Discovery of new pharmaceutical agents using in silico approaches: PASS, GUSAR, PharmaExpert and Way2Drug platform”

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Moscow, Russia

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Proteomics & Mass-spectrometry
Towards the human proteome

Personalized medicine
Digital "-omics" technologies: prevention and early diagnosis of socially significant diseases

Nanotechnology
Improving the efficiency of existing drugs

Bioinformatics
For identify biomarkers, pharmacological targets and the basic structures of new drugs

Biochemistry
Enzymes in pathological processes, biologically active compounds and vaccines

HUMAN PROTEOME PROJECT

Department for Bioinformatics

The Department of Bioinformatics carries out the investigations related to bioinformatics and computer-aided drug design & discovery. The skilled personnel, original and commercially available software & databases, and high performance computation facilities provide all pre-requisites for basic and applied research, covered the whole field "From genomes to drugs in silico"".
Department for Bioinformatics currently includes five laboratories:

- **Laboratory of Postgenomic Data Analysis** (Head - Dr.Sc. Elena Ponomarenko),
- **Laboratory of Bioinformational Technologies** (Head - Dr.Sc. Andrey Lisitsa),
- **Laboratory of Molecular Graphics and Drug Design** (Head - Dr.Sc. Alexander Veselovsky),
- **Laboratory of Structure-Function Based Drug Design** (Head - Prof. Dr. Vladimir Poroikov),
- **Laboratory of Parallel Computing and Informational Technology** (Head - Ph.D. Vladlen Skvortsov).

The associates are taking active participation in teaching students (special courses and practicums) from Medical-Biological Faculty of Russian State Medical University and some other Moscow Universities.

www.ibmc.msk.ru

Overview

1. Historical reflections
2. PASS (Prediction of Activity Spectra for Substances)
3. PharmaExpert
4. GUSAR (General Unrestricted Structure-Activity Relationships)
5. Some examples of applications
6. Our web-services based on PASS, GUSAR, etc.
7. Way2Drug.com: further progress

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System for Registration and Biological Testing of New Chemical Compounds

"The system of biological tests of physiologically active substances developed under the supervision of Piruzyan allows the use of relatively simple methods of investigation requiring minimal expenditures of time and substances to eliminate substances that are of little promise for pharmacology from a great number of new compounds and select those that may become medicinal drugs".

Lev Aramovich Piruzyan (On his 70th birthday)
http://link.springer.com/article/10.1134/S0362119707050192

Some historical reminiscences


НАУЧНО-ИССЛЕДОВАТЕЛЬСКИЙ ИНСТИТУТ
ПО БИОЛОГИЧЕСКИМ ИСПЫТАНИЯМ ХИМИЧЕСКИХ СОЕДИНЕНИЙ

ПРОСПЕКТ

СИСТЕМА
БИОЛОГИЧЕСКИХ ИСПЫТАНИЙ
ХИМИЧЕСКИХ СОЕДИНЕНИЙ
И СОЗДАНИЯ ЛЕКАРСТВ

МОСКВА, 1981


ГОСУДАРСТВЕННЫЙ КОМИТЕТ СССР ПО НАУКЕ И ТЕХНИКЕ

ПОСТАНОВЛЕНИЕ

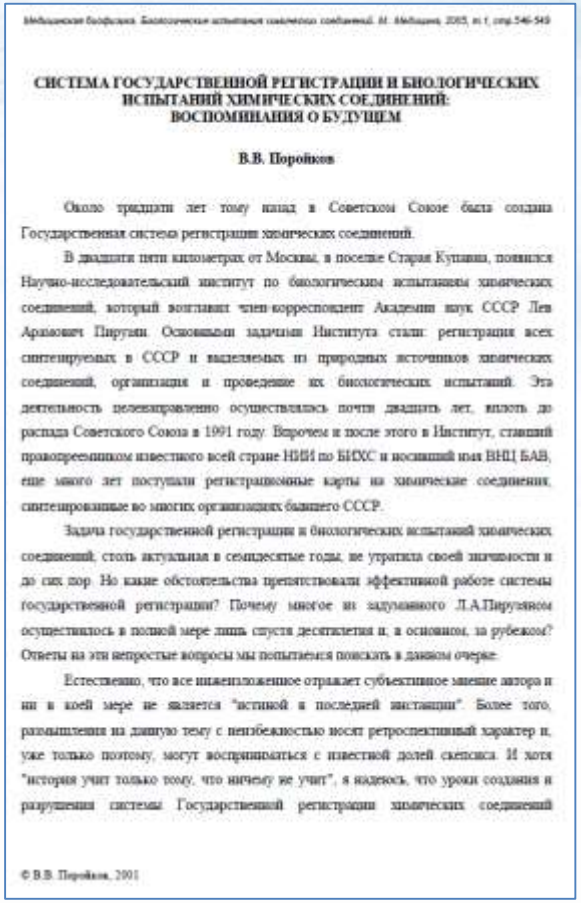
от 25 апреля 1989г. № 269

Об утверждении Положения о порядке государственной регистрации, биологических испытаний и отбора новых получаемых в СССР химических соединений

Государственный комитет СССР по науке и технике ПОСТАНОВЛЯЕТ:

Утвердить согласованное с Гособразованием СССР, Академией наук СССР, Минздравом СССР, Минсельхозпромом СССР, Минмедбиопромом СССР Положение о порядке государственной регистрации, биологических испытаний и отбора новых получаемых в СССР химических соединений согласно приложению.

Председатель
Государственного комитета СССР
по науке и технике
Е.П.Велихов


Медицинская биофизика. Биологические испытания химических соединений. М.: Медицина, 2005, кн.1, стр.546-549

СИСТЕМА ГОСУДАРСТВЕННОЙ РЕГИСТРАЦИИ И БИОЛОГИЧЕСКИХ ИСПЫТАНИЙ ХИМИЧЕСКИХ СОЕДИНЕНИЙ: ВОСПОМИНАНИЯ О БУДУЩЕМ

В.В. Поройков

Около тридцати лет тому назад в Советском Союзе была создана Государственная система регистрации химических соединений.

В двадцати пяти километрах от Москвы, в поселке Старая Купавна, появился Научно-исследовательский институт по биологическим испытаниям химических соединений, который возглавил член-корреспондент Академии наук СССР Лев Аронович Пирузян. Основными задачами Института стали: регистрация всех синтезируемых в СССР и выделяемых из природных источников химических соединений, организация и проведение их биологических испытаний. Эта деятельность целенаправленно осуществлялась почти двадцать лет, вплоть до распада Советского Союза в 1991 году. Впрочем и после этого в Институт, ставший правопреемником известного всей стране НИИ по БИХС и носивший имя ВНЦ БАВ, еще много лет поступали регистрационные карты на химические соединения, синтезированные во многих организациях бывшего СССР.

Задача государственной регистрации и биологических испытаний химических соединений, столь актуальная в семидесятые годы, не утратила своей значимости и до сих пор. Но какие обстоятельства препятствовали эффективной работе системы государственной регистрации? Почему многое из задуманного Л.А.Пирузяном осуществилось в полной мере лишь спустя десятилетия и, в основном, за рубежом? Ответы на эти непростые вопросы мы попытаемся поискать в данном очерке.

Естественно, что все нижеизложенное отражает субъективное мнение автора и ни в коей мере не является "истиной в последней инстанции". Более того, размышления на данную тему с неизбежностью носят ретроспективный характер и, уже только поэтому, могут восприниматься с известной долей скепсиса. И хотя "история учит только тому, что ничему не учит", я надеюсь, что уроки создания и разрушения системы Государственной регистрации химических соединений

© В.В. Поройков, 2001

PASS History: Persistent updating and improvement

1972	*Collection of the training set started (USSR National System of New Chemical Compounds Registration).*
1976-1992	*Early versions of different computer programs for biological activity spectra prediction (V.A. Avidon, V.E. Golender & A.B. Rosenblit).*
1993	First version of PASS: 9,314 compounds; 114 activities, accuracy of prediction AP=76%.
1998	PASS C&T version 4.0: 30,537 compounds; 541 activities, AP=82%.
2005	PASS Pro 2005: >60,000 compounds; >2500 activities, AP=89%.
2009	PASS Pro v. 9.1: >200,000 compounds; >3500 activities, AP =95%.
2014	**PASS Pro 2014: >950,000 compounds; >7000 activities, AP =95%.**

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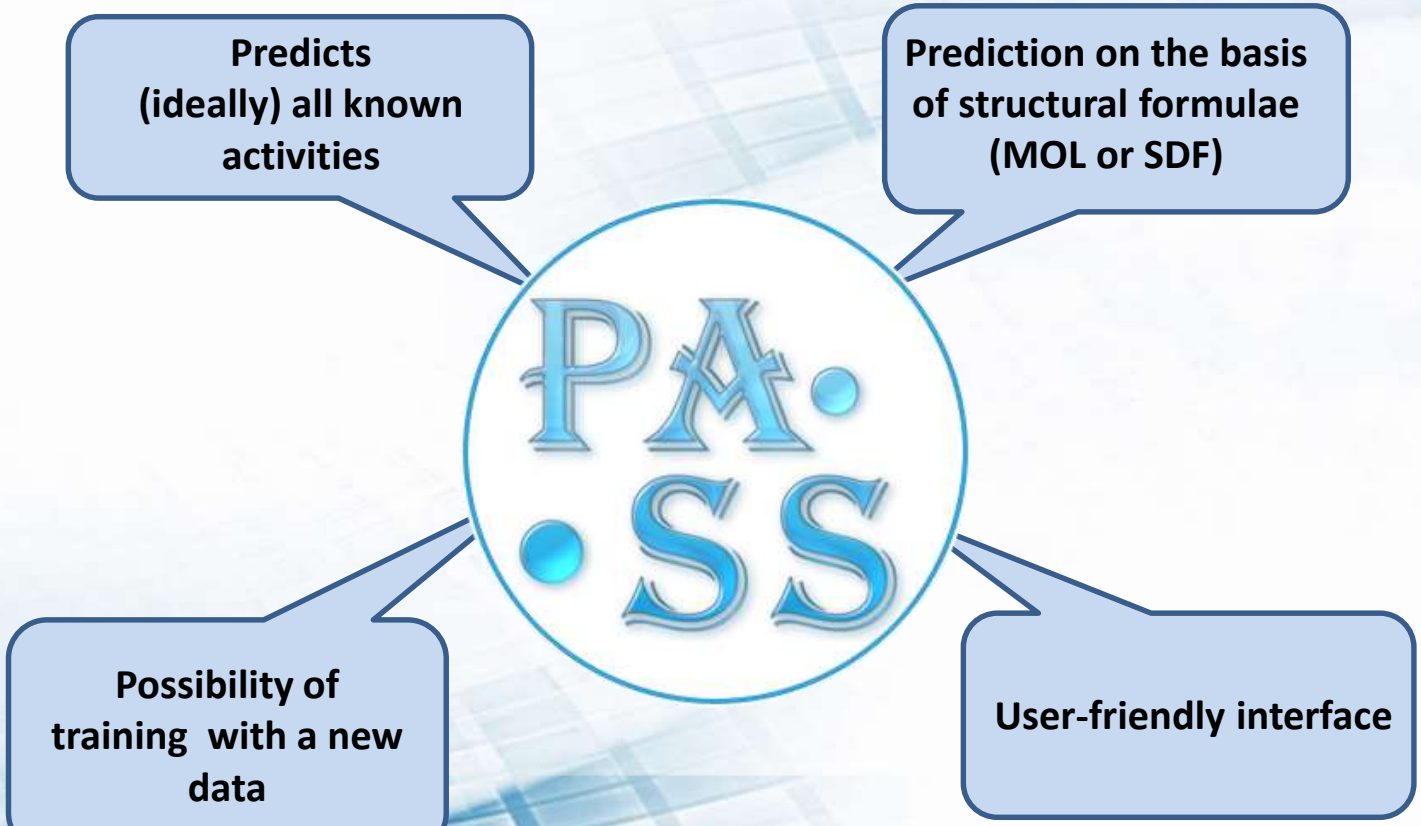
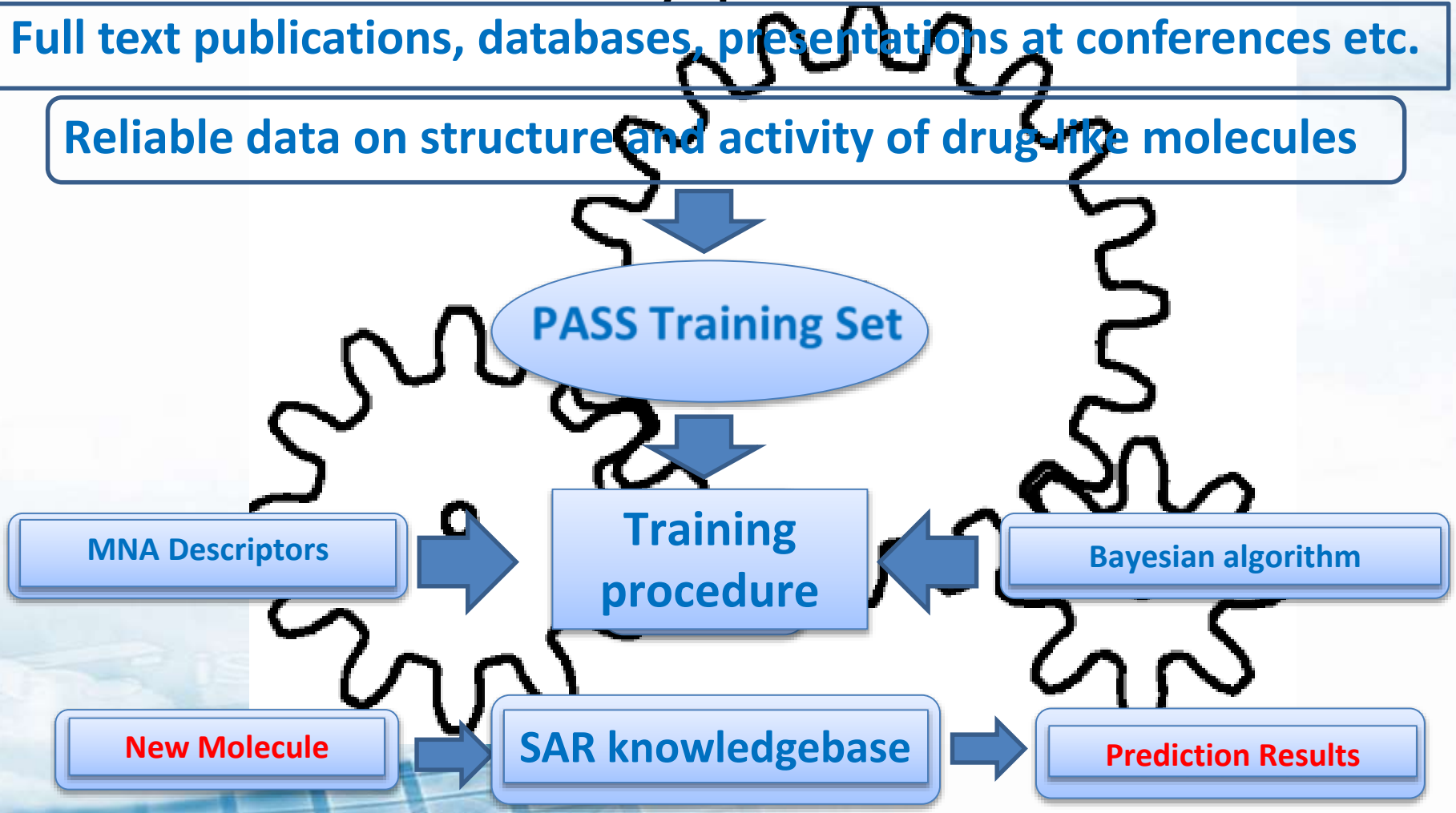
Requirements for a computer program evaluated biological activity profiles (spectra)



Computer program PASS: Prediction of Activity Spectra for Substances

Full text publications, databases, presentations at conferences etc.

Reliable data on structure and activity of drug-like molecules



Filimonov D.A. et al. *Chem. Heterocycl. Comps.*, 2014, **50**: 444-457.

PASS 2014 Characteristics

Training Set	959,801 drugs, drug-candidates, pharmacological and toxic substances comprise the training set
Biological Activity	7,158 biological activities can be predicted (Active vs. Inactive)
Chemical Structure	Multilevel Neighborhoods of Atoms (MNA) descriptors [1, 2]
Mathematical Algorithm	Bayesian approach was selected by comparison of many different methods [2]
Validation	Average accuracy of prediction in LOO CV for the whole training set is ~95% [2]; robustness was shown using principal compounds from MDDR database [3]

1. Filimonov D.A. et al. J. Chem. Inform. Computer Sci., 1999, 39: 666-670.
2. Filimonov D.A., Poroikov V.V. Chemoinformatics Approaches to Virtual Screening, 2008, 182-216.
3. Poroikov V.V. et al. J. Chem. Inform. Computer Sci., 2000, 40: 1349-1355.

Concept of biological activity spectrum

Biological Activity Spectrum is the intrinsic property of the compound reflected all biological activities, which can be found in the compound's interaction with biological entity.

Poroikov V.V., Filimonov D.A., Boudunova A.P. *Automatic Documentation and Mathematical Linguistics*. Allerton Press Inc., 1993, 27: 40-43.

Filimonov D.A., Poroikov V.V., Karaicheva E.I. et. al. *Experimental and Clinical Pharmacology*, 1995, 58: 56-62 (Rus).

Filimonov D.A., Poroikov V.V. In: *Bioactive Compound Design: Possibilities for Industrial Use*, BIOS Scientific Publishers, Oxford (UK), 1996. pp. 47-56.

Non-synonymous definitions in literature

Lewi P.J. Spectral mapping, a technique for classifying biological activity profiles of chemical compounds. *Arzneimittelforschung*. 1976; 26 (7):1295-1300.

Battistini A. et al. **Spectrum of biological activity** of interferons. *Annali dell'Istituto Superiore di Sanità*. 1990; **26** (3-4):227-253.

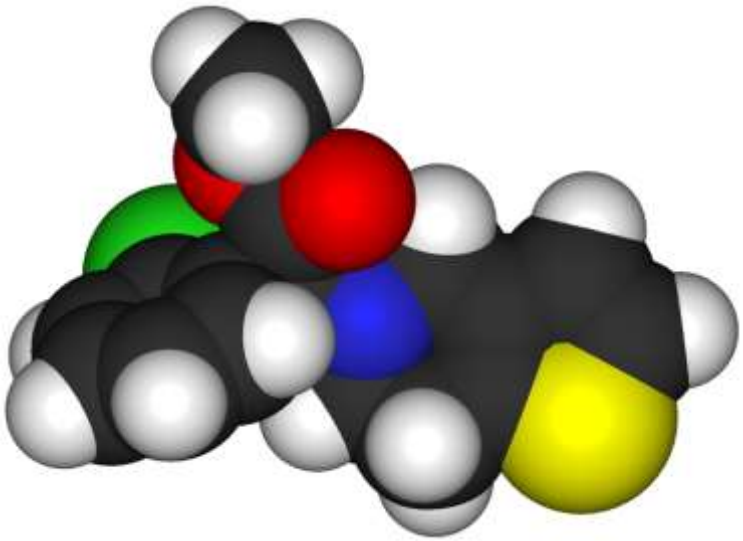
Gringorten J.L. et al. **Activity spectra** of Bacillus thuringiensis delta-endotoxins against eight insect cell lines. *In Vitro Cell. Dev. Biol. Anim*. 1999; **35** (5):299-303.

Fliri A.F. et al. **Biological spectra** analysis: Linking **biological activity profiles** to molecular structure *Proc. Natl. Acad. Sci. USA*. 2005; **102** (2): 261–266.

Rana A. Benzothiazoles: A new **profile of biological activities**. *Indian J. Pharm. Sci.* 2007; **69**:10-17.

Fedichev P., Vinnik A. **Biological Spectra** Analysis: Linking **Biological Activity Profiles** to Molecular Toxicity. 2007; http://www.q-pharm.com.

Chemical Structure Representation

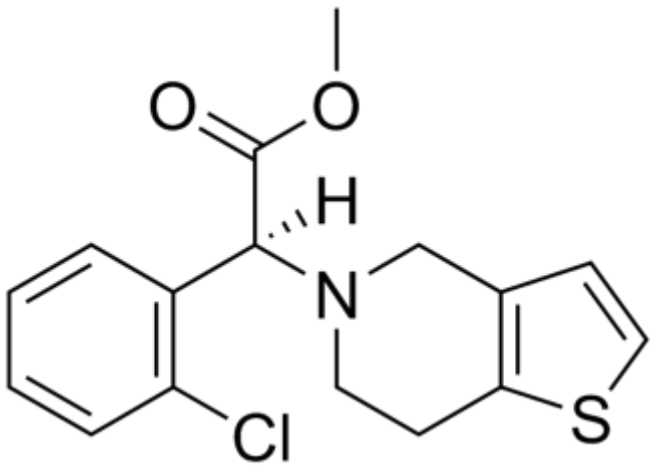


Spatial configuration of a free uncharged molecule in the ground state in vacuum is the necessary and sufficient description of its structure.

To use this molecular structure description one needs the substantial computational resources for molecular modeling and/or quantum-chemical calculations.

However, the basis of all calculations is the traditional structural formula.

Chemical structure representation



The structural formula unambiguously determines all properties of the organic molecule.

Environment? – Structural formula determines at least potential, “intrinsic” properties.

Neighborhoods of atoms descriptors

The most biological activities of organic compounds are the result of molecular recognition, which in turn depends on the correspondence between the particular atoms of the ligand and the target.

MOLECULAR BIOLOGY
QUANTUM CHEMISTRY
QUANTUM FIELD THEORY

$$M = V + VgM = V + VgV + VgVgV + VgVgVg + \ldots$$

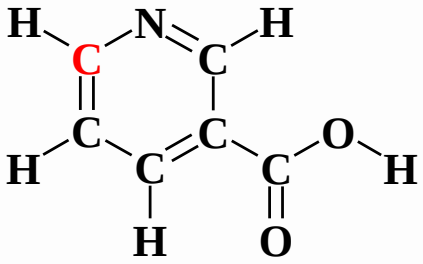
$$M_i = V_i + V_igM = V_i + V_ig(M_1 + M_2 + \ldots + M_m)$$

Descriptors are based on the concept of atoms' of molecule taking into account the influence of the neighborhoods:

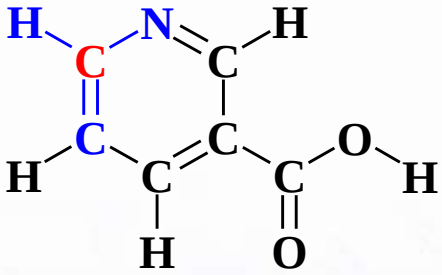
MNA - **multilevel neighborhoods of atoms**
QNA - **quantitative neighborhoods of atoms**

Filimonov D.A., Poroikov V.V. Probabilistic approach in activity prediction. *In: Chemoinformatics Approaches to Virtual Screening.* Eds. Alexandre Varnek and Alexander Tropsha. Cambridge (UK): RSC Publishing, 2008, 182-216.
Filimonov D.A., Zakharov A.V., Lagunin A.A., Poroikov V.V. QNA based 'Star Track' QSAR approach. *SAR and QSAR Environ. Res.*, 2009, 20 (7-8), 679-709.

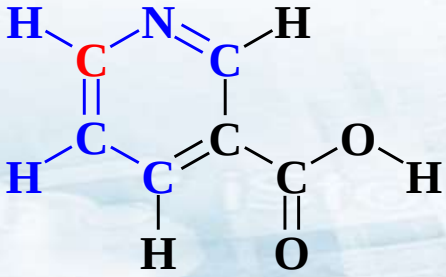
MNA: Multilevel Neighborhoods of Atoms



MNA/0: C



MNA/1: C(CN-H)

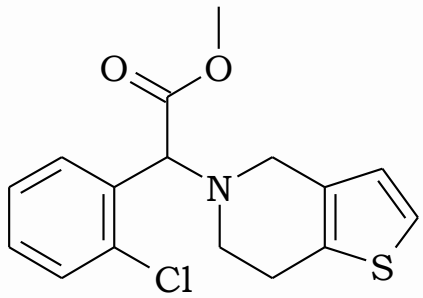


MNA/2: C(C(CC-H)N(CC)-H(C))

Filimonov D.A. et al. *J. Chem. Inform. Computer Sci.*, 1999, **39**: 666-670.

