

## PharmaExpert

This is an optional extension of the PASS system, allowing for a systematic data mining and biological interpretation of PASS results.

PharmaExpert analyzes mechanism-effect relationships, identifies the probable drug-drug interactions for pairs of molecules, and searches for molecules acting on multiple targets. The software can also help to identify molecules with desired activities and without toxic or side effects.

The analysis is based on a "mechanism-effect(s)" relationship knowledgebase (MER base) that is collected by experts from literature of more than 15 years.

## PASS

The acronym PASS stands for "Prediction of Activity Spectra for Substances". Upon entering a structural formula of a chemical substance, the program returns the potential biological activities of this compound.

## PharmaExpert allows to:

- Select compounds with required therapeutic, but without adverse effects;
- Comparatively analyze compounds with similar structures;
- Select compounds with multiple mechanisms of action;
- Assess drug-drug interactions with regard to their pharmacokinetic, pharmacodynamic, and adverse effects.

## About geneXplain

GeneXplain's mission is to provide a comprehensive platform for bioinformatic, systems biological and cheminformatic tools. The raison d'être of this platform is to assist translational research in the life sciences, mainly in the context of personalized medicine and pharmacogenomics. We intend to make our expertise available to academic and commercial partners in collaborative research projects.

## To achieve this, geneXplain offers:

•The geneXplain platform providing a large number of bioinformatic and systems biological data analysis workflows. Unique is geneXplain's Upstream Analysis for causal interpretation of expression data.

•TRANSFAC®, the most comprehensive database on eukaryotic transcription regulation. TRANSFAC® is now also available under the geneXplain platform, providing the most comprehensive collection of TF DNA-binding profiles.

•TRANSPATH®, one of the largest pathway/network databases presently available, particularly well suited for geneXplain's proprietary *Upstream Analysis*.

•HumanPSD, a rich information resource connecting pathways with targets, drugs and clinical trials.

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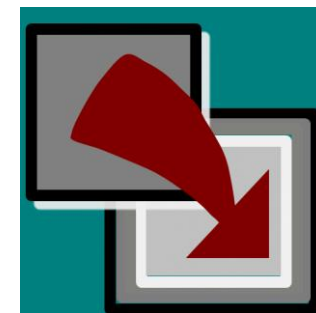
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# PharmaExpert

*The tool for estimation of safety and efficacy of new pharmaceutical agents*



geneXplain

# PharmaExpert - a tool for the estimation of safety and efficacy of new pharmaceutical agents

How to select the most promising compounds among those predicted to interact with the selected target(s) and to cause the required pharmacotherapeutic effect(s)?

PharmaExpert, as a pharmacological knowledge-based tool, provides *in silico* screening of compounds using the PASS prediction of their biological activities.

## PASS and PharmaExpert: The optimal combination

In a first step, PASS has predicted biological activities for chemical compounds based on a library containing more than 300,000 structures (known drugs and drug-like compounds).

As the next step, PharmaExpert selects those chemical compounds that exhibit the required biological activity spectra with low probability of adverse or toxic effects.

Out of the thousands of biological activities predicted by PASS, PharmaExpert identifies rational combinations of multi-targeted action and finds the suitable pharmaceutical agents among commercially available chemical compounds.

## Mechanism-effect relationships

PharmaExpert comes with a database, manually curated by experts, containing mechanism-effect relationships (MER), which is used to analyze the PASS prediction data.

In this MER base, biological activities are described as mechanisms of action and/or pharmacological effects, and their records contain lists of relationships with other types of biological activity, including references to publications.

