PASS: Prediction of Activity Spectra for Substances

Twenty Years of Development

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http://www.way2drug.com/passonline

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Acknowledgements to the key persons

Dmitry Filimonov, Ph.D.

Tatyana Gloriozova, M.Sc.

Alexey Lagunin, Dr. Sci.

and to many other colleagues who help us in PASS development

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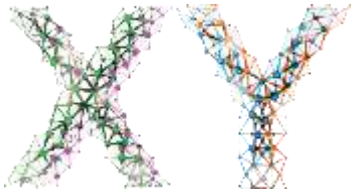
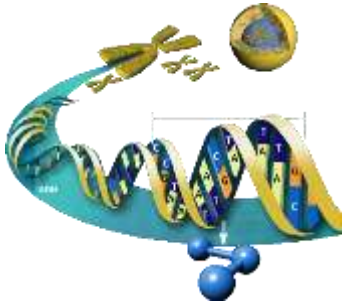
ACS Natl. Meetings	Titles of our Presentations
245th (2013)	Virtual high-throughput screening of novel pharmacological agents based on PASS predictions
239th (2010)	Fragment-based drug design using PASS approach
237th (2009)	Public molecular databases: How can their value be increased by generation of additional data *in silico*
235th (2008)	RoadMap data: New possibilities for computer-aided drug discovery
229th (2005)	Why relevant chemical information cannot be exchanged without disclosing structures
225th (2003)	Computer-aided discovery of compounds with combined mechanism of pharmacological action in large chemical databases
223th (2002)	Computer-aided prediction of activity spectra for substances (PASS)
222th (2001)	Computer-assisted mechanism-of-action analysis of large databases, including 250,000 chemical compounds registered by NCI

We are living in the time of Big biomedical and chemical Data

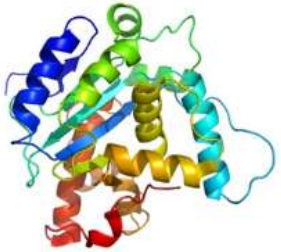
Potential biomarkers and pharmacological targets



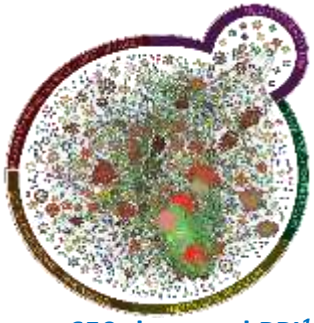
23 chromosomes



≈20-25 thousand genes



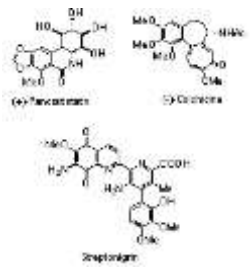
≈2 mln proteins



≈650 thousand PPI[1]

Potential chemical probes and pharmaceutical substances

≈12-15 thousand drug substances



≈1,5 mln biologically active substances

≈60 mln commercially available chemical samples

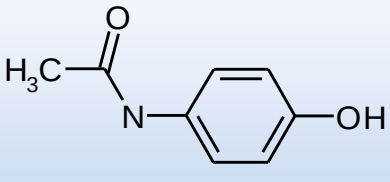
≈ 166 bln structures generated *in silico* [2]

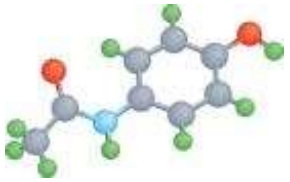
≈ 10^{120} theoretically possible structures [3]

1. PNAS, 2008, 105: 6959-6964. *2. JCIM, 2012, 53: 56-65.* *3. JCICS, 2003, 43: 374-380.*

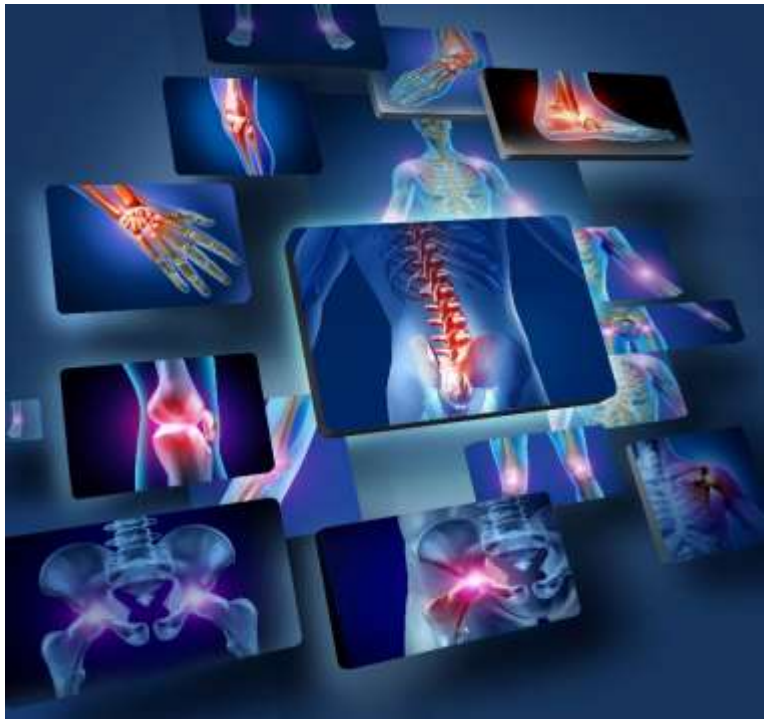
Most of pharmaceutical substances exhibit pleiotropic effects, which may become the reason:

E.g,
Acetaminophen





a) For treatment of certain pathology due to the desirable actions.



b) For adverse/toxic actions caused severe disorders or even death.

Antipyretic

Analgesic

NSAID

Antiosteoporotic

Antineoplastic

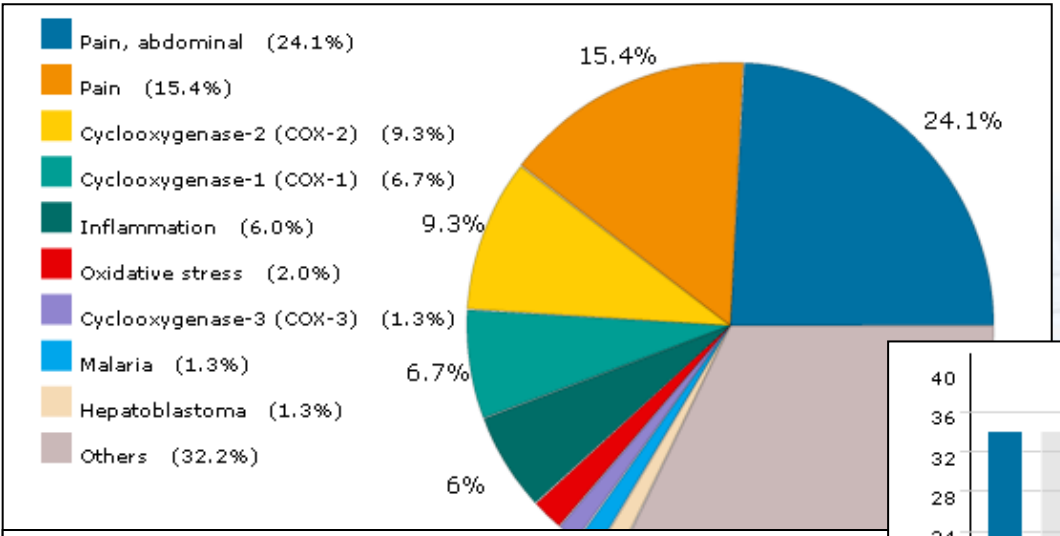
COX inhibitor

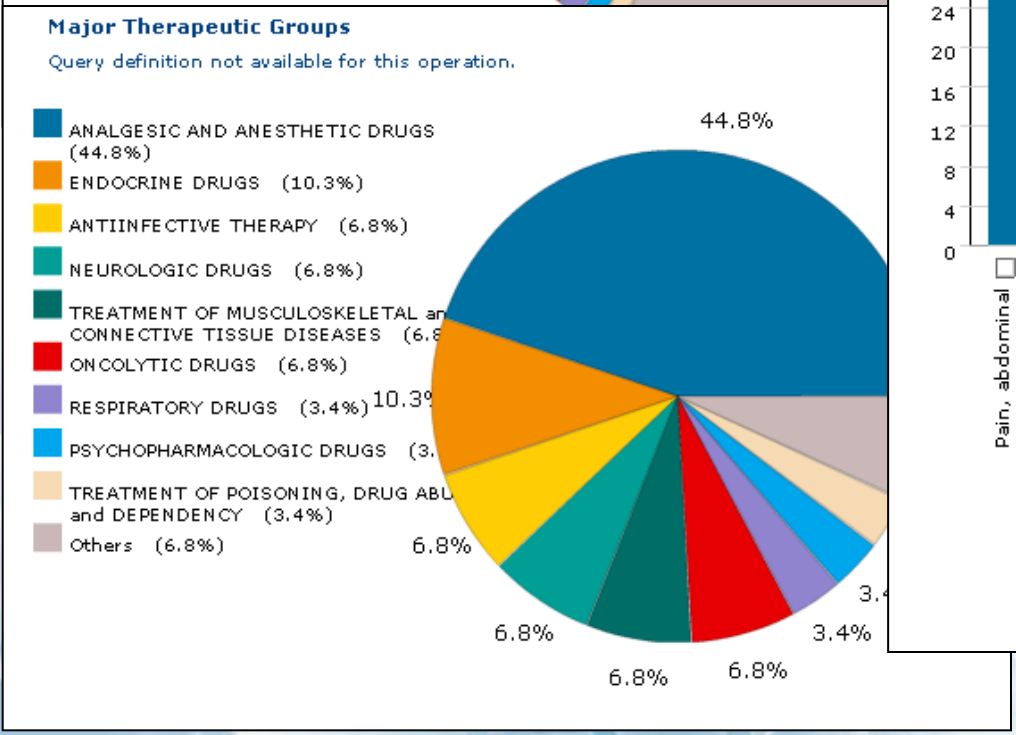
. . .

