Computer-Aided Discovery of Hidden Pharmacotherapeutic Potential in Phytoconstituents from Traditional Medicine

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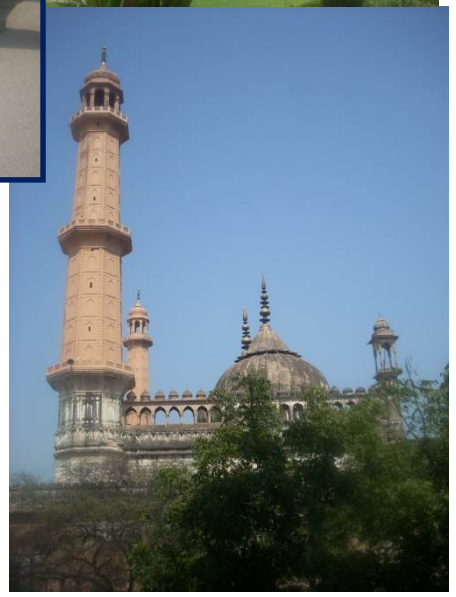
СПХФА
САНКТ-ПЕТЕРБУРГСКАЯ ГОСУДАРСТВЕННАЯ ХИМИКО-ФАРМАЦЕВТИЧЕСКАЯ АКАДЕМИЯ

Computer-Aided Discovery of Hidden Pharmacotherapeutic Potential in Phytoconstituents from Traditional Indian Medicine (TIM)

Supported by RFBR-DST
grant No. 11-04-92713-IND_a/RUSP-1176

Meeting with Prof. Rajesh K. Goel at CRDRI (Feb. 2010)



Some Information About Natural Compounds

- ✓ **At the end of XX century about 80 percent of the world population to some extend are using natural compounds as medicines[1].**
- ✓ **Pharmaceuticals of vegetable or microbial origin make up more than 30% of global sales[2].**
- ✓ **About 70% of NCEs were obtained on the basis of natural products in 1981-2006[3].**

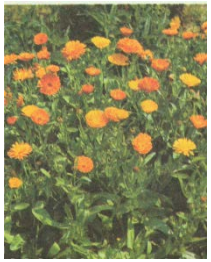
[1] World Health Organization

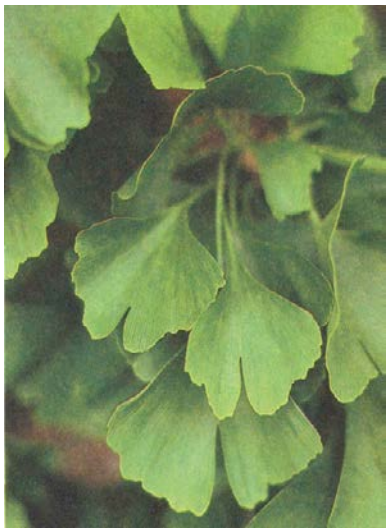
[2] Sneader W. Drug Discovery: A History. Wiley: Chichester, 2005, 88-150.

[3] Newman D.J., Cragg G.M. J. Nat. Prod., 2007, 70:461-477.

Advantages of Natural Compounds

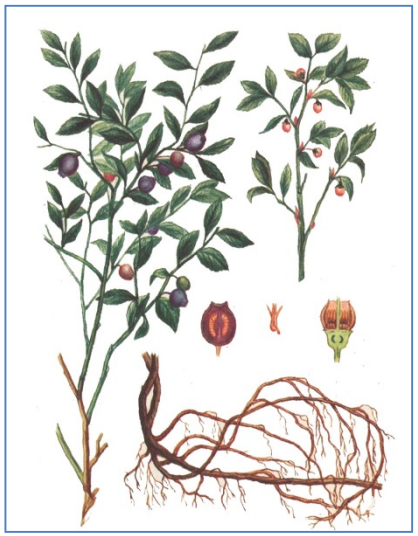
- ✓ Greater chemical diversity in comparison with the compounds obtained using only synthetic methods.
- ✓ Better ADME/T characteristics.





Гинкго двулопастной
Ginkgo biloba

Зверобой продырявленный
Hypericum perforatum



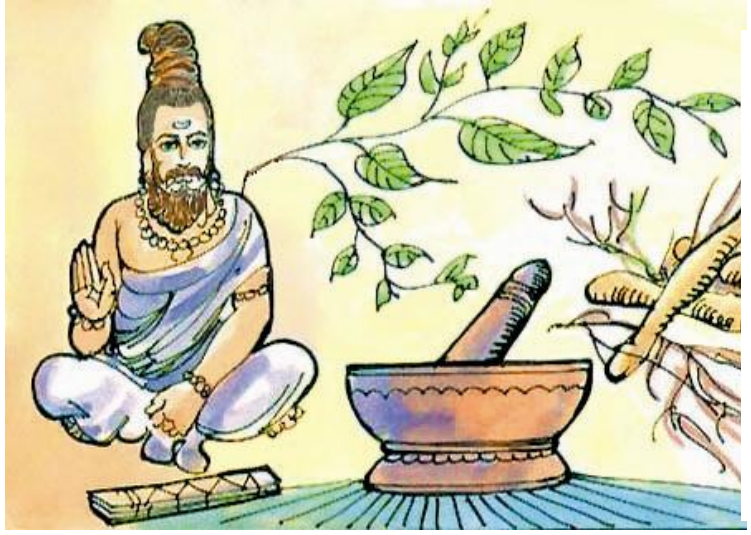
Черника обыкновенная
Vaccinium myrtillus

Эхинацея пурпурная
Echinacea purpurea

Traditional Indian Medicine (Ayurveda)

- ✓ **A lot of empirical knowledge about pharmacotherapeutic properties of natural products is accumulated in Traditional Indian Medicine (TIM) Ayurveda, which is known earlier than 1000 years BC.**

- ✓ **Some Ayurvedic plants are included into the list of national Indian priorities.**



Problems with Study of Phytocomponents

- ✓ **Utilization of extracts in a folk medicine.**
- ✓ **The difficulty of separation of each component in pure form.**
- ✓ **Changes in composition of components depending on the location and time of collection.**
- ✓ **Pleiotropic (multitargeted) action.**

Analysis of Ayurvedic (TIM) Medicines Using In Silico Approaches

The empirical knowledge contained in Ayurveda can be currently analyzed using modern computer-aided methods.

