SAR and QSAR in Environmental Research,
Vol. 18, Nos. 1–2, January–March 2007, 101–110

Taylor & Francis
Taylor & Francis Group

PASS: identification of probable targets and mechanisms of toxicity†

V. POROIKOV*, D. FILIMONOV, A. LAGUNIN, T. GLORIOZOVA and A. ZAKHAROV

Institute of Biomedical Chemistry of Russian Academy of Medical Sciences, Pogodinskaya Street 10, Moscow, 119121, Russia

(*Received 11 May 2006; in final form 16 August 2006*)

Toxicity of chemical compound is a complex phenomenon that may be caused by its interaction with different targets in the organism. Two distinct types of toxicity can be broadly specified: the first one is caused by the strong compound's interaction with a single target (e.g. AChE inhibition); while the second one is caused by the moderate compound's interaction with many various targets. Computer program PASS predicts about 2500 kinds of biological activities based on the structural formula of chemical compounds. Prediction is based on the robust analysis of structure-activity relationships for about 60,000 biologically active compounds. Mean accuracy exceeds 90% in leave-one-out cross-validation. In addition to some kinds of adverse effects and specific toxicity (e.g. carcinogenicity, mutagenicity, etc.), PASS predicts ~2000 kinds of biological activities at the molecular level, that providing an estimated profile of compound's action in biological space. Such profiles can be used to recognize the most probable targets, interaction with which might be a reason of compound's toxicity. Applications of PASS predictions for analysis of probable targets and mechanisms of toxicity are discussed.

Keywords: PASS; Biological activity spectra; Specific toxicity; Targets and mechanisms of toxicity; Acetylcholinesterase (AChE) inhibitor; Carcinogenicity; Computer-aided prediction

1. Introduction

Toxicity of chemical compound is a complex phenomenon that may be caused by its interaction with different targets in the organism.

Sometimes, it is possible to identify a single target, interaction with which may be a cause for the compound's toxicity. For example, well-known chemical weapon sarin (*O*-isopropylmethylphosphonofluoridate) is an extremely potent acetylcholinesterase (AChE) inhibitor with high specificity and affinity for the enzyme [1]. Sarin is a highly toxic nerve agent that causes human death due to anoxia resulting from airway

*Corresponding author. Email: vladimir.poroikov@ibmc.msk.ru
†Presented at the 12th International Workshop on Quantitative Structure-Activity Relationships in Environmental Toxicology (QSAR2006), 8–12 May 2006, Lyon, France.

SAR and QSAR in Environmental Research
ISSN 1062-936X print/ISSN 1029-046X online
DOI: 10.1080/10629360601054032

obstruction, weakness of the muscles of respiration, convulsions and respiratory failure. A second example came from pharmacology and is present by matrix metalloproteinase inhibitors that act as strong zinc binding agents and, due to the lack of selectivity, exhibit unacceptable toxicities shown in clinical trials [2]. A third example (also from pharmacology) is a toxicity of barbituric acid derivatives that in moderate amounts mimics the alcohol intoxication inhibiting the alcoholdehydrogenase in the organism [3].

There exist, of course, a lot of additional examples when inhibition/blockage of a *d'une importance vitale* biomacromolecular target leads to toxicity that may cause severe injuries and even death of a human being [4]. However, in many cases compound's toxicity is not caused by a strong interaction with a single biological macromolecule; instead of that compound demonstrates a moderate interaction with many different targets. As a result, more complex toxicity phenomena are observed, when no one unique mechanism of toxicity can be identified.

To describe a toxicity when a single molecular target is unknown, more general terms are widely used. Such terms describe either particular effects of compounds' action, e.g. arrhythmogenicity, ulcerogenicity, carcinogenicity, etc.; and/or specific organ/issue where a toxic effect is exhibited, e.g. cardiotoxicity, hepatotoxicity, nephrotoxicity, etc.

It is necessary to establish priorities of chemical compounds testing as well as "filtering out" the leads with high probability of adverse/toxic effects at the early stages of research and development. To achieve these purposes, computer methods are widely used [5–8]. One of such methods entitled PASS (Prediction of Activity Spectra for Substances) is developed for structure-activity relationships (SAR) analysis in diverse sets of chemical compounds with many different types of biological activities [9]. Here we present the possibilities of PASS application for computer-aided prediction of targets and mechanisms of toxicity.