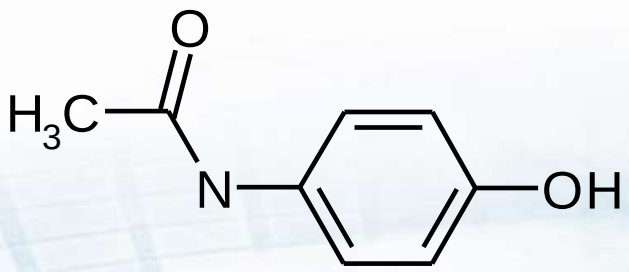
Hepatotoxic

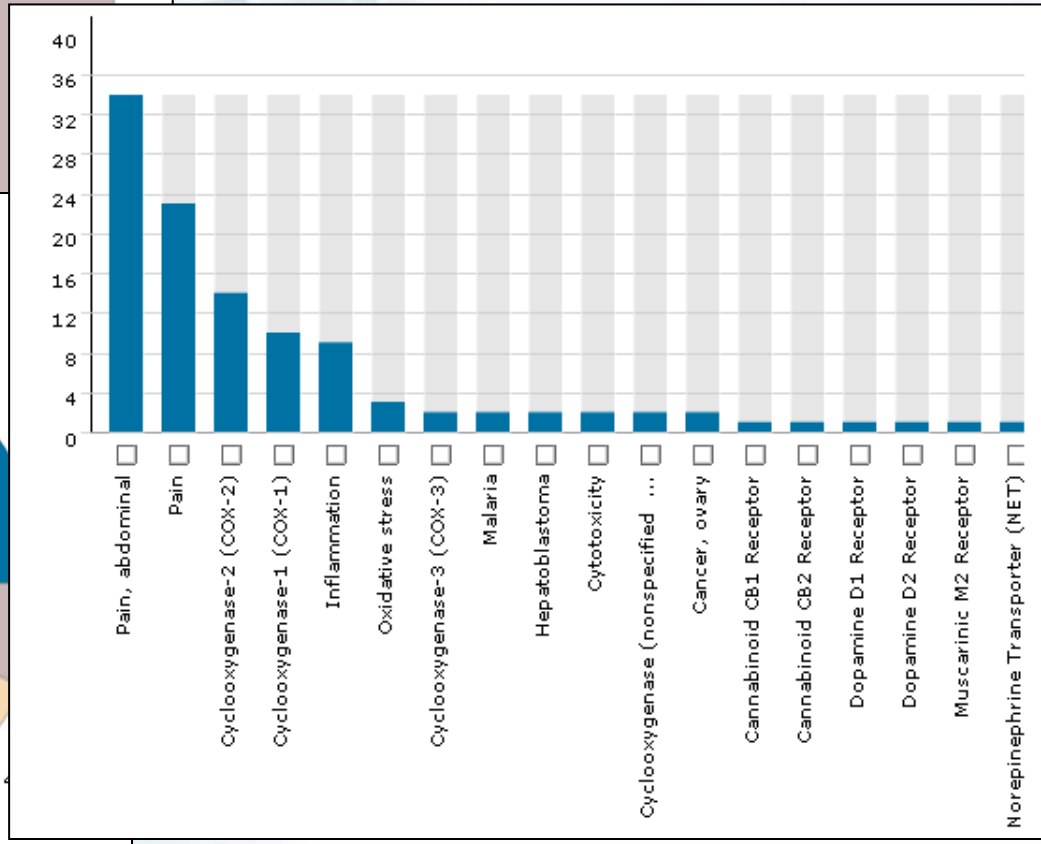
. . .

Pharmacological Studies of Acetaminophen









https://integrity.thomson-pharma.com/

To estimate the biological potential of the compound in silico, we proposed the 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 found 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.

Requirements to the creating such program

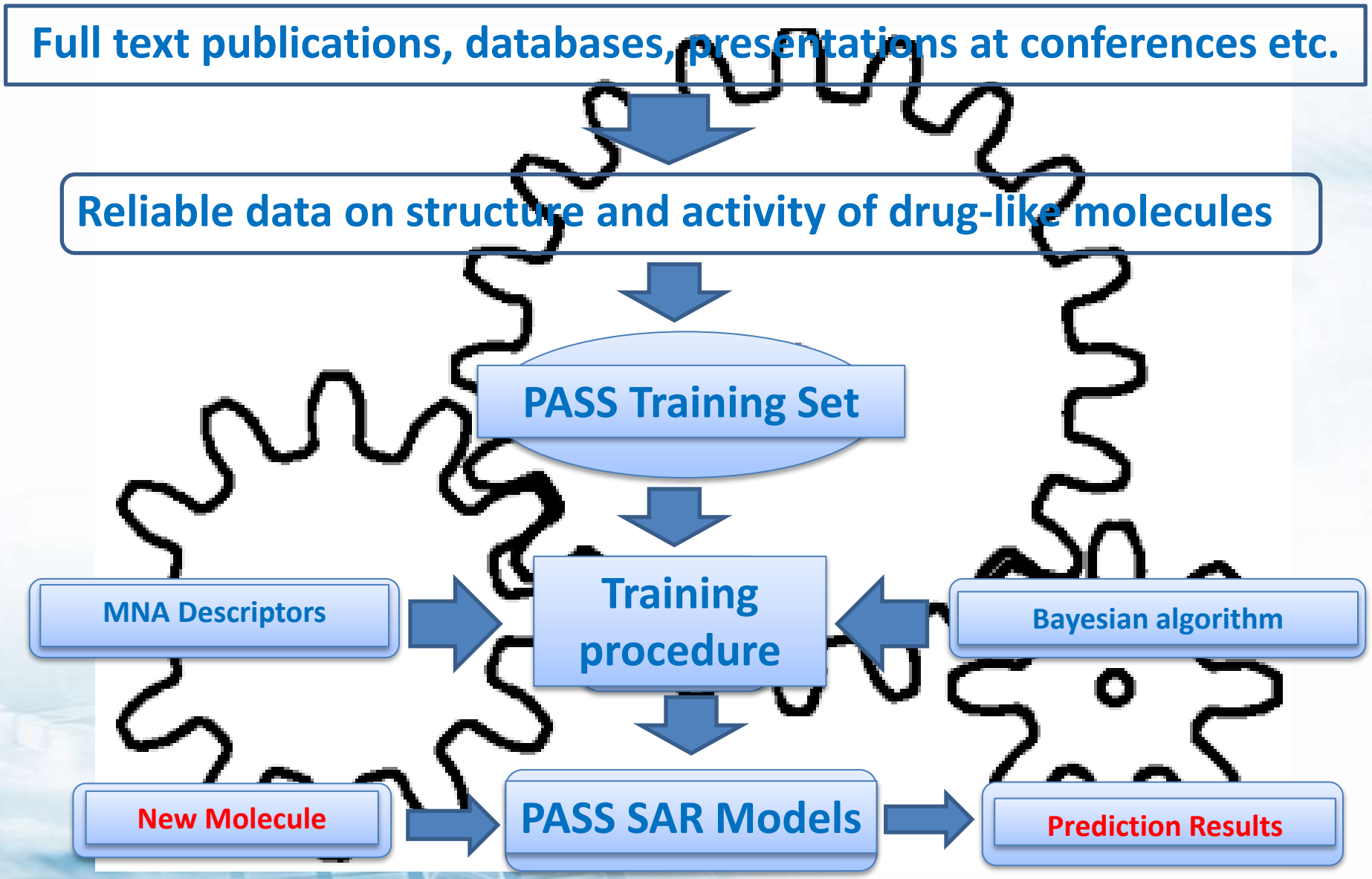
Predicts many (ideally, all known) activities

Uses only structural formula as input data (MOL or SDF)

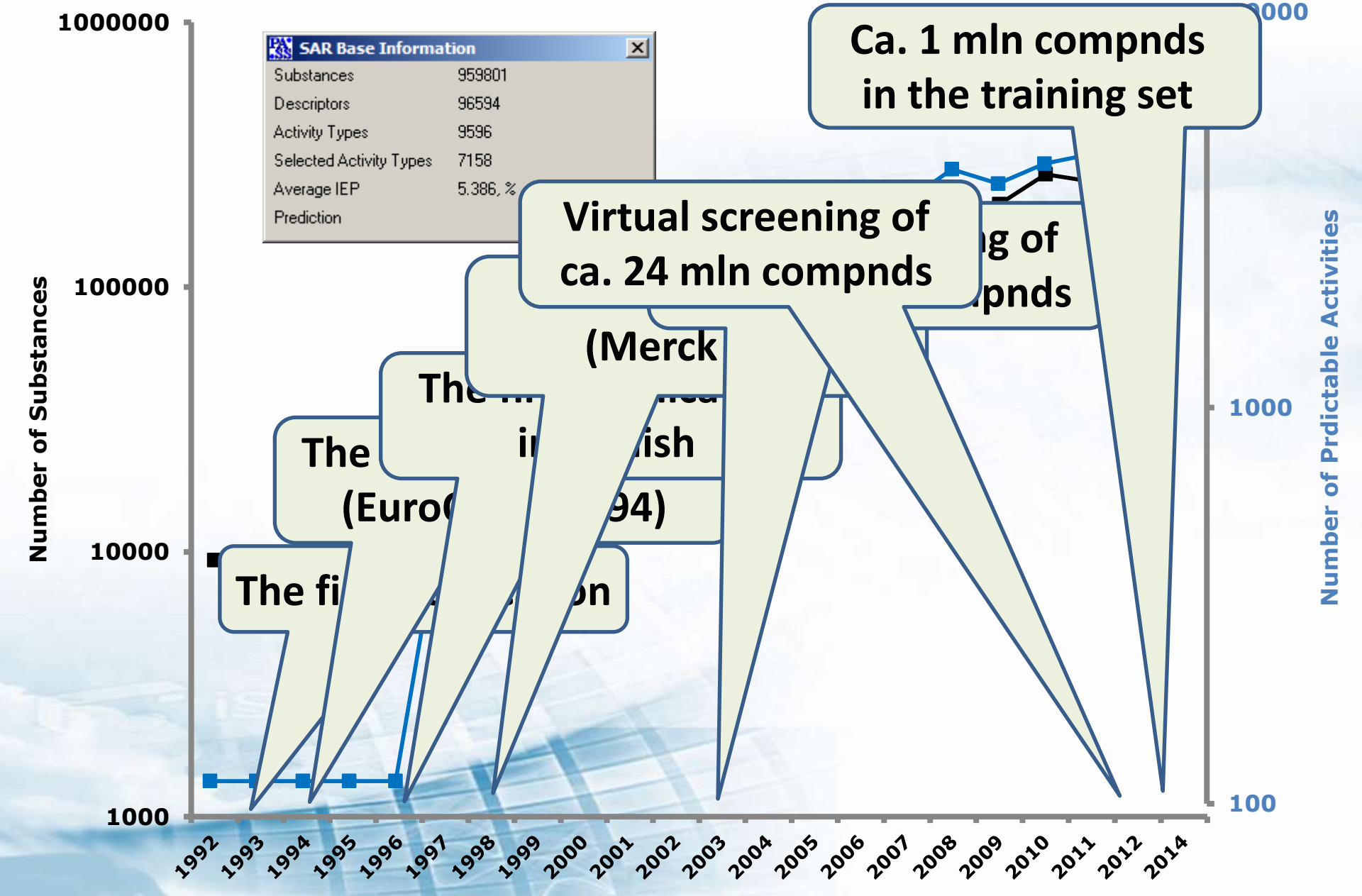
Can be re-trained with new data sets

Has user-friendly interface (“one click” to get prediction)

