PharmaExpert.Ru:Web-Services for Prediction of Biological Activity and Toxicity

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INTRODUCTION

Computer-aided prediction of biological activity, toxicity and physical-chemical properties of chemical compounds are widely used in modern drug design & discovery and environmental chemical toxicology.

METHODS

One of the first web-services in this field [1] has been developed on the basis of computer program PASS. PASS (Prediction of Activity Spectra for Substances) [2] currently predicts more than 4,000 pharmacotherapeutic effects, mechanisms of action, specific toxicities, interaction with metabolic enzymes, influence on gene expression, etc. with mean accuracy about 95%. Prediction is based on the analysis of structure-activity relationships for the training set consisted of over 250,000 drugs, drug-candidates, leads, and toxic compounds. Professional version of PASS provides the option for addition of new structures with their activities to the existing training set or creation of new training set and re-training the program, to develop a user- or problem-specific SAR knowledgebase.

Web-Service on Biological Activity Prediction with PASS

http://pharmaexpert.ru/passonline/

How does PASS predict Biological Activity Spectrum?

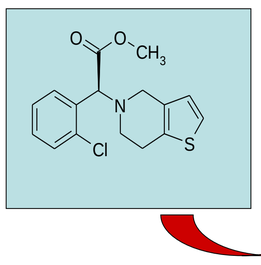
Structure of the compound

↓

Estimating the probability that it has a particular biological activity

↓

Predicted biological activity spectrum for Clopidogrel

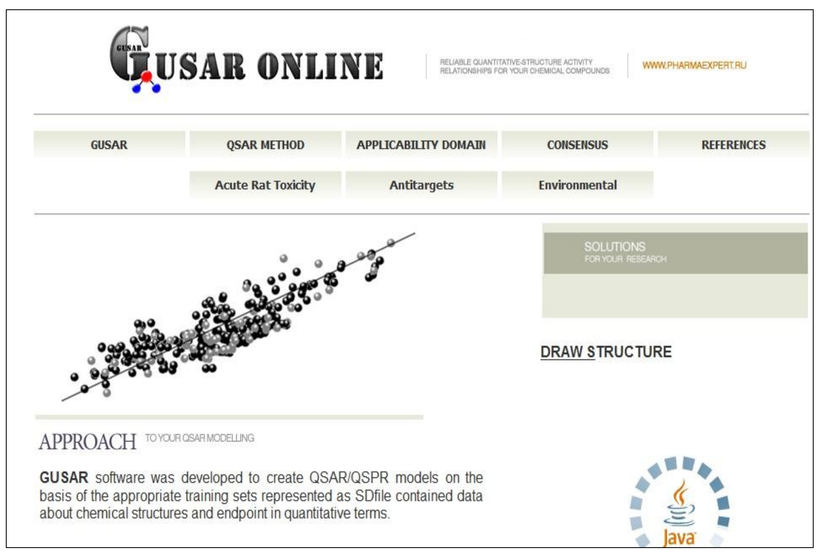


Antithrombotic
Angiogenesis inhibitor
Analgesic
…

Pa	Pi	Predicted activities	Known activities
0.947	0.005	Neuroprotector	+
0.801	0.007	Antithrombotic	+
0.697	0.005	Platelet aggregation inhibitor	+
0.679	0.013	Atherosclerosis treatment	
0.597	0.010	Angiogenesis inhibitor	+
		…	

Recently we developed a new web-service based on the GUSAR (General Unrestricted Structure-Activity Relationships) approach [3].

GUSAR-Based Web-Service



http://pharmaexpert.ru/gusar/

In contrast to PASS, which predicts activity in qualitative mode (active/inactive), GUSAR examines the Quantitative Structure-Activity Relationships for the appropriate training sets, and creates QSAR models for prediction of quantitative values (IC_{50}, Ki, LD_{50}, etc.). GUSAR web-service predicts rats' acute toxicity [4] and a few environmental chemical toxicity endpoints (96-hour 50% lethal concentration for Fathead Minnow, 48-hour 50% lethal concentration for Daphnia Magna, 50% growth inhibition concentration for Tetrahymena Pyriformis, Bioaccumulation Factor).

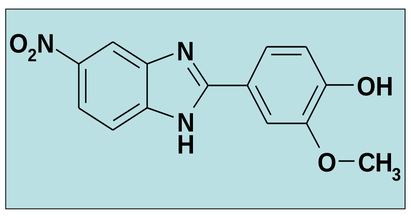
RESULTS

Currently PASS web-service is exploited by ~8,700 registered users from more than 70 countries. The number of organic compounds, for which predictions have been obtained, exceeded 250,000. There are over 40 publications, where the users of our web-service presented the results on experimental verification of computational predictions for compounds from different chemical classes with different kind of biological activities. In the vast majority of cases the results of prediction coincided with the experiment.

Example:

Navarrete-Vazquez G., Hidalgo-Figueroa S., Torres-Piedra M., et al. (2010). Synthesis, vasorelaxant activity and antihypertensive effect of benzo[d]imidazole derivatives. *Bioorganic & Medicinal Chemistry*, **18** (11): 3985–3991.