Substance representation

Structural formula of Clopidogrel



Activity Spectrum of Clopidogrel

Abdominal pain
Acute neurologic disorders treatment
Agranulocytosis
Allergic reaction
Anaphylaxis
Anemia
Angioedema
Angiogenesis inhibitor
Antianginal
Antiarthritic
Anticoagulant
Antineoplastic
Antipsoriatic
Antithrombotic
. . .
112 known activities in PASS SAR Base

MNA Descriptors of Clopidogrel

HC	C(C(CCC)C(CC-H-H)S(CC))
CHHHO	C(C(CCC)C(CS-H)-H(C))
CHHCC	C(C(CCC)N(CC-C)-H(C)-H(C))
CHHCN	C(C(CCS)C(CC-H)C(CN-H-H))
CHCC	C(C(CCS)C(CN-H-H)-H(C)-H(C))
CHCCN	C(C(CC-H-H)N(CC-C)-H(C)-H(C))
CHCS	C(C(CC-H)C(CC-H)-H(C))
CCCC	C(C(CC-H)C(CC-C)-H(C))
CCCS	C(C(CC-H)C(CC-C)-Cl(C))
CCCCl	C(C(CC-H)C(CC-Cl)-H(C))
CCOO	C(C(CC-H)C(CC-Cl)-C(CN-H-C))
NCCC	C(C(CC-H)S(CC)-H(C))
OC	N(C(CN-H-H)C(CN-H-H)-C(CN-H-C))
OCC	S(C(CCS)C(CS-H))
SCC	-H(C(CC-H))
ClC	-H(C(CC-H-H))
	-H(C(CN-H-H))
	-H(C(CS-H))
	-H(-C(CN-H-C))
	-H(-C(-H-H-H-O))
	-C(C(CC-C)N(CC-C)-H(-C)-C(-C-O-O))
	-C(-H(-C)-H(-C)-H(-C)-O(-C-C))
	-C(-C(CN-H-C)-O(-C)-O(-C-C))
	-O(-C(-H-H-H-O)-C(-C-O-O))
	-O(-C(-C-O-O))
	-Cl(C(CC-Cl))

Prediction of Biological Activity Spectra

According to the Bayes' theorem, the probability P(A|S) that the compound S has activity (or inactivity) A, equals to:

$$P(A|S) = P(S|A) \cdot P(A)/P(S)$$

If the descriptors of organic compound D_1, ..., D_m are independent, then:

$$P(S|A) = P(D_1, ..., D_m|A) = \Pi_i P(D_i|A)$$

P(A) and P(A|D_i) are calculated as sums through all compounds of the training set:

$$P(A \mid D_i) = \frac{\sum_k g_k(D_i) w_k(A)}{\sum_k g_k(D_i)}$$

$$P(A) = \frac{\sum_i \sum_k g_k(D_i) w_k(A)}{\sum_i \sum_k g_k(D_i)}$$

Filimonov D.A. et al. *Chem. Heterocycl Compnds.*, 2014, 50: 444-457.
Filimonov D.A., Poroikov V.V. (2006). *Rus. J. Gen. Chem.*, 2006, 50: 66-75.

Biological activities predicted by PASS

- **Pharmacotherapeutic effects**
  (antihypertensive, hepatoprotective, antiinflammatory etc.);
- **Mechanisms of action**
  (5-HT1A agonist, cyclooxygenase 1 inhibitor, adenosine uptake inhibitor, etc.);
- **Specific toxicities**
  (mutagenicity, carcinogenicity, teratogenicity, etc.);
- **Interaction with Antitargets**
  (HERG channel blocker, etc.);
- **Metabolic terms**
  (CYP1A substrate, CYP3A4 inhibitor, CYP2C9 inducer, etc.);
- **Influence on gene expression**
  (APOA1 expression enhancer, NOS2 expression inhibitor, etc.);
- **Action on transporters**
  (Dopamine transporter antagonist, Sodium/bile acid cotransporter inhibitor, etc.).

PASS algorithm description

Filimonov D.A., Lagunin A.A., Gloriozova T.A., Rudik A.V., Druzhilovskiy D.S., Pogodin P.V., Poroikov V.V. (2014). Prediction of the biological activity spectra of organic compounds using the PASS online web resource. *Chemistry of Heterocyclic Compounds*, 50: 444-457.

Filimonov D.A., Poroikov V.V. (2008). Probabilistic Approach in Virtual Screening. In: *Chemoinformatics Approaches to Virtual Screening*. Alexander Varnek and Alexander Tropsha, Eds. RSC Publishing, 182-216.

Filimonov D.A., Poroikov V.V. (2006). Prediction of biological activity spectra for organic compounds. *Russian Journal of General Chemistry*, 50: 66-75.

Descriptors (1999)

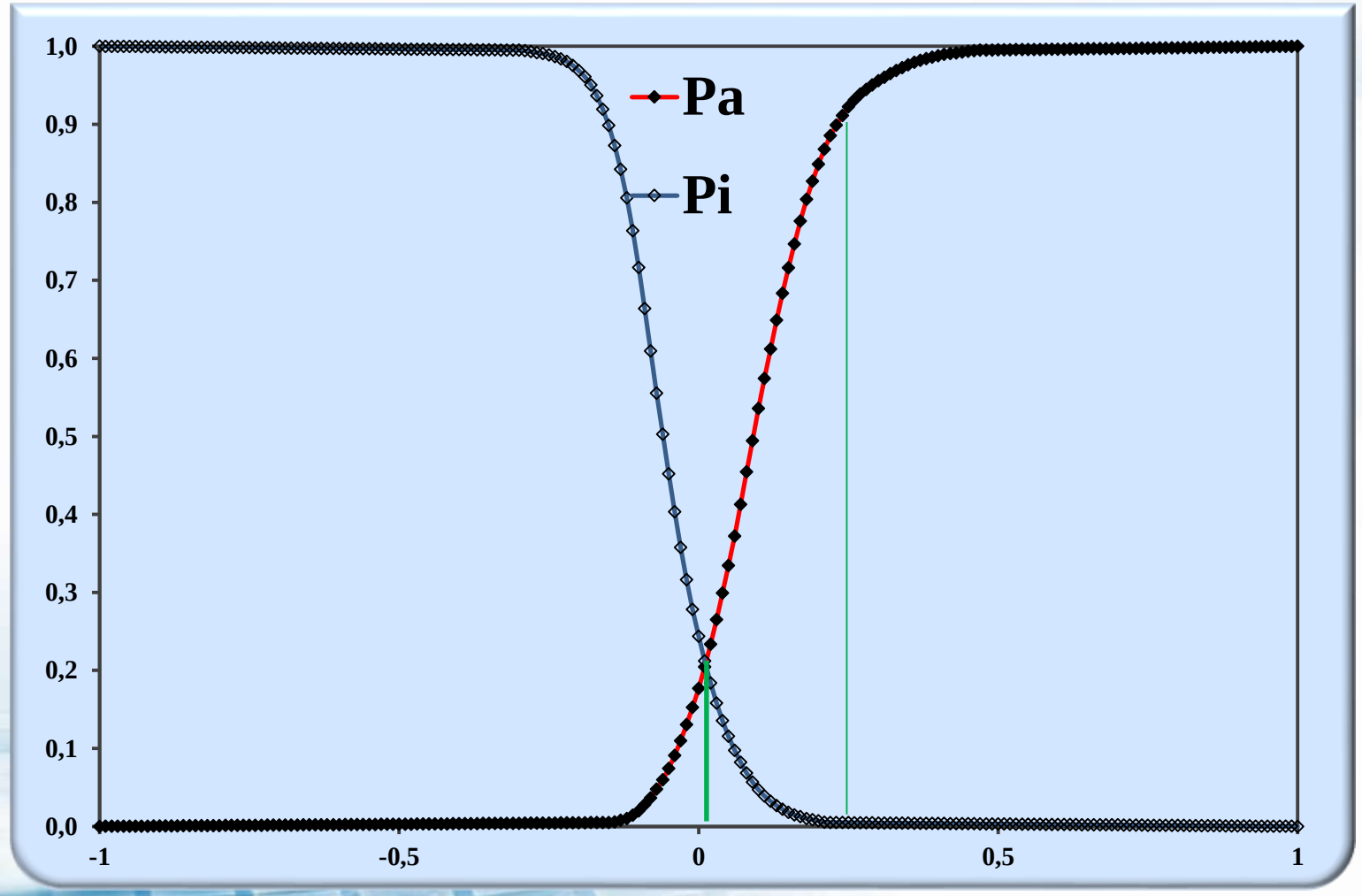
Robustness (2000)

PASS Online (2000)

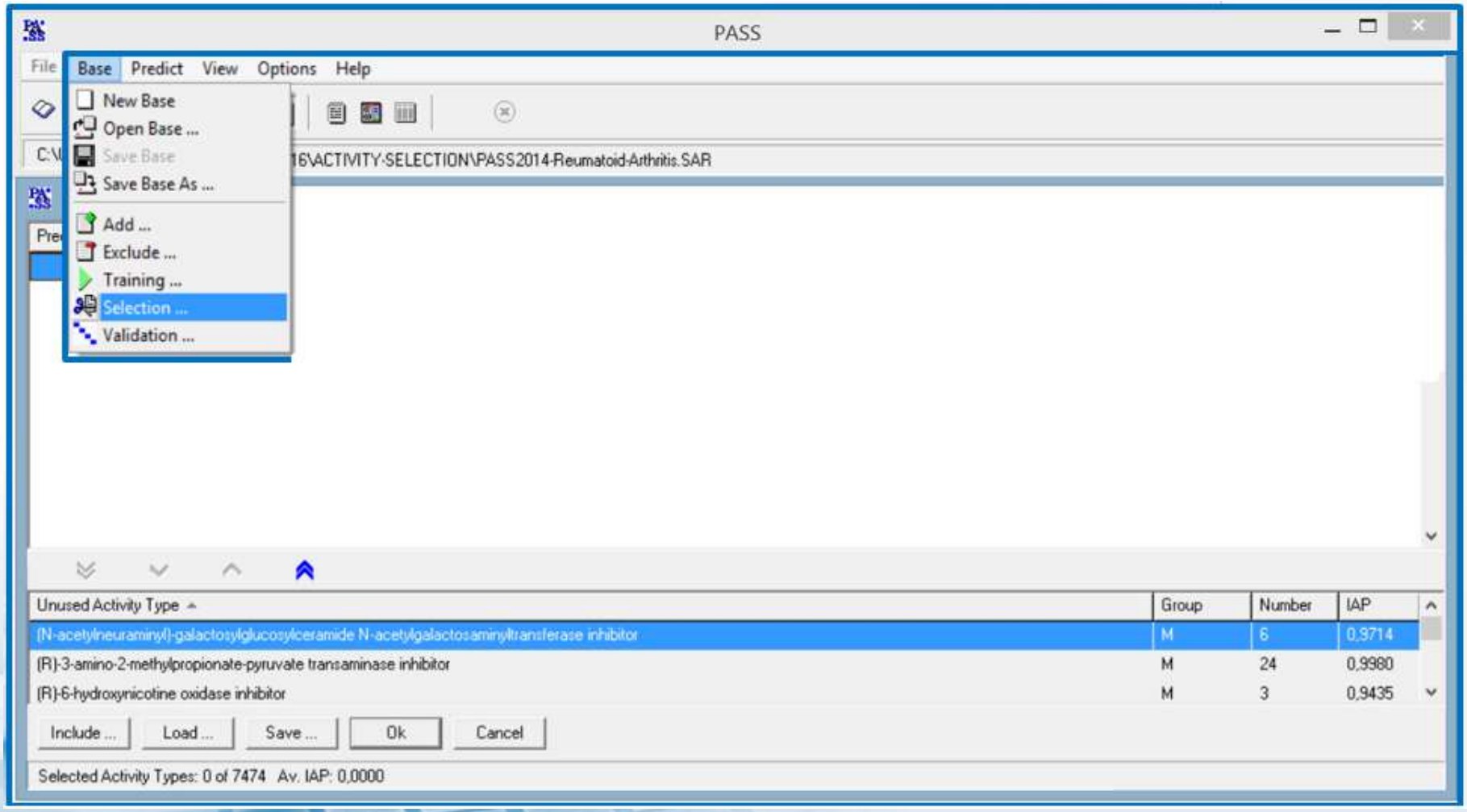
Drug-likeness (2001)

NCI Browser (2003)

Threshold selection: active/inactive?



PASS: Selection of the desirable activities



Rheumatoid arthritis treatment: PASS activities

5-Lipoxygenase inhibitor
Adenosine A3 receptor agonist
Adenosine deaminase inhibitor
Angiogenesis inhibitor
Antiinflammatory
Antimetabolite
Antioxidant
Apoptosis agonist
Autoimmune disorders treatment
Beta amyloid protein antagonist
Bisphosphonate
Bruton tyrosine kinase inhibitor
Calcineurin inhibitor
Cannabinoid receptor agonist
Cathepsin K inhibitor
CC chemokine 1 receptor antagonist
CC chemokine 2 receptor antagonist
Cell adhesion inhibitor
Cell adhesion molecule inhibitor
Chemokine receptor antagonist
Collagenase inhibitor
Complement inhibitor
Corticosteroid-like
Corticotropin releasing factor antagonist
CXC chemokine 2 receptor antagonist
CXC chemokine 4 receptor antagonist
Cyclin-dependent kinase 1 inhibitor
Cyclin-dependent kinase 2 inhibitor
Cyclin-dependent kinase 5 inhibitor
Cyclin-dependent kinase 7 inhibitor
Cyclin-dependent kinase 9 inhibitor
Cyclooxygenase 2 inhibitor
. . .
VLA-4 antagonist

Totally: 110 activities

Selection of activities for RA treatment

Select Activity Types to be Predicted

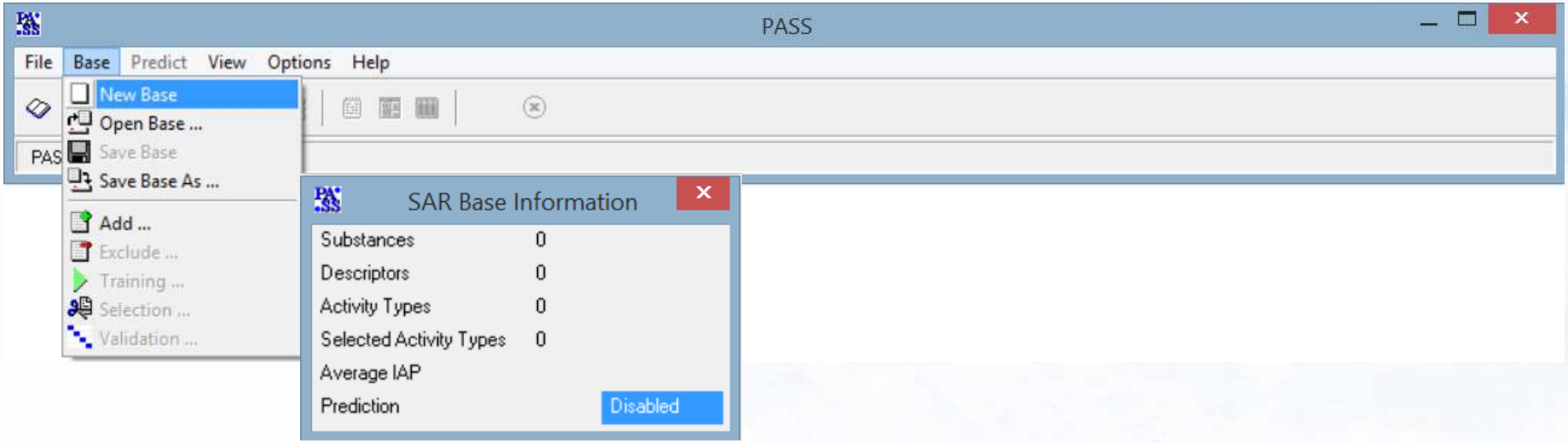
Predictable Activity Type	Group	Number	IAP
5-Lipoxygenase inhibitor	M	2834	0,9811
Adenosine A3 receptor agonist	M	163	0,9944
Adenosine deaminase inhibitor	MA	225	0,9903
Angiogenesis inhibitor	EM	4489	0,9223
Antiinflammatory	E	5983	0,8471
Antimetabolite	EM	732	0,9908
Antioxidant	EM	843	0,9494
Apoptosis agonist	E	1299	0,8877
Autoimmune disorders treatment	E	3972	0,8875
Beta amyloid protein antagonist	M	122	0,9805

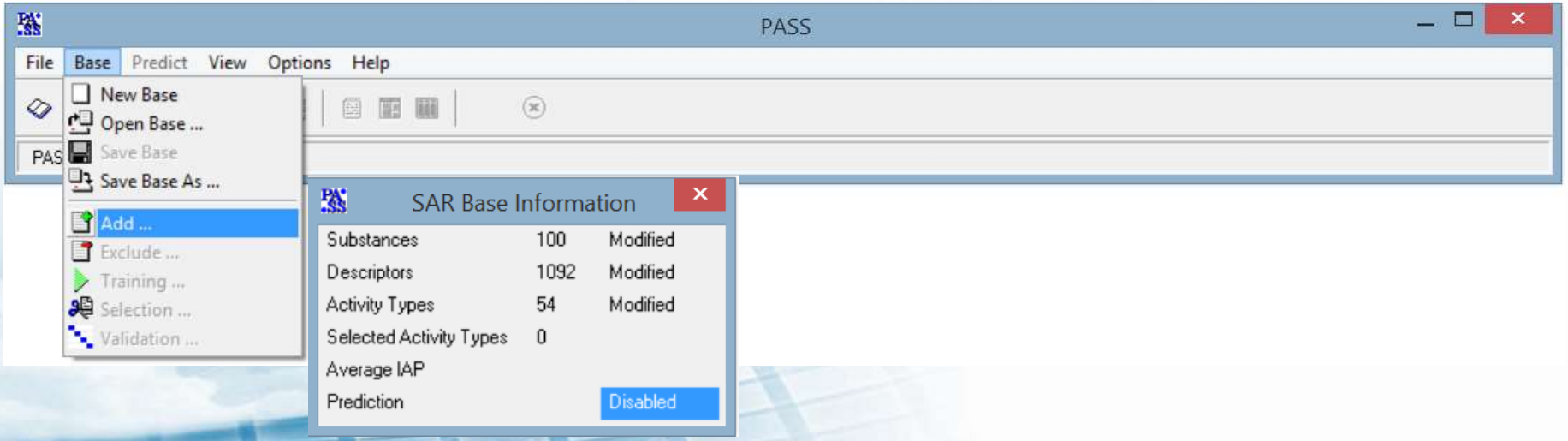
Unused Activity Type	Group	Number	IAP
(N-acetylneuraminyl)-galactosylglucosylceramide N-acetylgalactosaminyltransferase inhibitor	M	6	0,9714
(R)-3-amino-2-methylpropionate-pyruvate transaminase inhibitor	M	24	0,9980
(R)-6-hydroxynicotine oxidase inhibitor	M	3	0,9435
(R)-Pantolactone dehydrogenase (flavin) inhibitor	M	8	0,8780
(R)-aminopropanol dehydrogenase inhibitor	M	10	0,9939
(R)-limonene 6-monooxygenase inhibitor	M	3	0,9980
(R,R)-butanediol dehydrogenase inhibitor	M	3	0,9966
(S)-2-Methylmalate dehydratase inhibitor	M	4	0,9980
(S)-2-hydroxy-acid oxidase inhibitor	M	28	0,9336
(S)-3-amino-2-methylpropionate transaminase inhibitor	M	8	0,9607

Include ... | Load ... | Save ... | Ok | Cancel

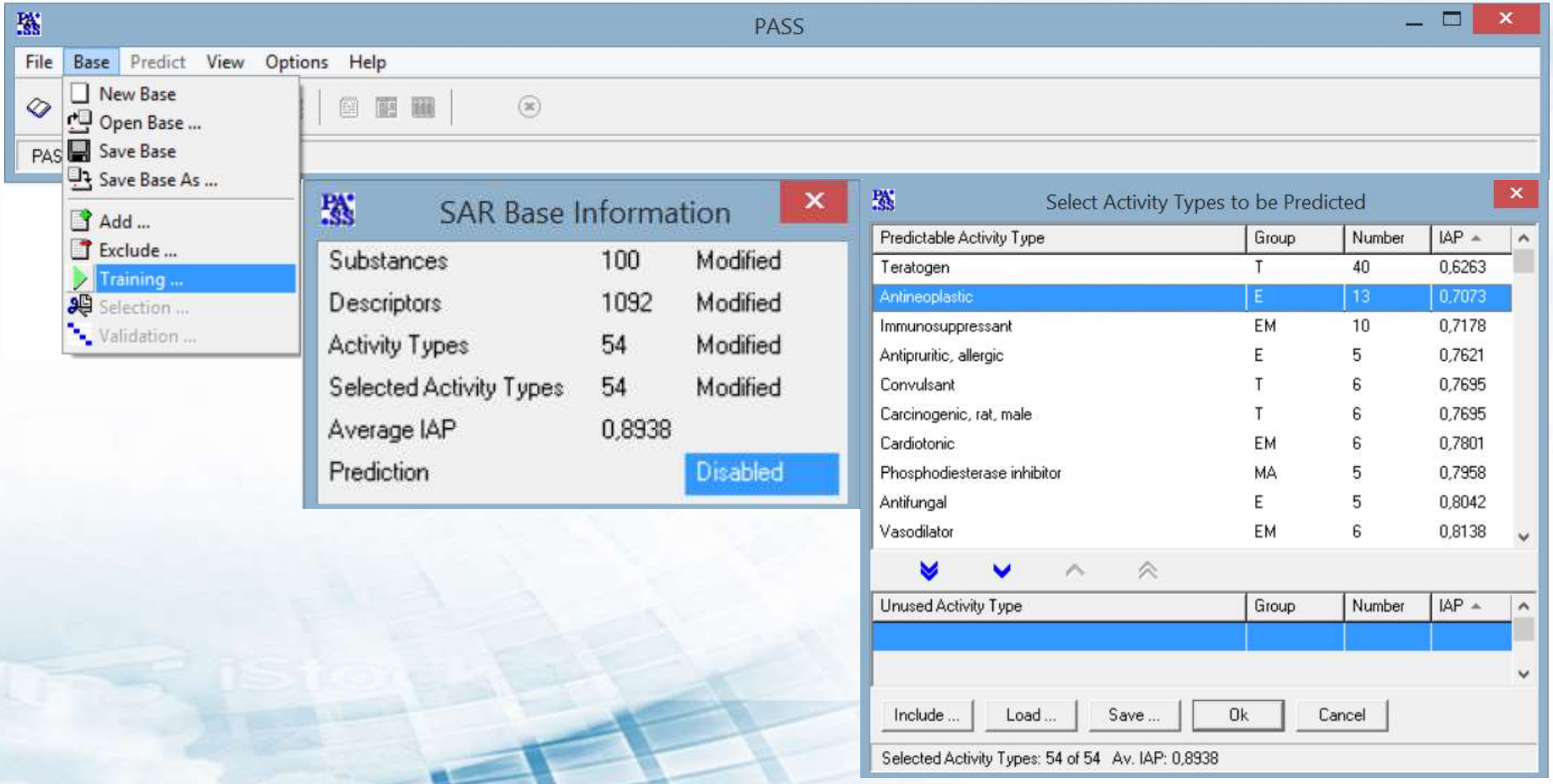
Selected Activity Types: 110 of 7474 Av. IAP: 0,9697