PASS is based on the ligand-based drug design approach



PASS training set is regularly updated and growing



PASS 2014 Characteristics

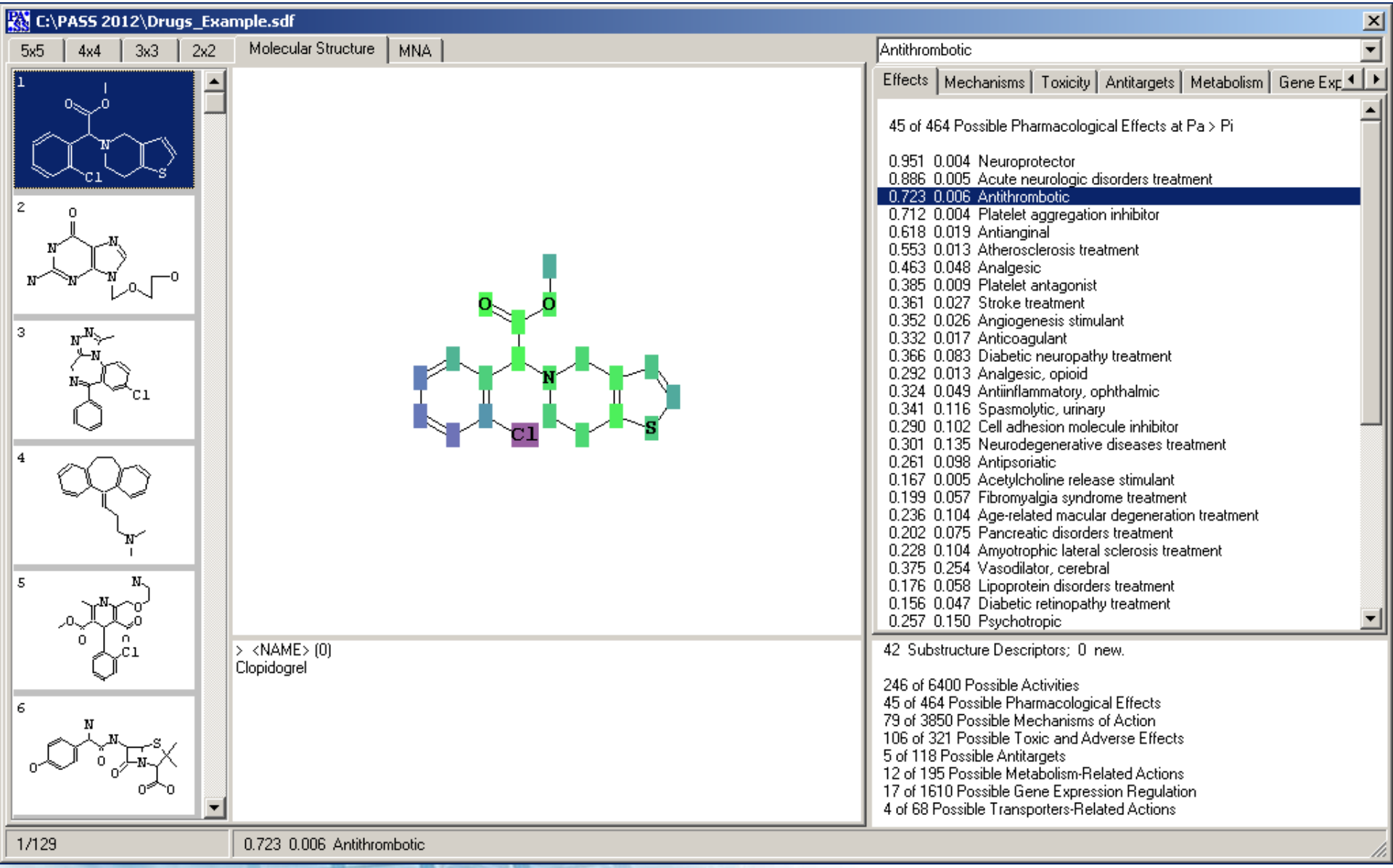
Training Set	**959,801 drugs, drug-candidates, pharmacological and toxic substances comprise the training set**
Biological Activity	**7,158 biological activities can be predicted (Active vs. Inactive)**
Chemical Structure	**Multilevel Neighborhoods of Atoms (MNA) descriptors [1, 2]**
Mathematical Algorithm	**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.
2. *Filimonov D.A., Poroikov V.V. In:* Chemoinformatics Approaches to Virtual Screening. RSC Publ., 2008, 182-216.
3. Poroikov V.V. et al. *J. Chem. Inform. Computer Sci.*, 2000, 40, 1349.

Types of biological activity predicted by PASS

- **Main pharmacological effects**
  (antihypertensive, hepatoprotective, anti-inflammatory 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.).

Results of PASS Prediction for Clopidogrel



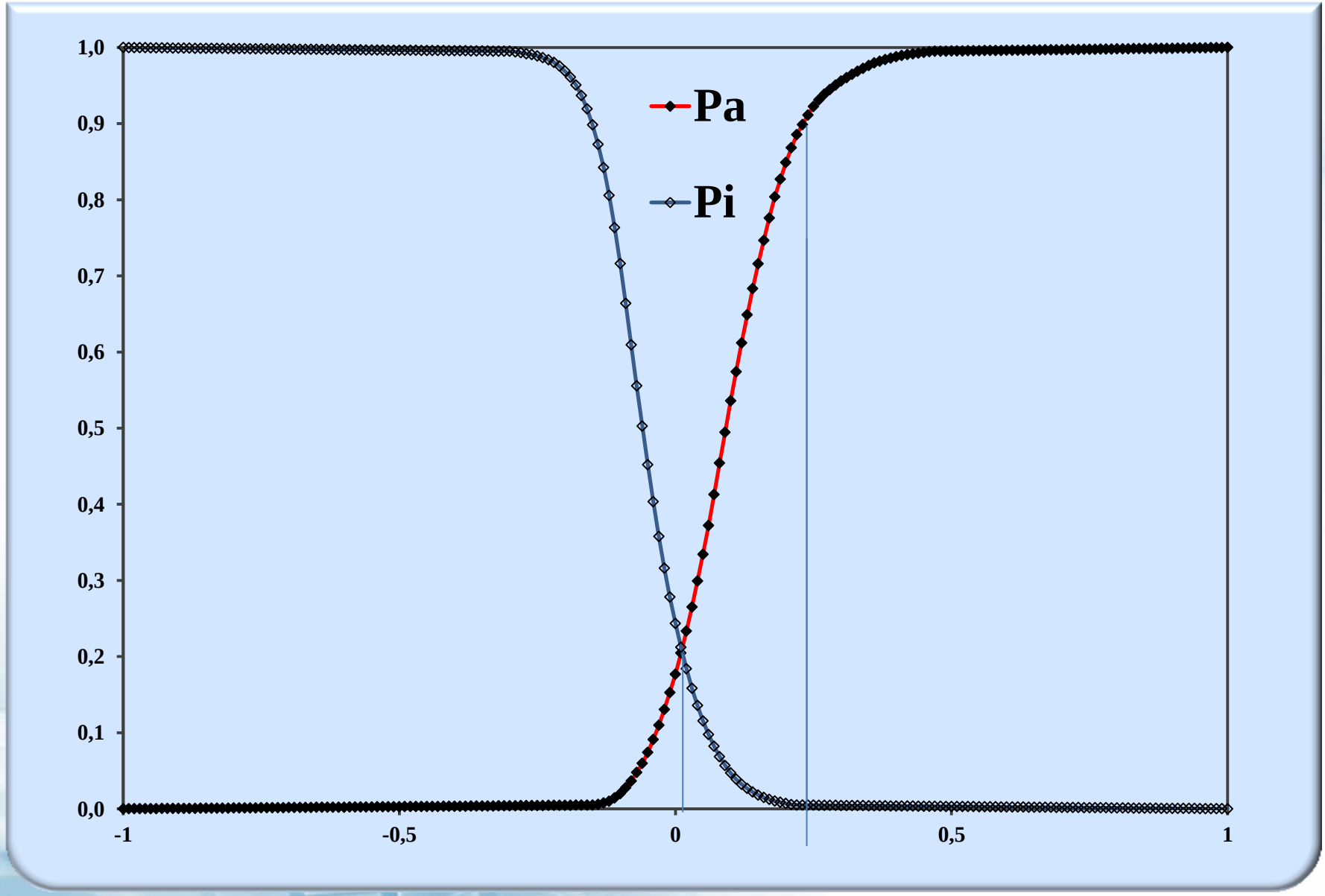
Results of PASS Prediction for Clopidogrel

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
Neuroprotector
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.

Distributions of Pa and Pi for Antineoplastic activity as functions of initial Bayesian estimates



Some publications, where PASS algorithm was described

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 (2), 66-75.

Poroikov V., Filimonov D. (2005). PASS: Prediction of Biological Activity Spectra for Substances. In: *Predictive Toxicology*. Ed. by Christoph Helma. N.Y.: Taylor & Francis, 459-478.

Descriptors (1999)

Robustness (2000)

Drug-likeness (2001)

PASS Online (2002)

NCI Browser (2003)

Examples of PASS-based search for new biologically active compounds

J. Chem. Inf. Comput. Sci. **2003**, *43*, 228−236

PASS Biological Activity Spectrum Predictions in the Enhanced Open NCI Database Browser

Vladimir V. Poroikov,[‡] Dmitrii A. Filimonov,[‡] Wolf-Dietrich Ihlenfeldt,[#] Tatyana A. Gloriozova,[‡] Alexey A. Lagunin,[‡] Yulia V. Borodina,[‡] Alla V. Stepanchikova,[‡] and Marc C. Nicklaus*[,†]

Laboratory of Structure-Function Based Drug Design, V.N. Orekhovich Institute of Biomedical Chemistry of the Russian Academy of Medical Sciences, 10 Pogodinskaya Street, Moscow 119121, Russia, Computer Chemistry Center and Institute for Organic Chemistry, University of Erlangen-Nürnberg, Nägelsbachstrasse

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Bioorganic & Medicinal Chemistry
Bioorganic & Medicinal Chemistry 12 (2004) 6559–6568

Design, synthesis, computational and biological evaluation of new anxiolytics

Athina Geronikaki,[a,*] Eugeni Babaev,[b] John Dearden,[c] Wim Dehaen,[d] Dmitrii Filimonov,[e] Irina Galaeva,[f] Valentina Krajneva,[f] Alexey Lagunin,[e] Fliur Macaev,[g] Guenadiy Molodavkin,[f] Vladimir Poroikov,[e] Serghei Pogrebnoi,[g]

Design of New Cognition Enhancers: From Computer Prediction to Synthesis and Biological Evaluation

Athina A. Geronikaki,*[,†] John C. Dearden,[‡] Dmitrii Filimonov,[§] Irina Galaeva,[§] Taissia L. Garibova,[§] Tatiana Gloriozova,[§] Valentina Krajneva,[§] Alexey Lagunin,[§] Fliur Z. Macaev,[⊥] Guenadij Molodavkin,[||] Vladimir V. Poroikov,[§] Serghei I. Pogrebnoi,[⊥] Felix Shepeli,[⊥] Tatiana A. Voronina,[§] Marta Tsitlakidou,[†] and Liudmila Vlad[⊥]

School of Pharmacy, Department of Pharmaceutical Chemistry, Aristotle University of Thessaloniki, Thessaloniki, Greece,

Chemistry of Heterocyclic Compounds, Vol. 42, No. 5, 2006

SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY OF ETHYNYLTHIAZOLES

A. Geronikaki[1], S. Vasilevsky[2], D. Hadjipavlou-Litina[1], A. Lagunin, and B. V. Poroikov[3]

A series of acetylene derivatives of thiazole using the Sonogashira cross-coupling method was synthesized and evaluated in vivo for their anti-inflammatory activity. Four compounds exhibited good anti-inflammatory activity and two inhibited soybean lipoxygenase.