Fifteen benzo[d]imidazole derivatives have been designed, synthesized and tested as vasorelaxant agents in order to obtain potential antihypertensive compounds. Vasodilatory and phosphodiesterase inhibiting actions for the designed compounds have been predicted by PASS. Vasodilatory activity of the synthesized compounds has been confirmed by the experiment (ex vivo relaxant response in intact aortic rings); the most potent effect has been observed for all the nitro derivatives. 2-Methoxy-4-[5-nitro-1H-benzo[d]imidazol-2-yl]phenol (compound 13) was the most potent derivative of the series.

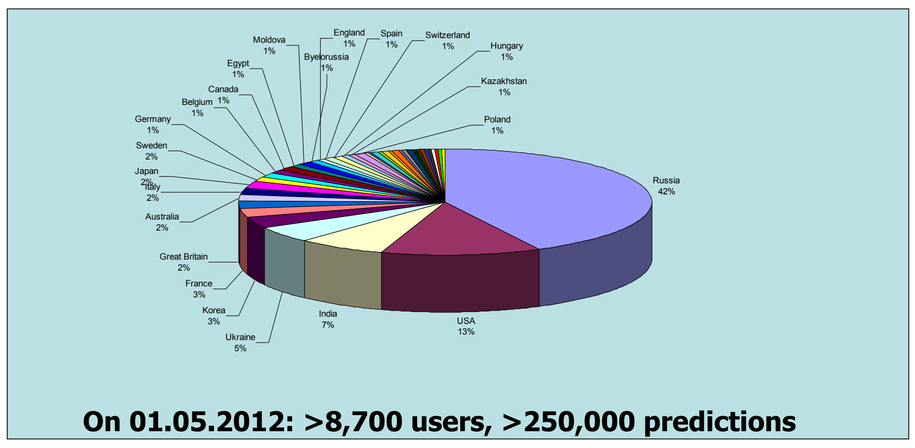


Compound 13: EC50=1.81 mkM
Emax=91.7%

PASS prediction results:

Pa	Pi	Activity
0.788	0.059	Vasodilator
0.631	0.006	Phosphodiesterase inhibitor

PASS Web-Service Users/Compounds Statistics



Reasonable results obtained by GUSAR modelling for different biological endpoints [3] suggest the possibility of using this method to the modelling of acute rodent toxicity. It was found that our consensus approach has some benefits against single QSAR predictive models for acute rat toxicity (LD_{50} values in mmol/kg). Comparison of the proposed approach with the results of T.E.S.T. 3.0 program (Toxicity Estimation Software Tool) (5828 compounds in the training set and 1458 compounds in the test set were used):

	R^2_{test}	$RMSE_{test}$	Coverage
GUSAR	**0.639**	**0.581**	**0.952**
Hierarchical QSAR*	0.573	0.654	0.847
Nearest neighbour*	0.546	0.662	0.995
FDA approach*	0.555	0.658	0.987
Consensus (Hierarchical QSAR, Nearest neighbor, FDA)*	0.620	0.596	1.000

* Given from User's Guide for T.E.S.T. (Toxicity Estimation Software Tool), a program to estimate toxicity from molecular structure, Version 3.0, U.S. Environmental Protection Agency, 2008.

A few reasons to use PASS&GUSAR commercial package instead of Online SERVICE:

	Online version	PASS	PASS Pro	GUSAR
Input – SD files	-	+	+	+
Security	-	+	+	+
Much more options	-	+	+	+
Selection of compounds by activities	-	+	+	+
The latest version of program	-	+	+	+
Use of own training set	-	+	+	+
Use of PharmaExpert for analysis of prediction results	-	+	+	+
Solution of technical problems, consultation	-	+	+	+

CONCLUSIONS

√ Computer-aided approaches are useful for finding of hits and their optimization to lead compounds.

√ PASS predictions allow to identify the most relevant biological screens for testing of particular chemical compounds.

√ GUSAR can be used as an universal tool for solving various QSAR/QSPR problems.

√ Predictive web-services are freely available from http://pharmaexpert.ru

ACKNOWLEDGEMENT

The study was partly supported by RFBR grant No. 12-07-00597.

REFERENCES

[1] Lagunin, A.; Stepanchikova, A.; Filimonov, D.; Poroikov, V *Bioinformatics*, *16*, **2000**, 647-648.

[2] Filimonov, D.; Poroikov, V. *In: Chemoinformatics Approaches to Virtual Screening*. Cambridge (UK): RSC Publishing, **2008**, 182-216.

[3] Filimonov, D.; Zakharov, A.; Lagunin, A.; Poroikov, V. *SAR and QSAR Environ. Res.*, *20*, **2009**, 679-709.

[4] Lagunin, A.; Zakharov, A.; Filimonov, D.; Poroikov, V. *Molecular Informatics*, *30*, **2011**, 241–250.

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