Such studies could give information about the basic mechanisms of TIM actions, providing the basis for rational design of new medicinal plant combinations, and identification of new lead compounds for future pharmaceuticals.

Some Publications on Computational Studies of TIM

J-AIM
Journal of Ayurveda and Integrative Medicine

J Ayurveda Integr Med. 2010 Oct-Dec; 1(4): 257–265.
PMCID: PMC3117
doi: 10.4103/0975-9476.74435

Beyond reverse pharmacology: Mechanism-based screening of Ayurvedic drugs

R. D. Lele

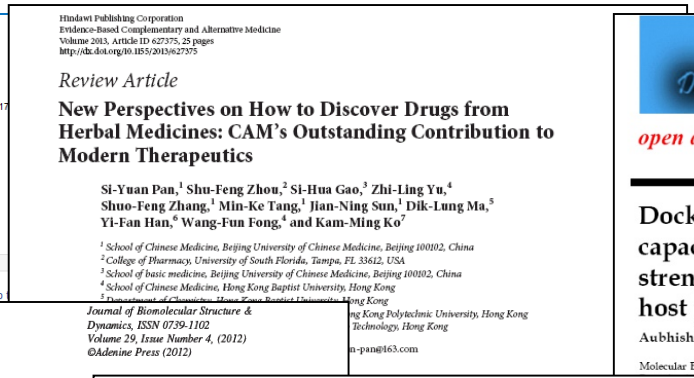
Author information ▶ Article notes ▶ Copyright and License information ▶

This article has been cited by other articles in PMC.

Abstract

This paper reviews the background of Europe history through the w Sarpaghanda. The oft lag between proof of p elucidation of mechar sometimes took almos relevance to public he presented so the comp forskolin and baicalein anti-oxidants and the pathway and its impli from turmeric is expla emphasizes the impor the significance of aha becomes clear. Under paradigm.

Keywords: Ayurved



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Volume 2013, Article ID 627375, 25 pages
http://dx.doi.org/10.1155/2013/627375

Review Article

New Perspectives on How to Discover Drugs from Herbal Medicines: CAM's Outstanding Contribution to Modern Therapeutics

Si-Yuan Pan,[1] Shu-Feng Zhou,[2] Si-Hua Gao,[3] Zhi-Ling Yu,[4] Shuo-Feng Zhang,[1] Min-Ke Tang,[1] Jian-Ning Sun,[1] Dik-Lung Ma,[5] Yi-Fan Han,[6] Wang-Fun Fong,[4] and Kam-Ming Ko[7]

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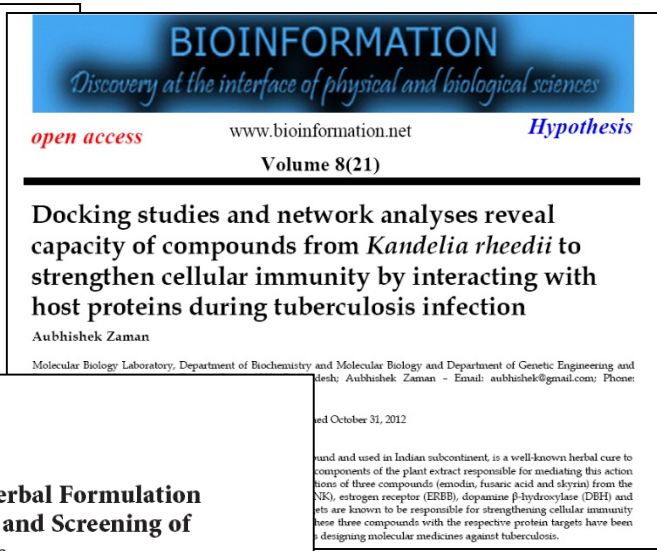


BIOINFORMATION
Discovery at the interface of physical and biological sciences

open access www.bioinformation.net Hypothesis

Volume 8(21)

Docking studies and network analyses reveal capacity of compounds from *Kandelia rheedii* to strengthen cellular immunity by interacting with host proteins during tuberculosis infection

Aubhishek Zaman

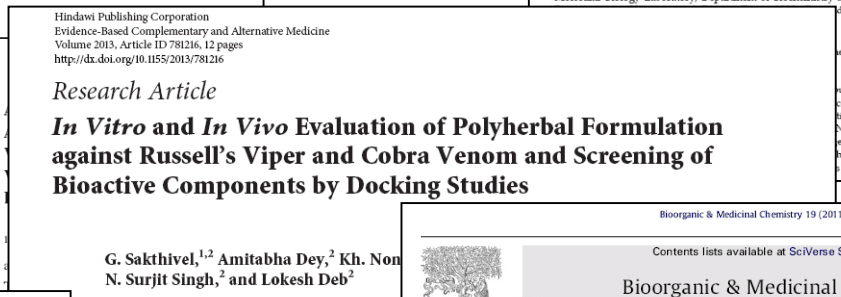
Molecular Biology Laboratory, Department of Biochemistry and Molecular Biology and Department of Genetic Engineering and