**Selection of compounds with required therapeutic effects and without toxic effects**

Pa	Pi	Activity	Probability
0.985	0.003	Dexamethasone	0.990 0.001 Hypersglycemic
0.979	0.004	Ibuprofen	0.990 0.002 Irritant
0.854	0.005	Naproxen	0.985 0.002 Embryotoxic
0.842	0.005	Meloxicam	0.982 0.002 Teralogen
0.827	0.005	Etidolac	0.982 0.001 CYP2B2 substrate
0.783	0.008	Diclofenac	0.983 0.002 CYP2B1 substrate
0.763	0.009	Montelukast	0.982 0.002 Respiratory failure
0.747	0.010	Indometacin	0.983 0.003 Antiallergic
0.720	0.013	Celecoxib	0.980 0.001 Trans-1,2-dihydrobenzene-1,2-diol dehydrogenase inhibitor
0.709	0.014	Nitroglycerin	0.981 0.004 Hematotoxic

**Selection of compounds with multitargeted action**

No	Pa	Number	Activity type	Activity type
1	0.944	3	5 Hydroxytyptamine 2 antagonist	Alpha adrenoceptor agonist
2	0.944	3	5 Hydroxytyptamine 2 antagonist	Alpha adrenoceptor antagonist
3	0.944	3	5 Hydroxytyptamine 2 antagonist	Beta 1 adrenoceptor antagonist
4	0.944	3	5 Hydroxytyptamine 2 antagonist	Beta adrenoceptor agonist
5	0.944	3	5 Hydroxytyptamine 2 antagonist	Beta adrenoceptor antagonist
6	0.944	3	5 Hydroxytyptamine 2 antagonist	Calcium channel blocker
7	0.944	3	5 Hydroxytyptamine 2	
8	0.944	3	5 Hydroxytyptamine 2	
9	0.944	3	5 Hydroxytyptamine 2	
10	0.944	3	5 Hydroxytyptamine 2	
11	0.897	1	Alpha adrenoceptor	

## Search function

The search mask of PharmaExpert allows to find any number of desired activities with specified thresholds of the probability to be active (Pa). At the same time, it is possible to exclude unwanted activities by simply setting their Pa to equal zero.

## Multitarget selection

With PharmaExpert it is possible to identify substances with multitargeted actions. Simply choose a desired effect and a number of mechanisms that should lead to it will be displayed automatically. The software will then return a list of substances displaying more than one mechanism leading to the effect.

## Drug-drug interactions

PharmaExpert provides a comfortable interface to reveal the most important types of drug-drug interactions for pairs of pharmaceutical agents.

A dedicated option allows to classify interactions of the compounds with metabolic enzymes and protein transporters, thus facilitating the estimation of *pharmacokinetic drug-drug interactions*.

*Pharmacodynamic interactions* are estimated with respect to molecular targets and pharmacotherapeutic effects.

*Synergistic or additive effects* of two compounds are provided for *adverse and toxic effects* as well.

A slide show with screenshots can be found on our homepage ([www.genexplain.com](http://www.genexplain.com)) and also on our Facebook account ([www.facebook.com/genexplain](http://www.facebook.com/genexplain)), and recommendations from experts for the PASS software can be found on our LinkedIn profile (<http://www.linkedin.com/company/genexplain/products>).

**Drug-Drug Interactions**

**Additive or Synergistic Effects and Actions**

Effect	Probability
Antiinflammatory	0.879 0.004
Lipid metabolism regulator	0.879 0.004
Antitubercotic	0.879 0.004
Antipyretic	0.879 0.004
Antacid	0.879 0.004
Antiinflammatory	0.854 0.005
Membrane permeability inhibitor	0.734 0.030
Cyclooxygenase 3 inhibitor	0.896 0.001

**Pharmacokinetic Drug-Drug Interactions**

Metabolism	Probability
CYP2C8 substrate	0.805 0.015
CYP2B2 substrate	0.714 0.035
CYP212 substrate	0.805 0.015
UGT2B1 substrate	0.714 0.035

**Additive or Synergistic Toxic and Side Effects**

Effect	Probability
Apnea	0.722 0.011
Glaucoma	0.722 0.011
Hypercholesterolemia	0.722 0.011
Hypercholesterolemic	0.722 0.011
Subarachnoid hemorrhage	0.722 0.011
Ocular toxicity	0.900 0.004
Conjunctivitis	0.900 0.004

**Pharmacodynamic Drug-Drug Interactions**

Effect	Probability
Insulin growth factor agonist	0.881 0.041
Chlorocone reductase inhibitor	0.815 0.080
Transferase stimulant	0.881 0.041
Protein disulfide-isomerase inhibitor	0.815 0.080