2. Methods

2.1 *General description of PASS*

Contrary to many other existing methods of SAR/QSAR/QSPR analysis focused on the prediction of a single type of biological activity within the same chemical series, PASS predicts the whole biological activity spectra of a molecule under study. The biological activity spectrum of the compound reflects all kinds of its biological activities, which can be found in the compound's interaction with biological entities [9].

PASS approach is based on the analysis of structure-activity relationships for the training set currently including about 60,000 drugs, drug-candidates, leads and toxic compounds whose biological activity is determined experimentally [10]. These SAR are obtained during the training procedure and are stored in the knowledge base called SAR Base. New biologically active compounds and new types of biological activity can be added to the PASS training set upon appearance in literature. Re-training of the program gives an updated SAR Base with the improved quality of prediction.

Used in PASS chemical descriptors are the so-called Multilevel Neighbourhoods of Atoms (MNA) published elsewhere [11]. The set of MNA descriptors is generated on the basis of structural formula (formulas) presented in MOL-file (SDF-file) form [12], which are used as PASS input. Since MNA descriptors are generated for each

compound *de novo*, new descriptors can be obtained upon presentation of a novel structural feature in the compound under study.

A detailed description of the mathematical algorithm used in the current version of PASS was published earlier [9, 10] and is also available on the web site [13].

The user obtains the results of prediction as a list of activity types, with the probabilities of presence (Pa) and absence (Pi) for each particular activity. By definition the probabilities Pa and Pi can be also interpreted as the measures of belonging to fuzzy subsets of ''active'' and ''inactive'' compounds, or as the probabilities of the 1st and 2nd kinds of errors of prediction. Both interpretations of probabilities Pa and Pi are equivalent and can be used for interpreting the results of prediction. Interpretation of the prediction results and criteria of activity/inactivity is rather flexible, and depends on the purpose of a particular investigation. By default, $Pa > Pi$ value is used as a threshold that provides the mean accuracy of prediction about 90% in leave-one-out cross-validation for all approximately 60,000 compounds and 2500 activities from the PASS training set.

PASS (version 2005) predicts 369 pharmacotherapeutic effects, 2055 biochemical mechanisms of action, 39 adverse effects and toxicities, 66 metabolic terms. Complete list of biological activities predicted by PASS is available at the web-site [13].

It is important to mention that, to estimate how robust is PASS approach, special experiments were performed with MDDR database [14]. It was shown that despite the incompleteness of the training set SAR analysis provided by PASS, it has a reasonable accuracy [14]. Thus, PASS can be applied for predicting of biological activity spectra for new compounds.

PASS is successfully applied in the pharmacological field, where a dozen of predictions were afterwards confirmed by the experiment. For example, new angiogenesis inhibitors [15], cognition enhancers [16], anxiolytics [17, 18], antileishmanial agents [19, 20] were discovered on the basis of PASS predictions. These provide additional evidences that PASS could be also used for prediction of adverse and toxic effects in chemical compounds under study.

3. Results and discussion

3.1 *Prediction of specific toxicity with PASS*

The list of adverse and toxic effects predicted by PASS with the results of leave-one-out cross-validation are given in table 1. The number of compounds per one adverse and toxic effects varies from 8 (Bradycardic) to 1531 (Teratogen), with an average of ~285. Independent Error of Prediction (IEP) varies from 4.6% (Bradycardic) to 30.9% (Hematotoxic), with average IEP $\approx$ 13.8%.

It is necessary to emphasize that PASS training set was created initially with a goal to find new compounds with useful pharmacotherapeutic action; therefore information about adverse and toxic effects may be incomplete for some types of activity. However, as was mentioned above, due to the robustness of PASS approach [14] one may rely on the positive results of prediction (if any type of activity is predicted with reasonable probability it has a good chance to be confirmed by the experiment). Moreover, since PASS is open for addition of new compounds and new types of activity to the training

Table 1. List of adverse and toxic effects predicted by PASS version 2005.