Computational Evidence to Inhibition of Human Acetyl Cholinesterase by Withanolide A for Alzheimer Treatment

http://www.jbsdonline.com

Abstract

Alzheimer's disease (AD), a neurodegenerative disorder, is the most common cause of



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Research Article

***In Vitro* and *In Vivo* Evaluation of Polyherbal Formulation against Russell's Viper and Cobra Venom and Screening of Bioactive Components by Docking Studies**

G. Sakthivel,[1,2] Amitabha Dey,[2] Kh. Non
N. Surjit Singh,[2] and Lokesh Deb[2]

[1] Department of Nanotechnology, Noorul Islam Centre for
[2] Pharmacology Laboratory, Medicinal Plants & Horticultu
Department of Biotechnology, Government of India, Tak

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ELSEVIER

Pharmacophore-based discovery of FXR-agonists. Part II: Identification of bioactive triterpenes from *Ganoderma lucidum*

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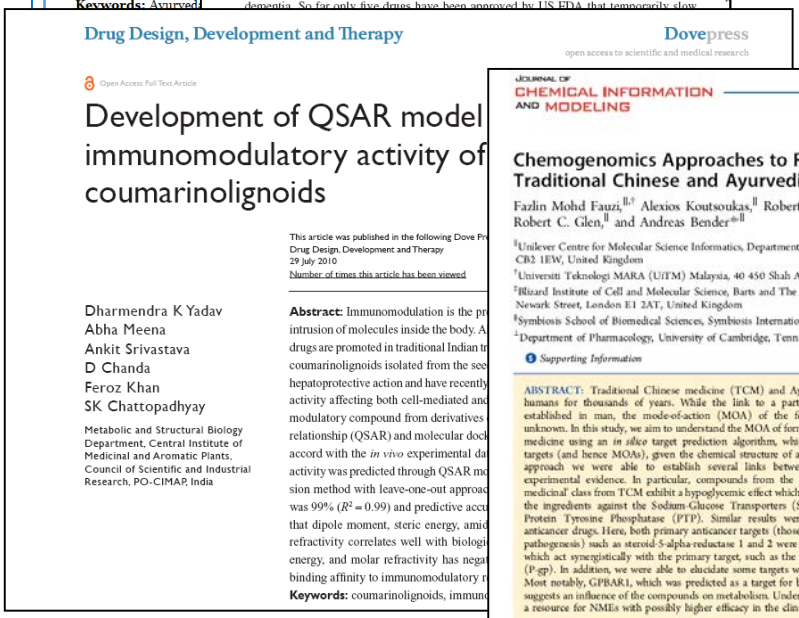
Lanostane triterpenes
Ganoderic acids
Molecular modeling
Virtual screening
Natural products

ABSTRACT

The farnesoid X receptor (FXR) belonging to the metabolic subfamily of nuclear receptors is a ligand-induced transcriptional activator. Its central function is the physiological maintenance of bile acid homeostasis including the regulation of glucose and lipid metabolism. Accessible structural information about its ligand-binding domain renders FXR an attractive target for in silico approaches. Integrated to natural product research these computational tools assist to find novel bioactive compounds showing beneficial effects in prevention and treatment of, for example, the metabolic syndrome, dyslipidemia, atherosclerosis, and type 2 diabetes. Virtual screening experiments of our in-house Chinese Herbal Medicine database with structure-based pharmacophore models, previously generated and validated, revealed mainly lanostane-type triterpenes of the TCM fungus *Ganoderma lucidum* Karst. as putative FXR ligands. To verify the prediction of the in silico approach, two *Ganoderma* fruit body extracts and compounds isolated thereof were pharmacologically investigated. Pronounced FXR-inducing effects were observed for the extracts at a concentration of 100 μg/mL. Intriguingly, five lanostanes out of 25 secondary metabolites from *G. lucidum*, that is, ergosterol peroxide (**2**), lucidumol A (**11**), ganoderic acid TR (**12**), ganodermanontriol (**13**), and ganoderiol F (**14**), dose-dependently induced FXR in the low micromolar range in a reporter gene assay. To rationalize the binding interactions, additional pharmacophore profiling and molecular docking studies were performed, which allowed establishing a first structure–activity relationship of the investigated triterpenes.



Drug Design, Development and Therapy
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Open Access Full Text Article

Development of QSAR model immunomodulatory activity of coumarinolignoids

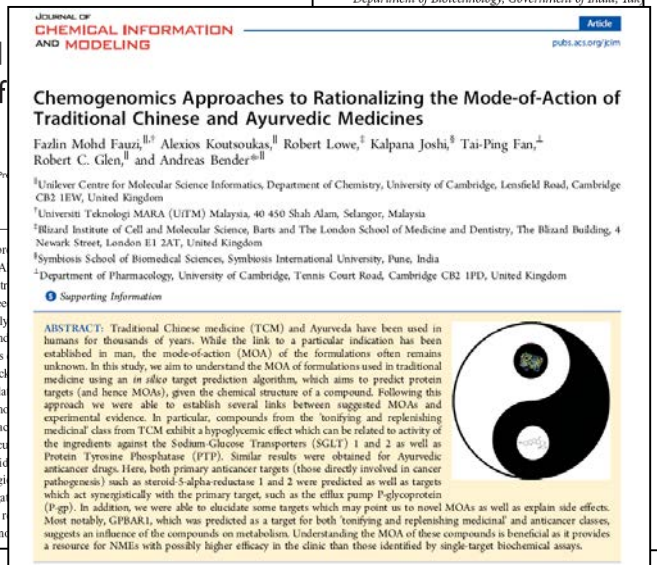
This article was published in the following Dove Pr
Drug Design, Development and Therapy
29 July 2010
Number of times this article has been viewed

