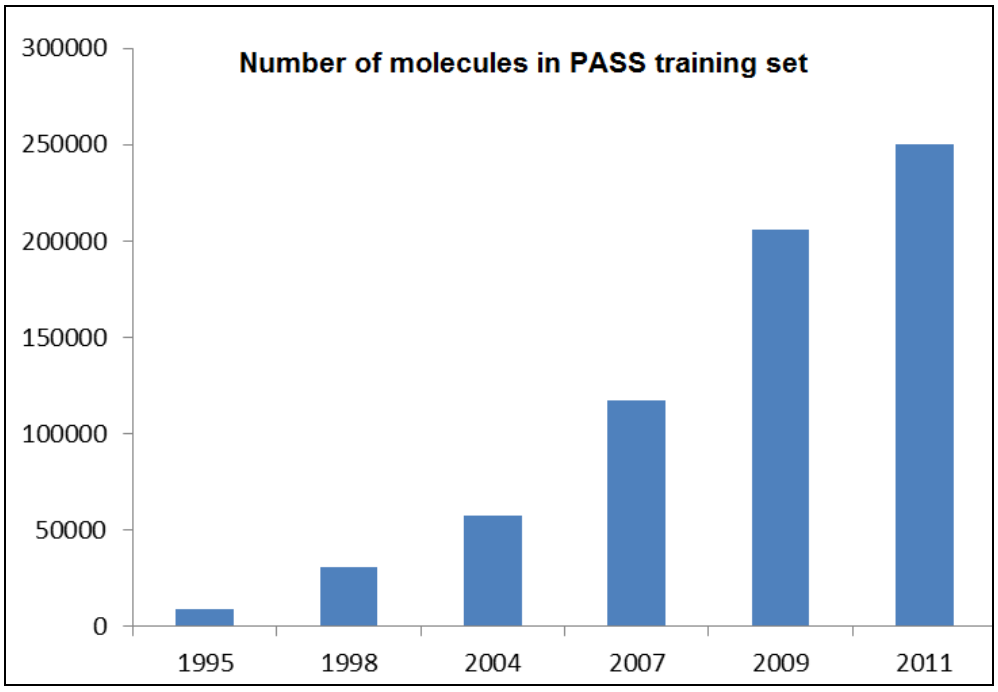
PASS: Prediction of Activity Spectra for Substances

Brief history of PASS. PASS (PASS Program Package, 2011) is the product of ideas which were originated about 40 years ago in the framework of National Registration System of New Chemical Compounds synthesized in the USSR (see for review: Burov et al., 1990). We started to work on this project in 1989 taking into account the experience of our precursors (Avidon, 1974; Avidon et al., 1978a, 1978b, 1983; Golender and Rosenblit, 1978, 1984).

During the past years we investigated thousands of chemical descriptors and hundreds of mathematical methods, to develop a uniform approach that could create accurate and robust SAR models by analysis of a training set consisting of thousands of organic molecules from different chemical series exhibiting plenty of biological activities. The PASS team is permanently collecting and evaluating the information about new pharmaceutical substances and lead compounds, to update the PASS training set and extend PASS predictive abilities on new chemical classes and novel biological activities.

Due to these efforts, the current version of PASS (11.4.12) predicts 4,366 kinds of biological activity with an average prediction accuracy of about 95%. PASS could predict 3,750 activities in 2009, 3,300 activities in 2007, 2,500 activities in 2005, 541 activities in 1998, and only 114 activities in 1996. PASS 11.4.12 training set included 250,407 known biologically active substances (drugs, drug-candidates, pharmaceutical leads, and toxic compounds); while in 1996 it included only about 9,500 biologically active substances (Figure 1).

List of activities predicted by PASS. In PASS 11.4.12 the default list of predictable biological activities includes: 497 terms related to main and side pharmacotherapeutic effects (e.g., *antihypertensive, hepatoprotective, sedative, etc.*); 3,378 terms related to biochemical mechanisms of action (e.g., *5-hydroxytryptamine agonist, acetylcholinesterase inhibitor, adenosine uptake inhibitor, etc.*); 274 terms related to specific toxicities (e.g., *carcinogenic, hallucinogenic, hepatotoxic, etc.*), 116 terms related to antitargets (e.g., *ATPase inhibitor, CYP3A4 inhibitor, HERG channel blocker, etc.*), 206 terms related to drug metabolism (e.g., *CYP1A substrate, CYP1A1 human substrate, CYP3A4 substrate, etc.),* 31 terms related to gene expression (e.g., *APOA1 expression enhancer, ErbB-2 expression inhibitor, etc.*), 49 terms related to drug transport (e.g., *P-glycoprotein substrate, P-glycoprotein inhibitor, P-glycoprotein inductor, etc.*).