N	*IEP (%)*	*Types of activity*
49	28.944	Arrhythmogenic
8	4.451	Bradycardic
1211	10.598	Carcinogenic
284	13.845	Carcinogenic, female mice
321	14.109	Carcinogenic, female rats
16	22.087	Carcinogenic, group 1
30	13.401	Carcinogenic, group 2A
184	7.973	Carcinogenic, group 2B
383	11.069	Carcinogenic, group 3
254	12.238	Carcinogenic, male mice
360	15.608	Carcinogenic, male rats
73	26.404	Cardiotoxic
137	25.329	Convulsant
234	6.875	Cytotoxic
741	14.940	Embryotoxic
451	8.160	Eye irritation, high
229	10.246	Eye irritation, moderate
44	8.405	Hallucinogen
25	30.948	Hematotoxic
10	21.367	Hypercalcaemic
232	12.687	Hypertensive
17	13.711	Hyperthermic
392	9.546	Hypnotic
24	15.145	Hypocalcaemic
804	6.530	Mutagenic
616	6.275	Mutagenic, Salmonella
102	9.860	Narcotic
22	18.566	Nephrotoxic
87	17.124	QT interval prolongation
295	6.084	Skin irritation, high
269	7.538	Skin irritation, moderate
19	9.124	Skin irritative effect
234	11.553	Spasmogenic
1531	17.631	Teratogen
37	24.219	Torsades de pointes
1239	17.985	Toxic
15	7.919	Toxic, respiratory center
27	10.314	Ulcerogenic
95	8.131	Vasopressor

N, the number of compounds in the training set; IEP, Independent Error of Prediction obtained in LOO CV.

set, the quality of prediction can be increased through the updating and re-training the vs program.

PASS abilities to predict carcinogenicity of chemical compounds was studied in details [21]. The data on structures and experimental results of two-year carcinogenicity assays for 412 chemicals from NTP (National Toxicological Program) and 1190 chemicals from CPDB (Carcinogenic Potency Database) were used for training and validation of the program. Quality of predictions, when information about species and sex of animals is taken into consideration, was also analyzed. Two procedures were used for evaluation of the accuracy of prediction: leave-one-out cross-validation (LOO CV) and leave 20% out cross-validation. In the last case we divided the studied set 20 times at random into two subsets. The data from the first subset containing 80% compounds

were added to the PASS training set, the second subset with 20% compounds was used as an evaluation set. The mean accuracy of prediction calculated by LOO CV is about 73% for NTP compounds in the equivocal category of carcinogenic activity and 80% for NTP compounds in the evidence category of carcinogenicity. The mean accuracy of prediction for the CPDB database is 89.9% calculated by LOO CV and 63.4% calculated by leave 20% out cross-validation. Influence of incorporation of species and sex data on the accuracy of carcinogenicity prediction was also investigated.

It was shown that the PASS algorithm can be successfully applied for prediction of carcinogenicity. Analysis of prediction results of rodent carcinogenicity showed that use of data on carcinogenicity together with data for drug-like compounds from the PASS training set, which are represented as possible non-carcinogens, increases accuracy of carcinogenicity prediction. Changing of ''Pa–Pi'' threshold leads to variation of sensitivity and specificity of carcinogenicity prediction that can be used to increase the number of correctly predicted carcinogens/non-carcinogens. The mean prediction accuracy calculated by LOO CV was 78.9% for ''equivocal'' and 86.7% for ''evident'' carcinogens. It was also shown that using more specific NTP data on species and sex did not increase the accuracy of carcinogenicity prediction. It is necessary to emphasize that such accuracy was achieved without expert evaluation of the prediction results and was comparable with the best currently available methods of carcinogenicity prediction [22, 23]. Example of carcinogenicity prediction for 4,6-dimethyl-2-(5-nitro-furan-2-Yl)-pyrimidine is given in figure 1. Predicted carcinogenicity in female rats coincide with the experimental data [24].

Based on this analysis of carcinogenicity prediction, one may extrapolate the abilities of PASS to predict any other adverse effect or specific toxicity. An expected quality of such predictions, which can be done by PASS version 2005, was estimated by LOO CV. These results are presented in table 1.