Dharmendra K Yadav
Abha Meena
Ankit Srivastava
D Chanda
Feroz Khan
SK Chattopadhyay

Metabolic and Structural Biology Department, Central Institute of Medicinal and Aromatic Plants, Council of Scientific and Industrial Research, PO-CIMAP, India

Abstract: Immunomodulation is the pr
intrusion of molecules inside the body. A
drugs are promoted in traditional Indian tr
coumarinolignoids isolated from the see
hepatoprotective action and have recently
activity affecting both cell-mediated and
modulatory compound from derivatives
relationship (QSAR) and molecular dock
accord with the *in vivo* experimental da
activity was predicted through QSAR m
sion method with leave-one-out approac
was 99% ($R^2 = 0.99$) and predictive accu
that dipole moment, steric energy, amid
refractivity correlates well with biologi
energy, and molar refractivity has nega
binding affinity to immunomodulatory r

Keywords: coumarinolignoids, immuno



JOURNAL OF CHEMICAL INFORMATION AND MODELING
Article
pubs.acs.org/jcim

Chemogenomics Approaches to Rationalizing the Mode-of-Action of Traditional Chinese and Ayurvedic Medicines

Fazlin Mohd Fauzi,[†,§] Alexios Koutsoukas,[‖] Robert Lowe,[‡] Kalpana Joshi,[§] Tai-Ping Fan,[⊥] Robert C. Glen,[‖] and Andreas Bender*[,‖]

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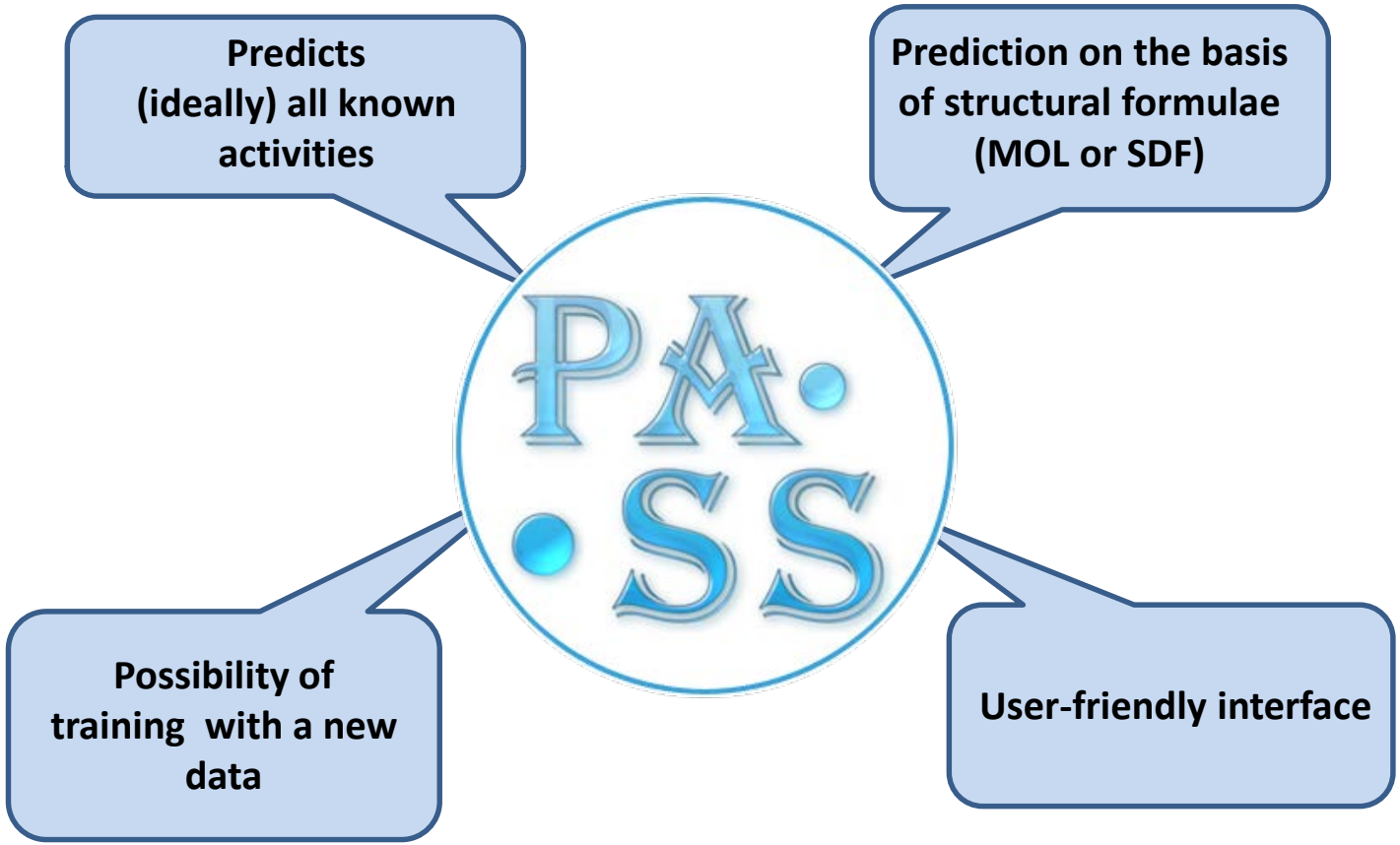
Supporting Information

