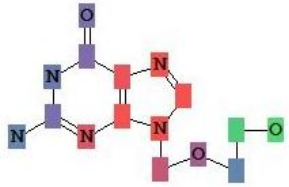


Activity Map | General | Effects | Mechanisms

718 of 4366 Possible Activities at Pa > Pi

0.993	0.003	Headache
0.988	0.001	Dysarthria
0.987	0.001	Pure red cell aplasia
0.988	0.003	Thrombocytopenia
0.988	0.004	Dizziness
0.987	0.004	Toxic, respiration
0.986	0.003	Agranulocytosis
0.984	0.003	Spasticity
0.984	0.004	Pain
0.982	0.003	Consciousness alteration
0.981	0.003	Coma
0.970	0.003	Leukopenia
0.957	0.006	Sensory disturbance
0.946	0.002	ADP-thymidine kinase inhibitor
0.943	0.003	Keratopathy
0.942	0.003	Allergic dermatitis
0.940	0.007	Emetic
0.935	0.004	Ataxia
0.922	0.004	Depression
0.922	0.005	Myoclonus
0.916	0.005	Necrosis
0.909	0.007	Anemia
0.910	0.012	Diarrhea
0.902	0.005	Drowsiness
0.898	0.002	Aldehyde oxidase substrate
0.901	0.009	Hyperthermic

All substructures have a positive impact on the activity „dizziness“ (green).