3.2 *Prediction of targets and mechanisms of toxicity*

From a mechanistic point of view, mechanisms of chemical compounds toxicity might be associated either with a strong action on a single target or with a moderate action on many different macromolecules in the organism. Since PASS predicts with reasonable accuracy more than 2000 types of activities at the molecular level it can be used for identification of potential targets that might cause the toxicity of compounds.

3.2.1 Predicted biological activity spectrum of sarin. Let us consider the results of biological activity spectrum predicted for sarin, well-known inhibitor of AChE (figure 2). From the data presented in figure 2, it is clear that 111 of 2413 possible activities are predicted for sarin with Pa > 40%. Acetylcholinesterase inhibitory activity has Pa = 0.477 and Pi = 0.007, which does not provide the top positions for this activity in the predicted activity list. Such result is not surprising because Pa value is an estimate of probability that the compound belongs to a particular class of ''active agents'', but Pa is not proportional to the appropriate potency. Since in the PASS training set AChE inhibitory activity is presented by 293 compounds, mostly used as pharmacological agents, Pa value 0.477 obtained for sarin means that this molecule does not resemble very close the most typical AChE inhibitors.

There are many other probable macromolecular targets in the predicted activity spectrum of sarin, including aryldialkylphosphatase inhibitor (Pa = 99.5%), cutinase

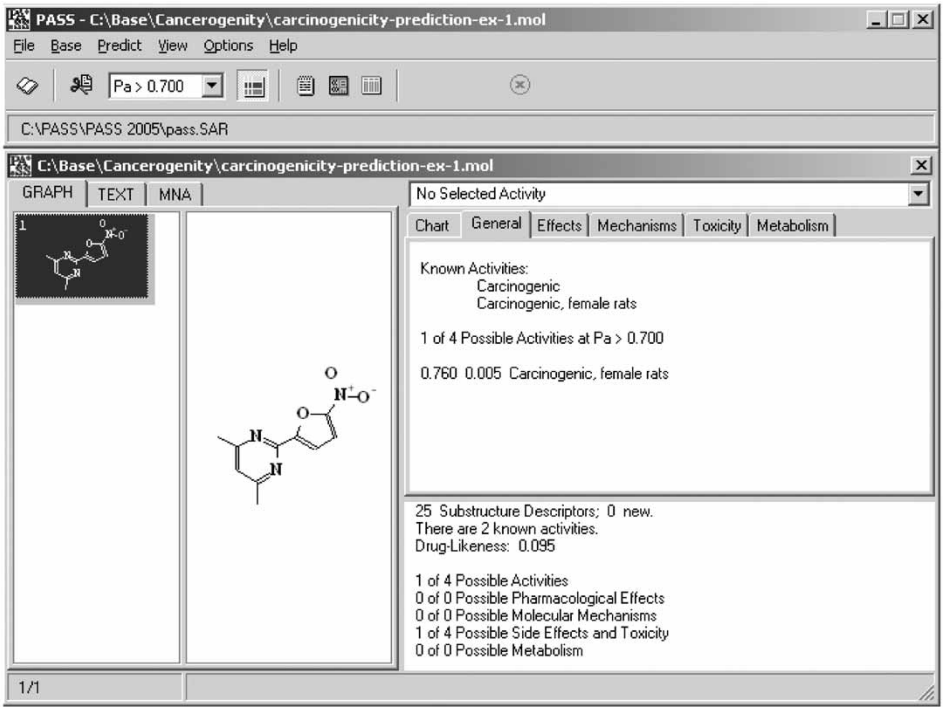


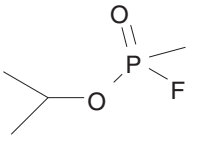
Figure 1. PASS interface and carcinogenicity prediction for 4,6-dimethyl-2-(5-nitro-furan-2-yl)-pyrimidine.

inhibitor (Pa = 99.3%), cathepsin G inhibitor (Pa = 98.6%), creatinase inhibitor (Pa = 98.4%), *n*-carbamoyl-L-amino-acid hydrolase inhibitor (Pa = 98.3%), phospholipase A2 inhibitor (Pa = 98.2%), etc. Despite many experimental studies of sarin biological action [1], due to its high toxicity, sarin was probably never tested *in vitro* against all these targets.