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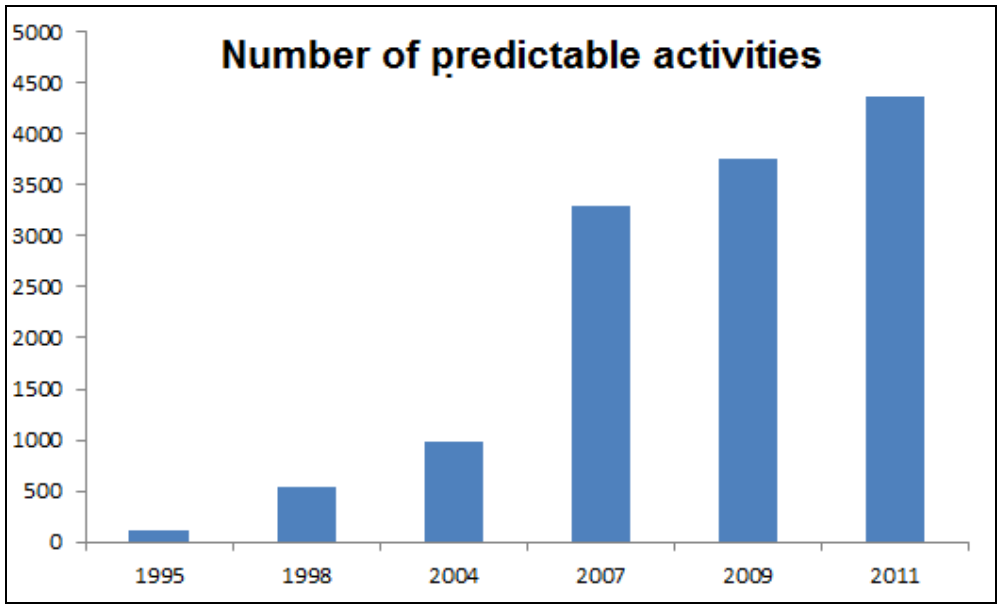


B

Figure 1. Growth of the numbers of compounds in the PASS training set (A), and predictable activities (B).

Presentation of biological activities in PASS. Biological activities in PASS are described qualitatively ("yes'/"no", "active"/"inactive"). The qualitative presentation allows integrating information concerning biologically active compounds collected from many different sources into the general PASS training set. Any property of chemical compounds, which is determined by their structural peculiarities, can be used for prediction by PASS. It was shown that the applicability of PASS is broader than the prediction of biological activities. For instance, this approach was successfully used for the prediction of a general property of organic molecules such as drug-likeness (Anzali et al., 2001).

Chemical structure description in PASS. The 2D structural formulae of compounds were chosen as the basis for the description of chemical structures, because this is the only information available at the early stages of research. Thus, using the structural formula as input data, one can obtain the estimates of biological activity profiles even for virtual molecules, prior to their chemical synthesis and biological testing.

Many different characteristics of chemical compounds can be calculated on the basis of structural formulae. In the earliest versions of PASS (Poroikov et al., 1993; Filimonov et al., 1995; Filimonov and Poroikov, 1996) we used the Substructure Superposition Fragment Notation (SSFN) codes (Avidon et al., 1982). However, SSFN, like many other structural descriptors, reflects rather an abstraction of chemical structure by a human than the nature of ligand-target interactions, which are the molecular mechanisms of biological activities.

The Multilevel Neighborhoods of Atoms (MNA) descriptors (Filimonov et al., 1999) have certain advantages in comparison with SSFN. These descriptors are based on the molecular structure representation, which includes the hydrogen atoms according to the valences and partial charges of other atoms and does not specify the types of bonds. MNA descriptors are generated as a recursively defined sequence:

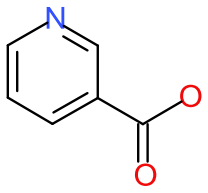
- zero-level MNA descriptor for each atom is the mark A of the atom itself;
- any next-level MNA descriptor for the atom is the sub-structure notation $A(D_1 D_2 ... D_i ...)$,

where D_i is the previous-level MNA descriptor for the i–th immediate neighbors of the atom A.