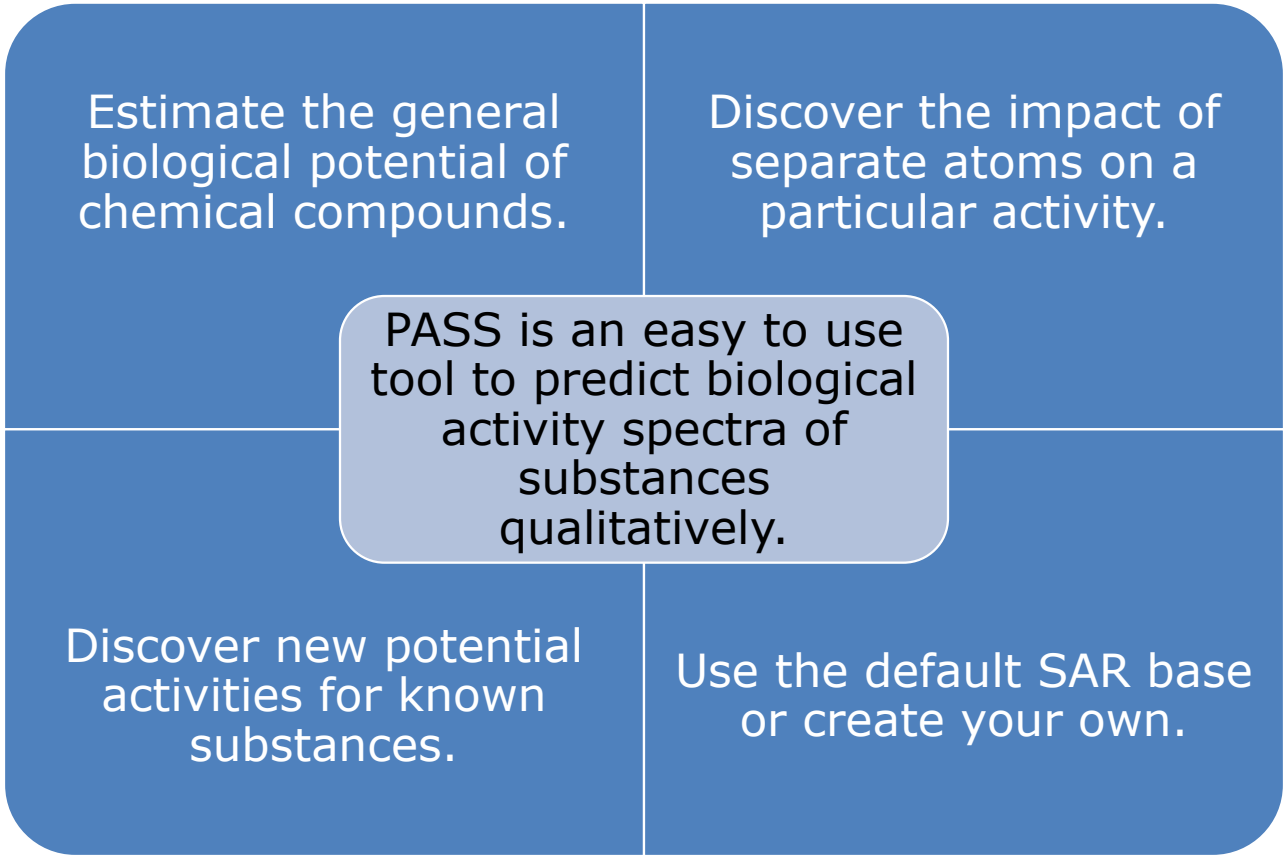


Activity Map | General | Effects | Mechanisms

0.085	0.076	Antiviral (Hepatitis C)
0.142	0.133	Aurora-C kinase inhibitor
0.327	0.319	CDP-glycerol glycerophosphotrans
0.023	0.016	Multiple inositol-polyphosphate pho
0.157	0.150	Quinoprotein glucose dehydrogena
0.011	0.004	CDK2/cyclin A3 inhibitor
0.045	0.039	Asparagine synthetase inhibitor
0.094	0.088	Aryl-aldehyde dehydrogenase (NAI
0.127	0.121	4-Chlorobenzoyl-CoA dehalogenas
0.276	0.270	Macrophage colony stimulating fac
0.241	0.236	Antiviral (Influenza A)
0.008	0.003	GTP cyclohydrolase IIa inhibitor
0.009	0.004	Phosphoribosylglycinamide formyltr
0.077	0.072	2-Methylcitrate synthase inhibitor
0.107	0.102	Thiol S-methyltransferase inhibitor
0.018	0.013	Methionyl-tRNA formyltransferase i
0.014	0.010	FMN adenylyltransferase inhibitor
0.192	0.188	Mediator release inhibitor
0.072	0.069	Inositol 1,4,5-triphosphate receptor
0.037	0.034	Purinergic P2Y1 antagonist
0.092	0.089	Glyceraldehyde-3-phosphate dehy
0.067	0.064	6-Phosphofructo-2-kinase inhibitor
0.218	0.216	Peptide agonist
0.063	0.061	UDP-glucose 6-dehydrogenase inh
0.098	0.097	Glycerone-phosphate O-acyltransf
0.043	0.043	Arginine-tRNA ligase inhibitor
0.041	0.040	rRNA (adenosine-2'-O-)-methyltran
0.022	0.022	Factor IXa inhibitor

Many atoms have a negative impact on the activity “peptide agonist” (red).

Summary


Estimate the general biological potential of chemical compounds.
Discover the impact of separate atoms on a particular activity.
PASS is an easy to use tool to predict biological activity spectra of substances qualitatively.
Discover new potential activities for known substances.
Use the default SAR base or create your own.