ABSTRACT: Traditional Chinese medicine (TCM) and Ayurveda have been used in humans for thousands of years. While the link to a particular indication has been established in man, the mode-of-action (MOA) of the formulations often remains unknown. In this study, we aim to understand the MOA of formulations used in traditional medicine using an *in silico* target prediction algorithm, which aims to predict protein targets (and hence MOAs), given the chemical structure of a compound. Following this approach we were able to establish several links between suggested MOAs and experimental evidence. In particular, compounds from the 'tonifying and replenishing medicinal' class from TCM exhibit a hypoglycemic effect which can be related to activity of the ingredients against the Sodium-Glucose Transporters (SGLT) 1 and 2 as well as Protein Tyrosine Phosphatase (PTP). Similar results were obtained for Ayurvedic anticancer drugs. Here, both primary anticancer targets (those directly involved in cancer pathogenesis) such as steroid-5-alpha-reductase 1 and 2 were predicted as well as targets which act synergistically with the primary target, such as the efflux pump P-glycoprotein (P-gp). In addition, we were able to elucidate some targets which may point us to novel MOAs as well as explain side effects. Most notably, GPBAR1, which was predicted as a target for both 'tonifying and replenishing medicinal' and anticancer classes, suggests an influence of the compounds on metabolism. Understanding the MOA of these compounds is beneficial as it provides a resource for NMEs with possibly higher efficacy in the clinic than those identified by single-target biochemical assays.

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

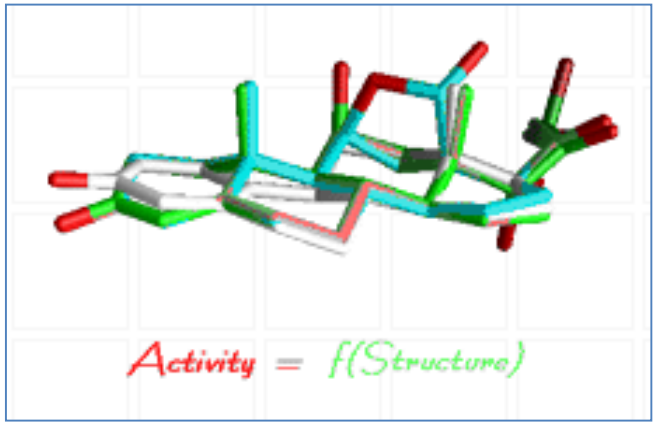


Biological activity spectra of organic compound

Biological activity is one of the most important characteristics of organic compound, which provides the basis for its use in therapeutic purposes. Biological activity reflects the result of interaction between the substance and biological object, and depends on substance structure and properties, biological object (species, sex, age), and mode of action (administration route, dose). Biological activity spectrum of an organic compound is the set of different kinds of biological activity that reflect the results of the compound's interaction with various biological entities. It represents the "intrinsic" property of a substance depending only on its structure. This is a qualitative characteristic property of a substance that depends only on its molecular structure.

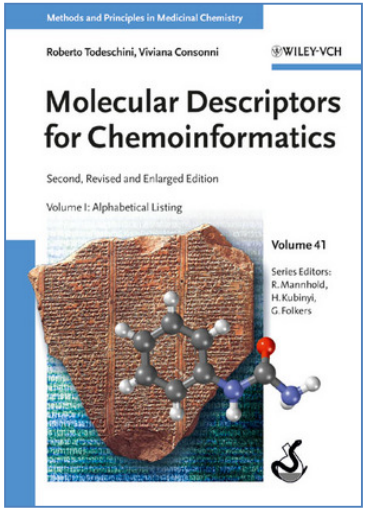
Poroikov V. et al. *Automatic Documentation and Mathematical Linguistics*, 1993, 27: 40-43.
Filimonov D. *Chemistry of Heterocyclic Compounds*, 2014, No. 3, 483-499.

Structure-activity relationships: (Q)SAR



Molecular descriptors

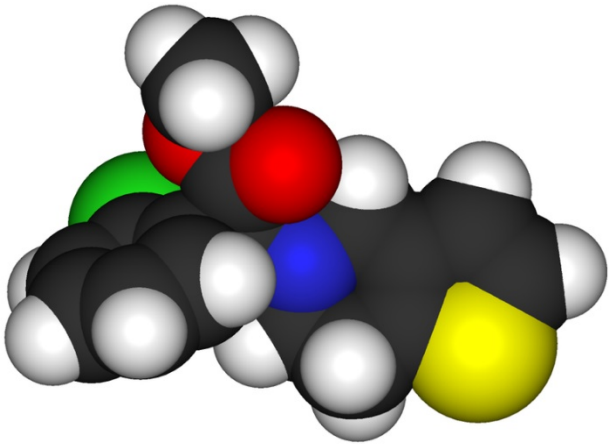
Sub-structural (-COO, -NH2, -OH, C6H5, и др.); physical-chemical (molecular weight, melting point, IR frequencies, chemical shifts in NMR, etc.); molecular connectivity, Wiener indices, Balaban indices, hydrophobicity constant, pKa, van der Waals volume, Log P, water solubility, etc. (several thousand).

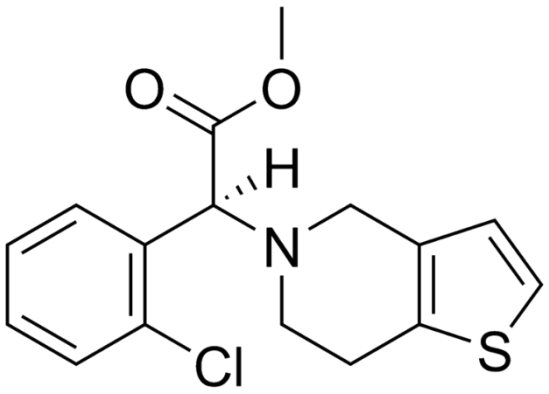


Mathematical methods

Multiple linear regression (MLR); non-linear regression; partial least squares (PLS); regression on principal components (PCR); artificial neural networks (ANN); similarity matrices; genetic algorithms; support vector machine (SVM); cluster analysis (CA); discriminant analysis; etc.