PASS Pro: Creating new SAR Base

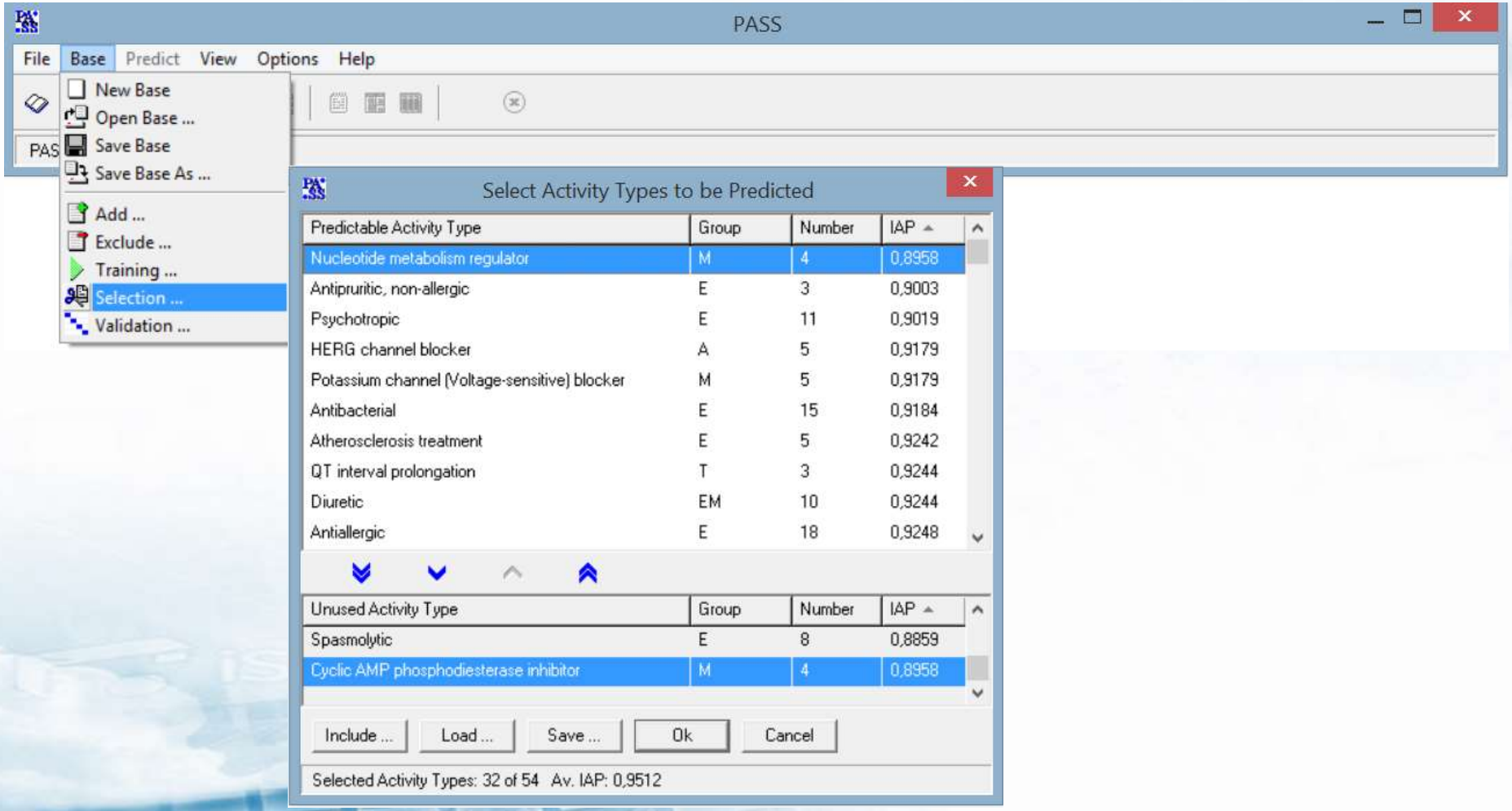




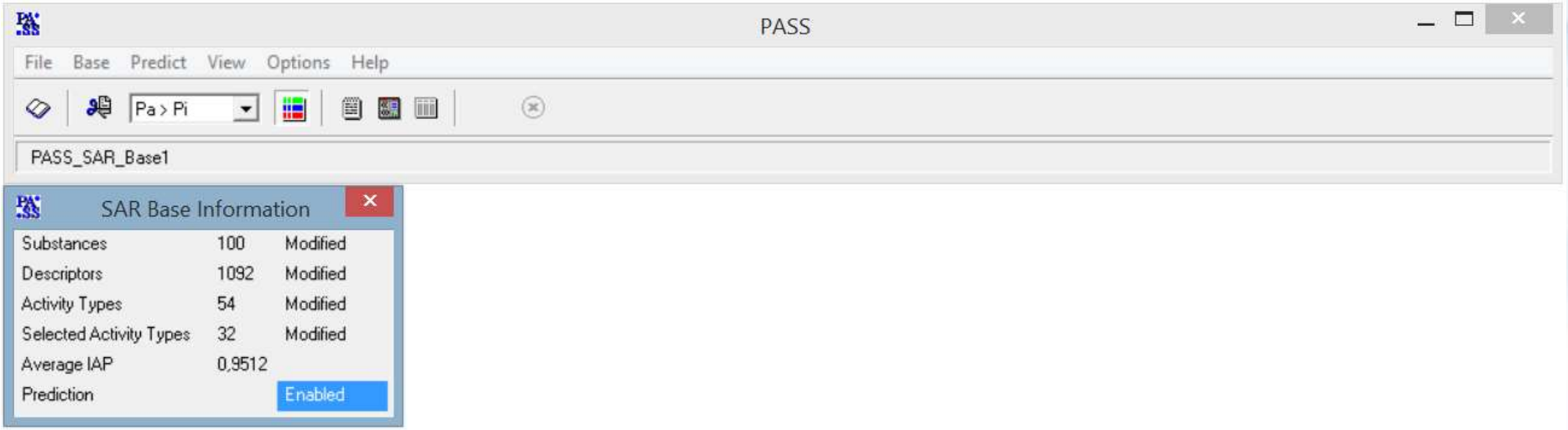
PASS Pro: Training



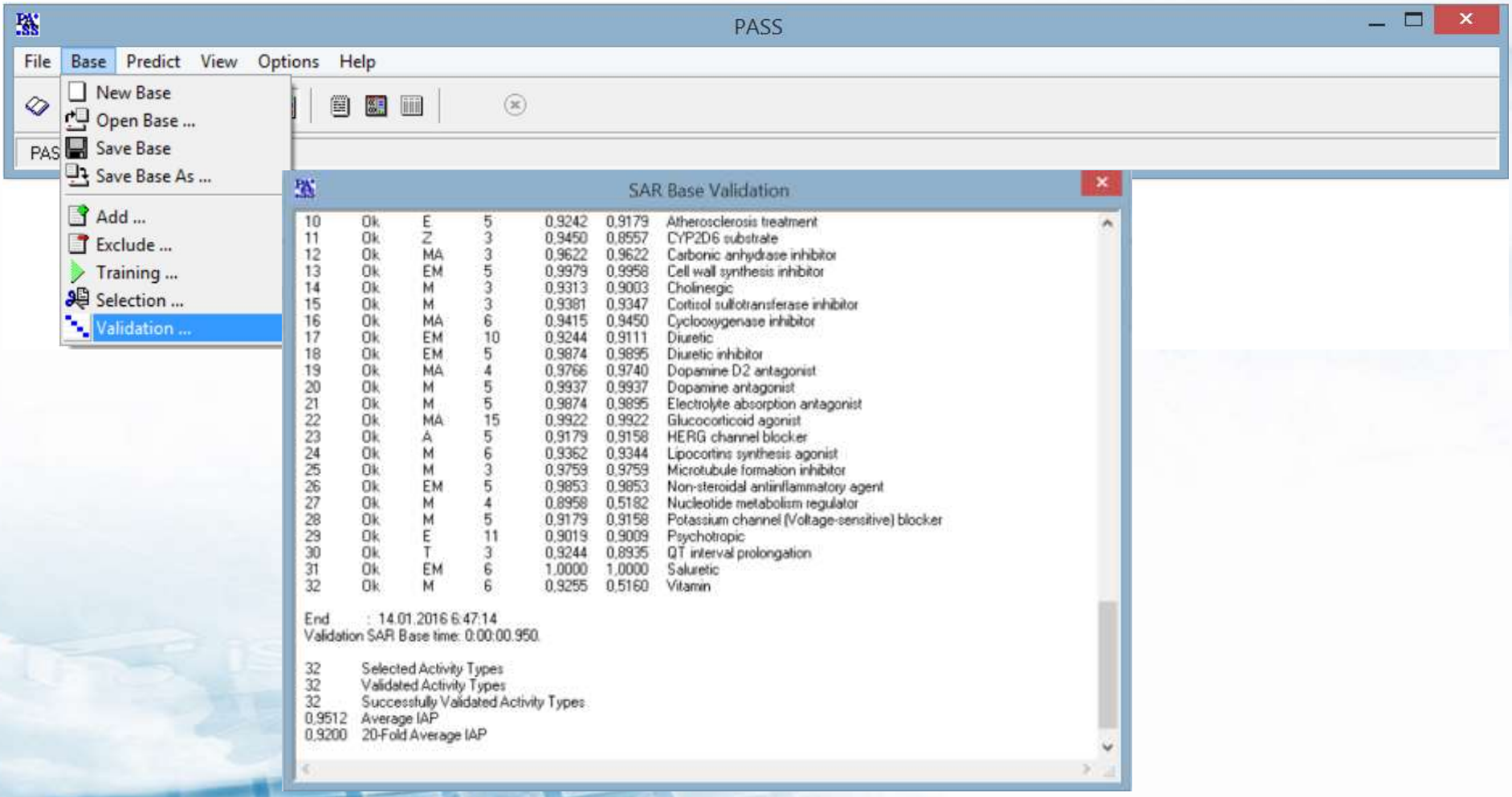
PASS Pro: Selection procedure



PASS Pro: Ready for Prediction



PASS Pro: 20-fold validation

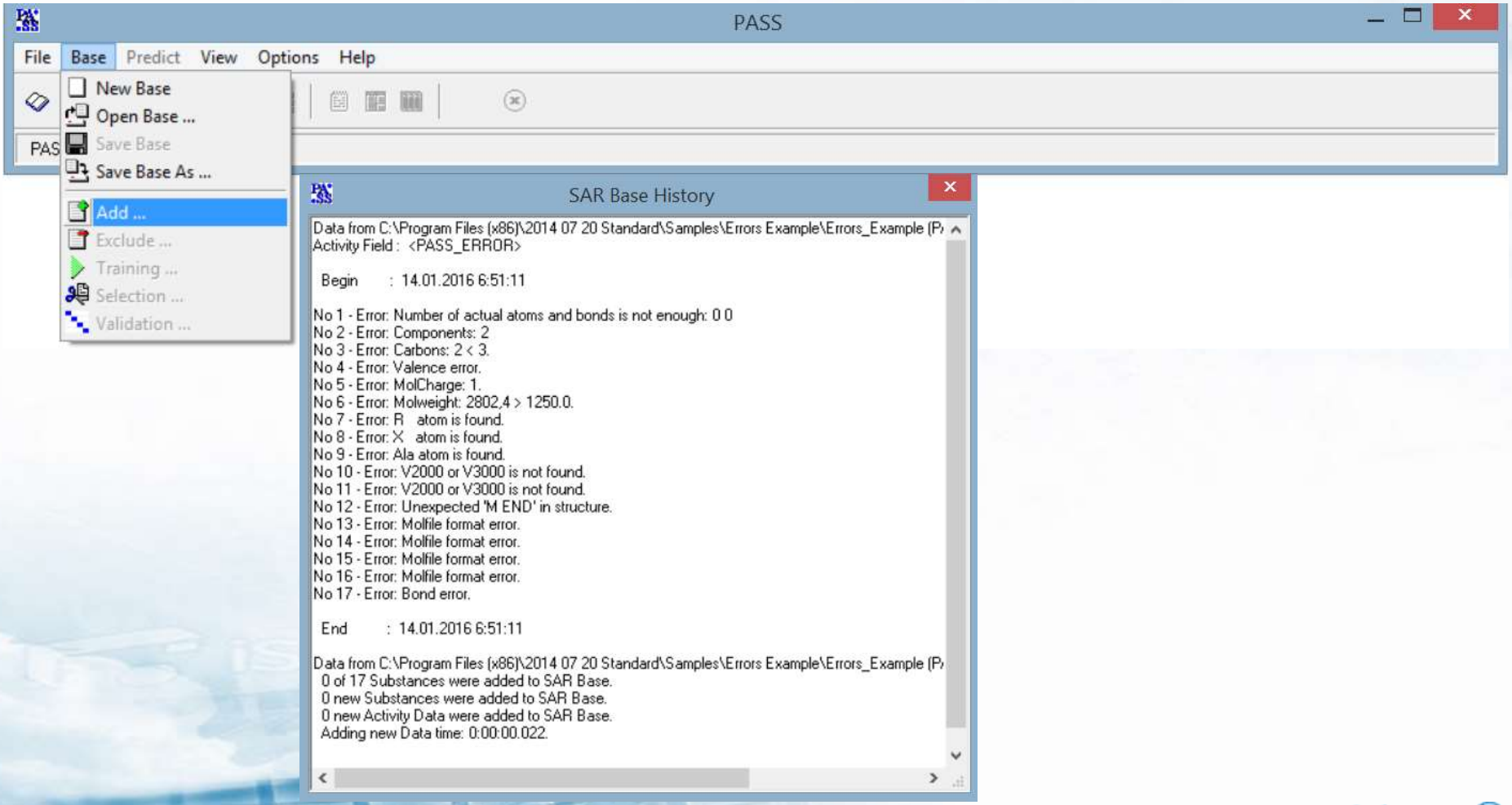


10	Ok	E	5	0,9242	0,9179	Atherosclerosis treatment
11	Ok	Z	3	0,9450	0,8557	CYP2D6 substrate
12	Ok	MA	3	0,9622	0,9622	Carbonic anhydrase inhibitor
13	Ok	EM	5	0,9979	0,9958	Cell wall synthesis inhibitor
14	Ok	M	3	0,9313	0,9003	Cholinergic
15	Ok	M	3	0,9381	0,9347	Cortisol sulfotransferase inhibitor
16	Ok	MA	6	0,9415	0,9450	Cyclooxygenase inhibitor
17	Ok	EM	10	0,9244	0,9111	Diuretic
18	Ok	EM	5	0,9874	0,9895	Diuretic inhibitor
19	Ok	MA	4	0,9766	0,9740	Dopamine D2 antagonist
20	Ok	M	5	0,9937	0,9937	Dopamine antagonist
21	Ok	M	5	0,9874	0,9895	Electrolyte absorption antagonist
22	Ok	MA	15	0,9922	0,9922	Glucocorticoid agonist
23	Ok	A	5	0,9179	0,9158	HERG channel blocker
24	Ok	M	6	0,9362	0,9344	Lipocortins synthesis agonist
25	Ok	M	3	0,9759	0,9759	Microtubule formation inhibitor
26	Ok	EM	5	0,9853	0,9853	Non-steroidal antiinflammatory agent
27	Ok	M	4	0,8958	0,5182	Nucleotide metabolism regulator
28	Ok	M	5	0,9179	0,9158	Potassium channel (Voltage-sensitive) blocker
29	Ok	E	11	0,9019	0,9009	Psychotropic
30	Ok	T	3	0,9244	0,8935	QT interval prolongation
31	Ok	EM	6	1,0000	1,0000	Saluretic
32	Ok	M	6	0,9255	0,5160	Vitamin

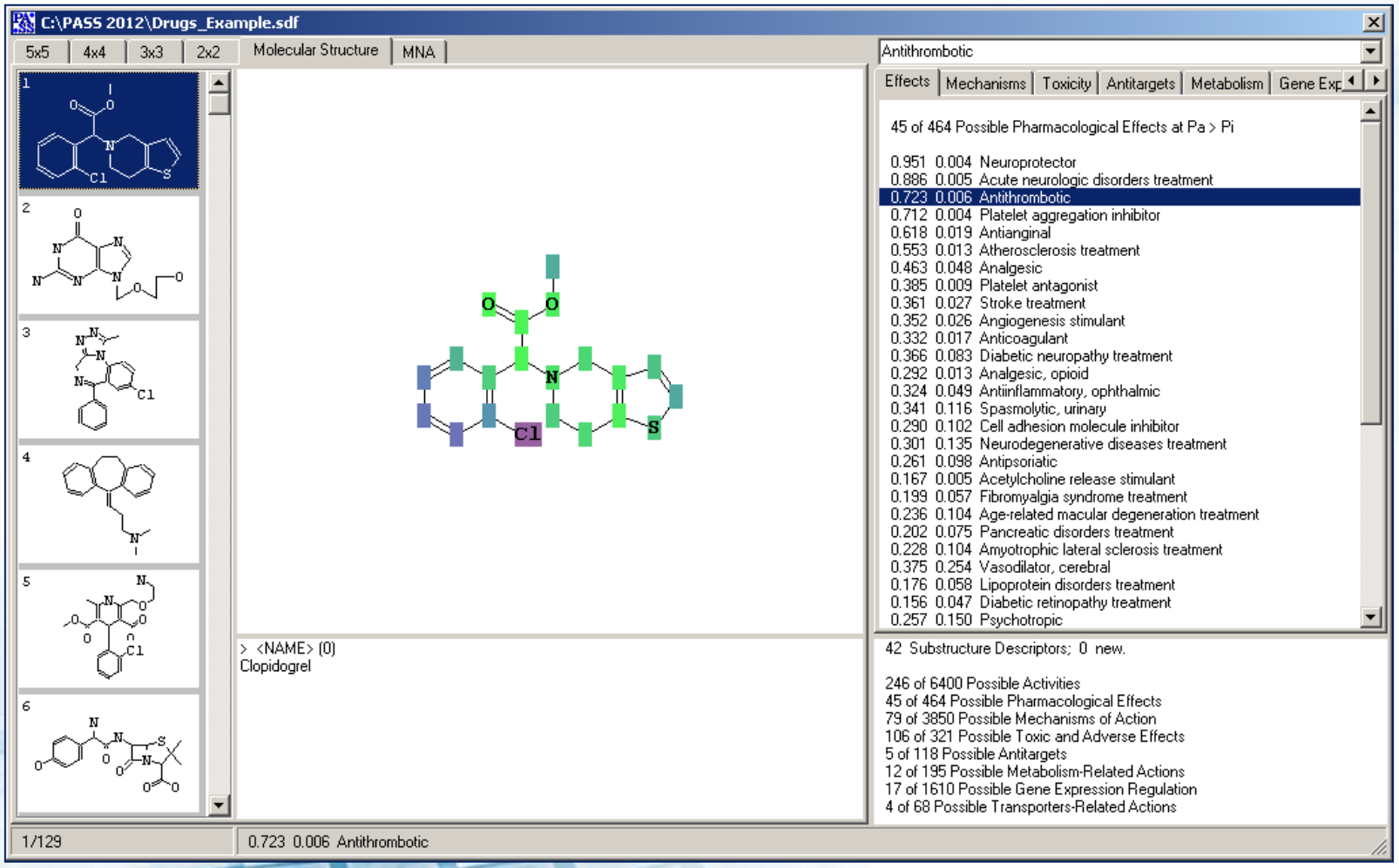
End : 14.01.2016 6:47:14
Validation SAR Base time: 0:00:00.950

32	Selected Activity Types
32	Validated Activity Types
32	Successfully Validated Activity Types
0,9512	Average IAP
0,9200	20-Fold Average IAP

PASS Pro: Quality Control



PASS predictions for Clopidogrel



Clopidogrel: predicted vs. known activities

Abdominal pain
Acute neurologic disorders treatment
Agranulocytosis
Allergic reaction
Anaphylaxis
Anemia
Angioedema
Angiogenesis inhibitor
Antianginal
Antiarthritic
Anticoagulant
Antineoplastic
Antipsoriatic
Antithrombotic
Anxiety
Arthralgia
Atherosclerosis treatment
Back pain
Behavioral disturbance
Blindness
Bronchoconstrictor
Cardiotoxic
Cataract
CCL4 expression enhancer
CCL5 expression enhancer
Chest pain
Colic
Colitis
Conjunctivitis
Consciousness alteration
Constipation
Cough
CYP2 substrate
CYP2C substrate
CYP2C19 inhibitor
CYP2C19 substrate
CYP2C9 inhibitor
CYP3A substrate
CYP3A4 substrate
Cytochrome P450 inhibitor
Dermatitis
Dermatologic
Dizziness
Drug eruption
Dyspepsia
Emetic
Eosinophilia
Erythema
Erythema multiforme
Exanthema
Flatulence
GP IIb/IIIa receptor antagonist
Hallucinogen
Headache
Heart failure
Hematotoxic
Hemorrhage
Henoch-Schonlein purpura
Hepatic failure
Hepatitis
Hepatotoxic
Hypertensive
Hyperthermic
Hypotension
Infection
Insomnia
Lassitude
Leukopenia
Lichen planus
Lichenoid eruption
Malaise
Menstruation disturbance
Myalgia
Nausea
Necrosis
Nephrotoxic
Neuroprotect
Neutropenia
Ocular toxicity
Pain
Pancreatitis
Pancytopenia
Platelet aggregation inhibitor
Platelet antagonist
Pruritus
Pulmonary embolism
Purinergic P2 antagonist
Purinergic P2T antagonist
Purinergic P2Y antagonist
Purinergic P2Y12 antagonist
Purinergic receptor antagonist
Purpura
Renal colic
Reproductive dysfunction
Rhinitis
Sensory disturbance
Serum sickness
Shock
Sinusitis
Sleep disturbance
Stomatitis
Syncope
THBS1 expression enhancer
Thrombocytopenia
Toxic
Toxic epidermal necrolysis
Toxic, gastrointestinal
TP53 expression enhancer
Urticaria
Vasculitis
Vertigo
Vision disturbance

Blue – predictions coincided with the experiment.
Black – unpredictable activities. **Red** – unpredicted activities.