The mark of atom may include not only the atomic type but also any additional information about the atom. In particular, if the atom is not included into the ring, it is marked by

"-". The neighbor descriptors $D_1D_2...D_i...$ are arranged in a unique lexicographic order. The iterative process of MNA descriptor generation can be continued covering first, second, etc. neighborhoods of each atom.

The molecular structure is represented in PASS by the set of unique MNA descriptors of the 1st and 2nd levels (Figure 2). The substances are considered to be *equivalent* in PASS if they have the same set of MNA descriptors. Since MNA descriptors do not represent the stereochemical peculiarities of a molecule, the substances whose structures differ only stereochemically, are formally considered as *equivalent*.



HC	**C(C(CC—H)C(CC—C)—H(C))**
HO	**C(C(CC—H)C(CN—H)—H(C))**
CHCC	**C(C(CC—H)C(CN—H)—C(C—O—O))**
CHCN	**C(C(CC—H)N(CC)—H(C))**
CCCC	**C(C(CC—C)N(CC)—H(C))**
CCOO	**N(C(CN—H)C(CN—H))**
NCC	**—H(C(CC—H))**
OHC	**—H(C(CN—H))**
OC	**—H(—O(—H—C))**
	—C(C(CC—C)—O(—H—C)—O(—C))
	—O(—H(—O)—C(C—O—O))
	—O(—C(C—O—O))

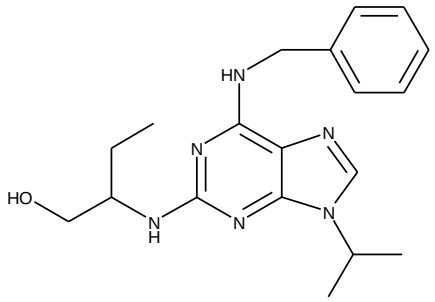
Figure 2. Structural formula of nicotinic acid and its MNA descriptors of the 1st (left column) and 2nd (right column) levels.

New QNA (Quantitative Neighborhoods of Atoms) descriptors were recently developed, which allow the analysis of quantitative structure-activity relationships (Filimonov et al., 2009).

Mathematical algorithm. The PASS algorithm of biological activity spectrum prediction is based on Bayesian estimates of probabilities of molecules belonging to the classes of active and inactive compounds, respectively. The mathematical method is described in several publications (Lagunin et al., 2000; Stepanchikova et al., 2003; Poroikov and Filimonov, 2005; Filimonov and Poroikov, 2006; Filimonov and Poroikov, 2008), and its details will not be discussed here. Only a general description necessary for the interpretation of prediction results is presented below.

Since the main purpose of PASS is the prediction of activity spectra for new molecules, the general principle of the PASS algorithm is the exclusion of substances from the SAR Base which are *equivalent* to the substance under prediction.

The structural formula of a molecule, for which PASS prediction should be carried out, is presented as a MOL file (for a set of molecules – as SDF file). The predicted activity spectrum is presented in PASS by the list of activities with probabilities "to be active" Pa and "to be inactive" Pi calculated for each activity (Figure 3). The list is arranged in descending order of Pa-Pi; thus, the more probable activities appear at the top of the list. Only activities with Pa>Pi are considered as possible for a particular compound. The list can be shortened at any desirable cutoff value, but Pa>Pi is used by default. If the user chooses a rather high value of Pa as a cutoff for selection of probable activities, the chance to confirm the predicted activities experimentally is high too, but many existing activities will be lost. For instance, if Pa>90% is used as a cutoff, about 90% of real activities will be lost; for Pa>80%, the portion of lost activities is 80%, etc.



> <PASS_RESULT_COUNT>

6 of 3300 Possible Activities at Pa > 0.500

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Pa	Pi	Activity
0.785	**0.002**	**Cyclin-dependent kinase inhibitor**
0.677	0.051	Systemic lupus erythematosus treatment
0.625	**0.001**	**Cyclin-dependent kinase 1 inhibitor**
0.555	0.065	Multiple sclerosis treatment
0.600	0.122	Hydrolase inhibitor
0.591	0.148	Myocardial ischemia treatment

. . .