Computer-Aided Selection of Potential Antihypertensive Compounds with Dual Mechanism of Action

Alexey A. Lagunin,* Oleg A. Gomazkov, Dmitrii A. Filimonov, Tatyana A. Gureeva, Elvira A. Dilakyan,

J. Med. Chem. **2008**, *51*, 1601–1609

Computer-Aided Discovery of Anti-Inflammatory Thiazolidinones with Dual Cyclooxygenase/Lipoxygenase Inhibition

Athina A. Geronikaki,[†] Alexey A. Lagunin,*[,‡] Dimitra I. Hadjipavlou-Litina,[†] Phaedra T. Eleftheriou,[†] Dmitrii A. Filimonov,[‡] Vladimir V. Poroikov,[‡] Intekhab Alam,[§] and Anil K. Saxena[§]

Department of Pharmaceutical Chemistry, School of Pharmacy, Aristotle University, Thessaloniki, 54124, Greece, Institute of Biomedical

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ELSEVIER
European Journal of Medicinal Chemistry 44 (2009) 473–481
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Original article

Evaluation of the local anaesthetic activity of 3-aminobenzo[*d*]isothiazole derivatives using the rat sciatic nerve model

Athina Geronikaki [a,*], Paola Vicini [b], Nikos Dabarakis [c], Alexey Lagunin [d], Vladimir Poroikov [d], John Dearden [e], Hassan Modarresi [e], Mark Hewitt [e], George Theophilidis [f]

European Journal of Medicinal Chemistry 47 (2012) 111–124
Contents lists available at SciVerse ScienceDirect
European Journal of Medicinal Chemistry
journal homepage: http://www.elsevier.com/locate/ejmech
ELSEVIER

Original article

Fragment-based design, docking, synthesis, biological evaluation and

Current Pharmaceutical Design, 2010, *16*, 1703-1717 1703

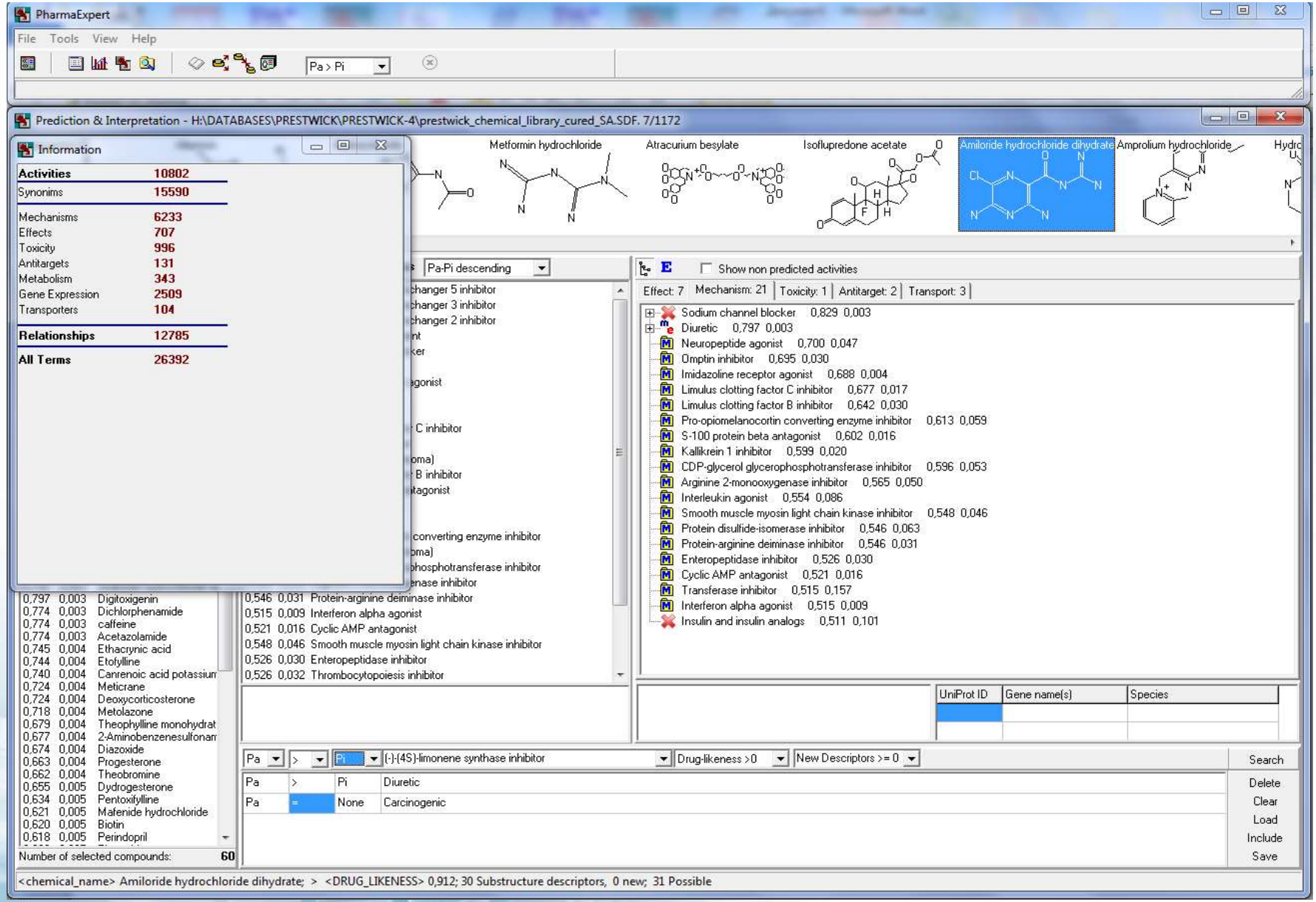
Multi-Targeted Natural Products Evaluation Based on Biological Activity Prediction with PASS

Alexey Lagunin, Dmitry Filimonov and Vladimir Poroikov*

Institute of Biomedical Chemistry of Rus. Acad. Med. Sci., 10, Pogodinskaya Str., Moscow, 119121, Russia

Abstract: Natural products found a wide use in folk medicine. Presently, when routine development of new drugs faced a considerable challenge, they become an inspiration and valuable source in drugs discovery. Rather complex and diverse chemical structures of natural compounds provide a basis for modulation of different biological targets. Natural compounds exhibit a multitargeted action that may lead

PharmaExpert: Tool for analysis of PASS prediction results



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

Pharmaceut. Chem. J., 2011, 45 (10), 605-611

Drug repositioning

PharmaExpert

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

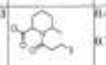
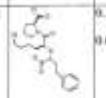
The search for new compounds with multiple mechanisms of action

J. Med. Chem., 2003, 46(15), 3326-3332

J. Med. Chem. 2008, 51(6), 1601-1609

Search for multitargeted compounds using PharmaExpert

Antihypertensive agents, ACE and NEP inhibitors

No	ID	Structure	Prediction		Experiment				
					IC_{50} ACE (M)			IC_{50} NEP (M)	
			Pa	Pi	Activity	purified ACE	blood serum	brain membr.	blood serum	brain membr.
I	587082		0.855	0.002	NEP inhibitor	$1 \cdot 10^{-7}$ 18%	$1 \cdot 10^{-6}$	$1 \cdot 10^{-6}$	-	$2 \cdot 10^{-7}$
			0.805	0.003	ACE inhibitor					
II	219863		0.440	0.005	NEP inhibitor	$1 \cdot 10^{-9}$	$2 \cdot 10^{-8}$	$1 \cdot 10^{-7}$	-	$2 \cdot 10^{-7}$
			0.773	0.003	ACE inhibitor					
III	119354		0.684	0.005	NEP inhibitor	$3 \cdot 10^{-7}$	$2 \cdot 10^{-6}$	$1 \cdot 10^{-6}$	$2 \cdot 10^{-7}$	$2 \cdot 10^{-6}$
			0.569	0.004	ACE inhibitor					
IV	119363		0.618	0.004	NEP inhibitor	$5 \cdot 10^{-6}$	$2 \cdot 10^{-6}$	$1 \cdot 10^{-6}$	$2 \cdot 10^{-7}$	$2 \cdot 10^{-6}$
			0.511	0.005	ACE inhibitor					
Lisinopril			0.115	0.012	NEP inhibitor		10^{-9}			
			0.607	0.004	ACE inhibitor					
Phosphoramidon			0.203	0.006	NEP inhibitor				10^{-7}	$2 \cdot 10^{-7}$
			0.151	0.017	ACE inhibitor					

3326 J. Med. Chem. 2003, 46, 3326−3332

Computer-Aided Selection of Potential Antihypertensive Compounds with Dual Mechanism of Action

Alexey A. Lagunin,* Oleg A. Gomazkov, Dmitrii A. Filimonov, Tatyana A. Gureeva, Elvira A. Dilakyan, Elena V. Kugaevskaya, Yulia E. Elisseeva, Nina I. Solovyeva, and Vladimir V. Poroikov

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

Received November 8, 2002

The prediction of biological activity spectra for substances as an approach for searching compounds with complex mechanisms of action was studied. New compounds with dual mechanisms of antihypertensive action were found by this approach. Biological activity spectra for substances were predicted on the basis of their structural formulas by the computer program PASS. Thirty molecular mechanisms of action of compounds from the MDDR 99.2 database, which cause the antihypertensive effect and can be predicted by PASS, have been identified. The analysis of predictions for compounds with 15 dual antihypertensive mechanisms of action from the MDDR 99.2 database has confirmed high accuracy of prediction. This approach was applied to databases of commercially available compounds (AsInEx and ChemBridge) and allowed us to select four substances that are potential inhibitors of angiotensin converting enzyme (ACE) and of neutral endopeptidase (NEP). At a later time, all these compounds were found to be the inhibitors of both ACE and NEP. The most potent compounds had IC_{50} of 10^{-7}−10^{-6} M for ACE and 10^{-5} M for NEP. New combinations of dual mechanisms of action never before found for antihypertensive compounds were predicted.

Antiinflammatory agents, COX-1, COX-2, LOX inhibitors

	anti-inflammatory (CPE)[a] activity and COX/LOX[b] inhibitory activity			
		inhibition %		
compd	CPE%	COX-1	COX-2	LOX
1	57.3 ± 3.4	62.0	0.0	44.0
2	72.7 ± 6.8	25.0	6.2	51.0
3	51.1 ± 4.2	8.0	2.5	22.4
4	66.1 ± 1.2	60.0	4.5	12.5
5	69.4 ± 2.3	25.0	12.1	76.0
6	54.2 ± 2.4	31.0	6.2	25.0
7	44.5 ± 1.8	90.0	30.4	12.0
8	62.0 ± 2.5	50.0	2.1	44.2
9		0.0	0.0	

J. Med. Chem. **2008**, *51*, 1601–1609 1601

Computer-Aided Discovery of Anti-Inflammatory Thiazolidinones with Dual Cyclooxygenase/ Lipoxygenase Inhibition

Athina A. Geronikaki,[†] Alexey A. Lagunin,*[,‡] Dimitra I. Hadjipavlou-Litina,[†] Phaedra T. Eleftheriou,[†] Dmitrii A. Filimonov,[‡] Vladimir V. Poroikov,[‡] Intekhab Alam,[§] and Anil K. Saxena[§]

Department of Pharmaceutical Chemistry, School of Pharmacy, Aristotle University, Thessaloniki, 54124, Greece, Institute of Biomedical Chemistry of Russian Academy of Medical Sciences, Pogodinskaya Street, 10, Moscow, 119121, Russia, and Medicinal Chemistry Division, Central Drug Research Institute, Chattar Manzil Palace, Lucknow-226 001, India

Received July 24, 2007

New anti-inflammatory agents possessing dual cyclooxygenase/lipoxygenase (COX/LOX) inhibition were discovered by computer-aided prediction of biological activity for 573 virtually designed chemical compounds. Prediction of biological activity was performed by PASS, and prediction results were analyzed with PharmaExpert software. Nine 2-(thiazole-2-ylamino)-5-phenylidene-4-thiazolidinone derivatives differing by the phenyl group substitution were selected for synthesis and experimental testing as potential COX/LOX inhibitors. Eight tested compounds exhibited anti-inflammatory activity in the carrageenin-induced paw edema. It was shown that seven tested compounds (77.8%) were LOX inhibitors, seven compounds were COX inhibitors (77.8%), and six tested compounds (66.7%) were dual COX/LOX inhibitors. Analysis of lipophilicity of the compounds showed a negative correlation with inhibition of edema formation. The binding modes of the most active compounds of this series (2-(thiazole-2-ylamino)-5-(*m*-chlorophenylidene)-4-thiazolidinone for COX-1 and COX-2, and 2-(thiazole-2-ylamino)-5-(*m*-nitrophenylidene)-4-thiazolidinone for 15-LOX) were proposed on the basis of docking studies.

Finding of nootropic effect in some antihypertensive drugs based on PASS prediction

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	-

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]

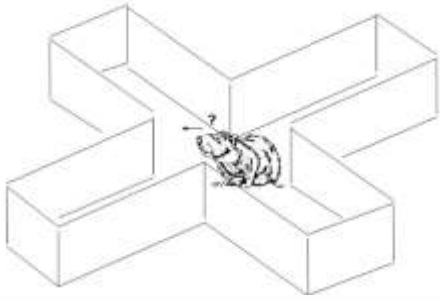
Author Affiliations

Correspondence to

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

Published 22 July 2013

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).



Kryzhanovskii S.A. et al. *Pharmaceutical Chemistry Journal*, 2012, 45: 605-611.