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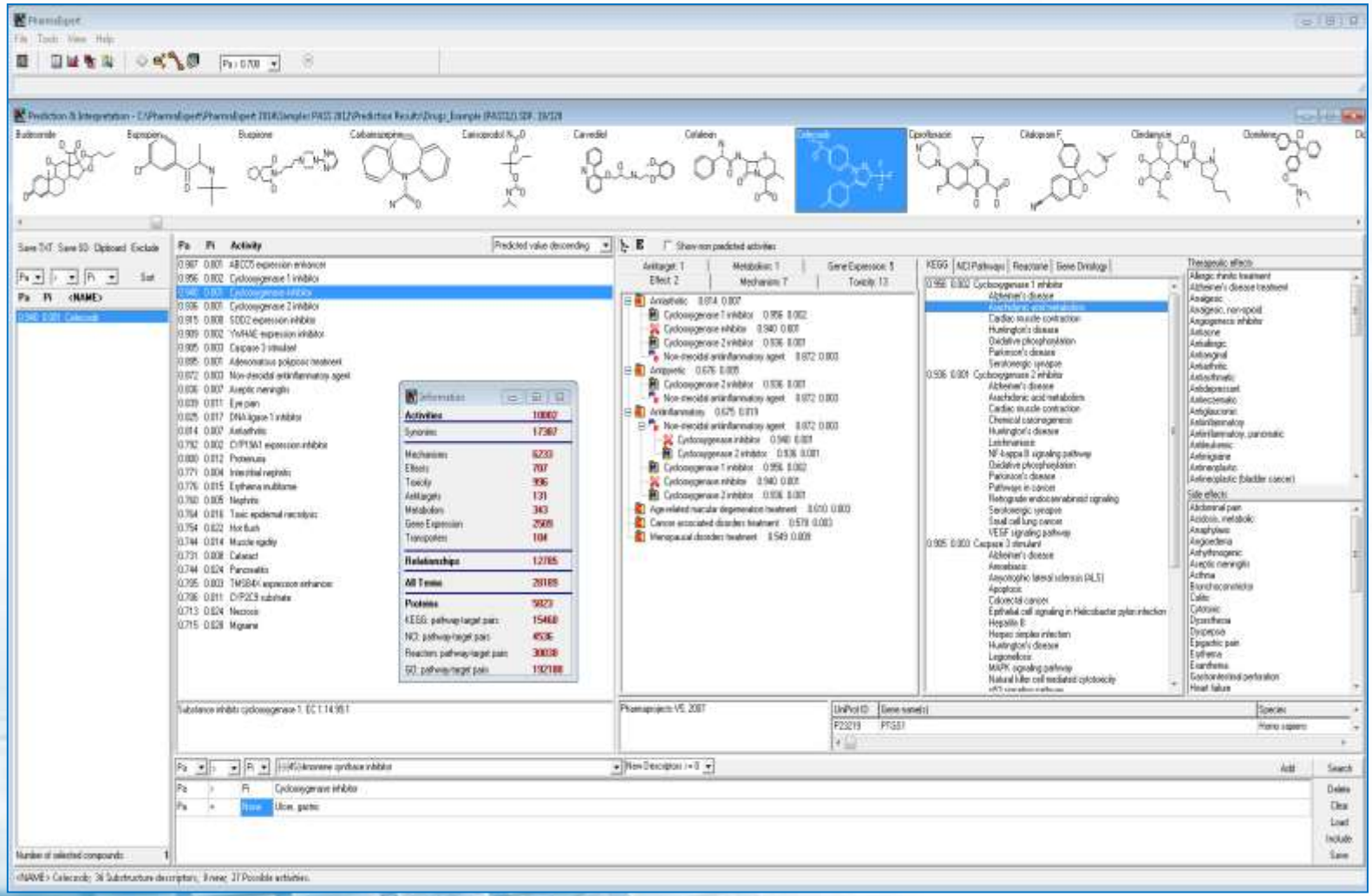
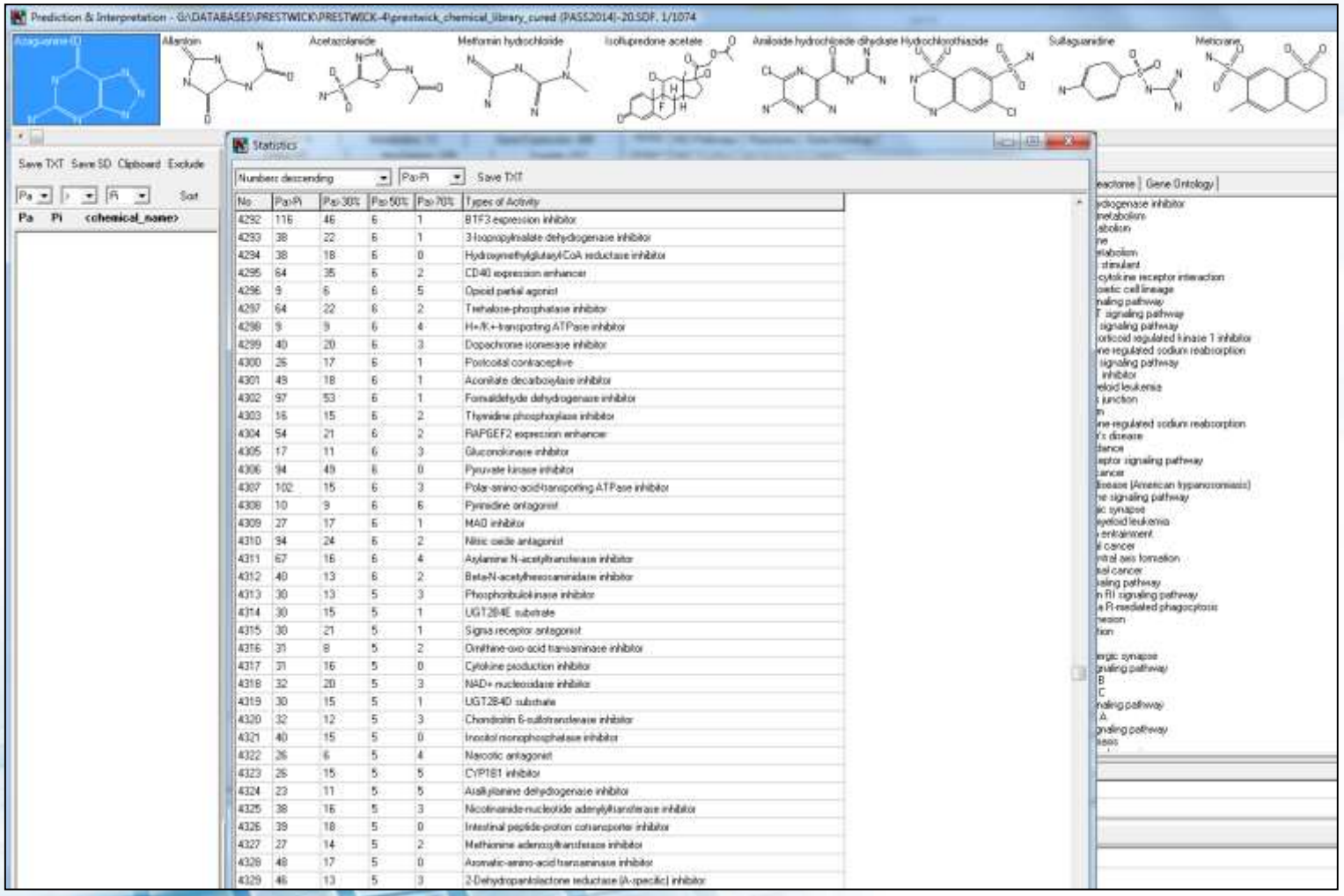
7. Way2Drug.com: further progress

PharmaExpert: Tool for analysis of PASS predictions

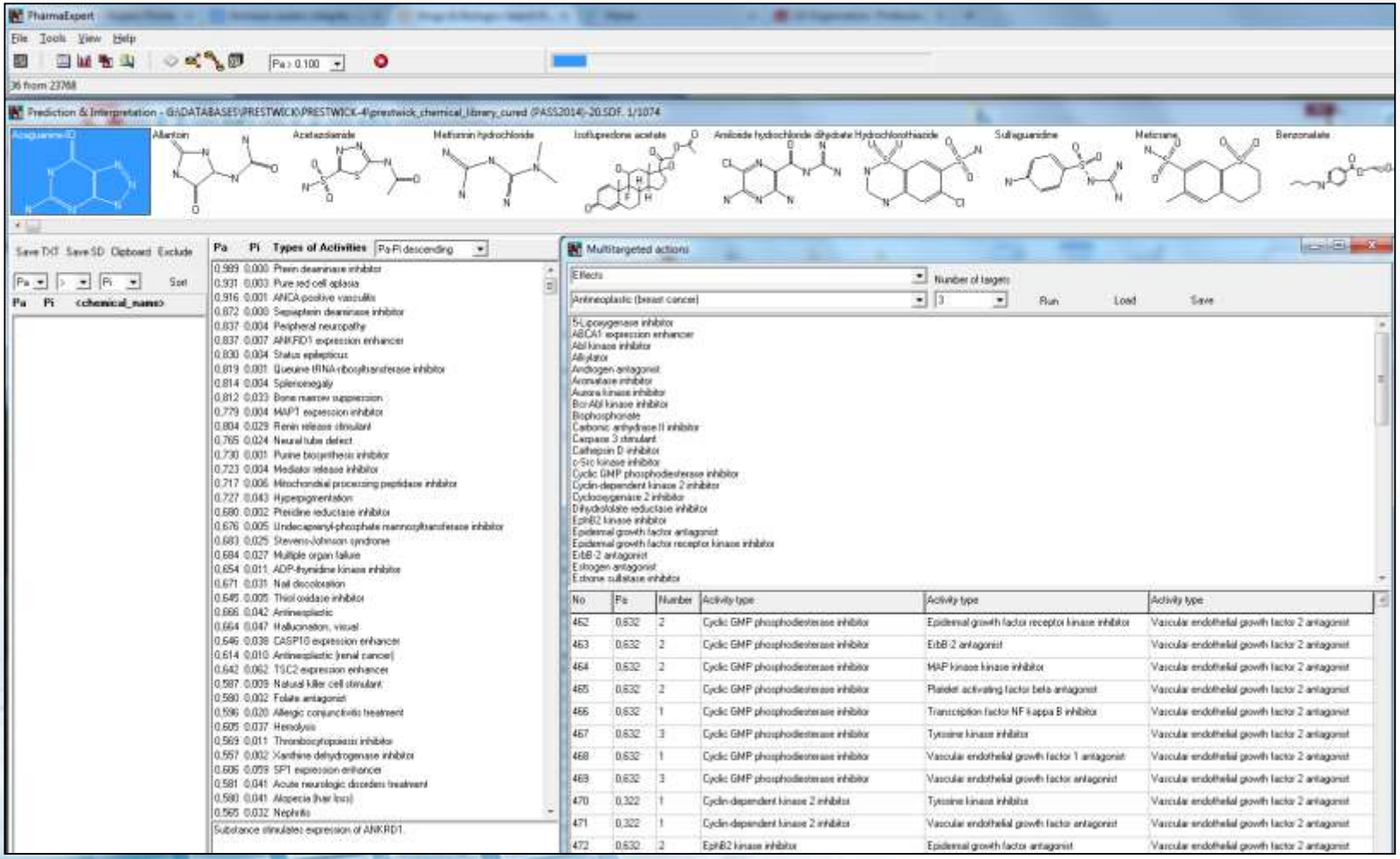


PharmaExpert: Statistics of predicted activities

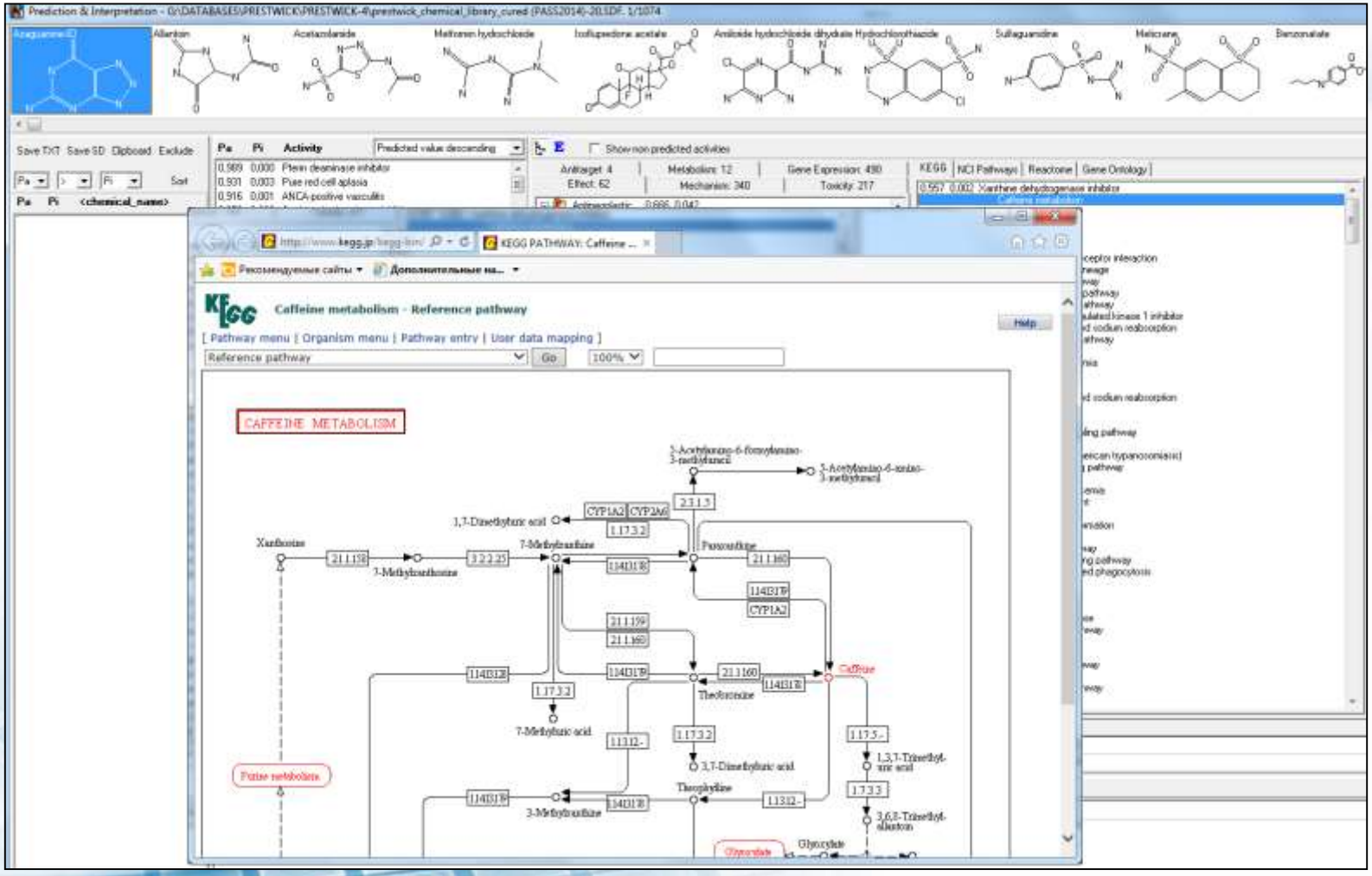


No	Pa>Pi	Pa>30%	Pa>50%	Pa>70%	Types of Activity
4292	116	46	6	1	BTF3 expression inhibitor
4293	38	22	6	1	3-Isopropylmalate dehydrogenase inhibitor
4294	38	18	6	0	Hydroxymethylglutaryl-CoA reductase inhibitor
4295	64	35	6	2	CD40 expression enhancer
4296	9	6	6	5	Opioid partial agonist
4297	64	22	6	2	Trehalose-phosphatase inhibitor
4298	9	9	6	4	H+/K+-transporting ATPase inhibitor
4299	40	20	6	3	Dopachrome isomerase inhibitor
4300	26	17	6	1	Postcoital contraceptive
4301	48	18	6	1	Aconitate decarboxylase inhibitor
4302	97	53	6	1	Formaldehyde dehydrogenase inhibitor
4303	16	15	6	2	Thymidine phosphorylase inhibitor
4304	54	21	6	2	RAPGEF2 expression enhancer
4305	17	11	6	3	Gluconokinase inhibitor
4306	94	49	6	0	Pyruvate kinase inhibitor
4307	102	15	6	3	Polar-amino-acid-transporting ATPase inhibitor
4308	10	9	6	6	Pyrimidine antagonist
4309	27	17	6	1	MAO inhibitor
4310	94	24	6	2	Nitric oxide antagonist
4311	67	16	6	4	Arylamine N-acetyltransferase inhibitor
4312	40	13	6	2	Beta-N-acetylhexosaminidase inhibitor
4313	30	13	5	3	Phosphoribulokinase inhibitor
4314	30	15	5	1	UGT2B4E substrate
4315	30	21	5	1	Sigma receptor antagonist
4316	31	8	5	2	Ornithine-oxo-acid transaminase inhibitor
4317	31	16	5	0	Cytokine production inhibitor
4318	32	20	5	3	NAD+ nucleosidase inhibitor
4319	30	15	5	1	UGT2B4D substrate
4320	32	12	5	3	Chondroitin 6-sulfotransferase inhibitor
4321	40	15	5	0	Inositol monophosphatase inhibitor
4322	26	6	5	4	Narcotic antagonist
4323	26	15	5	5	CYP1B1 inhibitor
4324	23	11	5	5	Alkylglycine dehydrogenase inhibitor
4325	38	16	5	3	Nicotinamide-nucleotide adenylyltransferase inhibitor
4326	39	18	5	0	Intestinal peptide-proton cotransporter inhibitor
4327	27	14	5	2	Methionine adenosyltransferase inhibitor
4328	48	17	5	0	Aromatic-amino-acid transaminase inhibitor
4329	46	13	5	3	2-Dehydropantolactone reductase (A-specific) inhibitor

PharmaExpert: Search for multitargeted antineoplastic agents



PharmaExpert: Link to the KEGG Pathway (example)



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7. Way2Drug.com: further progress

QNA: Quantitative Neighborhoods of Atoms

According to the Hellman-Feynman theorem, interatomic and intermolecular forces are electrical in nature.

Feynman R. Ph. *Phys. Rev.*, 1939, 56, 340-343.

$$P_i = B_i \sum_k (Exp(-½C))_{ik} B_k$$

$$Q_i = B_i \sum_k (Exp(-½C))_{ik} B_k A_k$$

$$A = ½(IP + EA)$$

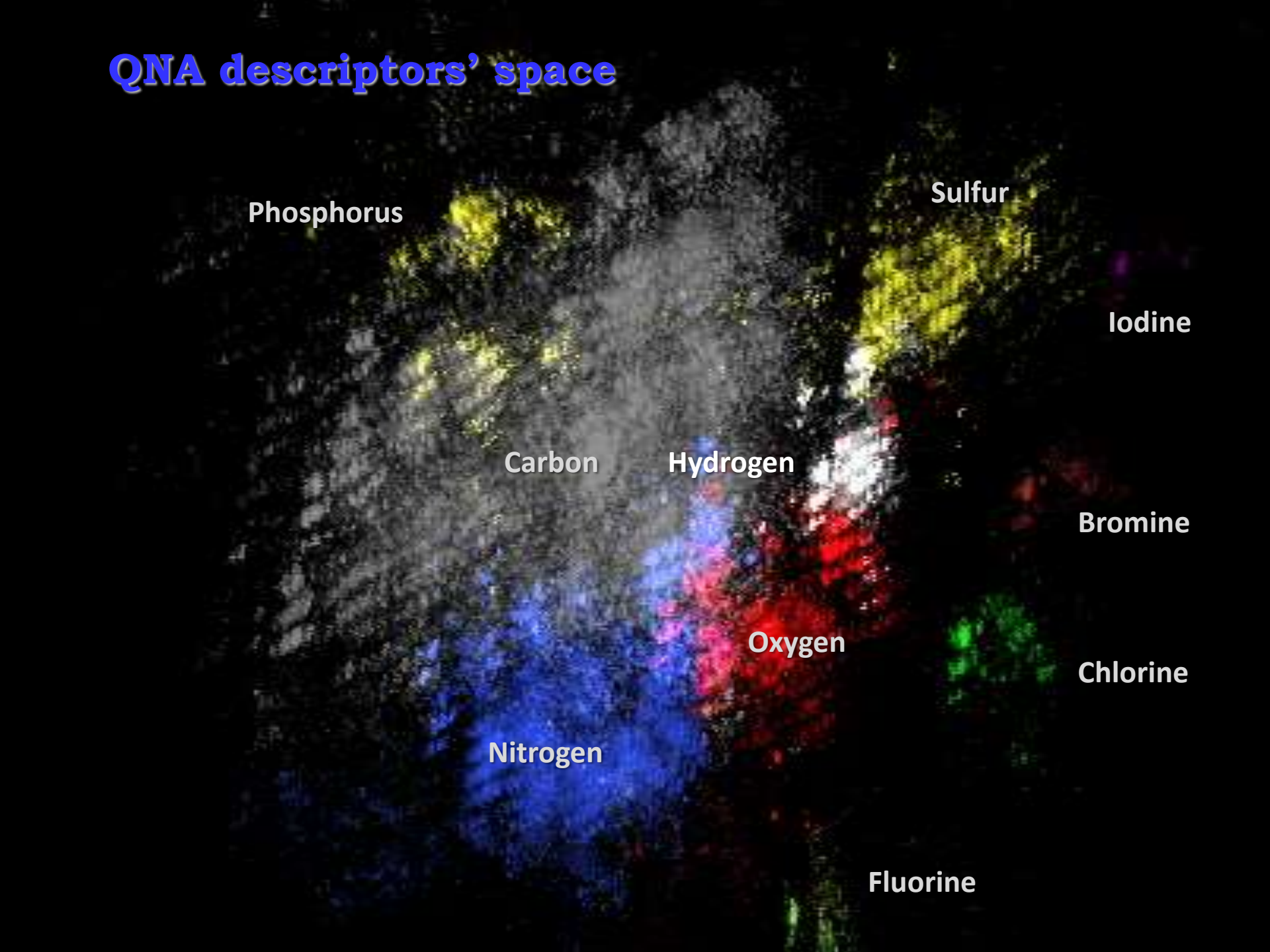
$$B = (IP - EA)^{-½}$$

IP is the first ionization potential,

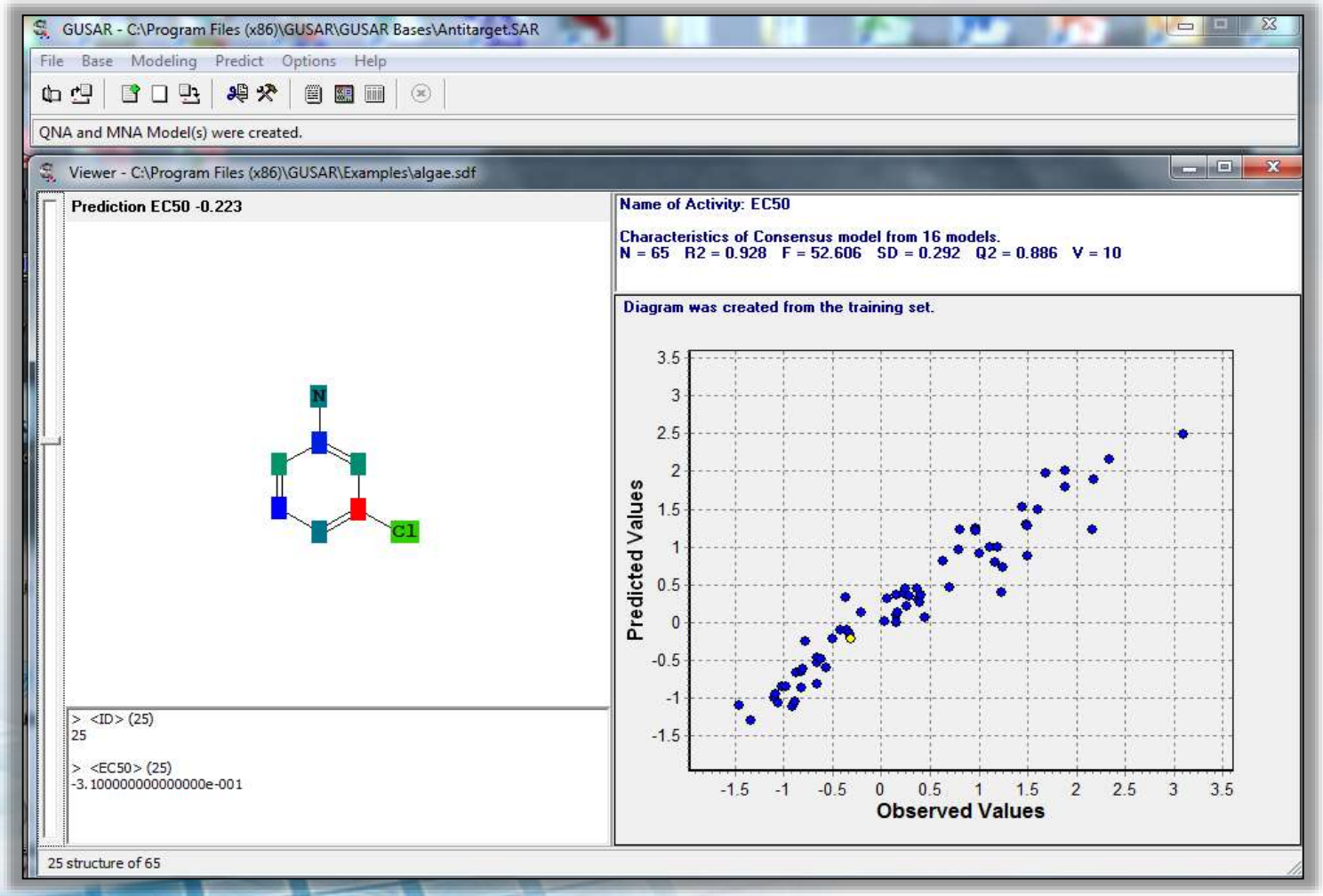
EA is the electron affinity.