Based on this example one may speculate that AChE might be not the only target of sarin in the organism as widely accepted [1], but sarin's action on other target was never studied because of acute effects caused by its AChE inhibitory activity. More general conclusion is that, on the basis of PASS predictions, it is not always easy to identify a single target that is currently considered as the most important because this target can be overlapped by many others that were never tested. However, even in such case PASS predictions significantly reduces the ''biological space'' providing the list of hints that might be considered as the most probable molecular targets. In the case of sarin only 108 molecular mechanisms (targets) from 2055 that can be predicted by PASS version 2005, that reduces the biological space for more than 20 times.

It is interesting to mention that there is also carcinogenic effect predicted for sarin with Pa = 0.987, however to exhibit such effect, the species should survive after the exposition to sarin, but this is not the case.

3.2.2 Biological activity spectrum predicted for barbituric acid. Barbiturates were very popular in the first half of the 20th century as sedative/hypnotic agents.

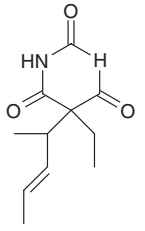


111 of 2497 Possible Activities at Pa > 0.400

Pa	Pi	for Activity:
0.995	0.000	Aryldialkylphosphatase inhibitor
0.993	0.000	Cutinase inhibitor
0.987	0.001	Carcinogenic
0.986	0.001	Cathepsin G inhibitor
0.984	0.000	Creatinase inhibitor
0.983	0.001	N-carbamoyl-L-amino-acid hydrolase inhibitor
0.982	0.002	Phospholipase A2 inhibitor
0.980	0.002	Phospholipase inhibitor
0.979	0.003	Pyroglutamyl-peptidase I inhibitor
0.978	0.001	Poly(3-hydroxybutyrate) depolymerase inhibitor
		. . .
0.477	**0.007**	**Acetylcholinesterase inhibitor**
0.464	0.010	Insecticide
0.498	0.060	Rhamnulose-1-phosphate aldolase inhibitor
0.443	0.008	Hypocalcaemic
0.457	0.036	Inositol-1(or 4)-monophosphatase inhibitor
0.567	0.155	(-)-(4S)-limonene synthase inhibitor
0.418	0.009	Tubulin GTPase inhibitor
0.471	0.071	H+-transporting two-sector ATPase inhibitor
0.459	0.062	Undecaprenyl-phosphate mannosyltransferase inhibitor
0.511	0.117	N-acetyllactosamine synthase inhibitor
0.441	0.066	Sphinganine-1-phosphate aldolase inhibitor
0.439	0.069	Transketolase inhibitor
0.442	0.074	ATP adenylyltransferase inhibitor
0.402	0.052	2-Dehydropantoate aldolase inhibitor
0.425	0.087	Aspartyl aminopeptidase inhibitor
0.415	0.084	Ethanolamine-phosphate cytidylyltransferase inhibitor
0.417	0.106	Sulfate adenylyltransferase (ADP) inhibitor
0.409	0.163	Mannotetraose 2-alpha-N-acetylglucosaminyltransferase inhibitor

Figure 2. Structural formula and biological activity spectrum predicted for sarin (known activity is given in bold).

Amobarbital, butabarbital, butalbital, hexobarbital, methyl phenobarbital, pentobarbital, phenobarbital are just a few examples of launched drugs. However, less than 10% of all sedative/hypnotic prescriptions in the United States are for barbiturates today; barbiturates are also used as anticonvulsants and for the induction of anesthesia. Decrease of popularity of these drugs is due to the toxicity and addiction potential of barbiturates. It is known that in moderate amounts these drugs produce a state of intoxication that is remarkably similar to alcohol intoxication [3].