Figure 3. Structural formula and part of PASS predicted activity spectrum for Seliciclib (R-Roscovitine, Cyclacel Ltd.). Known activities are marked in bold.

It is necessary to keep in mind that the probability Pa reflects the similarity of the molecule under prediction with the structures of molecules which are the most typical in a sub-set of "actives" in the training set. Therefore, usually there is no direct correlation between the Pa values and quantitative characteristics of activities.

Even for an active and potent compound, whose structure does not resemble the typical structures of "actives" from the training set, a low Pa value could be obtained during the prediction (in some cases negative Pa-Pi values can be observed). This may be explained by the way how the appropriate estimates are constructed: the values Pa for "actives" and Pi for "inactives" are distributed uniformly. Taking this into account, the following interpretation of prediction results is possible. If, for instance, Pa=0.9, then the appropriate estimates for 90% of the "actives" from the training set are less than for this compound, and only for 10% of "actives" these values are higher. If one declines the suggestion that this compound is active, he will make a wrong decision with a probability of 0.1. In case of Pa<0.5, but Pa>Pi, the appropriate estimates for more than half of the "actives" from the training set are higher than for this compound. If one declines the suggestion that this compound is active, he will make a wrong decision with a probability of less than 0.5. In such a case, the probability to confirm this kind of activity in an experiment is small, but if it will be confirmed, the chances are more than 50% that this structure has a high novelty and may become NCE.

If the predicted biological activity spectrum is wide, the structure of the compound is quite simple, and does not contain peculiarities, which are responsible for the selectivity of its biological action.

If it appears that the structure under prediction contains several new MNA descriptors (in comparison with the descriptors from the compounds of the training set), then the structure has low similarity with any structure from the training set, and the results of prediction should be considered as rather rough estimates.

Based on these criteria, one may choose which activities have to be tested for the studied compounds on the basis of compromise between the novelty of expected pharmacological action and the risk to obtain a negative result in experimental testing. Certainly, one could also take into account a particular interest to some kinds of activity, experimental facilities, etc.

Validation of PASS. Leave one out cross-validation (LOO CV) for the whole PASS 11.4.12 training set, which includes about 250,000 substances with 4,366 kinds of biological activities, provides the estimates of PASS prediction accuracy during the training procedure. Average accuracy of prediction is about 95% according to the LOO CV estimation, while for the different kinds of activity prediction accuracy varies from 70.5% (Antineoplastic, head/neck cancer) to 99.9% (VEGF2 expression inhibitor).

The accuracy of PASS predictions depends on several factors, from which the quality of the training set seems to be the most important one. A perfect training set should include comprehensive information about all biological activities known or possible for each compound. In other words, the whole *biological activity spectrum* should be thoroughly investigated for each compound included into the PASS training set. Unfortunately, no database exists with information about biologically active compounds tested against each kind of biological activity. Therefore, **the information concerning known biological activities for any compound is always incomplete**.

We investigated the influence of the information's incompleteness on the prediction accuracy for new compounds. About 20,000 "principal compounds" from the MDDR database (SYMYX MDL) were used to create heterogeneous training and evaluation sets. At random 20, 40, 60, or 80% of the information were excluded from the training set. Either structural data or biological activity data were removed in two separate computer experiments. In both cases it was shown that even if up to 60% of the information is excluded, the results of the prediction are still satisfactory (Poroikov et al., 2000). Thus, **despite the incompleteness of information in the training set, the PASS algorithm is robust enough to get reasonable results of prediction.**

PASS predictions were performed for about 250,000 molecules from the Open NCI database (Poroikov et al., 2003). This information is presented at the NCI web-site (http://cactus.nci.nih.gov/ncidb2/) in a searchable mode. One can combine different terms in a query using Boolean operators. For example, with a query "Angiogenesis inhibitor AND Pa>0.9 AND Pi<0.2 NOT acid NOT amide" we identified 85 hits. Seven compounds were tested in NCI and four showed the Angiogenesis inhibitory activity at approximately 10-100 μM (Poroikov et al., 2003). Also, on the basis of results of anti-HIV testing of compounds from the Open NCI database, we estimated that, using PASS predictions, one could significantly (up to 17 times) increase the fraction of "actives" in the selected sub-set (Poroikov et al., 2003).