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

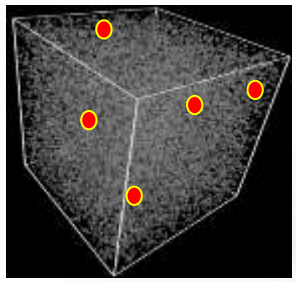
Annex I - "Description of Work"

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

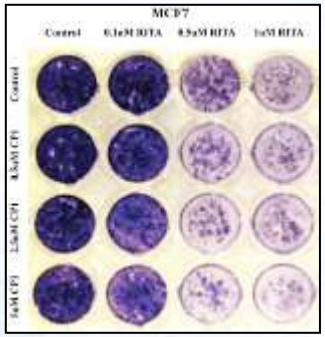
Operative commencement date of contract: February 1st, 2007

Participants: 9 teams from 8 countries



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

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



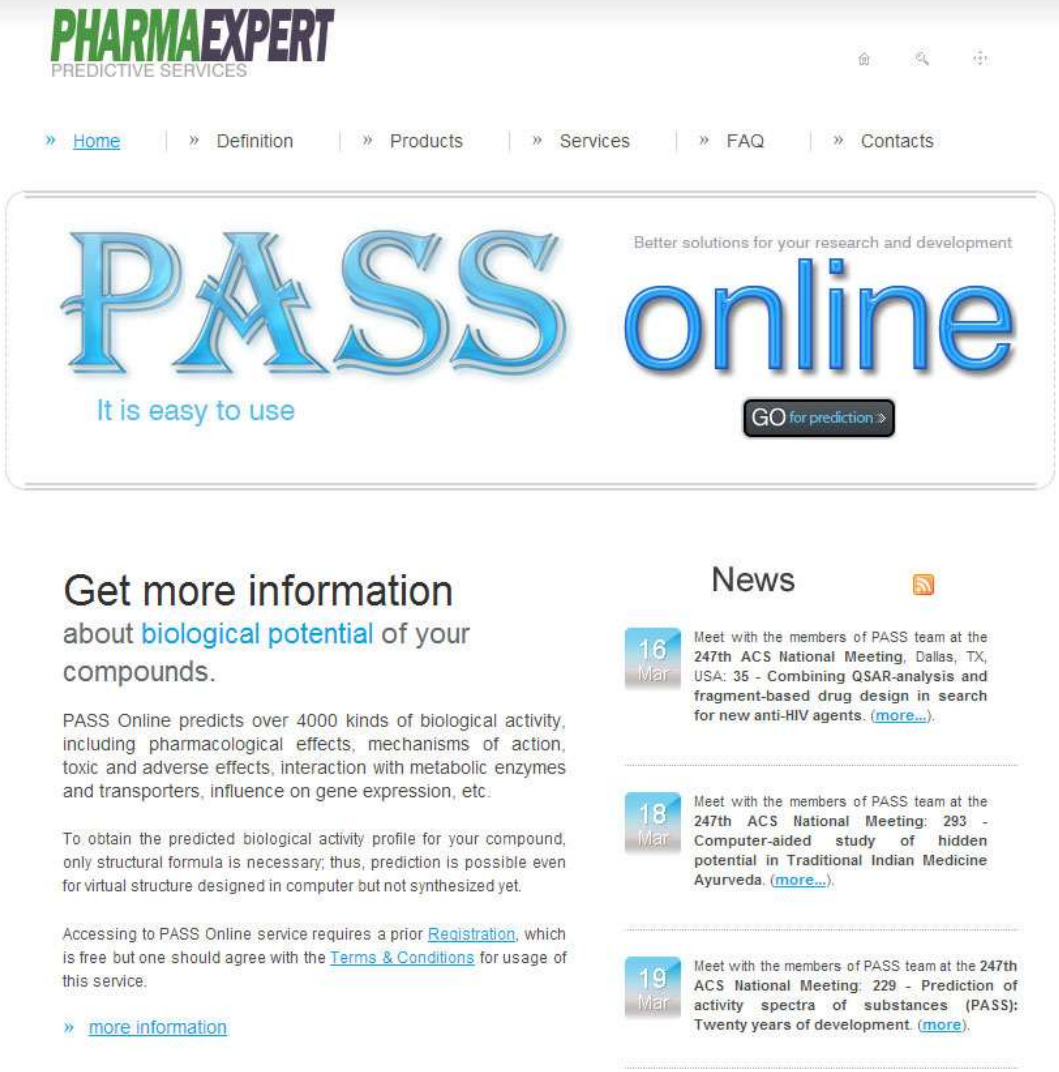
11 compounds tested in cellular assays

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

Further progress:

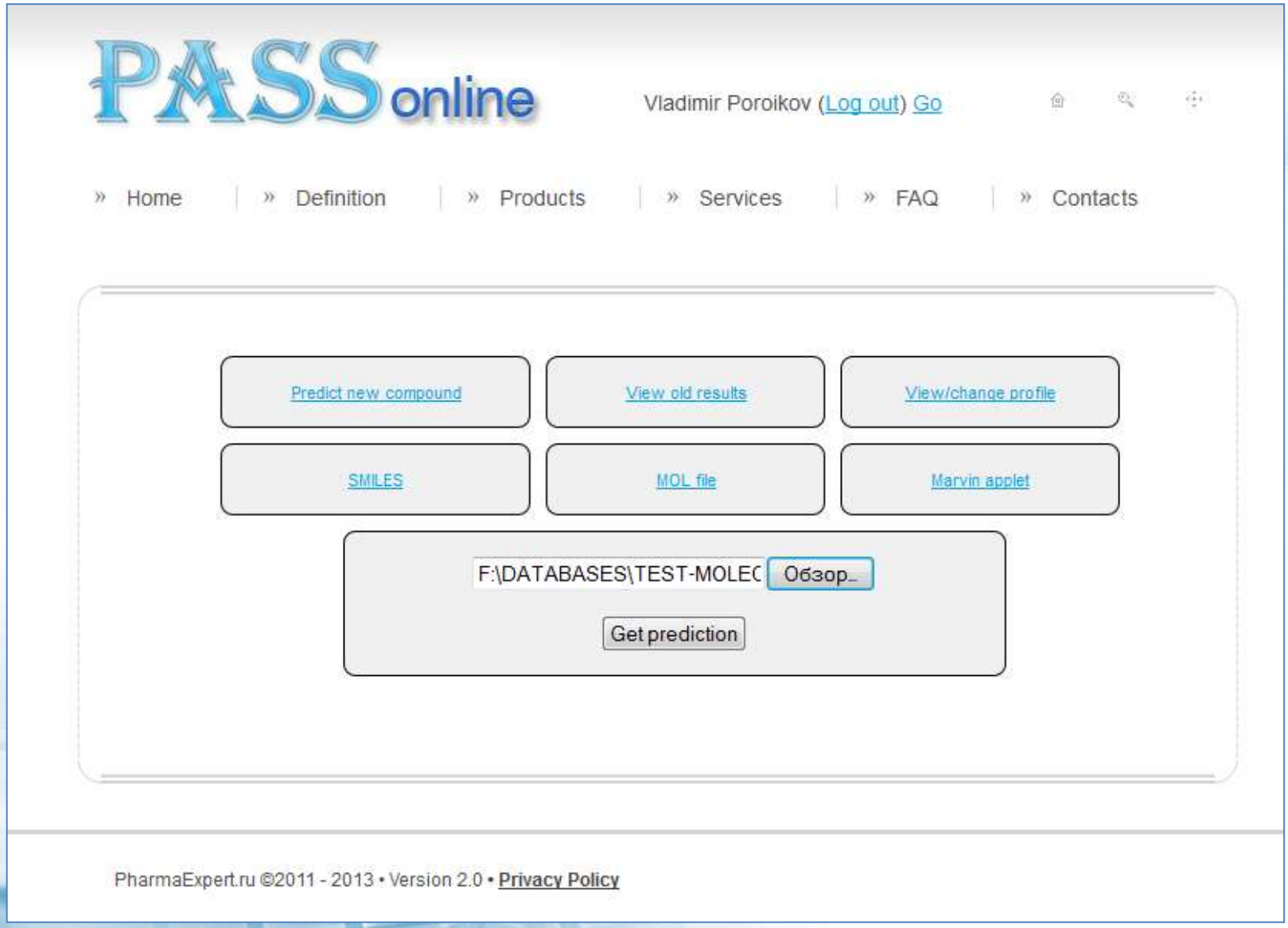
- Activity confirmed in experiments on mouse xenograft models
- ALab – resident of «Skolkovo» (2012)
- Grant of«Skolkovo» (2013)
- More active analogs (2014)