PharmaExpert

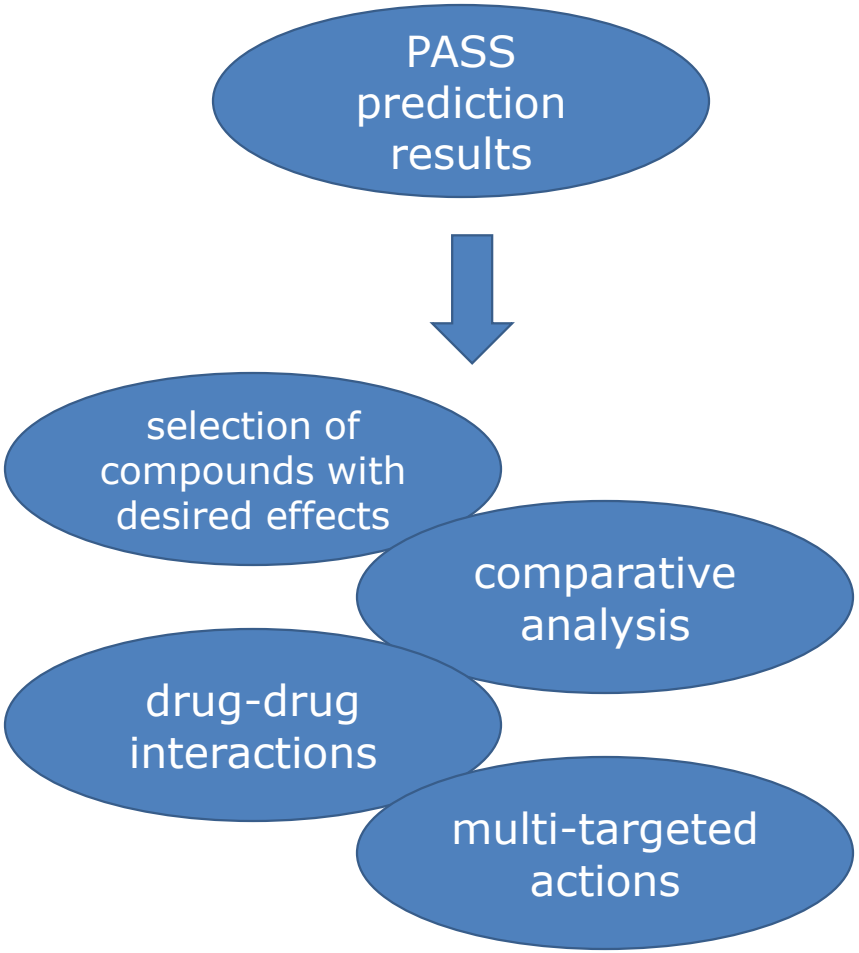
- A useful extension for PASS

General Information

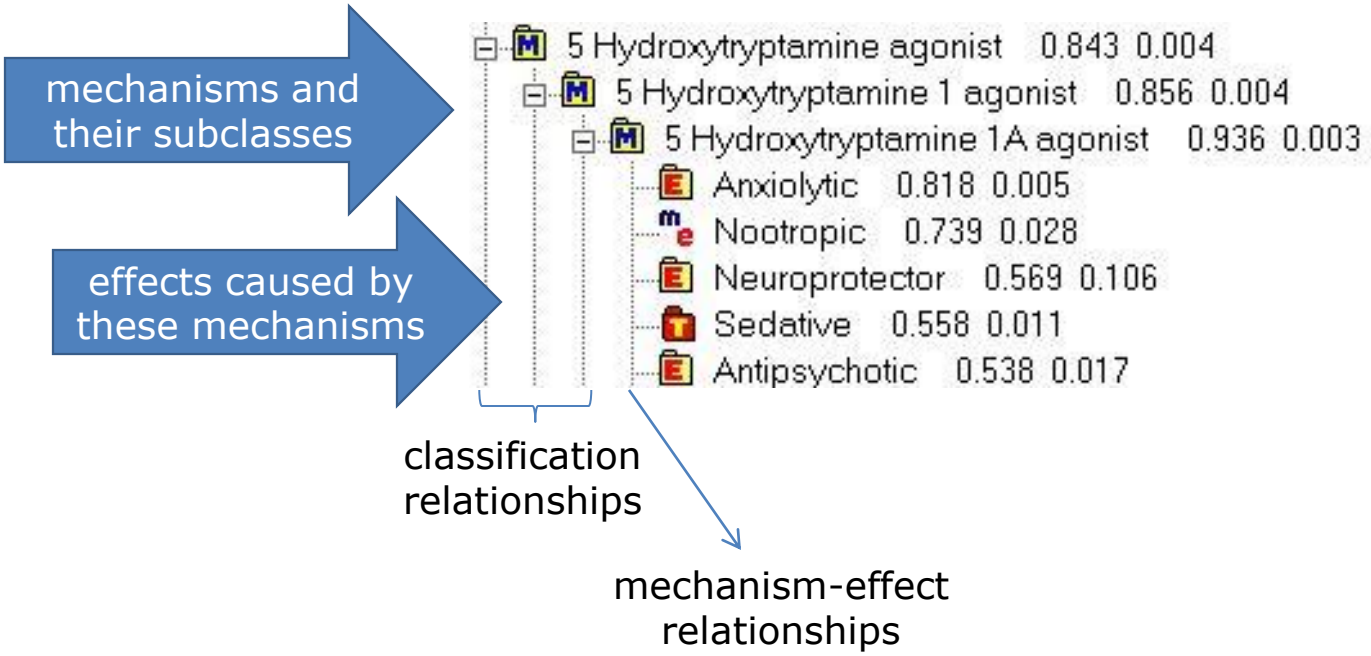
- PharmaExpert…
  - works with PASS prediction results as SD files.
  - analyses mechanism-effect relationships.
  - identifies drug-drug interactions for pairs of molecules.
  - searches for structures with required activity profile(s).
  - finds molecules that act on multiple targets.