PASS web-service (http://pharmaexpert.ru/passonline), providing the possibility for academic users to obtain PASS predictions freely via the Internet, was started in 2000 (Lagunin et al., 2000; Sadym et al., 2003; Filimonov and Poroikov, 2006; Geronikaki et al., 2008a). Submitting a MOL file or drawing the structural formula with a Marvin applet, the user obtains PASS predictions on his display. By August 1st, 2011 the number of registered users exceeded 7,500, and over 220,000 predictions were obtained. Based on the prediction results, the researchers select the most prospective substances for chemical synthesis and biological testing. Comparison of PASS prediction results with the experiments provides independent validation of the approach versus compounds from different chemical series with various kinds of biological activity. Currently, about forty independent papers have been published, where the coincidence of PASS predictions with experimental results is described. For example, due to the PASS predictions, new antileishmanial agents were found among 2 substitution-bearing 6-nitro- and 6-amino-benzothiazoles (Delmas et al., 2002), 7-substituted 9-chloro and 9-amino-2-methoxyacridines (Di Giorgio et al., 2003), beta-carboline alkaloids (Di Giorgio et al., 2004); new anxiolytics were found among quinazolines (Goel et al., 2005), thiazoles, pyrazoles, isatins, a-fused imidazoles and other chemical series (Geronikaki et al., 2004); new anti-inflammatory agents were found among substituted amides and hydrazides of dicarboxylic acids (Dolzhenko et al., 2003), 1-acylaminoalkyl-3,4-dialkoxybenzene derivatives (Labanauskas et al., 2005); etc. (see for review – Geronikaki et al., 2008a).

Also, on the basis of PASS predictions new antihypertensive and anti-inflammatory agents with dual mechanisms of actions were discovered (Lagunin et al., 2003; Geronikaki et al., 2008b), which demonstrated the capability of PASS in finding multitargeted agents exhibiting additive/synergistic effects. PASS applications for the prediction of biological activity spectra of organic molecules including known drug substances are described in detail (Poroikov et al., 2001; Poroikov and Filimonov, 2002; Poroikov et al., 2007).

PASS INet, however, does not provide the full functionality of the commercial version of PASS. In particular: an earlier version of the SAR Base is implemented into PASS INet; this program predicts a smaller number of biological activities; predictions can be obtained only for a single molecule using a MOL file as an input, while in the commercial version of PASS predictions can be obtained for a set of molecules represented as SDF file with further analysis of prediction results by PharmaExpert; PASS licensees can use the program (Figure 4)

in house and keep confidentiality (no submission of the structural formulae of the studied molecules via Internet).