PASS Online Resource

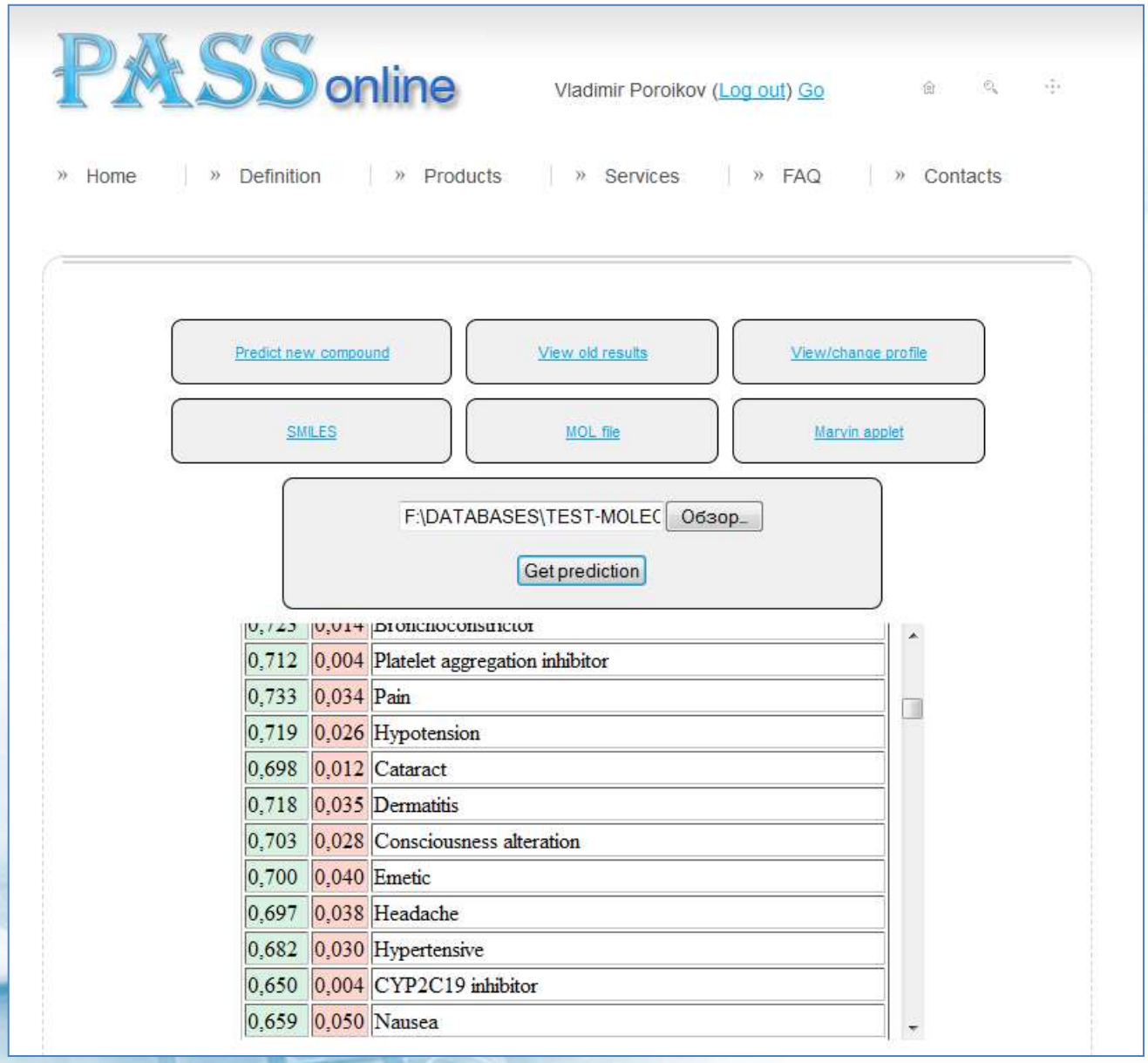


http://way2drug.com/passonline

Prediction for structure presented by MOL file

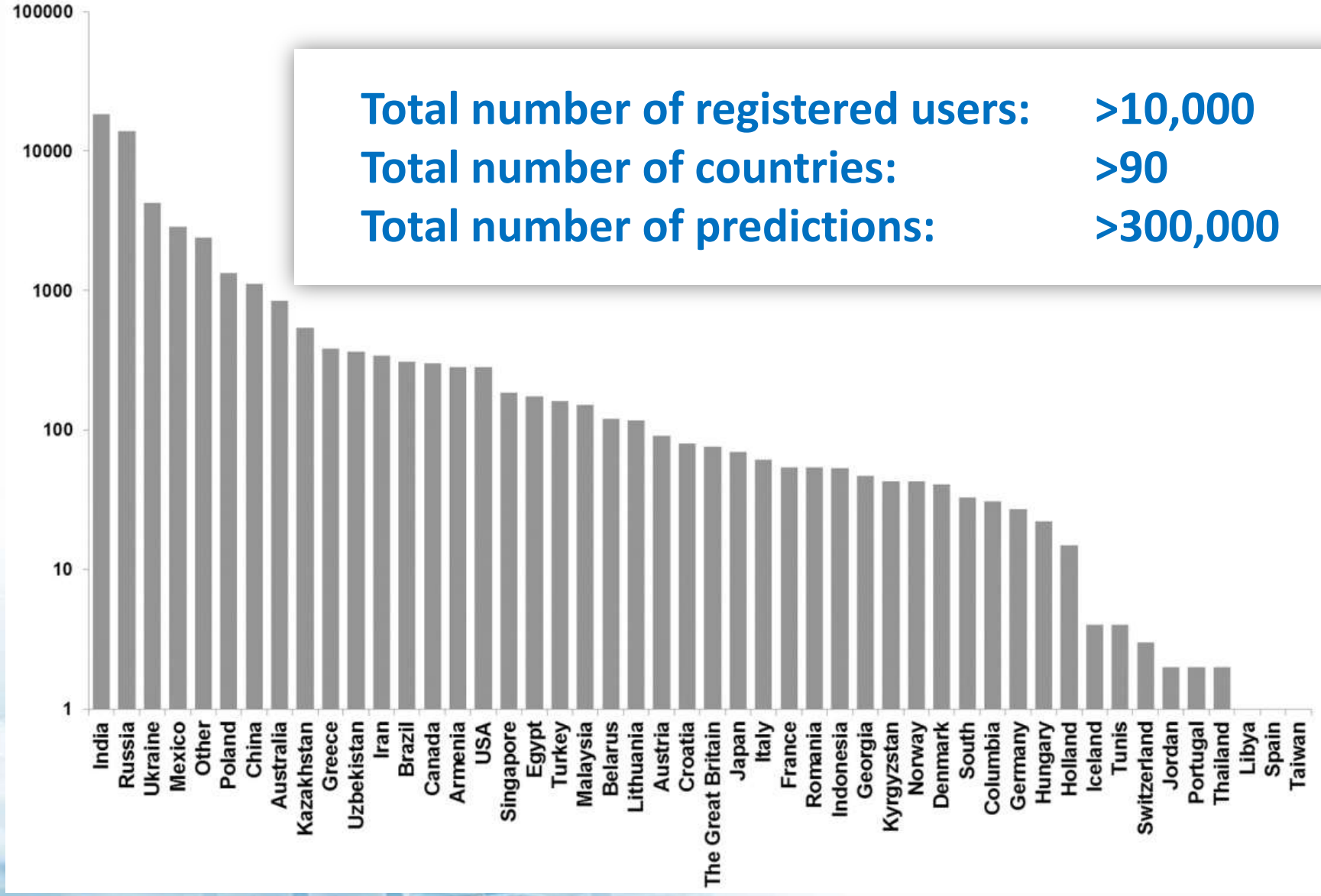


Prediction Results



0,712	0,004	Platelet aggregation inhibitor
0,733	0,034	Pain
0,719	0,026	Hypotension
0,698	0,012	Cataract
0,718	0,035	Dermatitis
0,703	0,028	Consciousness alteration
0,700	0,040	Emetic
0,697	0,038	Headache
0,682	0,030	Hypertensive
0,650	0,004	CYP2C19 inhibitor
0,659	0,050	Nausea

PASS Online Utilization in 2013

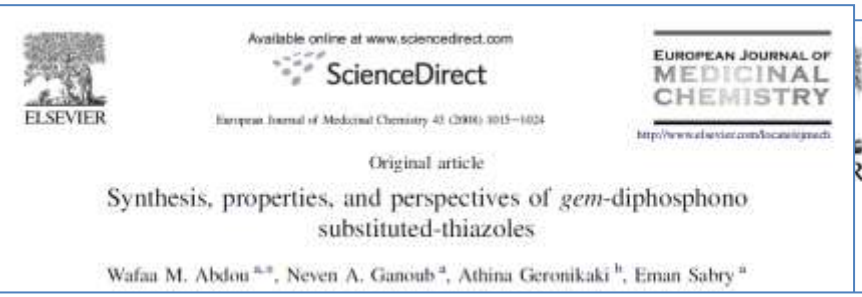


Total number of registered users: **>10,000**

Total number of countries: **>90**

Total number of predictions: **>300,000**

Over 150 independent publications with PASS online predictions (>50% papers with experimental testing of prediction results)

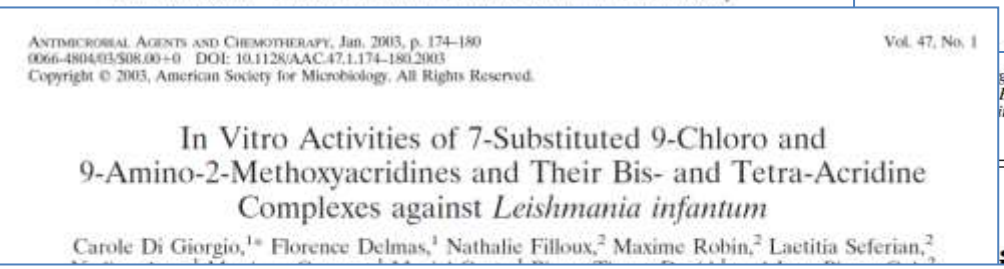


Available online at www.sciencedirect.com
ScienceDirect
European Journal of Medicinal Chemistry 45 (2010) 1015–1024
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Original article

Synthesis, properties, and perspectives of *gem*-diphosphono substituted-thiazoles

Wafaa M. Abdou [a,*], Neven A. Ganoub [a], Athina Geronikaki [b], Eman Sabry [a]



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2003, p. 174–180
0066-4804/03/$08.00+0 DOI: 10.1128/AAC.47.1.174–180.2003
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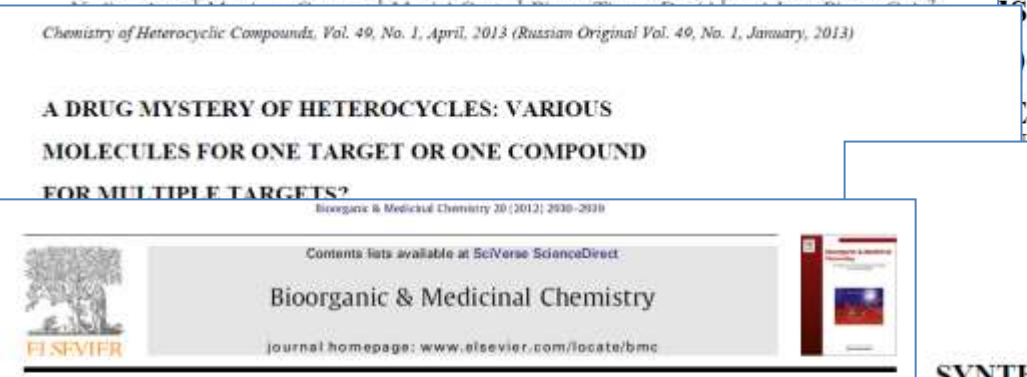
Vol. 47, No. 1

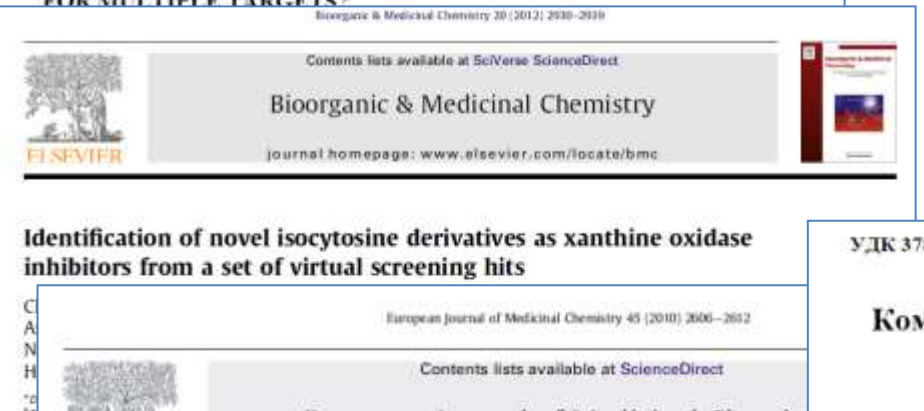
In Vitro Activities of 7-Substituted 9-Chloro and 9-Amino-2-Methoxyacridines and Their Bis- and Tetra-Acridine Complexes against *Leishmania infantum*

Carole Di Giorgio,[1]* Florence Delmas,[1] Nathalie Filloux,[2] Maxime Robin,[2] Laetitia Seferian,[2]



Chemistry of Heterocyclic Compounds, Vol. 49, No. 1, April, 2013 (Russian Original Vol. 49, No. 1, January, 2013)

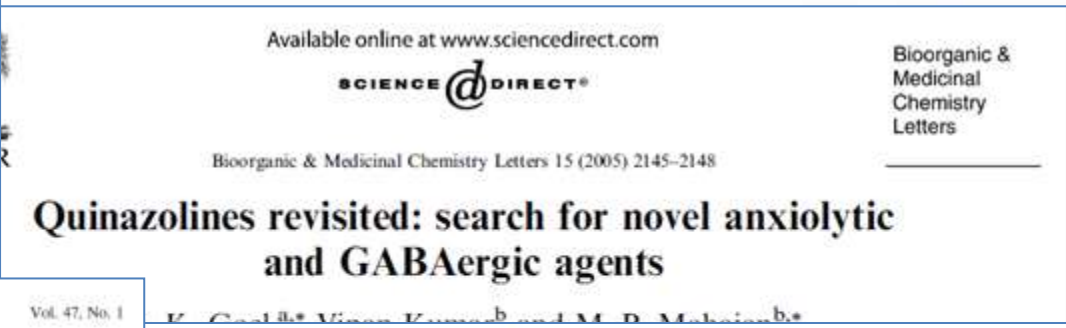
A DRUG MYSTERY OF HETEROCYCLES: VARIOUS MOLECULES FOR ONE TARGET OR ONE COMPOUND FOR MULTIPLE TARGETS?