Chemical structure representation





The spatial configuration of the free uncharged molecules in the ground state in a vacuum is a necessary and sufficient description of its structure.

The use of this molecular structure description requires substantial computational resources for molecular modeling and/or quantum-chemical calculations.

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

Thus, the structural formula uniquely determines all properties of the organic molecule.

Influence of the environment?

- Structural formula determines, at least, potential “intrinsic" properties of the molecule.

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 particular atoms of the ligand and the target.

MOLECULAR BIOLOGY

QUANTUM CHEMISTRY

QUANTUM FIELDS THEORY

D.A. Filimonov

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

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

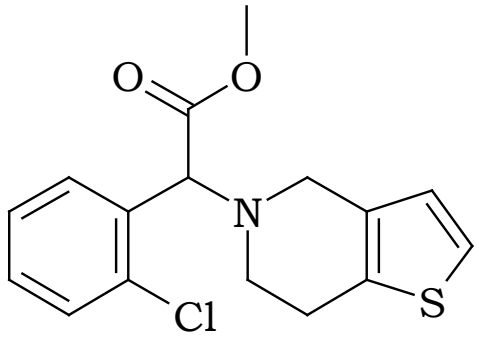
Descriptors are based on the concept of atoms' of molecule taking into account the influence of the neighborhoods:

MNA - **M**ultilevel **N**eighborhoods of **A**toms
QNA - **Q**uantitative **N**eighborhoods of **A**toms
LMNA - **L**abeled **M**ultilevel **N**eighborhoods of **A**toms

Filimonov D.A., Poroikov V.V. *In: Chemoinformatics Approaches to Virtual Screening.* Eds. Alexandre Varnek and Alexander Tropsha. Cambridge (UK): RSC Publishing, 2008, 182-216.
Filimonov D.A. et al. *SAR and QSAR Environ. Res.*, 2009, 20: 679-709.
Rudik A.V. et al. *J. Chem. Inform. Model.*, 2014, 54: 498–507.

Substance representation: Clopidogrel

Structural formula



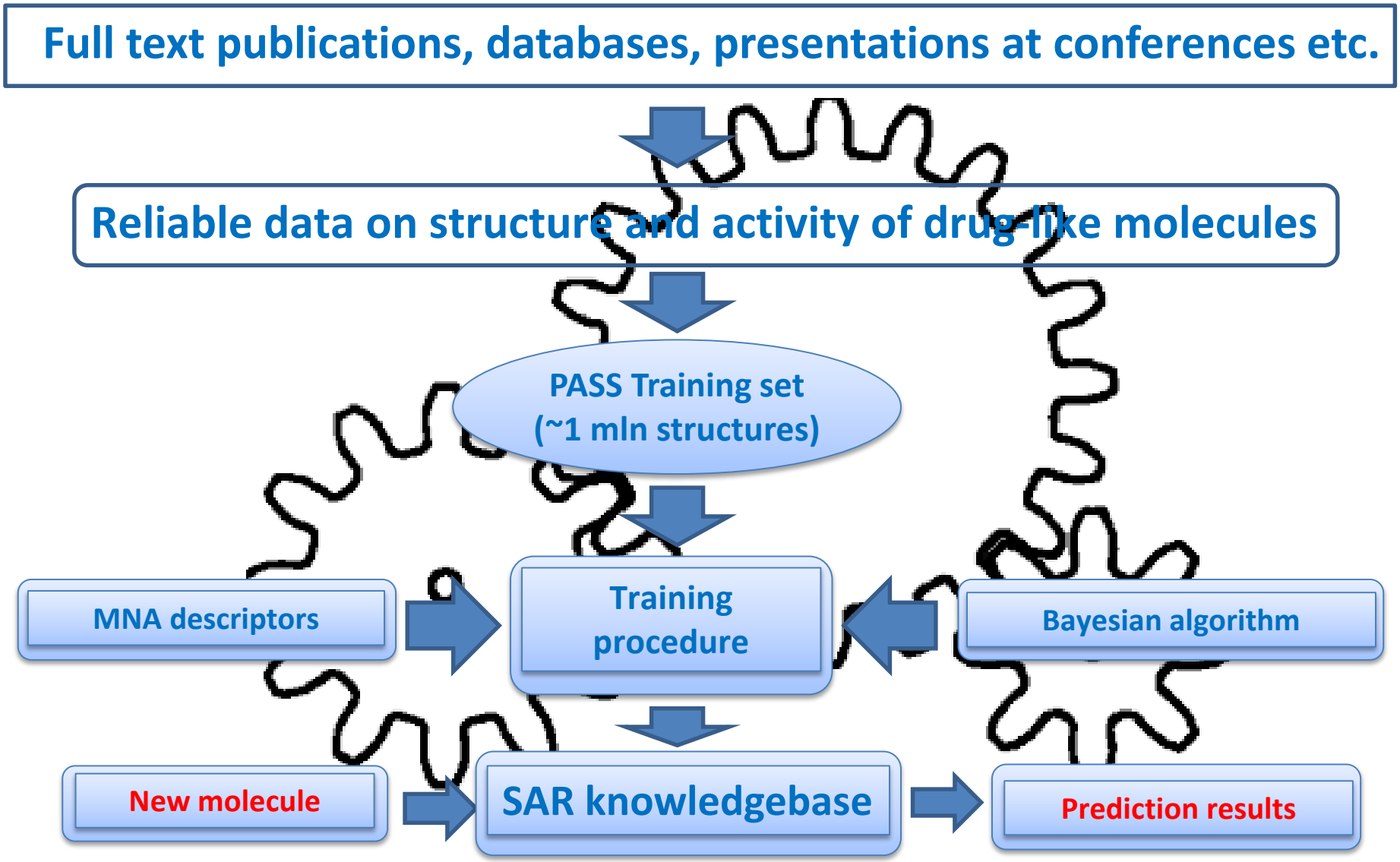
Activity Spectrum

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 (1st and 2nd levels)