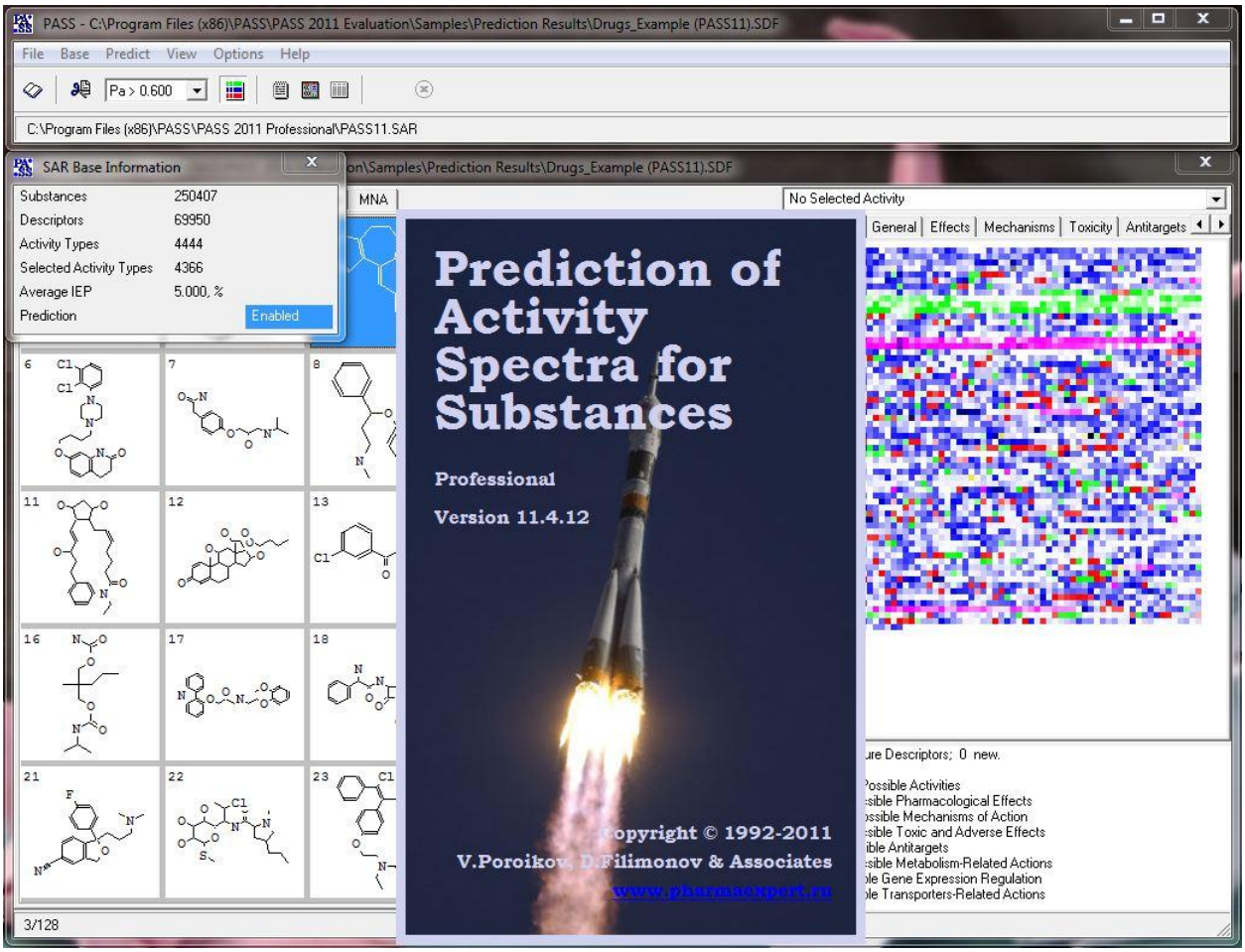

Figure 4. PASS user interface and example of prediction results (displayed in a graphic mode).

In the commercial version of PASS, the user can evaluate the contribution of each atom in a molecule to the required biological activity (Figure 5).

The color of each atom depends on the contribution of the atom to the activity.

Green	**Pa = 1, Pi = 0**
Red	**Pa = 0, Pi = 1**
Blue	**Pa = 0, Pi = 0**
Grey	**Pa = 0.33, Pi = 0.33**

Thus, **Green** means the positive impact of a particular fragment into the activity; **Red** means the positive impact of a particular fragment into the activity; **Blue** and **Grey** mean the

neutral impact of a particular fragment into the activity. Based on this information, medicinal chemists can modify the structure in order to increase the probability of a desirable pharmacological activity or decrease the probability of toxic action.