10 of 2497 Possible Activities at Pa > 0.700

Pa	Pi	for Activity:
0.933	0.003	(R)-Pantolactone dehydrogenase (flavin) inhibitor
0.912	0.004	Sedative
0.853	0.003	Hypnotic
0.835	0.013	Convulsant
0.823	0.003	Narcotic
0.799	0.008	Antiepileptic
0.737	0.013	Oxidoreductase inhibitor
0.719	**0.007**	**Alcohol dehydrogenase (NADP+) inhibitor**
0.704	0.005	1,5-Anhydro-D-fructose reductase inhibitor
0.700	0.015	Carbonyl reductase (NADPH) inhibitor

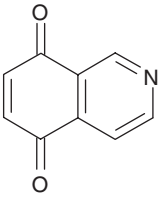
Figure 3. Structural formula and biological activity spectrum predicted for barbituric acid (known activity is given in bold).

It was interesting to analyze if we can identify the mechanisms of alcohol-like toxicity in biological activity spectra predicted for barbiturates. Predicted biological activity spectrum for barbituric acid is shown in figure 3. It is remarkable to note that in the biological activity spectrum of barbituric acid, in addition to well-known pharmacotherapeutic effects (sedative, hypnotic, anticonvulsant, etc.), alcohol dehydrogenase inhibitory activity is predicted with probability Pa = 71.9% (eight position in the predicted biological activity list), that provides the "proof-of-the-concept".

3.2.3 Biological activity spectrum predicted for 5,8-isoquinolinedione. This is rather toxic compound with a $LD_{50} = 25\,mg\,Kg^{-1}$ (mice, i.p.). It was interesting to see if there is any particular target, interaction with which might be a cause of 5,8-isoquinolinedione toxicity. With this purpose we predicted biological activity spectrum of 5,8-isoquinolinedione (figure 4). It appears that in the top part of predicted biological activity spectrum (17 types of activity are predicted with Pa > 70%), there is no single target action on which might cause such high toxicity. Instead of that, we have a probable action on many molecular targets, including NAD(P)+-arginine ADP-ribosyltransferase inhibitor (Pa = 89.1%), phosphatase inhibitor (Pa = 86.4%), kinase inhibitor (Pa = 80.7%), trans-cinnamate 4-monooxygenase inhibitor (Pa = 75.4%), ecdysone 20-monooxygenase inhibitor (Pa = 74.7%), interleukin 1 antagonist (Pa = 73.8%), etc. So, it seems that in case of 5,8-isoquinolinedione mechanism of toxicity is rather complex and associated with action on many different targets.

4. Conclusions

(1) Based on PASS predictions, specific adverse effects and/or toxicity of chemical compounds can be identified.



17 of 2497 Possible Activities at Pa > 0.700

Pa	Pi	for Activity:
0.891	**0.005**	**NAD(P)+-arginine ADP-ribosyltransferase inhibitor**
0.864	**0.018**	**Phosphatase inhibitor**
0.807	**0.006**	**Kinase inhibitor**
0.825	0.057	Antiseborrheic
0.761	**0.011**	**Trans-cinnamate 4-monooxygenase inhibitor**
0.754	**0.013**	**Mg-protoporphyrin IX monomethyl ester (oxidative) cyclase inhibitor**
0.747	**0.014**	**Ecdysone 20-monooxygenase inhibitor**
0.738	**0.007**	**Interleukin 1 antagonist**
0.728	**0.008**	**Secologanin synthase inhibitor**
0.718	**0.009**	**Nitrite reductase [NAD(P)H] inhibitor**
0.703	**0.002**	**Isoquinoline 1-oxidoreductase inhibitor**
0.727	**0.030**	**Quinoprotein glucose dehydrogenase inhibitor**
0.705	**0.010**	**2,5-Dihydroxypyridine 5,6-dioxygenase inhibitor**
0.731	0.036	Cardiovascular analeptic
0.705	**0.012**	**CYP2A3 substrate**
0.703	**0.016**	**Indole-3-acetaldehyde oxidase inhibitor**
0.708	**0.057**	**Arylalkyl acylamidase inhibitor**

Figure 4. Structural formula and biological activity spectrum predicted for 5,8-isoquinolinedione (known activity is given in bold).