Bioorganic & Medicinal Chemistry 20 (2012) 2030–2039
Contents lists available at SciVerse ScienceDirect
Bioorganic & Medicinal Chemistry
journal homepage: www.elsevier.com/locate/bmc

Identification of novel isocytosine derivatives as xanthine oxidase inhibitors from a set of virtual screening hits

European Journal of Medicinal Chemistry 45 (2010) 2606–2612
Contents lists available at ScienceDirect
European Journal of Medicinal Chemist



Available online at www.sciencedirect.com
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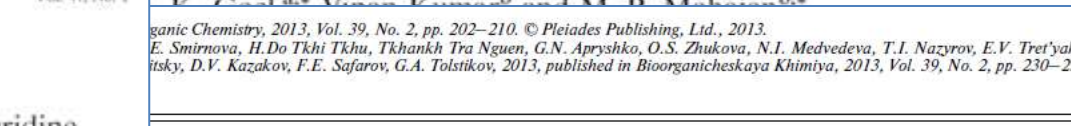
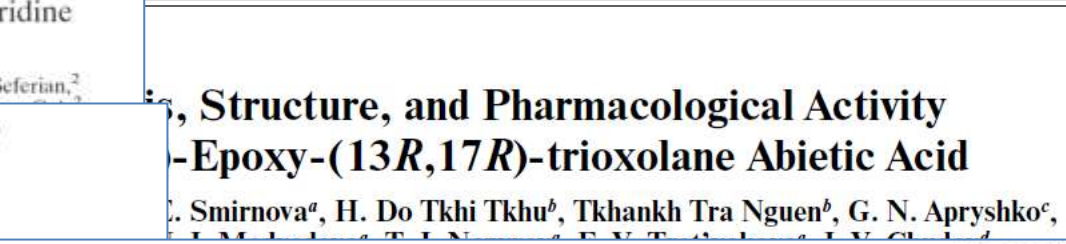
Bioorganic & Medicinal Chemistry Letters

Bioorganic & Medicinal Chemistry Letters 15 (2005) 2145–2148

Quinazolines revisited: search for novel anxiolytic and GABAergic agents

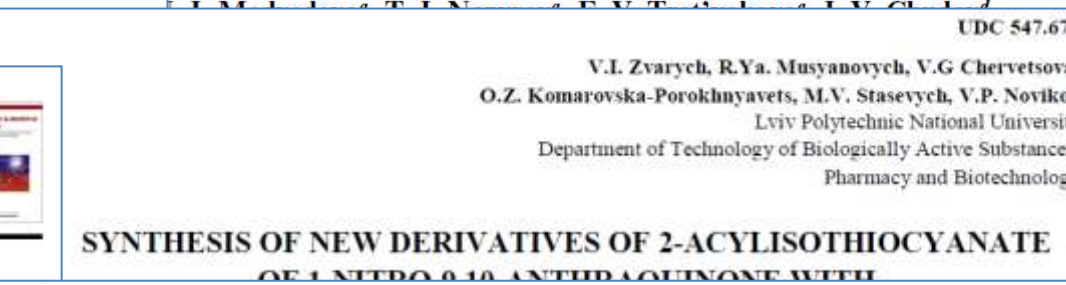


ganic Chemistry, 2013, Vol. 39, No. 2, pp. 202–210. © Pleiades Publishing, Ltd., 2013.
E. Smirnova, H.Do Tkhi Tkhu, Tkhankh Tra Nguen, G.N. Apryshko, O.S. Zhukova, N.I. Medvedeva, T.I. Nazyrov, E.V. Tret'yak
itsky, D.V. Kazakov, F.E. Safarov, G.A. Tolstikov, 2013, published in Bioorganicheskaya Khimiya, 2013, Vol. 39, No. 2, pp. 230–2



, Structure, and Pharmacological Activity
-Epoxy-(13*R*,17*R*)-trioxolane Abietic Acid

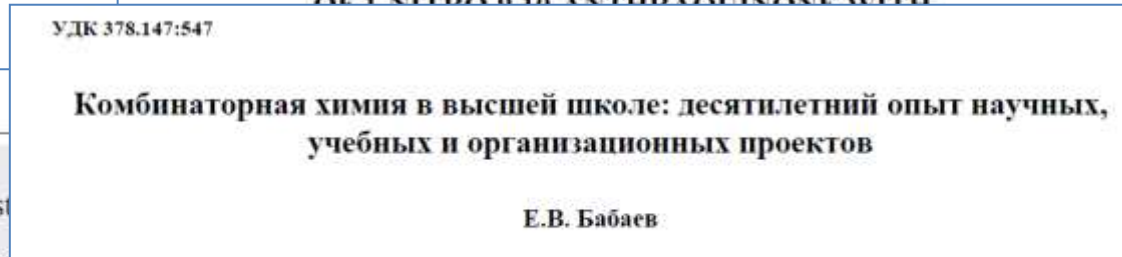
. Smirnova[a], H. Do Tkhi Tkhu[b], Tkhankh Tra Nguen[b], G. N. Apryshko[c],



UDC 547.67

V.I. Zvarych, R.Ya. Musyanovych, V.G Chervetsov
O.Z. Komarovska-Porokhnyavets, M.V. Stasevych, V.P. Novik
Lviv Polytechnic National Universi
Department of Technology of Biologically Active Substance
Pharmacy and Biotechnolog

SYNTHESIS OF NEW DERIVATIVES OF 2-ACYLISOTHIOCYANATE



УДК 378.147:547

Комбинаторная химия в высшей школе: десятилетний опыт научных, учебных и организационных проектов

Е.В. Бабаев

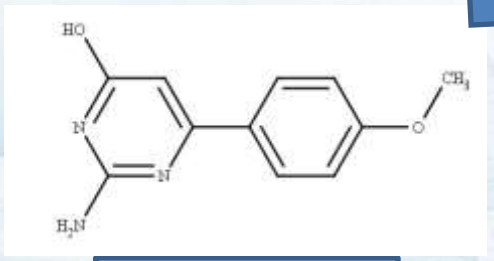
Example 1. Virtual screening of the synthetic library

2648 organic molecules

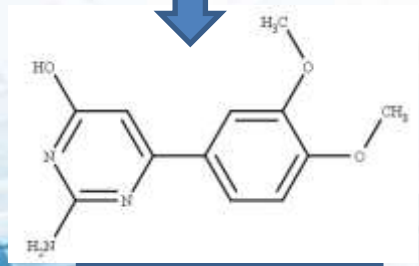
PASS Predictions
Xanthine oxidase inhibitors

32 hits; 24 tested

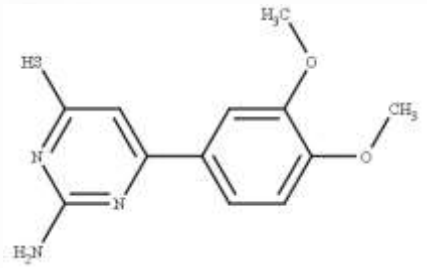
Reference drug
Allopurinol
IC_{50}=5,7 uM



IC_{50}=9,4 uM



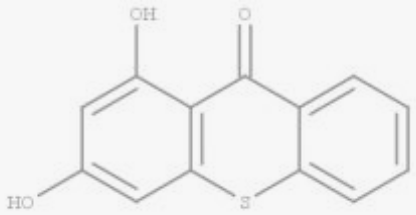
IC_{50}=30,2 uM



IC_{50}=1,4 uM

C. B-Rao et al. Bioorg. Med. Chem., ***20****, 2930 (2012).*

Example 2. Prediction of the most probable activities of xantones and thioxantones for testing *in vitro*



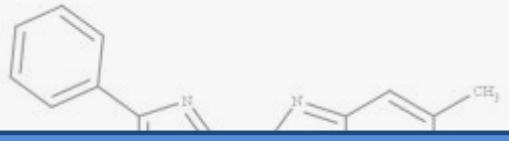
Activity	*Pa*	*Pi*
Antineurotoxic	0,859	0,005
Quercetin 2,3-dioxygenase inhibitor	0,543	0,005
Thioredoxin disulfide reductase inhibitor	0,541	0,007
FMO3 substrate	0,540	0,008
CF transmembrane conductance regulator inhibitor	0,539	0,005
Sulfotransferase substrate	0,505	0,004
Estrogen beta receptor agonist	0,501	0,001

The only activities that were tested are antimicrobial (S. aureus, S. pneumonia, S. pyogenes, M. catarrgalis, H. influenza, E. Coli) and cyrotoxic (HepG2 and Jurkat cell lines). No such activities were predicted and found experimentally).

Verbanac D. et al. Bioorg. Med. Chem., 20, 3180 (2012)

Mechani

Example 3. Prediction of the most probable activities of pyranopyrazole derivatives for testing *in vivo*



Analgesic and anti-inflammatory activity of these compounds was shown on experimental models in mice. Using docking the authors concluded that COX-2 inhibiting activity reduces in the following order: phenothiazolyl > benzothiazolyl > quinolyl> pyridiminyl > OCH_3 > Br > CH_3 > H. However, these conclusions require experimental verification.

Kumar A. et al. Eur. J. Med. Chem., 50, 81 (2012)

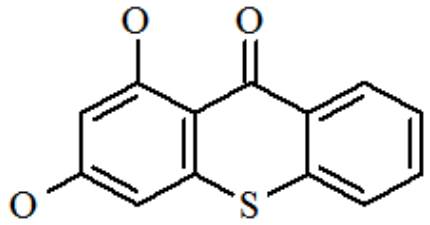
Complement factor D inhibitor	0,572	0,050
Immunomodulator	0,532	0,033
Immunosuppressant	0,454	0,044
Cyclooxygenase inhibitor	0,400	0,004
HCV IRES inhibitor	0,431	0,050

Systematic review of these >150 publications is accepted for publication by "Chemistry of Heterocyclic Compounds"

Graphical abstract

D. A. Filimonov, A. A. Lagunin, T. A. Gloriozova, A. V. Rudik, D. S. Druzhilovsky, P. V. Pogodin, V. V. Poroikov

Prediction of biological activity of organic compounds using web-resource PASS Online



PASS

Pa	Pi	Activity
0,859	0,004	Antineurotoxic
0,776	0,009	Fibrinolytics

Filimonov D.A. et al. Chemistry of Heterocyclic Compounds, No. 4 (2014).

In December 2013 we executed an interview of active PASS Online users

Please, fill in the Anonymous form below.