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))

PASS: Prediction of Activity Spectra for Substances



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

PASS 2014 Characteristics

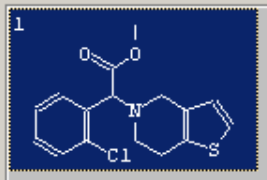
Training Set	959,801 drugs, drug-candidates, pharmacological and toxic substances comprise the training set
Biological Activity	7,158 biological activities can be predicted (Active vs. Inactive)
Chemical Structure	Multilevel Neighborhoods of Atoms (MNA) descriptors [1, 2]
Mathematical Algorithm	Bayesian 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]

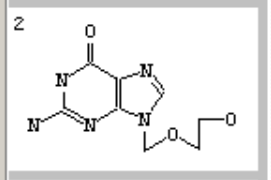
1. Filimonov D.A. et al. J. Chem. Inform. Computer Sci., 1999, 39: 666-670.
2. Filimonov D.A., Poroikov V.V. Chemoinformatics Approaches to Virtual Screening, 2008, 182-216.
3. Poroikov V.V. et al. J. Chem. Inform. Computer Sci., 2000, 40: 1349-1355.

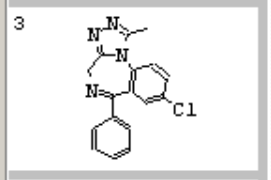
Results of PASS Prediction for Clopidogrel

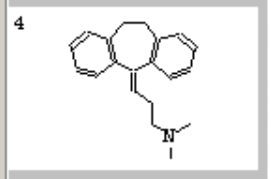
C:\PASS 2012\Drugs_Example.sdf

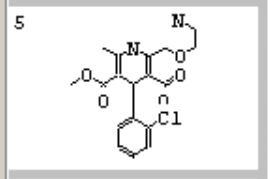
5x5 | 4x4 | 3x3 | 2x2 | Molecular Structure | MNA

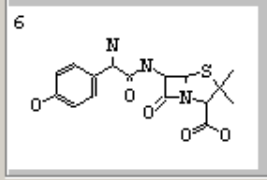


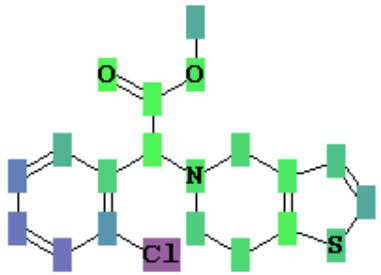












> <NAME> (0)
Clopidogrel

Antithrombotic

Effects | Mechanisms | Toxicity | Antitargets | Metabolism | Gene Exp

45 of 464 Possible Pharmacological Effects at Pa > Pi

0.951	0.004	Neuroprotector
0.886	0.005	Acute neurologic disorders treatment
0.723	0.006	Antithrombotic
0.712	0.004	Platelet aggregation inhibitor
0.618	0.019	Antianginal
0.553	0.013	Atherosclerosis treatment
0.463	0.048	Analgesic
0.385	0.009	Platelet antagonist
0.361	0.027	Stroke treatment
0.352	0.026	Angiogenesis stimulant
0.332	0.017	Anticoagulant
0.366	0.083	Diabetic neuropathy treatment
0.292	0.013	Analgesic, opioid
0.324	0.049	Antiinflammatory, ophthalmic
0.341	0.116	Spasmolytic, urinary
0.290	0.102	Cell adhesion molecule inhibitor
0.301	0.135	Neurodegenerative diseases treatment
0.261	0.098	Antipsoriatic
0.167	0.005	Acetylcholine release stimulant
0.199	0.057	Fibromyalgia syndrome treatment
0.236	0.104	Age-related macular degeneration treatment
0.202	0.075	Pancreatic disorders treatment
0.228	0.104	Amyotrophic lateral sclerosis treatment
0.375	0.254	Vasodilator, cerebral
0.176	0.058	Lipoprotein disorders treatment
0.156	0.047	Diabetic retinopathy treatment
0.257	0.150	Psychotropic

42 Substructure Descriptors; 0 new.

246 of 6400 Possible Activities
45 of 464 Possible Pharmacological Effects
79 of 3850 Possible Mechanisms of Action
106 of 321 Possible Toxic and Adverse Effects
5 of 118 Possible Antitargets
12 of 195 Possible Metabolism-Related Actions
17 of 1610 Possible Gene Expression Regulation
4 of 68 Possible Transporters-Related Actions