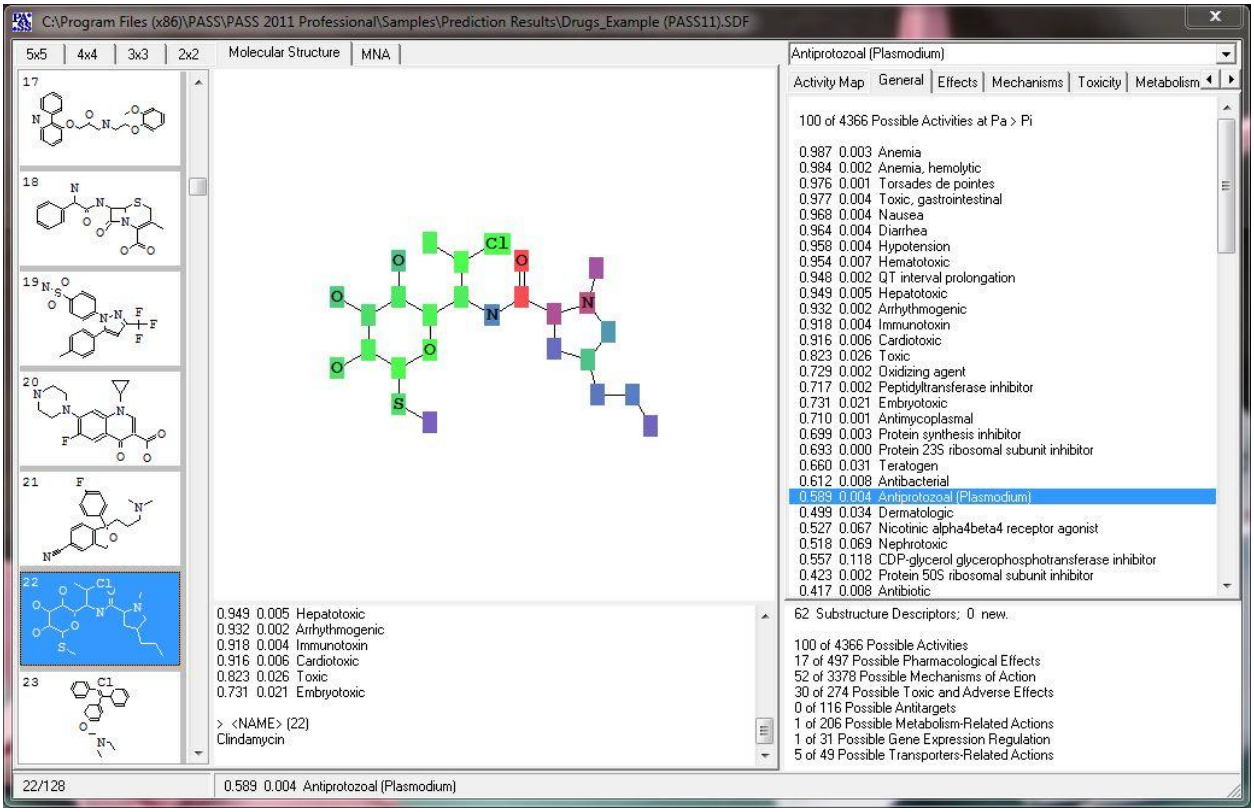

Figure 5. Influence of particular atoms in a molecule on a particular activity (Antiprotozoal (Plasmodium) in this example).

The PASS team provides continuous support of the licensees, supplying them with the latest versions of PASS when such versions appear.

PharmaExpert as a tool for the analysis of PASS predictions. PharmaExpert (Poroikov et al., 2005; PharmaExpert Program Package, 2011) was developed to analyze the biological activity spectra of substances predicted by the PASS program. This software provides a flexible mechanism for selecting compounds with the required biological activity profiles. Different kinds of biological activity are divided into seven classes: mechanisms of action, pharmacological effects, toxic/adverse effects, metabolic terms, antitargets, transporter terms and gene expression terms.

PharmaExpert analyzes the "mechanism-effect(s)" and "effect-mechanism(s)" relationships, identifies probable drug-drug interactions for pairs of molecules, and searches for molecules with required activity profile(s) and/or acting on multiple targets (Figure 6). The analysis is based on the "mechanism-effect(s)" relationships knowledgebase (MER base) that is collected from literature of more than 12 years and includes about 11,000 relationships at the present time.

PharmaExpert also contains a report generation option, which allows the user to prepare a draft report with the analysis of biological activity profiles for the set of compounds automatically.