Robert G. Parr et al. *J. Chem. Phys.*, 1978, 68(8), 3801-3807.
Gasteiger J, Marsili M. *Tetrahedron*, 1980, 36, 3219-3228.
Rappe A K and W A Goddard III. *J. Ph. Ch.*, 1991, 95, 3358-3363.

QNA descriptors' space

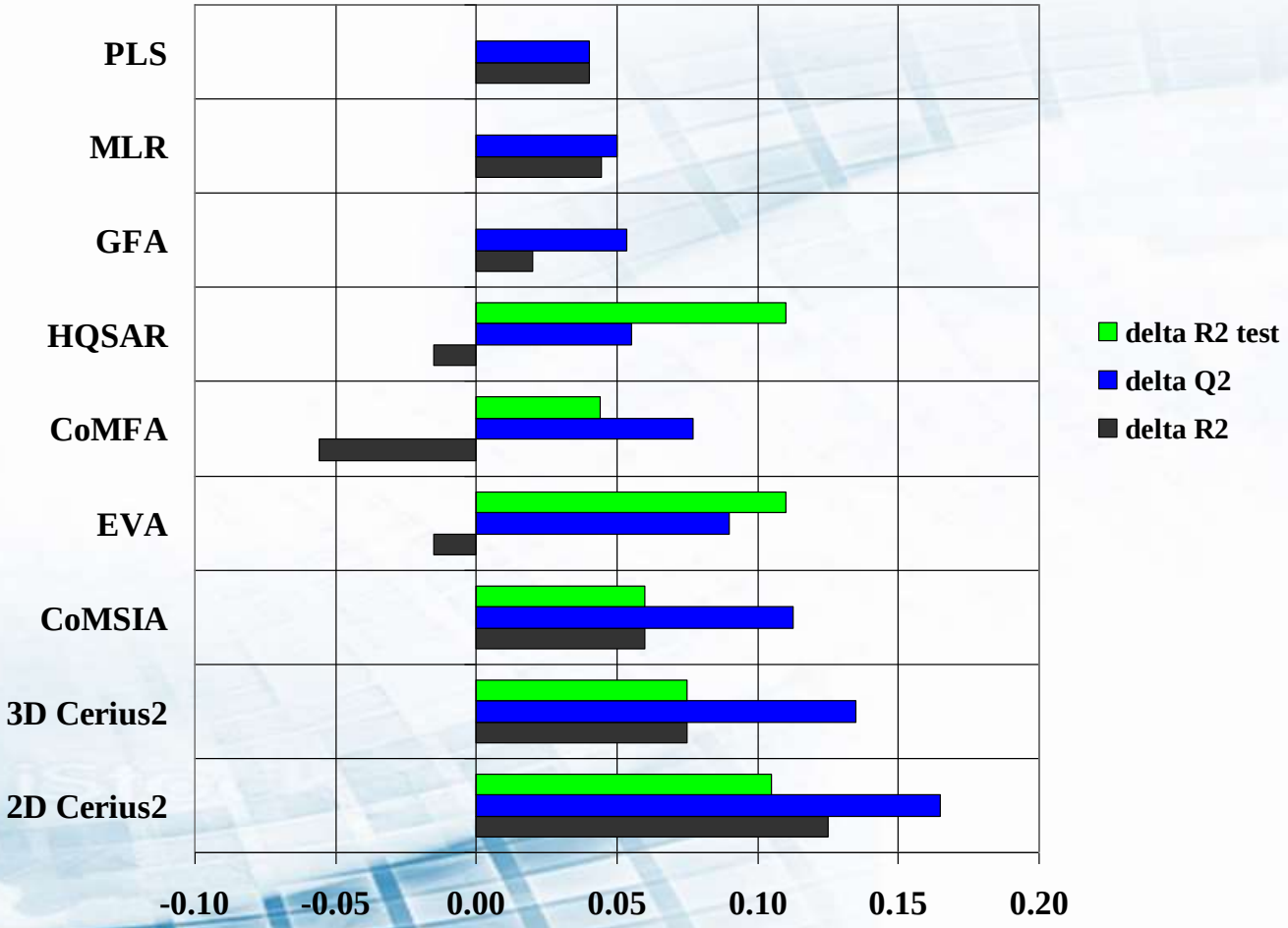


GUSAR: General Unrestricted Structure-Activity Relationships



Filimonov D.A. et al. *SAR and QSAR Environ. Res*., 2009, **20**: 679-709.

GUSAR: Superiority in performance in comparison with some other (Q)SAR methods



Filimonov D.A. et al. *SAR and QSAR Environ. Res*., 2009, **20**: 679-709.

Impacts of atoms into particular activity

For each atom in a molecule all MNA/QNA descriptors are generated. Using these descriptors for each particular activity Pa и Pi values are calculated.

Each atom is colored in accordance with the following:

Red	**: = 0.3+0.7*Pi**	**(negative impact on activity)**
Green	**: = 0.3+0.7*Pa**	**(positive impact on activity)**
Blue	**: = 1-0.7*(Pi+Pa)**	**(neutral impact on activity)**

This can be interpreted in the following way:

If Pa = 0 and Pi = 1, then Red = 1, Green = 0.3, Blue = 0.3 – bright red color;

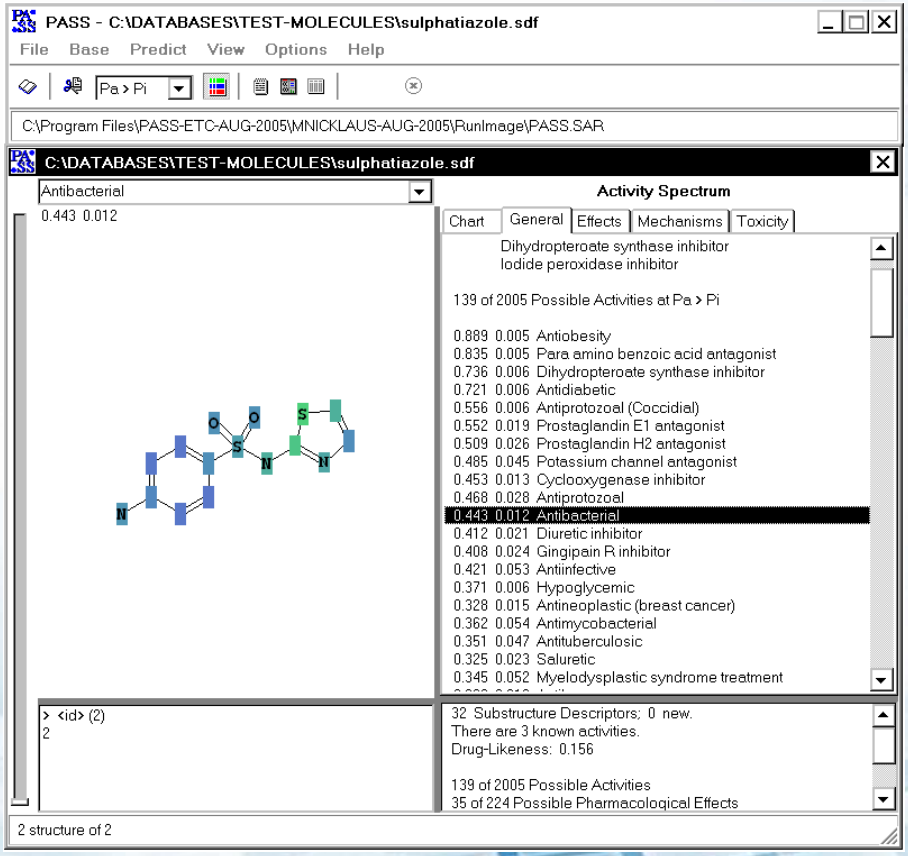
If Pa = 1 and Pi = 0, then Red = 0.3, Green = 1, и Blue = 0.3 – bright green color;

If Pa = 0 and Pi = 0, then Red = 0.3, Green = 0.3, Blue = 1 – bright blue color;

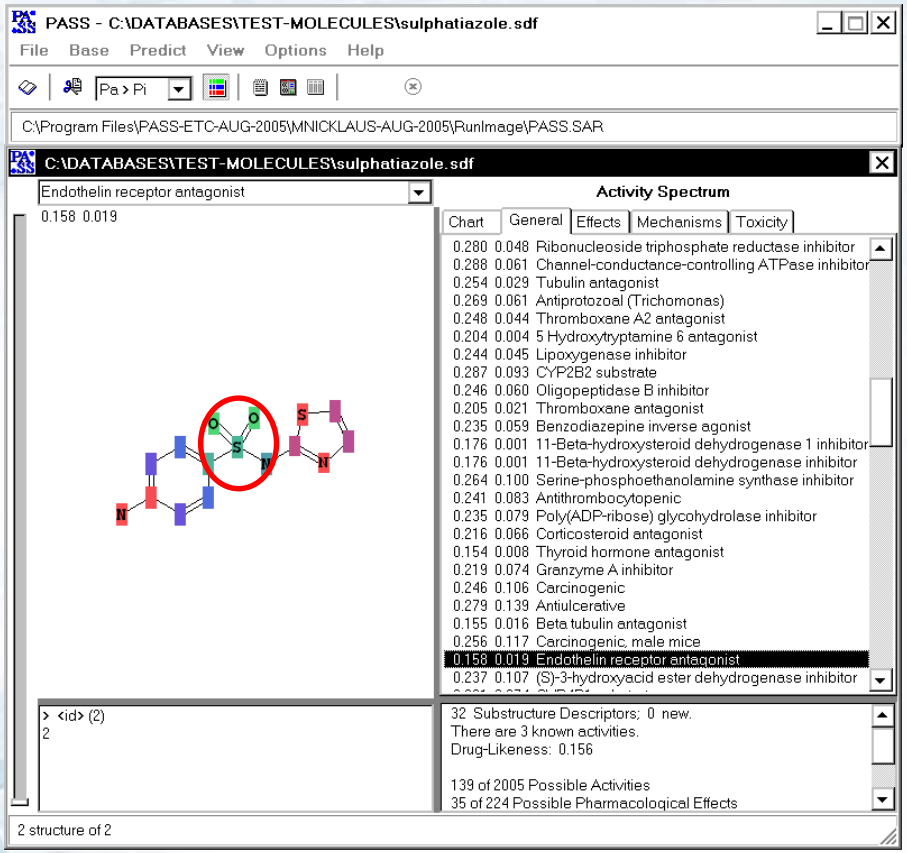
If Pa = 0.33 and Pi = 0.33, then Red = 0.53, Green = 0.53, Blue = 0.53 – grey color.

Case study: Sulfathiazole

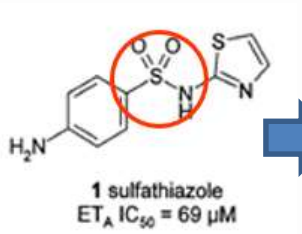
Antibacterial Activity



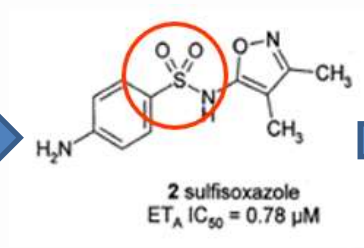
ET_A Receptor Antagonist



"Critical fragment" remains unchanged



1



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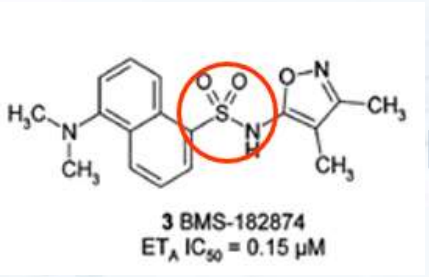

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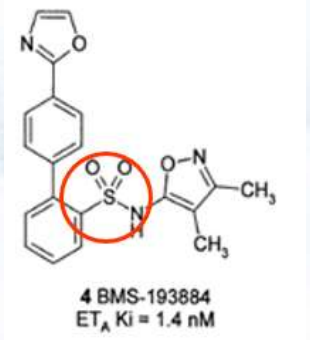

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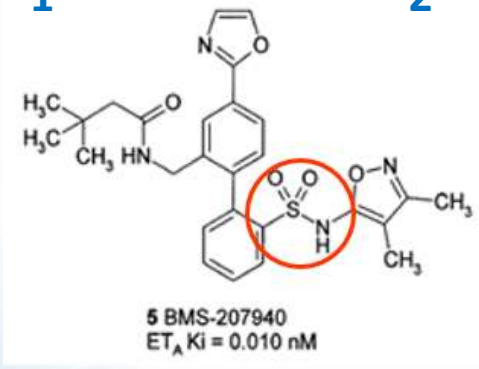

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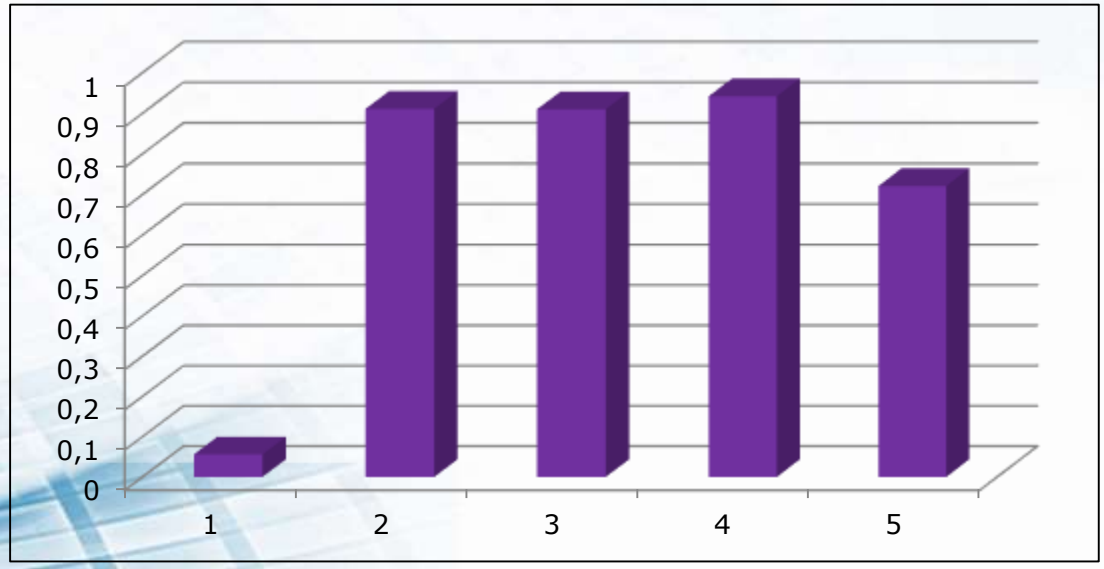

Wermuth C. *J. Med. Chem.*, 2004, 47: 1303-1314.

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GUSAR Application to the antifungal activities

Table 3. QSAR modeling of antifungal activities results.

Activity name	Number of compounds Training set/Test set	Number of models	R^2 training set	Q^2 training set	R^2 test set	Coverage,%	RMSE test
B.s.	12/5	4	0.89	0.72	0.57	80	35.74
F.m.	12/5	21	0.89	0.77	0.80	100	28.01
F.o.	12/5	3	0.85	0.68	0.66	100	17
R.s.	12/5	20	0.91	0.79	0.72	100	27.58
S.s.	12/5	11	0.89	0.79	0.81	100	37.29
V.i.	12/5	2	0.83	0.61	0.82	100	20.37

R^2 – determination coefficient

Q^2 – determination coefficient calculated for leave-one-out cross validation procedure

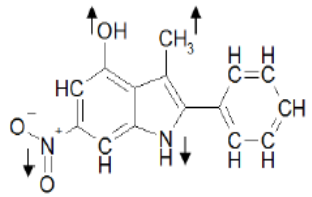

Figure 2. Atom contribution into the antifungal activity.

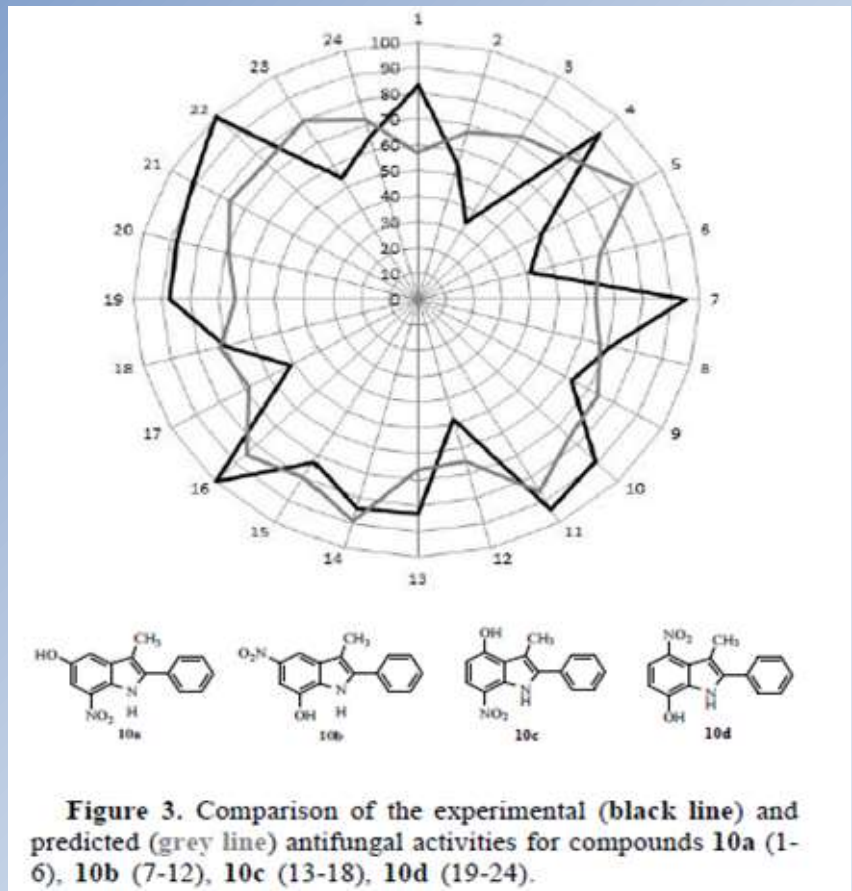

Figure 3. Comparison of the experimental (**black line**) and predicted (grey line) antifungal activities for compounds **10a** (1-6), **10b** (7-12), **10c** (13-18), **10d** (19-24).

Kokurkina G.V. et al. *Eur. J. Med. Chem.*, 2012, **46**: 4374-4382**.**

IBMC

SEVENTH FRAMEWORK PROGRAMME

Baltinfect
Unlocking infectious diseases research potential at Rīga Stradiņš University

RĪGAS STRADIŅA UNIVERSITĀTE

Drug repositioning

DRUG REPOSITIONING: IDENTIFYING AND DEVELOPING NEW USES FOR EXISTING DRUGS

Ted T. Ashburn and Karl B. Thor

Biopharmaceutical companies attempting to increase productivity through novel discovery

Drug News Perspect 22(2), March 2009

MEETING REPORT

DRUG REPOSITIONING SUMMIT: FINDING NEW ROUTES TO SUCCESS

Highlights from the Cambridge Healthtech Institute's Third Annual Drug Repositioning Summit, held October 6–7, 2008, in Boston

INSIGHT

THE VALUE OF DRUG REPOSITIONING IN THE CURRENT PHARMACEUTICAL MARKET

Repurp
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by Edward L. Tobinick

covery efforts efficiently has become of pri-

REVIEWS

Drug Discovery Today • Volume 16, Numbers 7/8 • April 2011

ELSEVIER

Reviews • KEYNOTE REVIEW

In silico repositioning of approved drugs for rare and neglected diseases

Sean Ekins[1,2,3,4],
Matthew D. Kras

OPEN ACCESS Freely available online

PLoS COMPUTATIONAL BIOLOGY

Drug Discovery Using Chemical Systems Biology: Repositioning the Safe Medicine Comtan to Treat Multi-Drug and Extensively Drug Resistant Tuberculosis

Sarah L. Kinnings[1]*, Nina Liu[2]*, Nancy Buchmeier[3]*, Peter J. Tonge[2], Lei Xie[4]*, Philip E. Bourne[4,5]*

1 Department of Biology, University of York, York, United Kingdom, 2 Institute of Chemical Biology & Drug Discovery, Department of Chemistry, Stony Brook University, Stony Brook, New York, United States of America, 3 Department of Chemistry and Biochemistry, University of California San Diego, La Jolla, California, United States of America, 4 San Diego Supercomputer Center, University of California San Diego, La Jolla, California, United States of America, 5 Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, La Jolla, California, United States of America

SAR and QSAR in Environmental Research
2001, Vol. 12, pp. 327–344
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TOP 200 MEDICINES: CAN NEW ACTIONS BE DISCOVERED THROUGH COMPUTER-AIDED PREDICTION?*

V. POROIKOV[a,b,†], D. AKIMOV[b], E. SHABELNIKOVA[b] and D. FILIMONOV[a]

[a]*Institute of Biomedical Chemistry of the Russian Academy of Medical Sciences, 10, Pogodinskaya Street, Moscow, 119832, Russia;* [b]*Medical and Biological Faculty of the Russian State Medical University, 1, Ostrovityanova Street, Moscow, 117869, Russia*

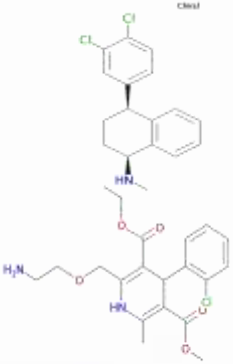
(Received 30 June 2000; In final form 31 March 2001)

Computer-aided prediction of the biological activity spectra by the program PASS was applied to a set of 130 pharmaceuticals from the list of the Top 200 medicines. The known pharmacological effects were found in the predicted activity spectra in 93.2% of cases. Additionally,

Drug repositioning based on PASS prediction

In 2001 we published predictions of new effects for 8 medicines from the list of Top200 Drugs [1].

Which predictions are confirmed? (informational search, September 2014)

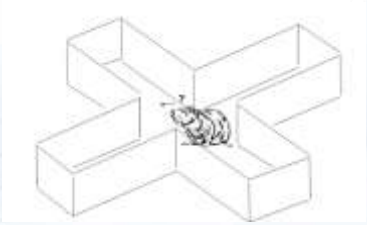


			Ref.
Sertraline	**Cocain dependency treatment**	+	[2]
Amlodipine	**Antineoplastic enhancer (moderate BCRP/ABCG2 inhibitor)**	+	[3]
Oxaprozin	**Interleukin 1 antagonist (Inhibitor of production of Interleukin 1β)**	+	[4]
Ramipril	**Antiarthritic**	+	[5]

1. Poroikov V. et al. SAR and QSAR Environ. Res., 2001, 12: 327-344.
2. Mancino M.J. et al. J. Clin. Psychopharmacol., 2014, 34: 234–239.
3. Takara K. et al. Mol. Med. Rep., 2012, 5: 603-609.
4. Rainsford K.D. et al. Inflammopharmacology, 2002, 10: 85–239.
5. Shi Q. et al. Arthritis Res. Ther., 2012, 14: R223.

Nootropic effect in some antihypertensive drugs?

Name	Pa (Nootropic effect), %
Captopril	44,6
Enalapril	65,5
Lisinopril	61,8
Perindopril	60,9
Quinapril	65,1
Ramipril	63,3
Monopril	30,9
Piracetam	81,7
Amlodipin	-
Hydrochlorothiazide	-



Perindopril in dose of 1 mg/kg, and quinapril and monopril in doses of 10 mg/kg improved the patrolling behavior in the maze, like piracetam and meclofenoxate (in doses of 300 and 120 mg/kg, respectively).