1. Where are you working?

- ☐ Academy (University)
- ☐ Research Institute
- ☐ Industry
- ☐ Regulatory Agency
- ☐ Other (Please, specify)

2. What is your field of activity?

- ☐ Organic Chemistry
- ☐ Medicinal Chemistry
- ☐ Pharmacology
- ☐ Toxicology
- ☐ Pharmacy
- ☐ Other (Please, specify)

3. What is your primary aim to use PASS Online service?

- ☐ Planning of Chemical Synthesis
- ☐ Planning of Biological Testing
- ☐ Finding New Actions of Known Compounds
- ☐ Chemical Safety & Risk Assessment
- ☐ Other (Please, specify)

4. How satisfied are you by PASS Online service?

Very Sat. *means that you are very satisfied by this aspect of PASS Online service.*
Sat. *means that you are satisfied by this aspect of PASS Online service.*
N. *means that you can't decide whether you are satisfied by this aspect of PASS Online service.*
Dissat. *means that you are dissatisfied by this aspect of PASS Online service.*
Very Dissat. *means that you are very dissatisfied by this aspect of PASS Online service.*

On PASS Online service how I feel about…	Very Dissat.	Dissat.	N.	Sat.	Very Sat.
Registration procedure	☐	☐	☐	☐	☐
Structure input	☐	☐	☐	☐	☐
Accessibility via Internet	☐	☐	☐	☐	☐
User interface	☐	☐	☐	☐	☐
Speed of response	☐	☐	☐	☐	☐
List of predictable activities	☐	☐	☐	☐	☐
Results of prediction	☐	☐	☐	☐	☐

5. To improve PASS Online service are you ready…

Very Likely *means that you will very likely to take part in this activity.*
Likely *means that you will likely to take part in this activity.*
N. *means that you can't decide whether you will take part in this activity or not.*
Unlikely *means that you will unlikely to take part in this activity.*
Very Unlikely *means that you will very unlikely to take part in this activity.*

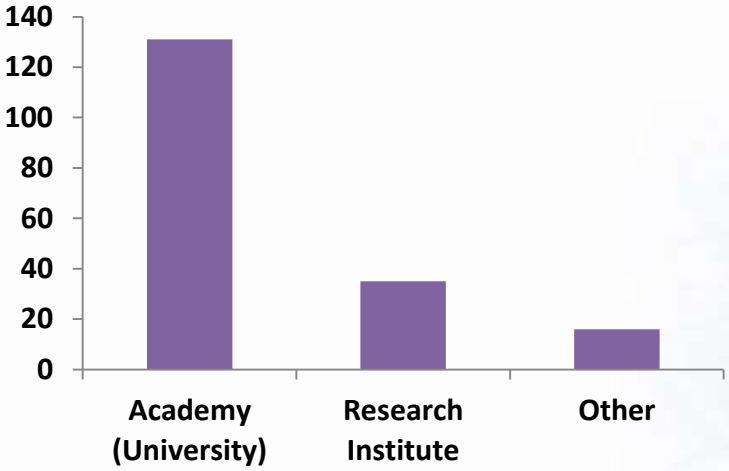
I am ready…	Very Unlikely	Unlikely	N.	Likely	Very Likely
To submit a feedback about correspondence of predictions with the experiment	☐	☐	☐	☐	☐
To submit the proposal what can be done for improvement of PASS Online	☐	☐	☐	☐	☐
To submit the proposal which biological activities should be covered by PASS Online	☐	☐	☐	☐	☐
To submit the proposal which chemical series should be covered by PASS Online	☐	☐	☐	☐	☐
Take part in a joint work to input data on active compounds from particular chemical series to update PASS Online training set	☐	☐	☐	☐	☐
To refer on PASS Online prediction results in my publications	☐	☐	☐	☐	☐
To recommend PASS Online service to other colleagues	☐	☐	☐	☐	☐

6. Are you willing to share some information about your activity, to find some partners for collaborative projects?

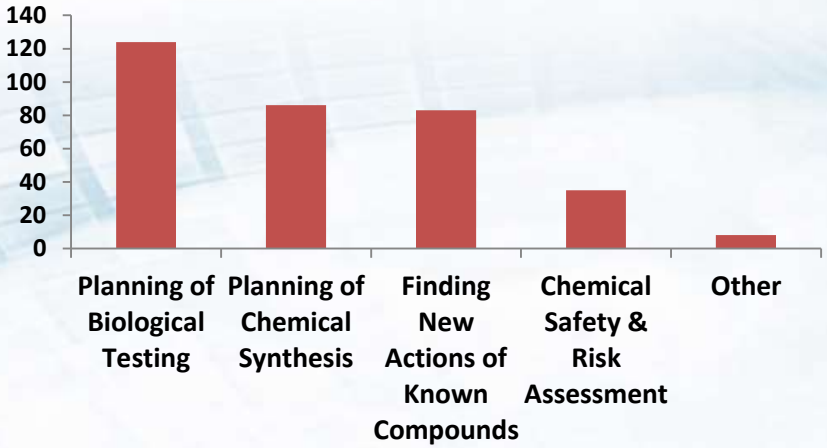
Very Likely *means that you will very likely to take part in this activity.*
Likely *means that you will likely to take part in this activity.*
N. *means that you can't decide whether you will take part in this activity or not.*
Unlikely *means that you will unlikely to take part in this activity.*
Very Unlikely *means that you will very unlikely to take part in this activity.*

Responses on the questions (1)

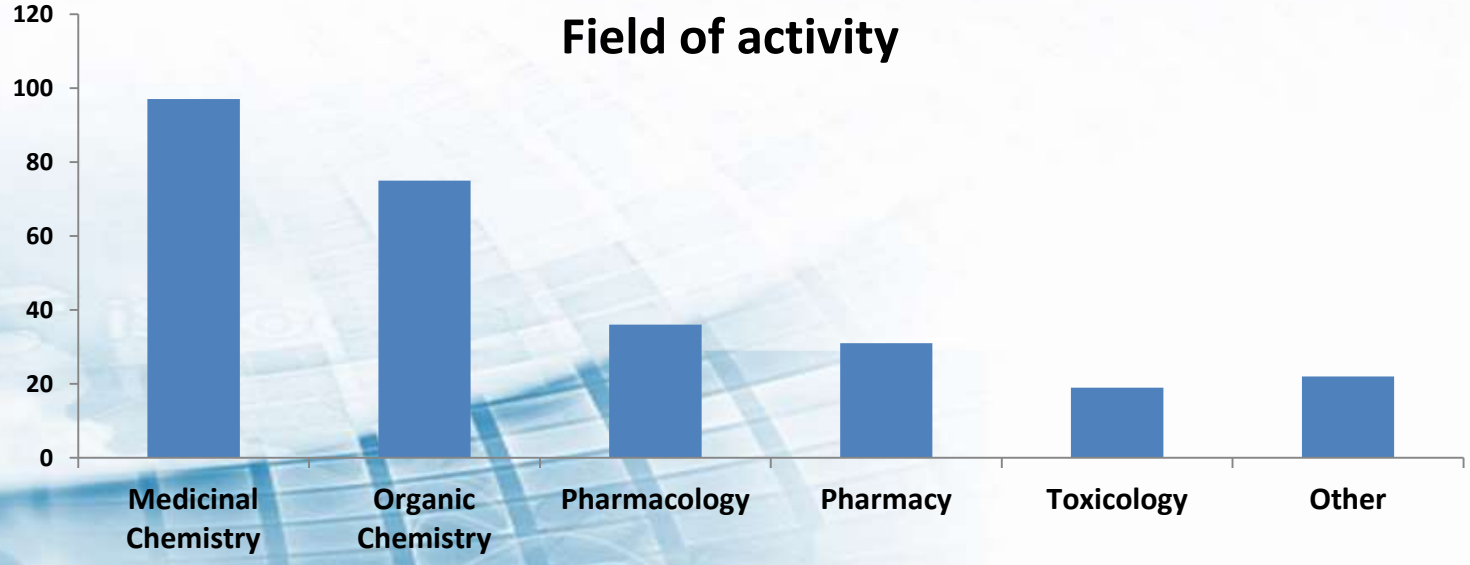
Where are you working?



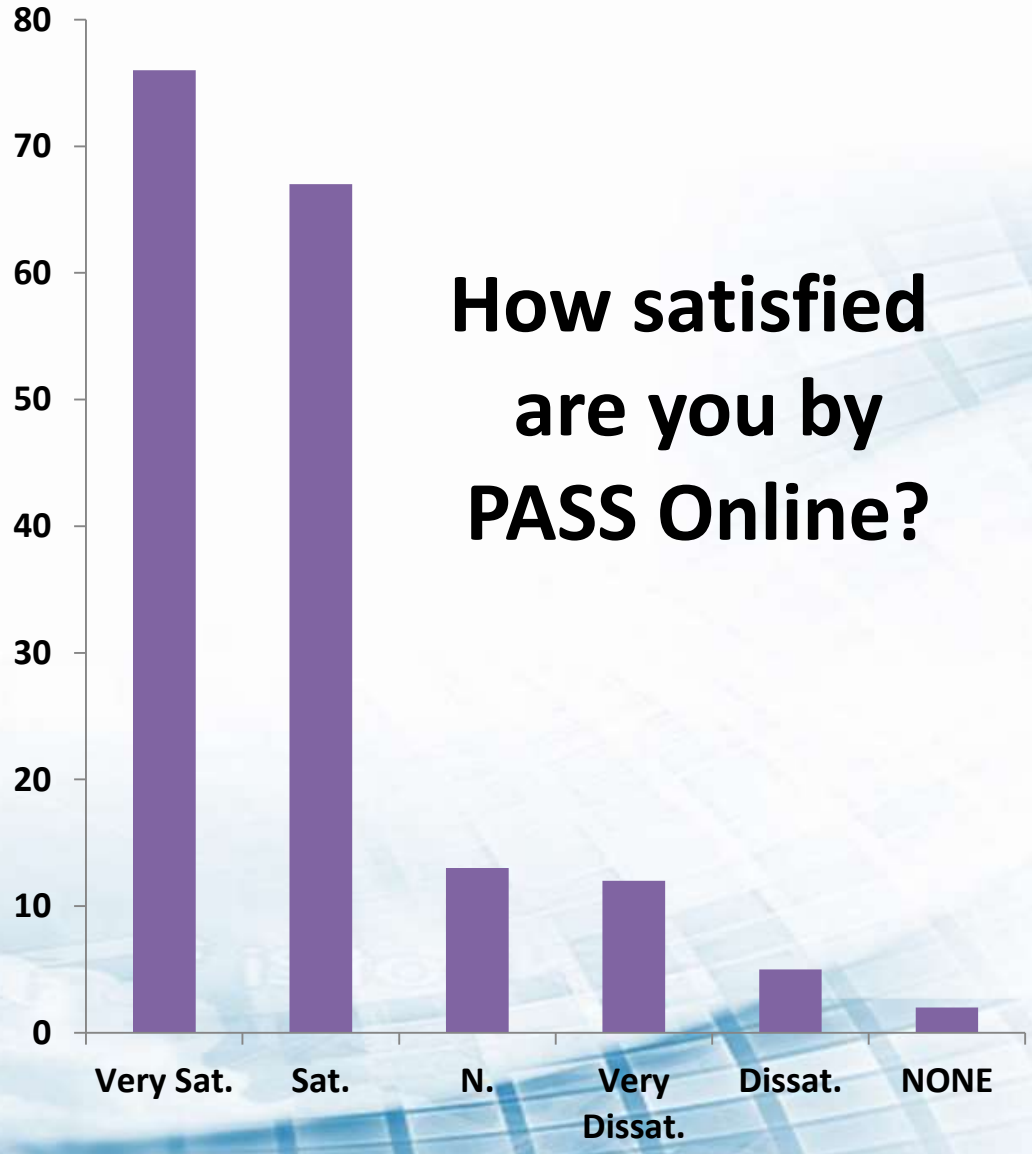
Primary aim to use PASS Online



Field of activity



Responses on the questions (2)



How satisfied are you by PASS Online?

Most of users are ready:

- To inform us about the experimental results
- To make suggestions how web-resource can be improved
- To add new information to the training set
- Refer in publications
- Recommend to colleagues
- Try to obtain joint grants

Major comments of the users

1. Acknowledgements etc.
2. Collaboration
3. Interface, general remarks
4. Presentation of the prediction results
5. Input of data
6. Training set
7. List of activities
8. Miscellaneous

Summary

1. PASS provides information about most probable biological activities based on structural formulae of organic compounds.
2. PASS predictions can be used for planning of synthesis and biological testing.
3. PASS Online is widely used by organic and medicinal chemists, pharmacologists etc.
4. Recommendations of PASS Online users provided during the interview can be used for further improvement of the web-resource.
5. PASS Online web-resource may become a platform for many collaborative projects in the field of drug discovery.

PASS

Thanks for your kind attention!

Visit our web-page:

www.way2drug.com/passonline

Your questions, pls., address to:

vladimir.poroikov@ibmc.msk.ru

20th EuroQSAR

Understanding Chemical-Biological Interactions