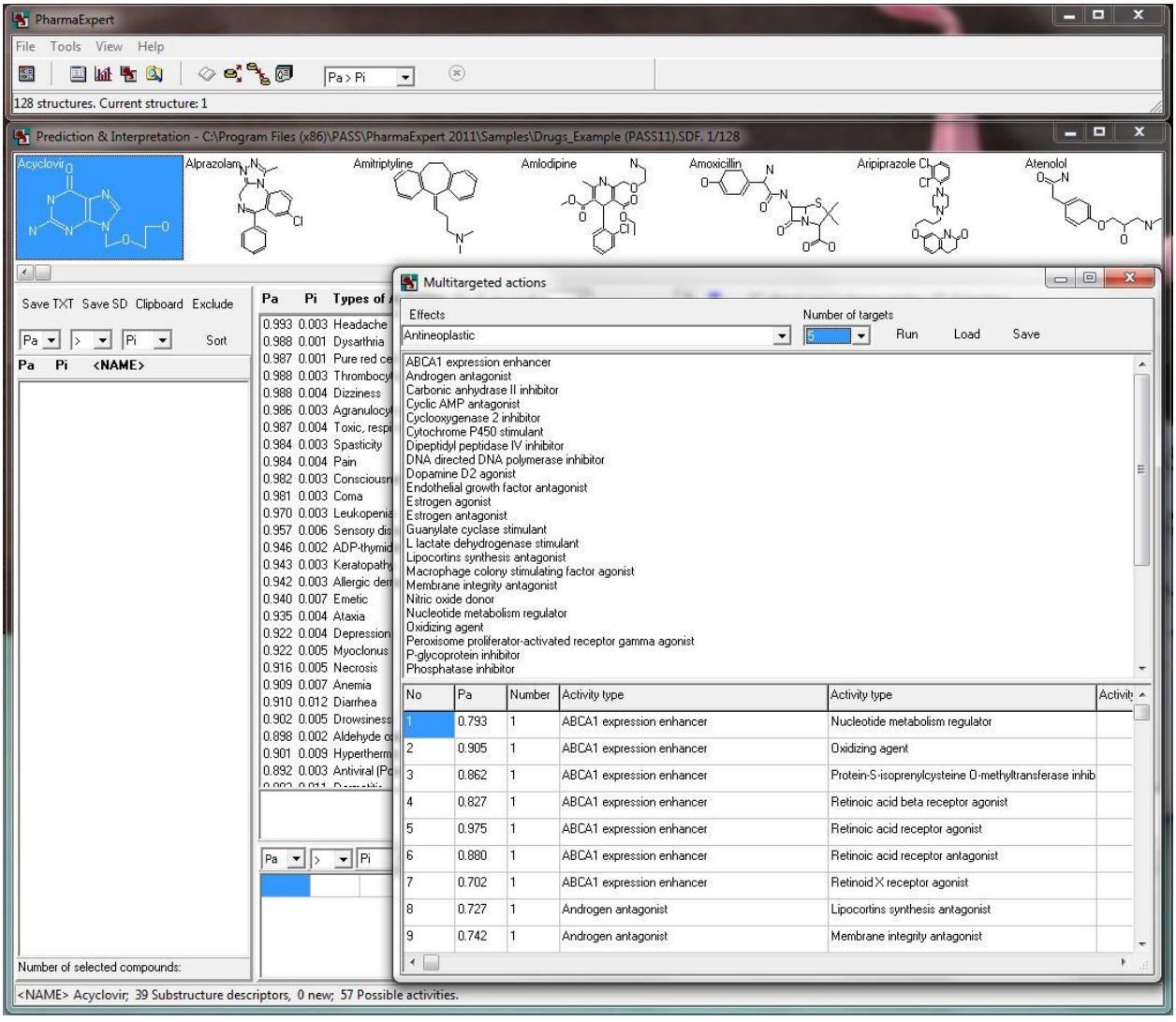

Figure 6. Example of a PharmaExpert search for antineoplastic multitargeted ligands.

PASS provides the following opportunities for licensed users:

- Determine the tests most relevant for a particular compound class.
- Reveal new effects and mechanisms of action for known substances in corporate and personal databases.
- Find new leads with given biological activity profiles among the compounds from in-house and commercial databases.
- Select the most promising compounds from available samples for high throughput screening.

Some advantages of PASS use in R&D:

Possibility of application at early stages of research. Because only the structural formula of a compound (hit) is necessary as input for PASS, computer prediction can be obtained at a very early stage of pharmaceutical R&D (ligand design) when no time and money are yet spent on chemical synthesis, biological testing, etc.

Reasonable accuracy of prediction. The average accuracy of prediction in leave one out cross-validation (for ~250,000 compounds and ~4,300 kinds of biological activity from the PASS training set) is about 95%. The PASS algorithm produces rather robust estimates of structure-activity relationships despite the incompleteness of the training set (Poroikov et al., 2000).

PASS parameters represent the biological space. PASS represents the properties of molecules in biological space in contrast to many other descriptors, which reflect the structural properties of molecules. PASS parameters can be used for clustering of compounds according to their biological properties, not according to their structural similarity.

Predictions are rather fast. Calculation of biological activity spectra for 10,000 compounds on an ordinary PC takes about 5 min; therefore, PASS can be effectively used to analyze databases consisting of millions of structures.

Standard structure formats are used. Standard SDF or MOL file formats (MDL) are used as input for PASS; therefore, the existing databases of chemical structures can be retrieved easily.

Only an ordinary PC is necessary. PASS and PharmaExpert work on personal computers under the operating systems Windows 98/NT/2000/XP/VISTA/7 with 1 GB RAM and 200 MB free hard disc space.

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