BMJ Open 2013;**3**:e002881 doi:10.1136/bmjopen-2013-002881

Geriatric medicine

Effects of centrally acting ACE inhibitors on the rate of cognitive decline in dementia

Yang Gao[1,2], Rónán O'Caoimh[1], Liam Healy[1], David M Kerins[3,4], Joseph Eustace[5], Gordon Guyatt[6], David Sammon[2], D William Molloy[1,7]

Author Affiliations

Correspondence to

Professor D William Molloy; w.molloy@ucc.ie

Published 22 July 2013

Kryzhanovskii S.A. et al. *Pharm. Chem. J.,* 2012, 45: 605-611.

www.way2drug.com

Dichotomic modelling of regulatory networks behavior

Active node

Inactive node

Inactive edge of activation

Active edge of inhibition

Active edge of activation

Edge property

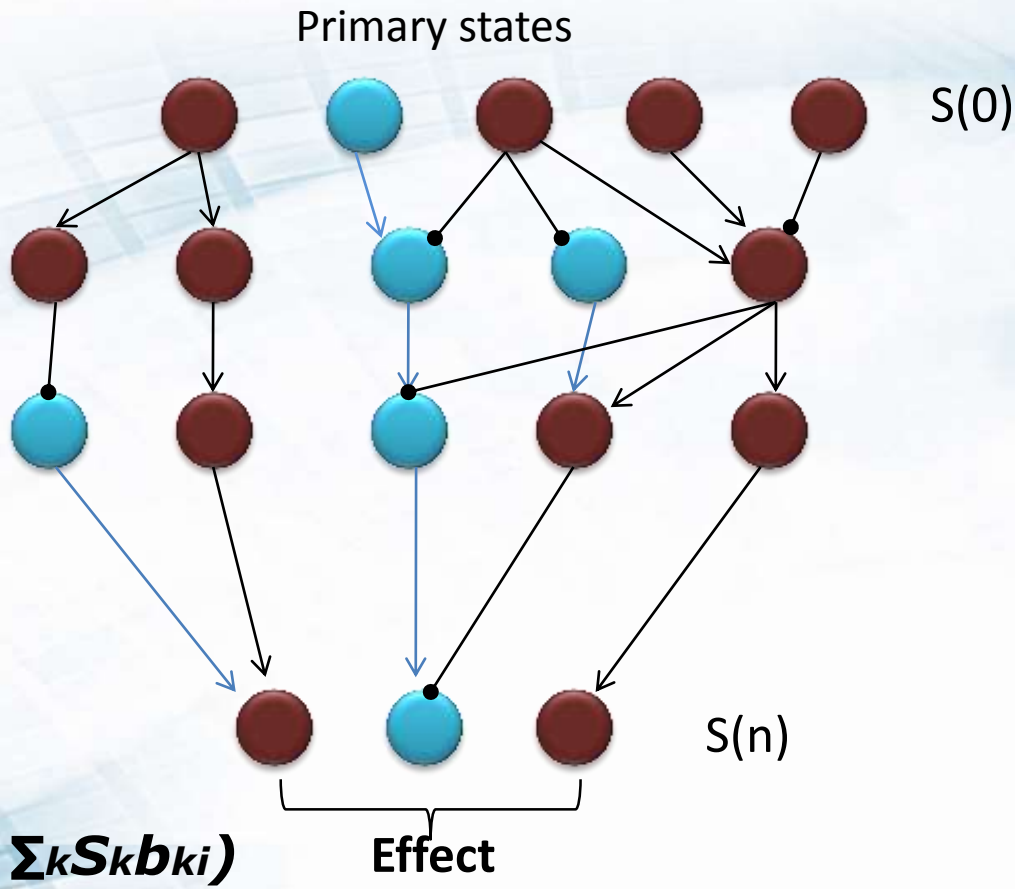
$b_{ik}=1$

$S_k=1$

$b_{ik}=-1$

$S_k=0$

State of node *i* $S_i=1$



$$F_i(S_1, S_2, \ldots, S_n) = \Theta(a_i + \sum_k S_k b_{ki})$$

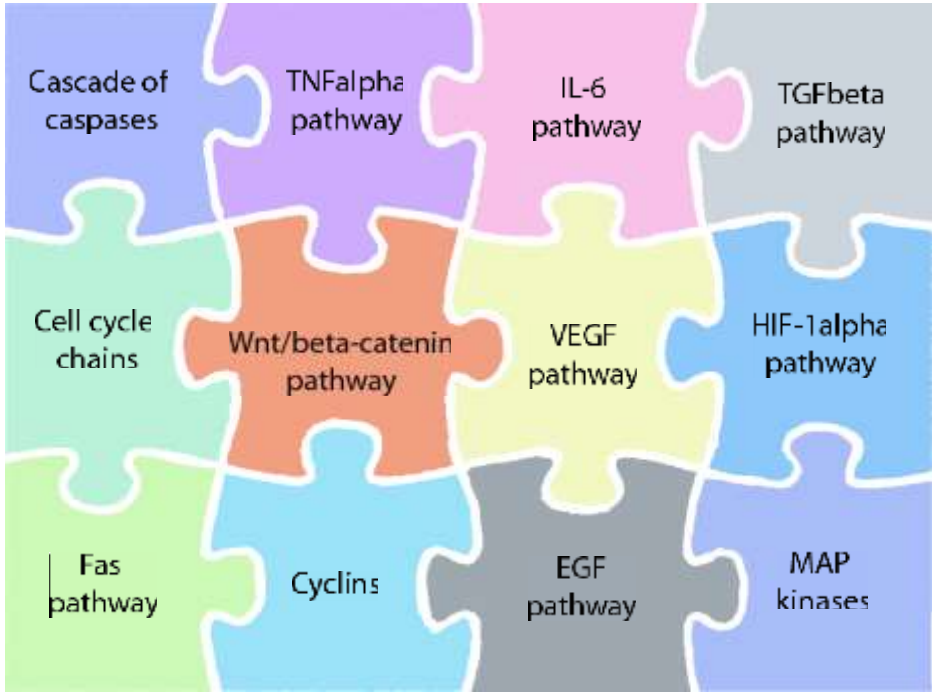
Koborova O.N. et al. SAR and QSAR Environ. Res., 2009, 20: 755-766.

Input Data for Breast Cancer Modeling

Regulatory network

TRANSPATH® database

Fragment: 2336 edges and 1405 nodes



Microarray data for breast cancer

Cyclonet database
http://cyclonet.biouml.org

- HER2/neu-positive breast carcinomas.
- Ductal carcinoma.
- Invasive ductal carcinoma and/or a nodal metastasis.
- Generalized breast cancer.

Koborova O.N. et al. SAR and QSAR Environ. Res., 2009, 20: 755-766.

Some Double and Triple Targets' Combinations Identified for Breast Cancer

No	Compounds	Action 1	Action 2	Action 3
1	4	Bcl2 antagonist	CDK-2 inhibitor	
2	10	Bcl2 antagonist	Myc inhibitor	
3	10	Bcl2 antagonist	Phosphatidylinositol 3-kinase beta inhibitor	
4	3	CDK-2 inhibitor	Myc inhibitor	
5	7	HIF-1 alpha inhibitor	Myc inhibitor	
6	10	HIF-1 alpha inhibitor	Phosphatidylinositol 3-kinase beta inhibitor	
7	10	Myc inhibitor	Phosphatidylinositol 3-kinase inhibitor	
8	10	Bcl2 antagonist	Myc inhibitor	Phosphatidylinositol 3-kinase beta inhibitor

Koborova O.N. et al. SAR and QSAR Environ. Res., 2009, 20: 755-766.

European project «From analysis of gene regulatory networks to drug» (Net2Drug)

SIXTH FRAMEWORK PROGRAMME
PRIORITY 1
LIFE SCIENCES, GENOMICS AND
BIOTECHNOLOGY FOR HEALTH

Contract for:

SPECIFIC TARGETED RESEARCH OR INNOVATION PROJECT DEDICATED TO SMEs

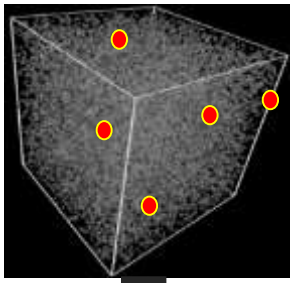
Annex I - "Description of Work"

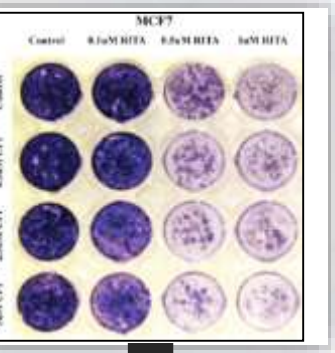
Project acronym: Net2Drug
Project full title: From gene regulatory networks to drug prediction.
Proposal/Contract no.: 037590
Related to other Contract no.:

Date of preparation of Annex I: November 5th, 2006

Operative commencement date of contract: February 1st, 2007

Participants: 9 teams from 8 countries





2 active compounds (BC, melanoma)
Synergism with RITA.

ChemNavigator database (~24,000,000 structures of organic compounds)

Virtual screening of potential multitarget anticancer substances (PASS, GUSAR)

11 compounds tested in cellular assays

Further progress:

Activity confirmed in experiments on mouse xenograft models

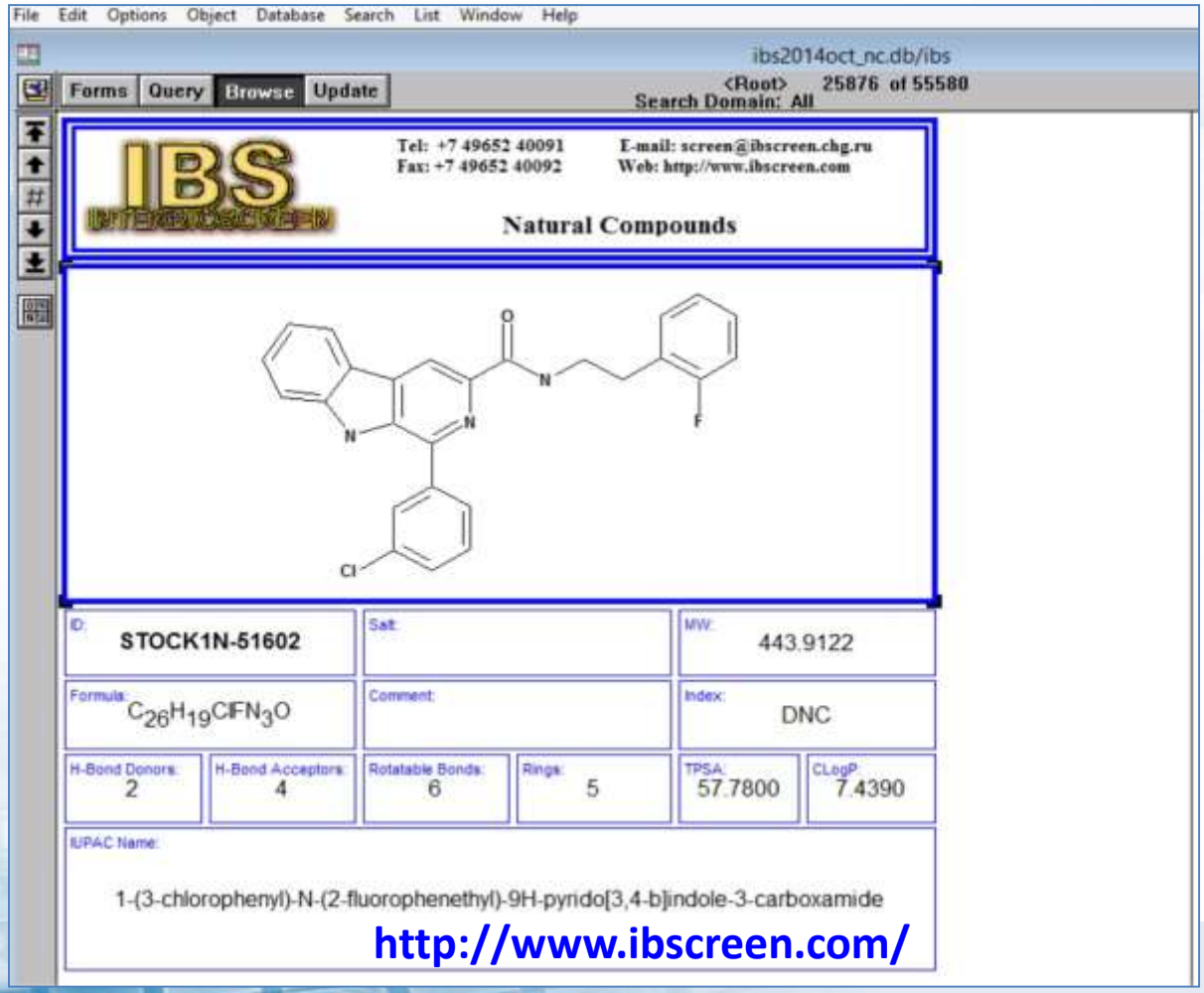
ALab – resident of «Skolkovo» (2012)

Grant of«Skolkovo» (2013)

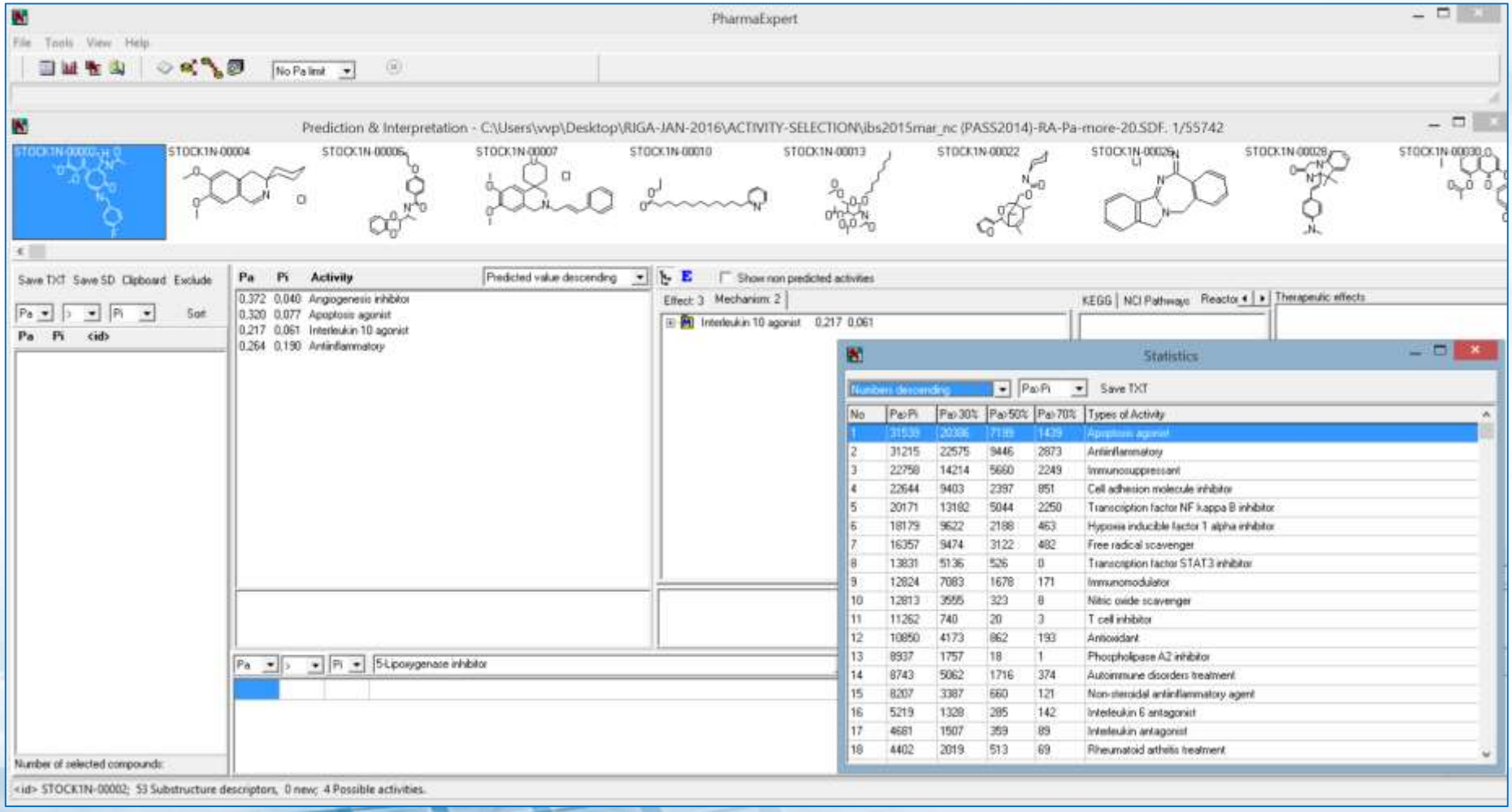
More active analogs (2014)

Mechanism(s) of action (2015)

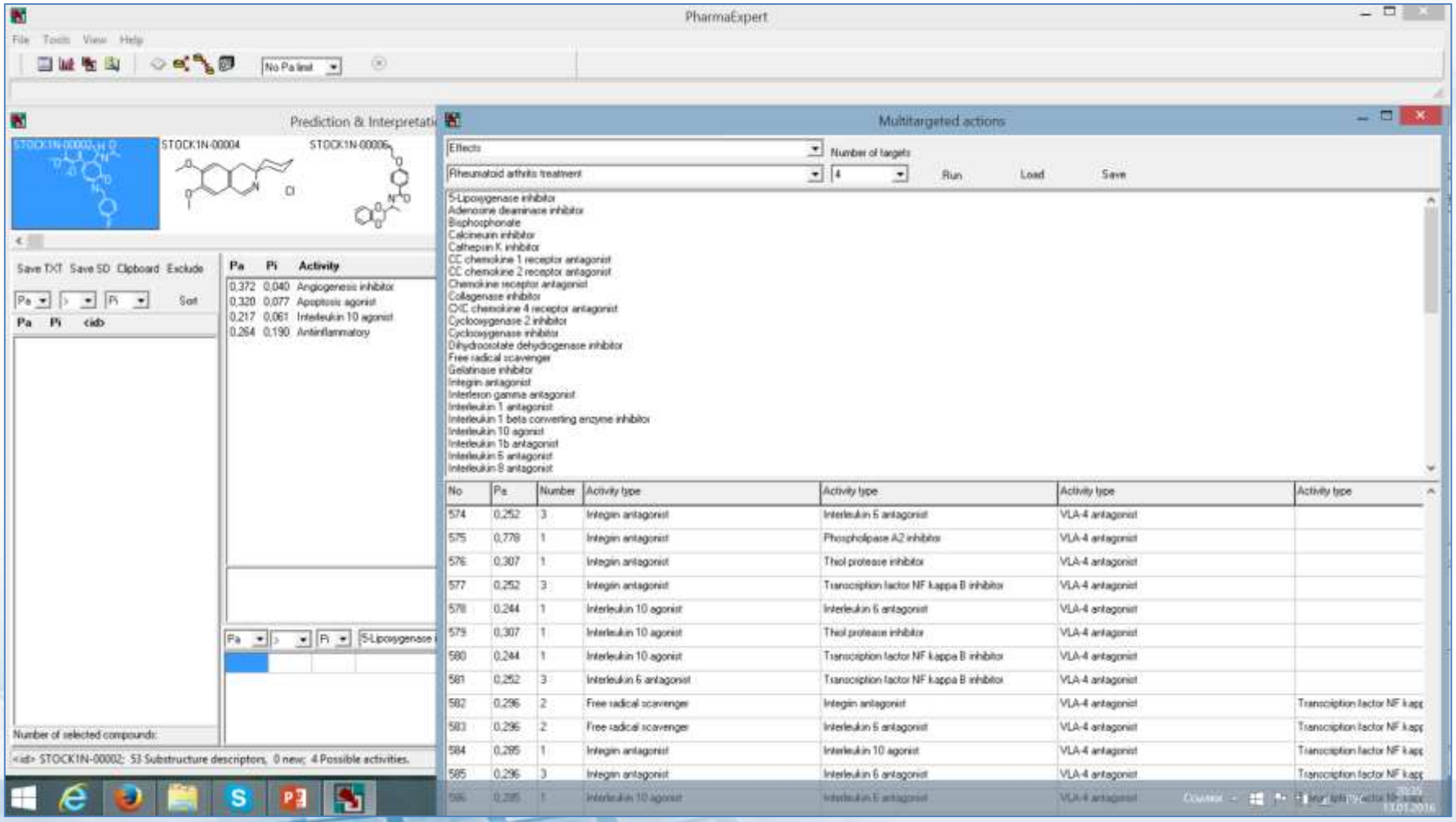
InterBioScreen library of natural compounds



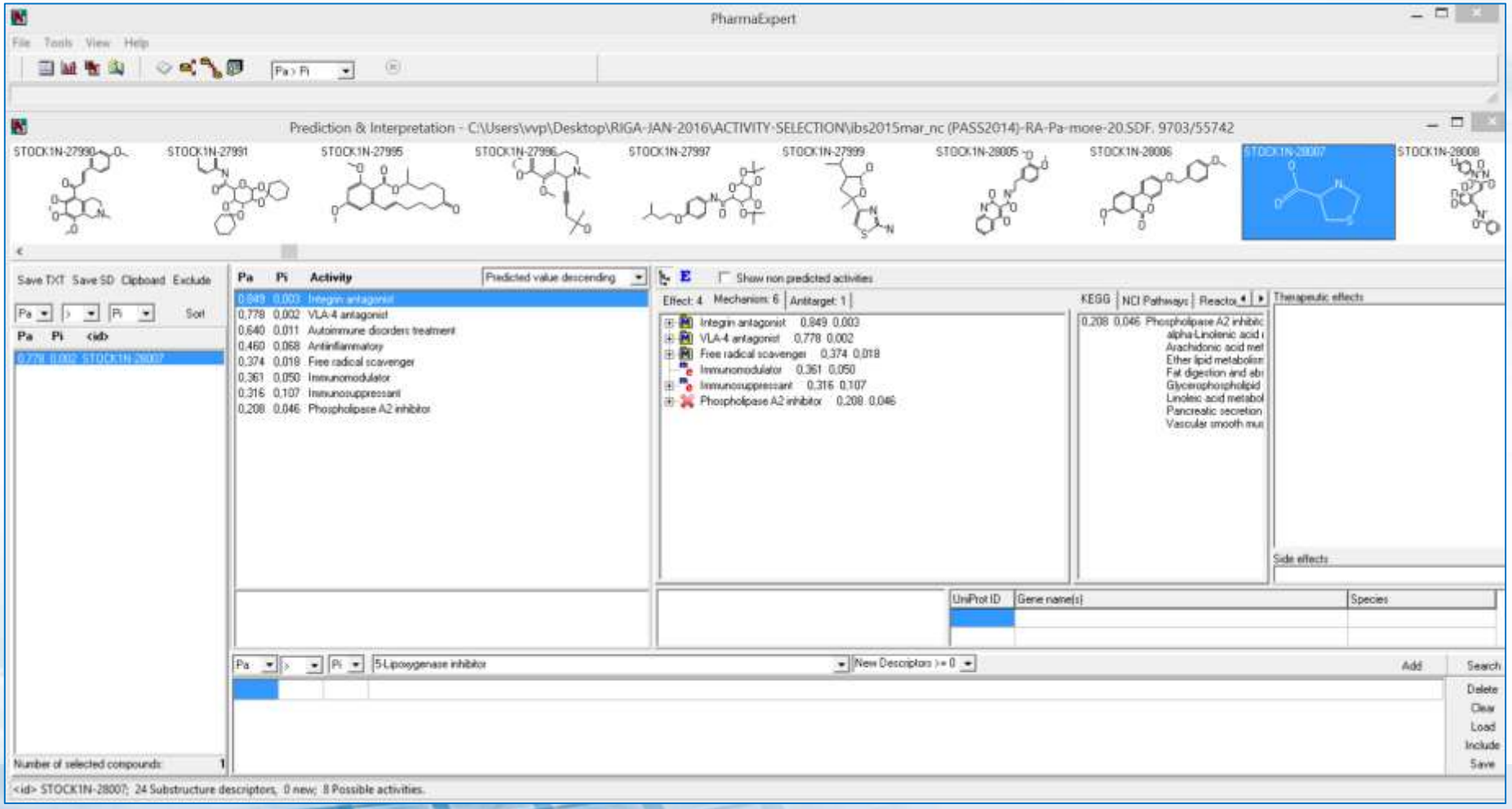
Predictions of RA associated activities for IBS library



Search for multitargeted agents for RA treatment



One promising hit for experimental validation



PASS + PharmaExpert

The search for new compounds with multiple mechanisms of action	*J. Med. Chem., 2003, 46(15), 3326-3332* *J. Med. Chem. 2008, 51(6), 1601-1609*
The search for new compounds with specific therapeutic effect(s) or/and interaction with specific target(s)	*J. Med. Chem., 2004, 47(11), 2870-2876* *Bioorg. Med. Chem., 2004, 12(24), 6559-6568* *Eur. J. Med. Chem., 2009, 44 (2), 473-481*
Drug repositioning	*Pharmaceut. Chem. J., 2011, 45 (10), 605-611*
Assessment of drug-drug interactions and between natural compounds - components of medicinal plants	*Curr. Pharm. Des. 2010, 16(15), 1703-1717* *Med. Chem. Res. 2011, 20(9), 1509-1514* *Cardiovascul. Therap. Prof., 2008, 7(5), 100-104*

More info: way2drug.com/suc_stor.php

Success Stories

Here you will find a brief overview of publications describing applications of our software. This overview provides you a guide how people use our tools, to achieve better results in their projects aimed at drug design & discovery or chemical safety assessment. Among the over 250 publications, there are many success stories about virtual screening, drug repurposing, revealing the hidden potential of natural products, chemical safety assessment, etc.