Key Data

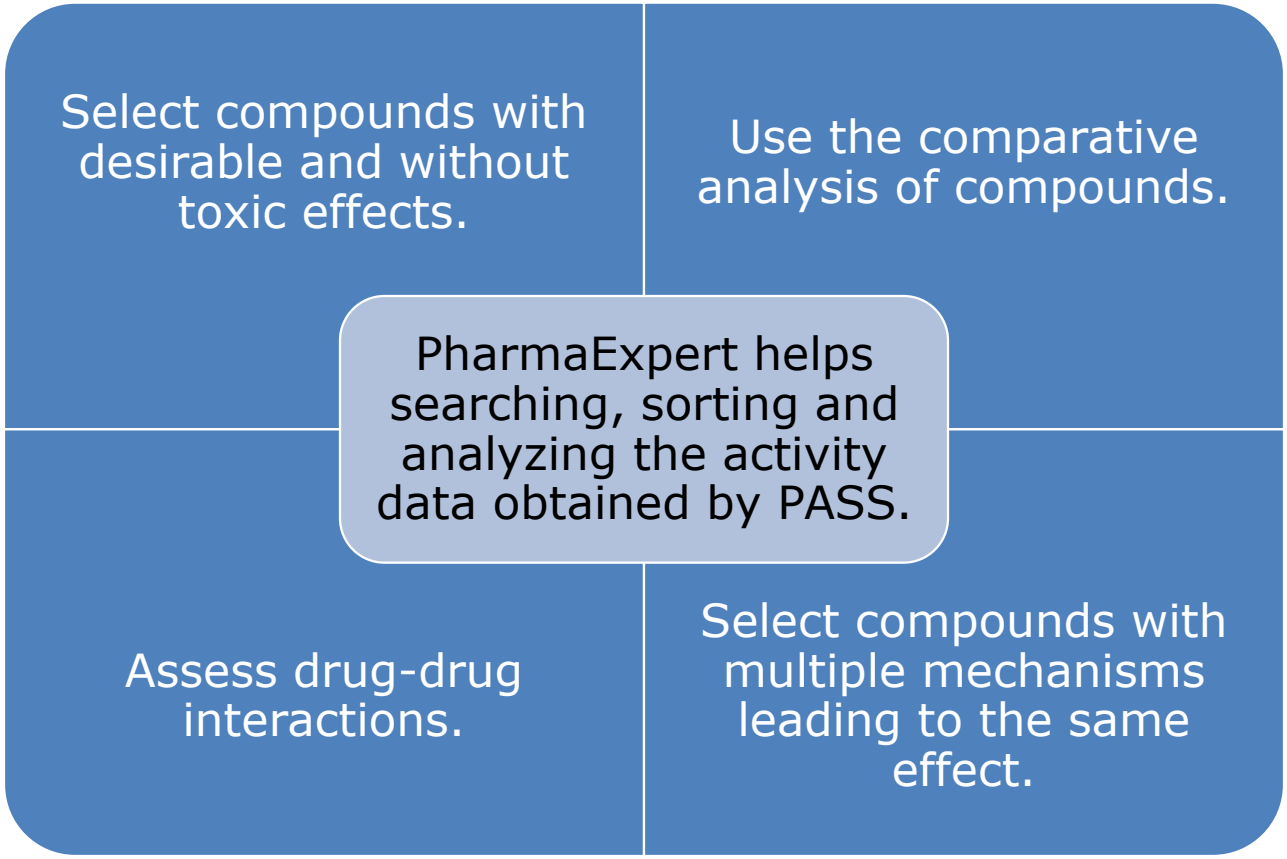
- 11,049 mechanism-effect relationships (MER)
- manually curated MER base containing 7,723 activities
  - 5,753 mechanisms of action
  - 715 pharmacological effects
  - 998 toxic and side effects
  - 133 antitargets
  - about 500 terms related to metabolism, gene expression and transporters



Activity Types and Relationships



Summary


Select compounds with desirable and without toxic effects.
Use the comparative analysis of compounds.
PharmaExpert helps searching, sorting and analyzing the activity data obtained by PASS.
Assess drug-drug interactions.
Select compounds with multiple mechanisms leading to the same effect.

Why You Should Give PASS and PharmaExpert a Try

- Advantages of the Software

Evaluate Drug-Like Compounds

- estimation of the general biological potential of drug-like chemical compounds, including newly synthesized and virtually designed substances
- discovery of new potential activities of known compounds
- dissecting the impact of separate atoms and groups on a particular activity
- selection of compounds with desirable activities and without adverse or toxic effects
- selection of compounds with multiple mechanisms of action
- comparative analysis of compounds
- assessing drug-drug interactions with regard to their pharmacokinetic, pharmacodynamic and adverse effects

Advantages of PASS/PharmaExpert

- Only the structural formula of a compound is required to predict its biological activity spectrum.
- Analysis options and filters help restricting the number of tested compounds and direct further experimental evaluations.
- The software is installed locally and runs on any ordinary PC.
- A proprietary SAR base can be created to generate a user-specific version of PASS.
- The algorithm is fast, 50,000 compounds can be screened in ten minutes.
- PASS is widely accepted by the community: applications of PASS are cited in over 200 independent publications, and in about 40 of them PASS predictions are experimentally verified.
  - A list of all third-party publications about PASS can be found here: *http://www.genexplain.com/sites/default/files/PASS%20-%20third-party%20publications.pdf*