(2) Biological activity spectra predicted by PASS significantly reduce the biological space due to the prioritization of the most probable targets, interaction with which may cause a toxicity.
(3) Currently, PASS approach cannot be applied for prediction of biological activity of inorganic compounds, coordinative compounds, multicomponent compounds or mixtures and polymers.

Acknowledgements

We are grateful for the support of this work by the Russian Ministry of Education and Science (grant # 02.434.11.1014), Russian Foundation in Basic Research (grant # 05-07-90123) and ISTC/BTEP (grant # 3197/111).

References

[1] A.W. Abu-Qare, M.B. Abou-Donia. *Food Chem. Toxicol.*, **40**, 1327 (2002).
[2] L.H. Foley, R. Palermo, P. Dunten, P. Wang. *Bioorg. Med. Chem. Lett.*, **11**, 969 (2001).
[3] http://www.wikipedia.org
[4] http://toxnet.nlm.mih.gov
[5] J.C. Dearden. *J. Comput. Aided Mol. Des.*, **17**, 119 (2003).

[6] T.W. Schultz, T.I. Netzeva, M.T. Cronin. *SAR QSAR Environ. Res*., **15**, 399 (2004).
[7] G. Klopman, A. Sedykh. In *Predictive Toxicology*, C. Helma (Ed.), pp. 415–422, Taylor & Francis, London (2005).
[8] R. Benigni. *Chem. Rev*., **105**, 1767 (2005).
[9] V. Poroikov, D. Filimonov. In *Predictive Toxicology*, C. Helma (Ed.), pp. 459–478, Taylor & Francis, London (2005).
[10] D. Filimonov, V. Poroikov. *Rus. Chem. J*., **50**, 66 (2006).
[11] D. Filimonov, V. Poroikov, Yu. Borodina, T. Gloriozova. *J. Chem. Inf. Comput. Sci*., **39**, 666 (1999).
[12] http://www.mdl.com
[13] http://www.ibmc.msk.ru/PASS
[14] V. Poroikov, D. Filimonov, Yu. Borodina, A. Lagunin, A. Kos. *J. Chem. Inf. Comput. Sci*., **40**, 1349 (2000).
[15] V. Poroikov, D. Filimonov, W.-D. Ihlenfeldt, T. Gloriozova, A. Lagunin, Yu. Borodina, A. Stepanchikova, M. Nicklaus. *J. Chem. Inf. Comput. Sci*., **43**, 228 (2003).
[16] A. Geronikaki, J. Dearden, D. Filimonov, I. Galaeva, T. Garibova, T. Gloriozova, V. Krajneva, A. Lagunin, F. Macaev, G. Molodavkin, V. Poroikov, S. Pogrebnoi, F. Shepeli, T. Voronina, M. Tsitlakidou, L. Vlad. *J. Med. Chem*., **47**, 2870 (2004).
[17] A. Geronikaki, E. Babaev, J. Dearden, D. Filimonov, I. Galaeva, V. Krajneva, A. Lagunin, F. Macaev, G. Molodavkin, V. Poroikov, V. Saloutin, A. Stepanchikova, T. Voronina. *Bioorg. Med. Chem*., **12**, 6559 (2004).
[18] R.K. Goel, V. Kumarb, M.P. Mahajan. *Bioorg. Med. Chem. Lett*., **15**, 2145 (2005).
[19] C. Di Giorgio, F. Delmas, N. Filloux, M. Robin, L. Seferian, N. Azas, M. Gasquet, M. Costa, P. Timon-David, J.-P. Galy. *Antimicrob. Agents Chemo*., **47**, 174 (2003).
[20] M. Meyer, J.C. Dore, A. Valentin, L. Acerbey, J. Devillers. Abstracts of 12th International Workshop on Quantitative Structure-Activity Relationships in Environmental Toxicology, Lyon, France, 8–12 May, p. 131 (2006).
[21] A. Lagunin, J. Dearden, D. Filimonov, V. Poroikov. *Mutat. Res*., **586**, 138 (2005).
[22] A.M. Richard, R. Benigni. *SAR QSAR Environ. Res*., **13**, 1 (2002).
[23] R. Benigni, R. Zito. *Mutat. Res*., **566**, 49 (2004).
[24] http://potency.berkeley.edu/cpdb.html