If you have some experience with the utilization of our software, please, tell us your story. Sharing of your experience, will support newcomers in their first steps to apply computer-aided drug discovery methods in practice, and will help us to improve our web-services.

General papers with references on our computational tools

"One of the first approaches in the field of in silico pharmacology was PASS (Prediction of Activity Spectra for Substances), which applies a set of 2D descriptors to compounds that are then correlated with a set of bioactivities."

Vegner L. et al. J. Med. Chem., 2013, 56, 8377. DOI: 10.1021/jm400813y

"Several ligand-based methods apply data mining methods in order to identify unknown drug–target interactions. One of the first initiatives in this field was PASS developed by Poroikov et al. (SAR & QSAR Environ. Res., 2007, 18: 101). It can predict the biological activity profile of a compound based on the analysis of structure–activity relationships for more than 250 000 biologically active substances."

Peragovics A. et al. J. Chem. Inform. Model., 2013, 53, 103. DOI: 10.1021/ci3004489

"Thorough studies have revealed pronounced differences between natural and synthetic compounds in terms of their structural and physicochemical properties, which renders the inference of targets for natural products from well-characterized drug-like compounds conceptually difficult. In fact, only a few select applications have been described." (One of the two mentioned publications is Lagunin A., Filimonov D., Poroikov V. Multi-targeted natural products

• • •

Overview

1. Historical reflections
2. PASS (Prediction of Activity Spectra for Substances)
3. PharmaExpert
4. GUSAR (General Unrestricted Structure-Activity Relationships)
5. Some examples of applications
6. **Our web-services based on PASS, GUSAR, etc.**
7. Way2Drug.com: further progress

Way2Drug web platform

We have proposed the local correspondence concept, which is based on the fact that most biological activities of organic compounds are the result of molecular recognition, which in turn depends on the correspondence between the particular atoms of the ligand and the target.

Using this concept, we have developed a consistent system of atom-centered neighborhoods of atoms descriptors including MNA, QNA, and LMNA, and have implemented them in several SAR/QSAR/QSPR modeling approaches.

➡ www.way2drug.com

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SEVENTH FRAMEWORK PROGRAMME

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Unlocking infectious diseases research potential at Rīga Stradiņš University

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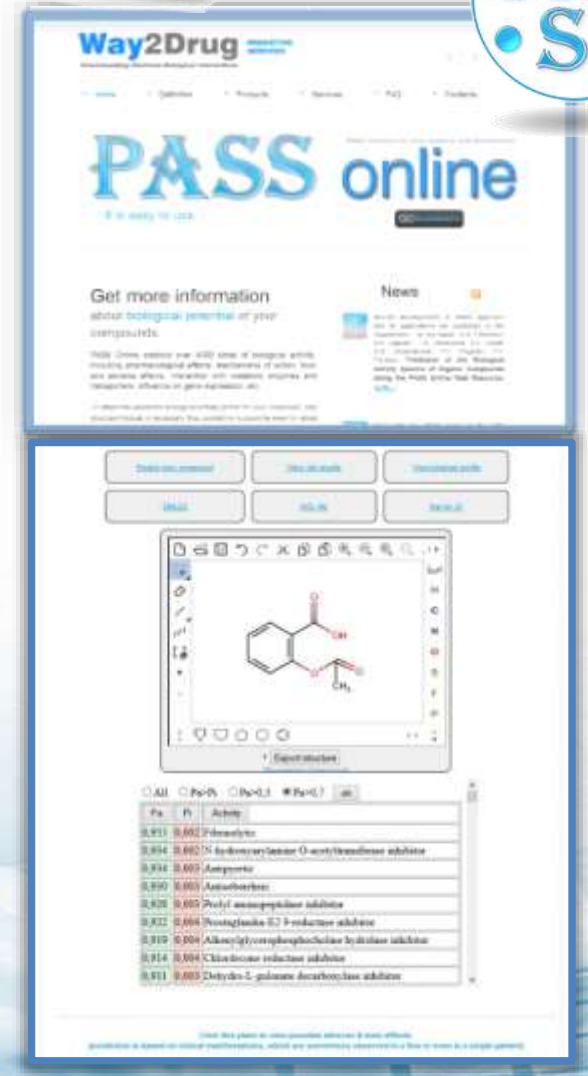
PASSOnline



Predicts about 4000 biological activity types of organic compounds by their structural formulas, including pharmacological effects, mechanisms of action, toxicity and side effects, interaction with metabolic enzymes, effects on gene expression, etc.

Training set with more than 313,000 known biologically active substances, belonging to different chemical classes.

Constantly working to improve the quality of prediction, updating the training set, and making changes in calculation methods.

average training set LOO CV: 0.95

Filimonov D.A. et al. *Chem. Heterocycl. Comp.*, 2014, No. 3, 483-499.

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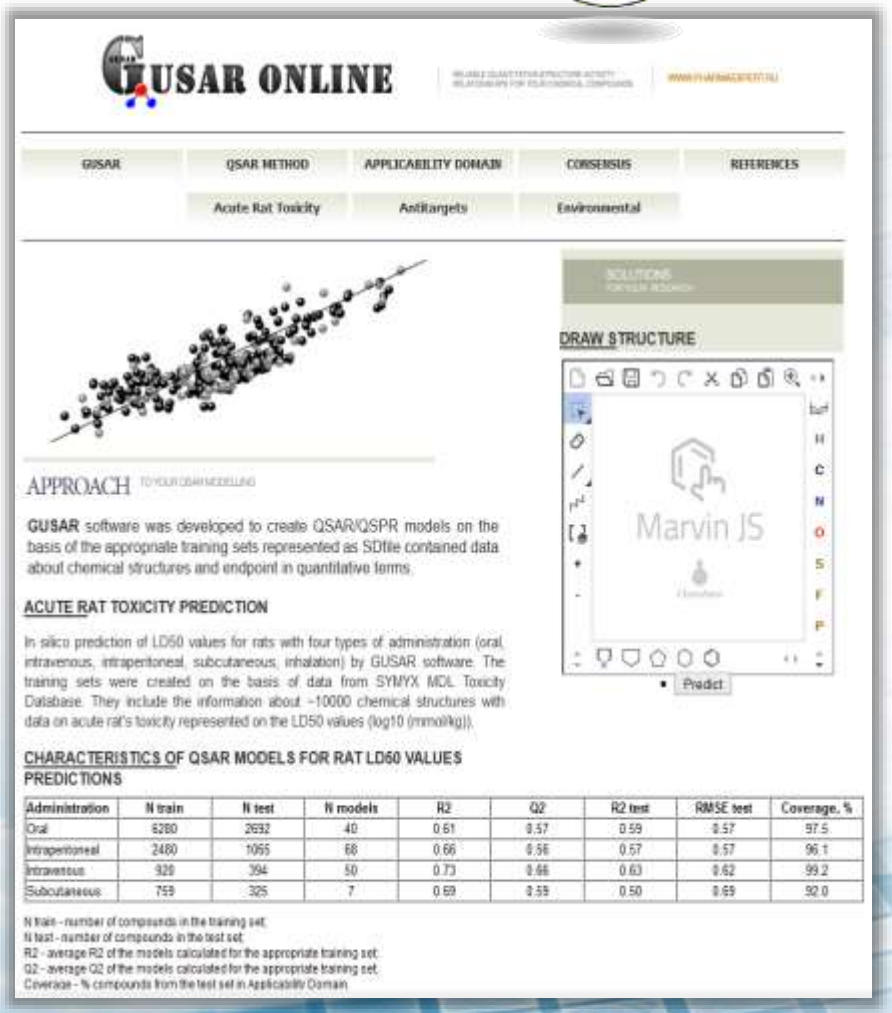
GUSAR Online

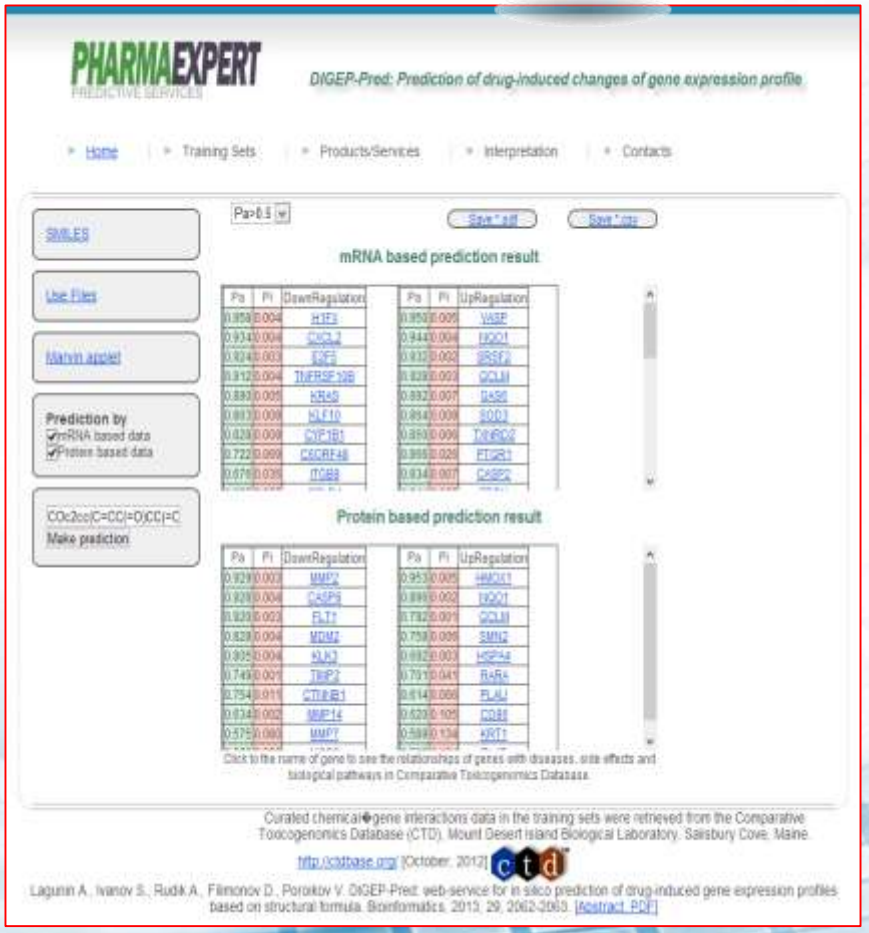


- GUSAR online presents: consensus prediction, applicability domain assessment, internal and external models validation and clearly interpretations of obtaining results.
- Developed to create QSAR/QSPR models on the basis of the appropriate training sets represented as SDF file format contained data about chemical structures and different endpoints in quantitative terms.
- Prediction of acute rat toxicity;
- Prediction of antitarget interaction profiles for chemical compounds;
- Prediction of ecotoxicity for chemical compounds.

➡ www.way2drug.com

Zakharov A.V. et al. *Chem. Res. Toxicol.*, 2012, **25**: 2378-2385.

DIGEP-Pred



- Gene expression profiles are used to solve various problems in pharmaceutical research, such as the repositioning of drugs, overcoming resistance, estimating toxicity and drug-drug interactions.

- **Training sets:**
  mRNA-based - 1385 compounds for 952 genes (500 up- and 475 downregulations);
  Protein-based - 1451 compounds for 129 genes (85 up- and 51 downregulations).

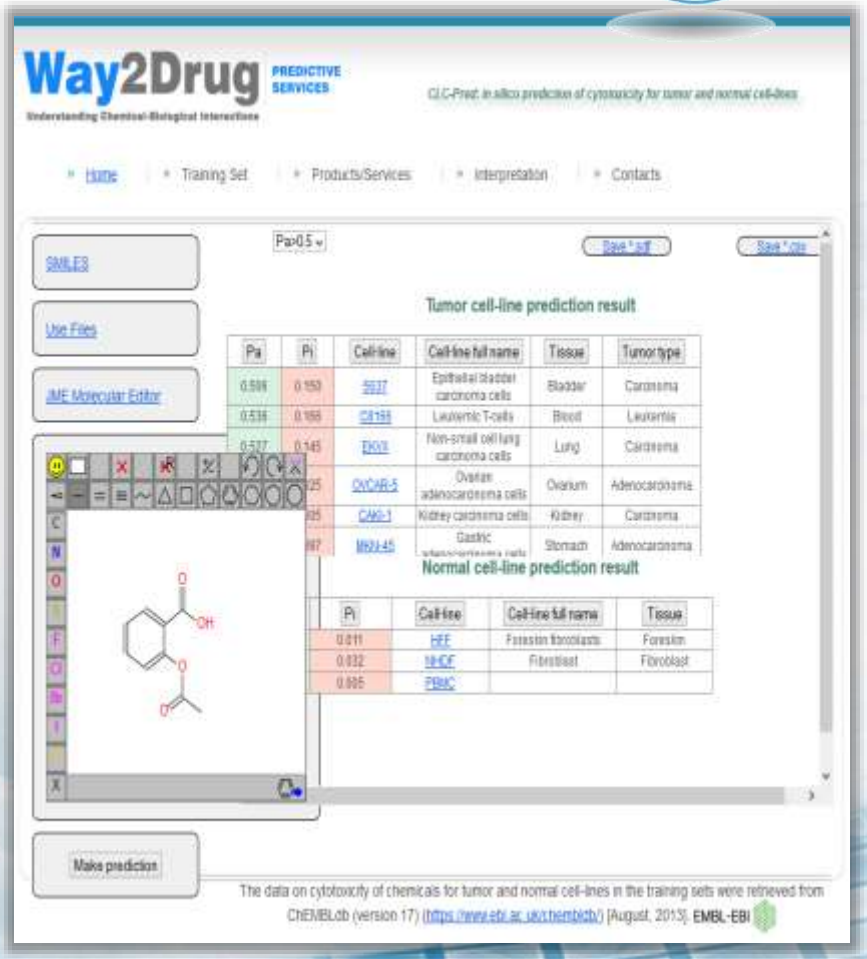
- **Results of prediction are linked to CTD (Comparative Toxicogenomics Database) for the purpose of their interpretation.**

- **mRNA-based training set LOO CV: 0.853**

➡ **www.way2drug.com**

Lagunin A.A. et al. *Bioinformatics*, 2013, **29**: 2062-2063.

CLC-Pred



- Web-service for *in silico* prediction of cytotoxicity to the tumor and non-tumor cell-lines based on structural formula of chemical compound.
- Training sets on the basis of DB ChEMBLdb (ver.17) were collected from 76804 chemical compounds, which reflected the current level of knowledge of the cytotoxicity of chemical compounds in relation to the 44 tumor and 48 non-tumor cell-lines.
- In this case, the spectrum of biological activity is the assessment of cytotoxicity in relation to different cell lines.

! **Training set LOO CV: 0.96**

➡ www.way2drug.com

Konova V.I. et al. *SAR and QSAR Environ. Res.*, 2015.

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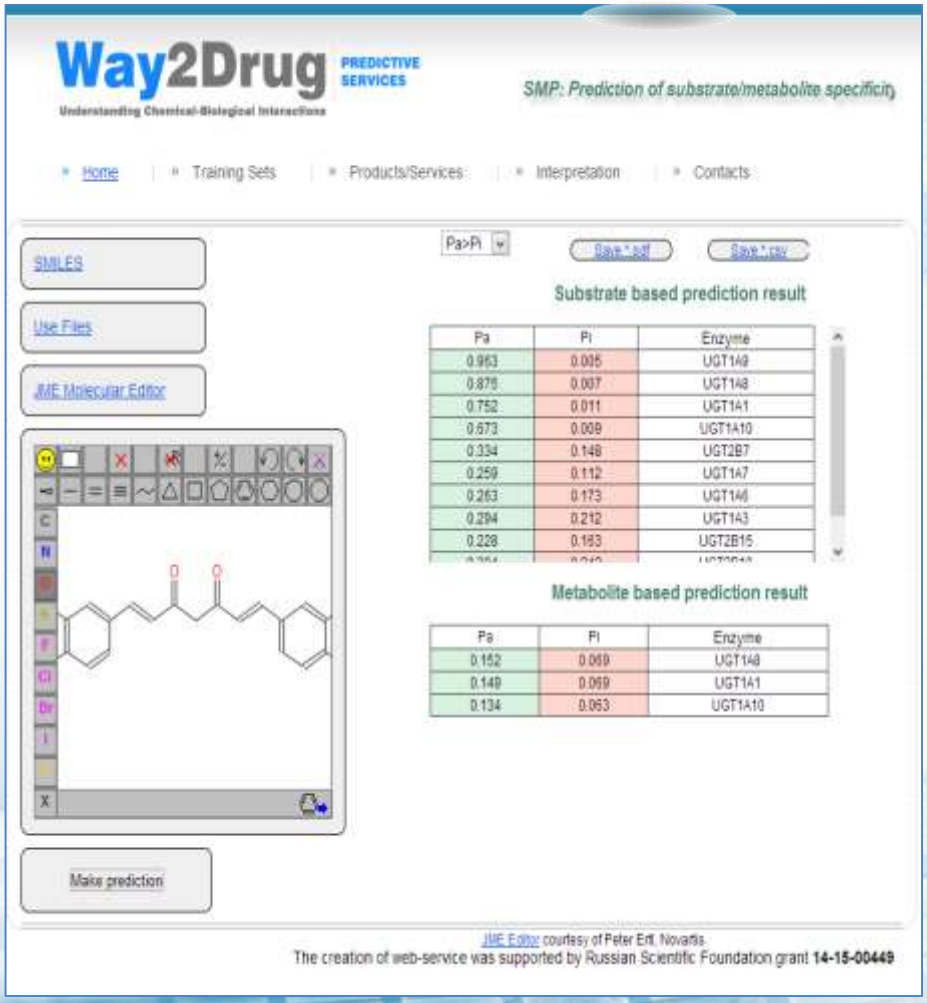
Meta-Pred



✓ **Prediction of interaction with 18 cytochrome P450 and UGT isoforms: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A10, UGT1A1, UGT2B7, UGT1A7, UGT2B15, UGT1A8, UGT1A4, UGT2B17, UGT2B10, UGT1A3, UGT1A9, UGT1A6, UGT2B4.**

✓ **Substrate training set – 3411 compounds.**

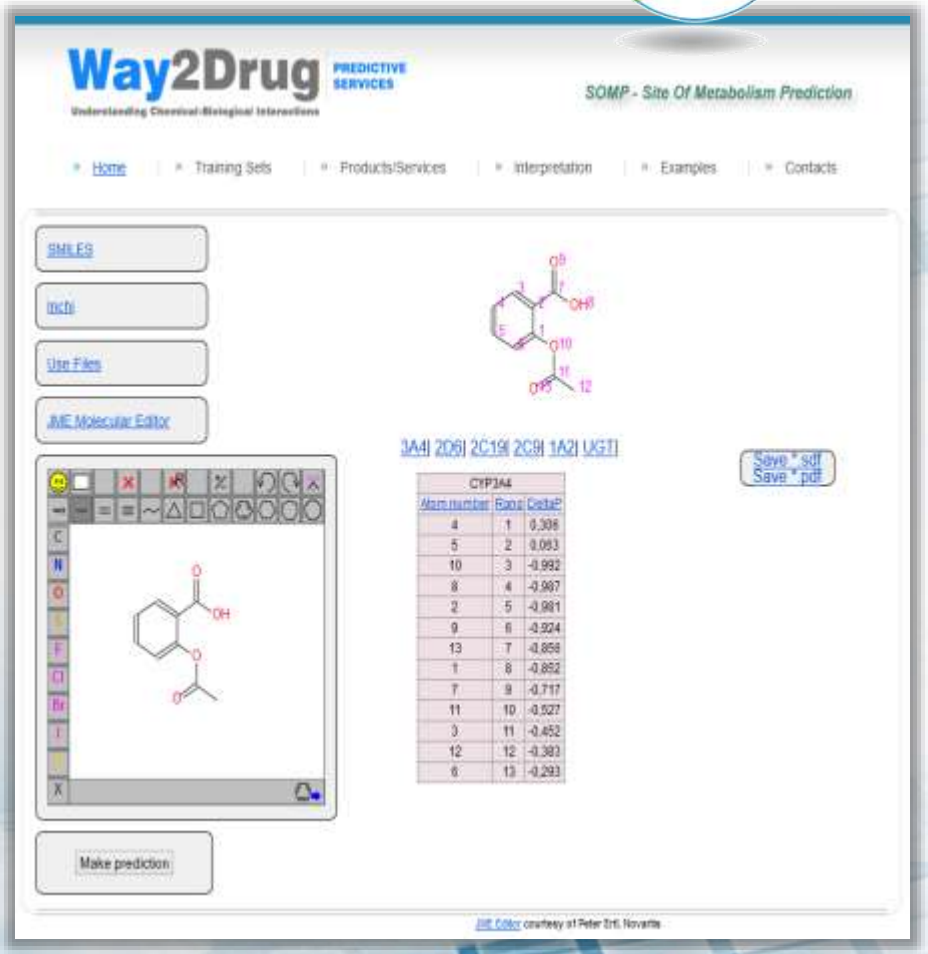
✓ **Metabolite-based training set – 2104 compounds.**

! **Training set LOO CV: 0.934**

➡ **www.way2drug.com**

Rudik A.V. et al., 2015, in preparation.

SOMP



Prediction of sites of metabolism for drug-like compounds for (five major human) cytochrome P450s: CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Also in the training set were included the sites of glucoronidation, catalyzed by UGT.

Enzyme	Substrate amount	LOO CV
CYP3A4	960	0.89
CYP2D6	588	0.92
CYP2C9	446	0.92
CYP2C19	388	0.93
CYP1A2	573	0.92
UGT	592	0.98

Rudik A.V. et al. *Bioinformatics*, 2015, **31**: 2046-2048.

The study is supported by RSF grant No. 14-15-00449.

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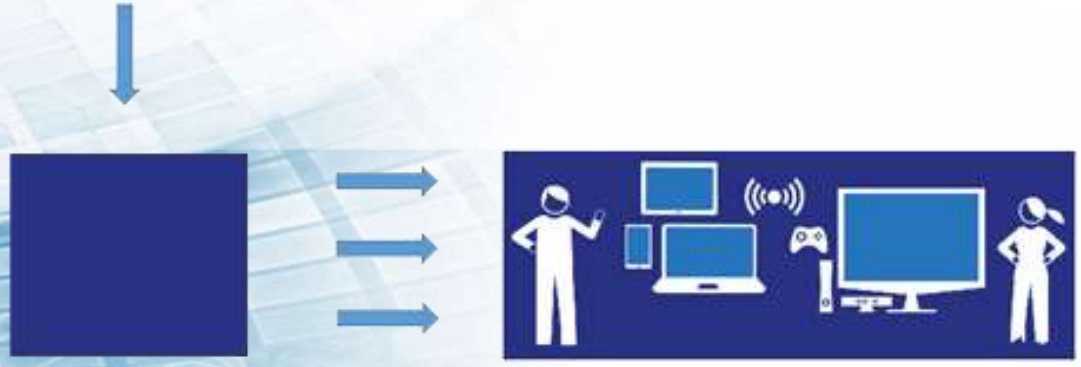
>500 K predictions

91 country

12 949 users

- India
- Russia
- Ukraine
- Mexico
- China
- United States
- Egypt
- Kazakhstan
- Brazil
- Other



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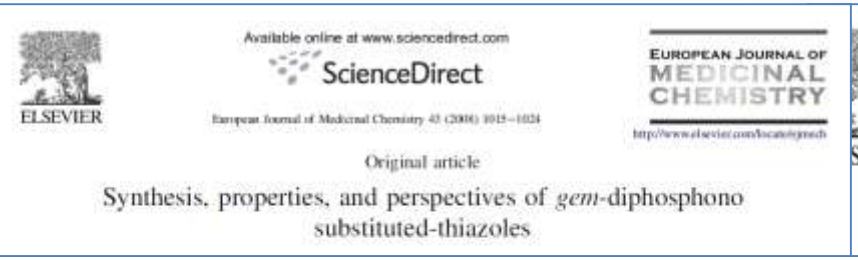
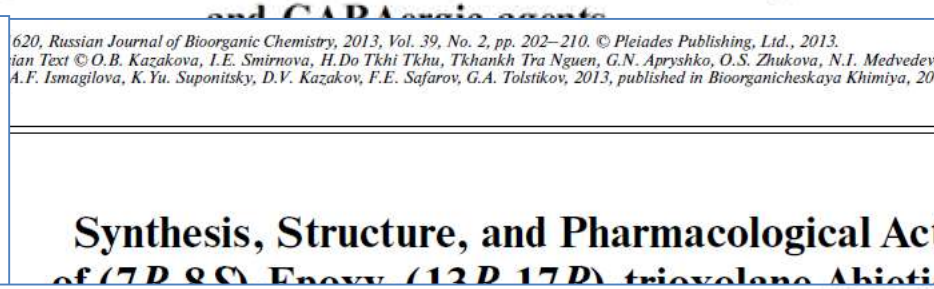
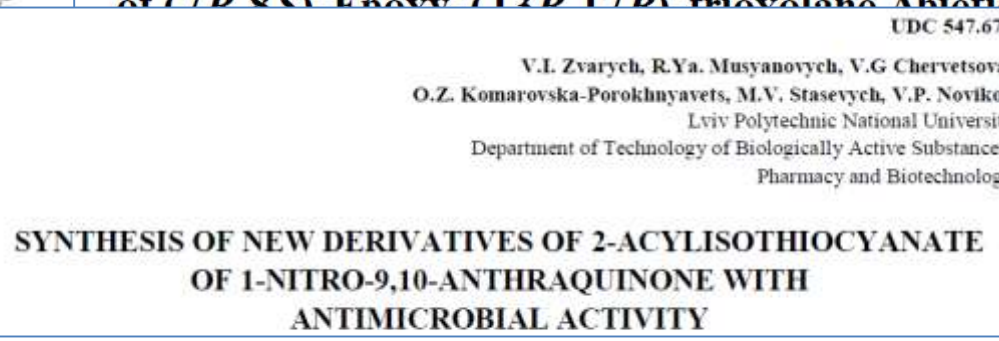
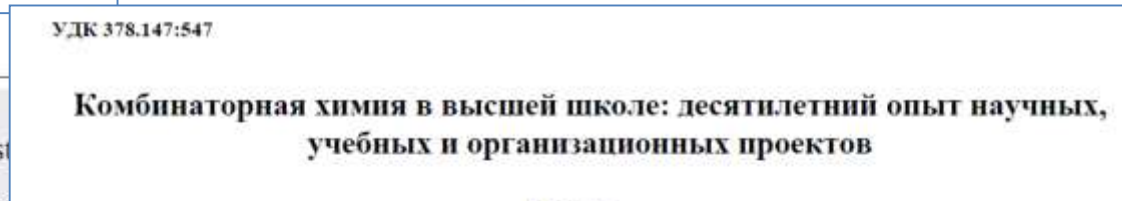
About 300 papers published citing our web-services (>50% with the experimental confirmation; the other 50% - just with the prediction results without experimental testing)









Overview

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6. Our web-services based on PASS, GUSAR, etc.
7. **Way2Drug.com: further progress**

Integration of all web-services (I)

Our Services

PASSOnline
biological potential of your compounds (more)

Gusar Online
create QSAR/QSPR models (more)

SMP
prediction subatrate/metabolite specificity (more)

DIGEP Pred
drug-induced changes of gene expression (more)

Meta-Pred
in silico prediction of sites of metabolism (more)

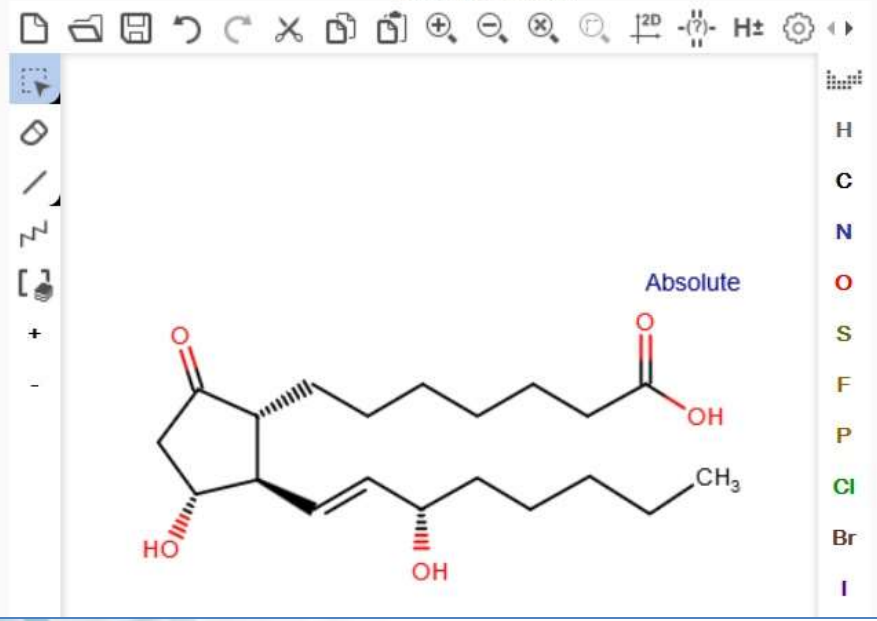
CLC-Pred

Predict activities/properties of your compound

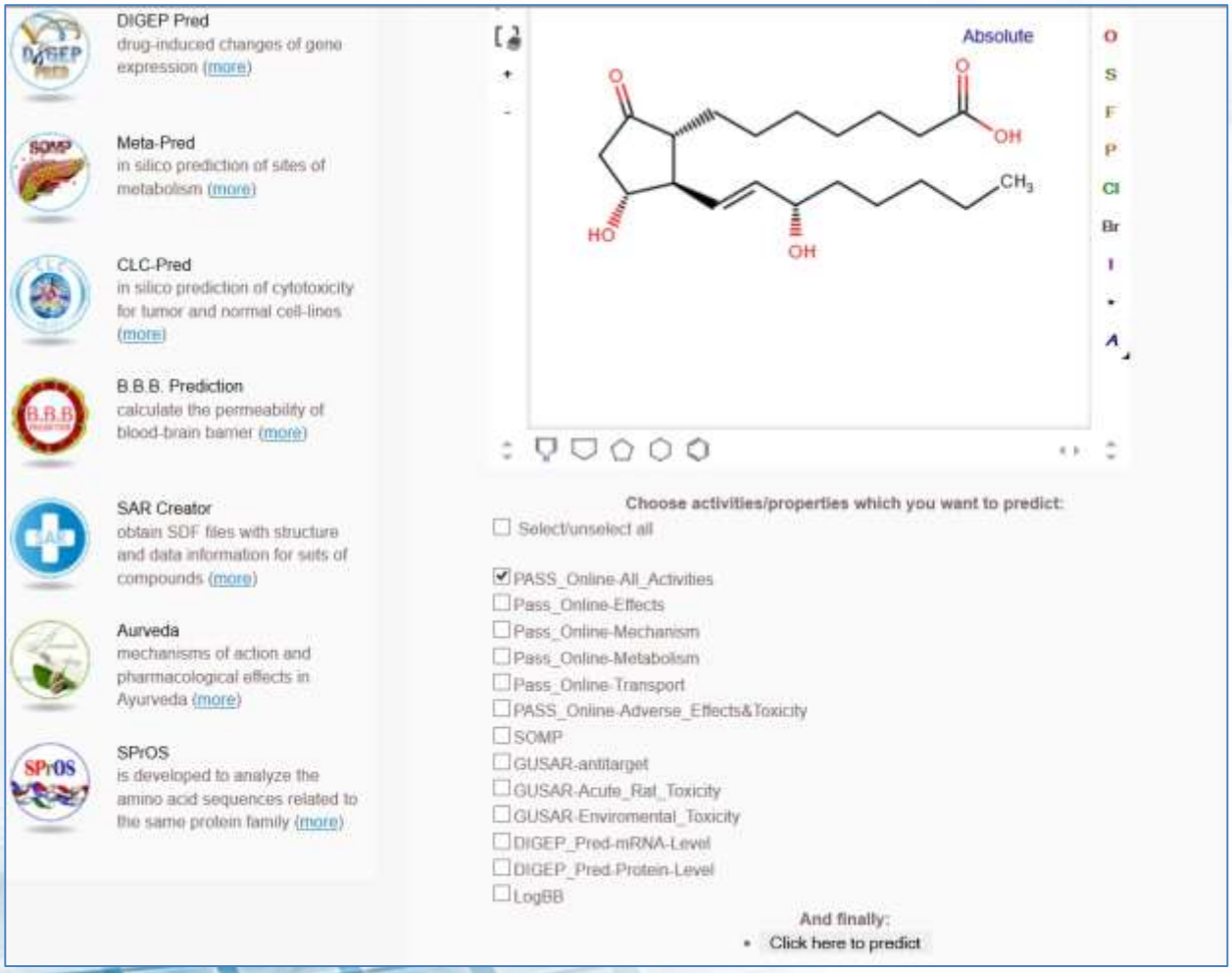
To recieve results, please, enter:

vvp1951@yandex.ru

Draw a structure:

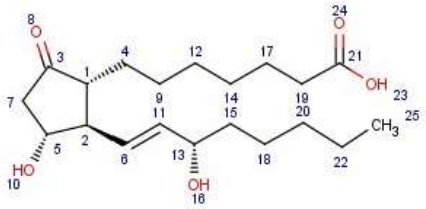


Integration of all web-services (II)



Integration of all web-services (III)

PASS_Online-All_Activities Web Server prediction results



Pa	Pi	Activity
0,980	0,001	Vasoprotector
0,980	0,001	Antisecretoric
0,979	0,001	Prostaglandin-E2 9-reductase inhibitor
0,976	0,002	Vasodilator, peripheral
0,975	0,001	GST A substrate
0,972	0,002	Mucomembranous protector
0,948	0,001	UGT2B1 substrate
0,944	0,002	Glutathione S-transferase substrate
0,937	0,001	CYP4A11 substrate
0,939	0,003	Vasodilator
0,934	0,002	Antithrombotic
0,933	0,001	Morphine 6-dehydrogenase inhibitor
0,927	0,001	Leukotriene-B4 20-monooxygenase inhibitor
0,923	0,000	CYP4F substrate
0,920	0,002	Antiulcerative
0,921	0,004	CYP2E1 substrate
0,914	0,001	Cytoprotectant
0,915	0,004	CYP2E substrate
0,913	0,001	GST M substrate
0,909	0,001	Gastrin inhibitor
0,912	0,006	Mucositis treatment
0,901	0,000	Oxytocic
0,901	0,002	CYP4A substrate
0,897	0,005	Antieczematic

. . .

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Computer-aided analysis of hidden potential in traditional Indian medicine Ayurveda

- Natural products are used in folk medicine since many thousands year. They represent a significant, though often underappreciated resource for the development of new medicines.

- Contents:
  (1) 50 medicinal plants;
  (2) structural formulae of 1906 phytochemicals;
  (3) biological activity of 288 phytochemicals.

- Criteria:
  (1) Ayurvedic /traditional medicinal use;
  (2) adequately explored for phytochemical analysis;
  (3) unexplored for pleiotropic pharmacological studies.

Lagunin A.A. et al. *Biomedical Chemistry*, 2015, **61:** 286-297.

Supported by RFBR-DST grant No. 11-04-92713_IND

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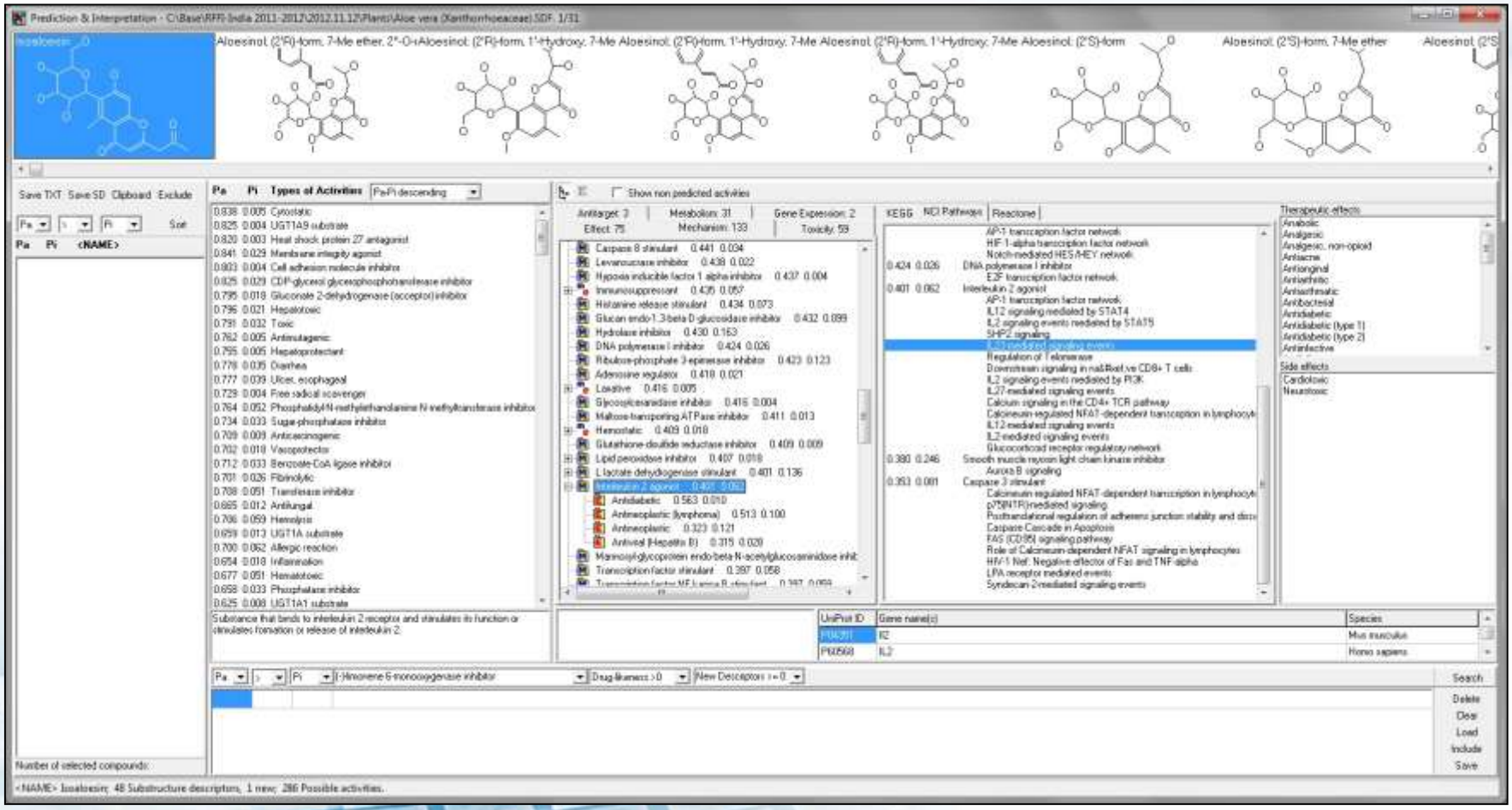
САНКТ-ПИТЕРБУРГСКИЙ ГОСУДАРСТВЕННЫЙ ТЕХНОЛОГИЧЕСКИЙ ИНСТИТУТ

New Features in PharmaExpert adopted to analysis of phytoconstituents of medicinal plants



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More information could be found in our joint publications

Med Chem Res (2011) 20:1509–1514
DOI 10.1007/s00044-010-9398-y

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

PASS-assisted exploration of new therapeutic potential of natural products

Rajesh Kumar Goel · Damanpreet Singh · Alexey Lagunin · Vladimir Poroikov

Received: 15 March 2010 / Accepted: 22 July 2010 / Published online: 6 August 2010

Abstract The use of drug substances derived from plants, fungi, bacteria, and marine organisms are "Mother Nature Gift" for diseases of mankind. Many of these are discovered serendipitously and have a long tradition in medicine. Till date, the use of natural products, their semisynthetic and synthetic derivatives have been mostly confined to their ethnic use. But it has been well known that each

Keywords Ayurveda · Biological activity spectrum · Herbal drugs · Natural products · PASS

Introduction

Natural products (NPs) are used in folk medicine since

European Journal of Pharmacology 704 (2013) 33–40

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Behavioural pharmacology

Ameliorative effect of Curcumin on seizure severity, depression like behavior, learning and memory deficit in post-pentylenetetrazole-kindled mice

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Компьютерная оценка скрытого потенциала фитокомпонентов лекарственных растений из традиционной индийской медицины Аюрведа

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Реферат

С целью изучения скрытого потенциала традиционной индийской медицины Аюрведа создан веб- (http://ayurveda.pharmaexpert.ru). В данных введена информация о 50 индийской медицине и входящих в их ивности 288 фитокомпонентов. ологической активности 946 видами биологической активности и о выборку компьютерной программы ифицированной обучающей выборки и по одному и кросс-валидация залось, что значения средней ошибки т значений, полученных при 5,395%, соответственно), что пециализированной версии программы раммы PASS получен прогноз спектров лекарственных растений ТИМ. С н анализ результатов прогноза для ИМ; для ряда растений проведено ми экстрактов из лекарственных рмакотерапевтические эффекты

Chemo- and Bioinformatics resources and *in silico* approaches for drug discovery from Plants used in Traditional Indian Medicine: A Critical Review.

Lagunin A.A.[1], Goel R.K.[2], Gawande D.Y.[2], Pahwa P.[2], Gloriozova T.A.[1], Dmitriev A.V.[1], Ivanov S.A.[1], Rudik A.V.[1], Konova V.I.[1], Pogodin P.V.[1,3], Druzhilovsky D.S.[1], Poroikov V.V.[1,3]

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Abstract

In silico studies are widely recognized as a useful stage of new drug discov appropriate databases. Here we review the significance of chemo- and bioinfor and *in silico* approaches for new drug discovery form medicinal plants used in Tr Medicine including reverse pharmacology, QSAR, structure- and ligand-based methods, ADME/T assessment and network analysis. The review contains a prac a combination of chemo- and bioinformatics methods in the study of therapeu

NPR

REVIEW

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ROYAL SOCIETY OF CHEMISTRY

Chemo- and bioinformatics resources for *in silico* drug discovery from medicinal plants beyond their traditional use: a critical review†

Alexey A. Lagunin,*[a,c] Rajesh K. Goel,*[b] Dinesh Y. Gawande,[b] Priynka Pahwa,[b] Tatyana A. Gloriozova,[a] Alexander V. Dmitriev,[a] Sergey M. Ivanov,[a] Anastassia V. Rudik,[a] Varvara I. Konova,[a] Pavel V. Pogodin,[a,c] Dmitry S. Druzhilovsky[a] and Vladimir V. Poroikov*[a,c]

Covering: up to 2014

IBMC

SEVENTH FRAMEWORK PROGRAMME

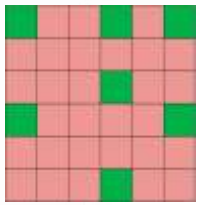
Baltinfect
Unlocking infectious diseases research potential at Rīga Stradiņš University

RĪGAS STRADIŅA UNIVERSITĀTE

PREDICTION

Training set

(Q)SAR Method



DATA

FALSE POSITIVES

TRUE POSITIVES

FALSE NEGATIVES

Accuracy of prediction depends on both issues

Lighthouses drawing by Olga Kiseleva (IBMC)

Study on quality of data in publicly and commercially available databases

JOURNAL OF CHEMICAL INFORMATION AND MODELING
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QSAR Modeling Using Large-Scale Databases: Case Study for HIV-1 Reverse Transcriptase Inhibitors

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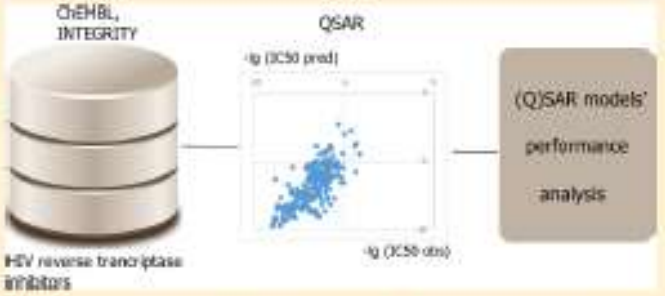
Supporting Information

ABSTRACT: Large-scale databases are important sources of training sets for various QSAR modeling approaches. Generally, these databases contain information extracted from different sources. This variety of sources can produce inconsistency in the data, defined as sometimes widely diverging activity results for the same compound against the same target. Because such inconsistency can reduce the accuracy of predictive models built from these data, we are addressing the question of how best to use data from publicly and commercially accessible databases to create accurate and predictive QSAR models. We investigate the suitability of commercially and publicly available databases to QSAR modeling of antiviral activity (HIV-1 reverse transcriptase (RT) inhibition). We present several methods for the creation of modeling (i.e., training and test) sets from two, either commercially or freely available, databases: Thomson Reuters Integrity and ChEMBL. We found that the typical predictivities of QSAR models obtained using these different modeling set compilation methods differ significantly from each other. The best



Summary

- Based on long-term projects in chemoinformatics (local correspondence concept, PASS, PharmaExpert, GUSAR, etc.), we have developed several web-services useful in computer-aided drug discovery.
- These web-services are widely used by many researchers from over 90 countries; more than 300 papers published with citations of our web-resources.
- Further development of these resources requires integration, curation of the information, improvement of functionality, etc.
- Active cooperation with the Way2Drug users will significantly enhance our initiatives.

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МИНИСТЕРСТВО ОБРАЗОВАНИЯ И НАУКИ
РОССИЙСКОЙ ФЕДЕРАЦИИ

РОССИЙСКИЙ НАУЧНЫЙ ФОНД
ПОДДЕРЖКА И РАЗВИТИЕ

RFBR RUSSIAN FOUNDATION FOR BASIC RESEARCH

Sk Сколково

And to many other colleagues who participate(d) in our projects

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Way2Drug
PREDICTIVE SERVICES
Understanding Chemical-Biological Interactions

Thank you for your kind attention!

We are open for collaboration; please, address your suggestions to:
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