1/129 | 0.723 0.006 Antithrombotic

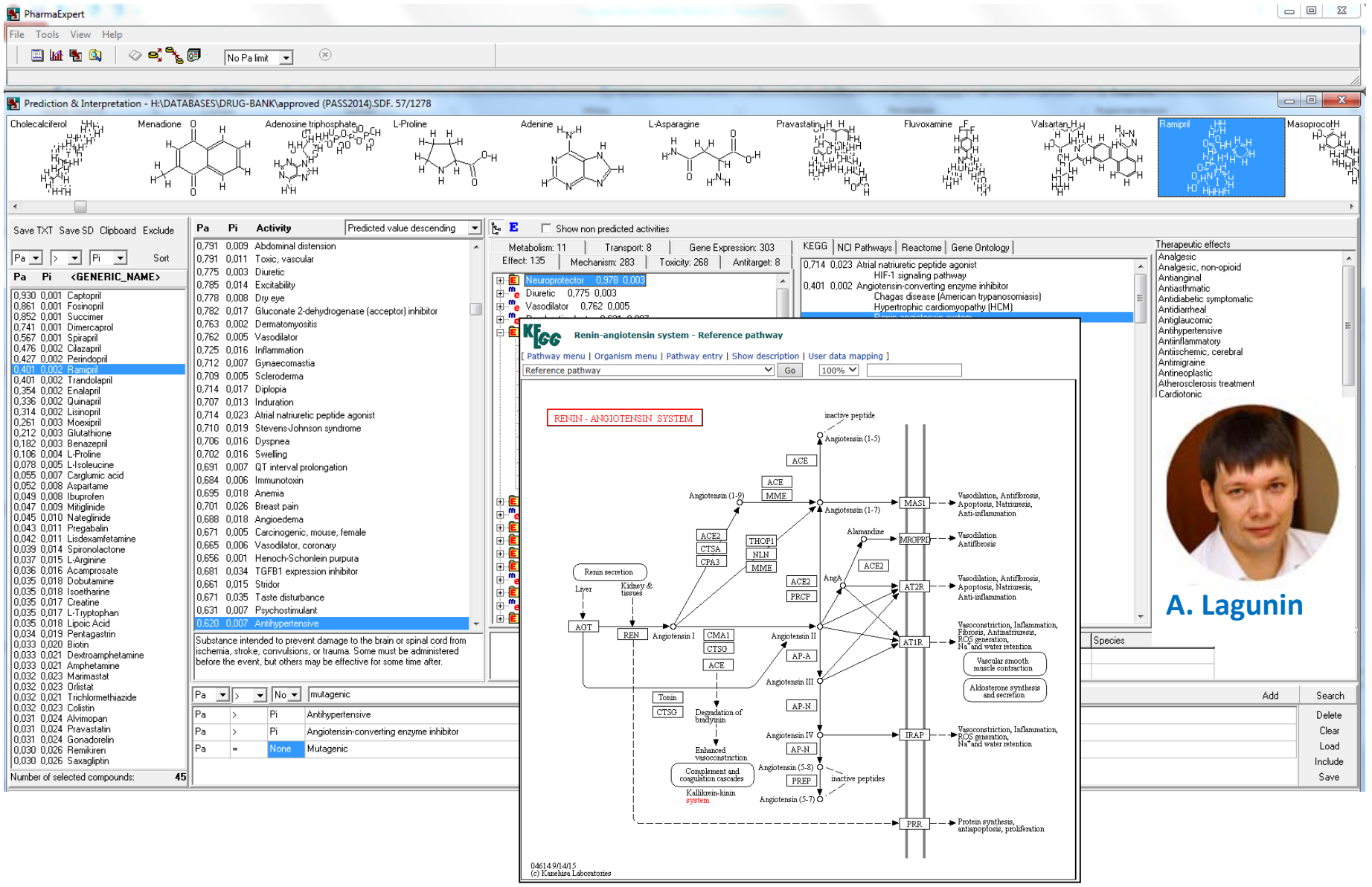
Results of PASS Prediction for Clopidogrel

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.

PharmaExpert: Interpretation of the prediction results



Web-services based on our methods

www.way2drug.com/Projects.php

D. Druzhilovsky

A. Rudik

A. Zakharov

Some examples of practical applications of biological activity spectra prediction

Athina Geronikaki,
AUT, Greece

Finding molecules with needed effects and MOA

Cur. Top. Med. Chem., 2015, 16: 441.

Marc Nicklaus,
NCI/NIH, USA

Search for multitarget drugs

J. Med. Chem. 2008, 51: 1601.

Drug reporpusing

Pharm. Chem. J. 2011, 45: 605.

Rajesh Goel,
PU, India

Sergey Kryzhanovsky,
Inst. of Pharmacol., Russia

Estimating drug-drug interactions for phytoconstituents of medicinal plants

Nat. Prod. Rep., 2014, 31: 1585.

Examples of search for new compounds based on predictions

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]

2870 *J. Med. Chem.* **2004,** *47,* 2870−2876

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,|| Maria 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.

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

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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]

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§

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 structure−activity relationships of 2-benzo/benzisothiazolimino-5-aryliden-4

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

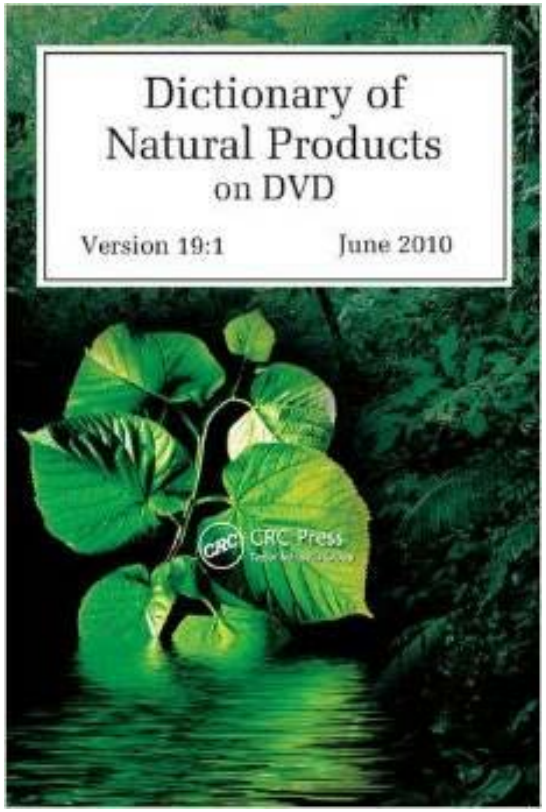
Multi-Targeted Natural Products Evaluation Based on Biological Activity Prediction with PASS

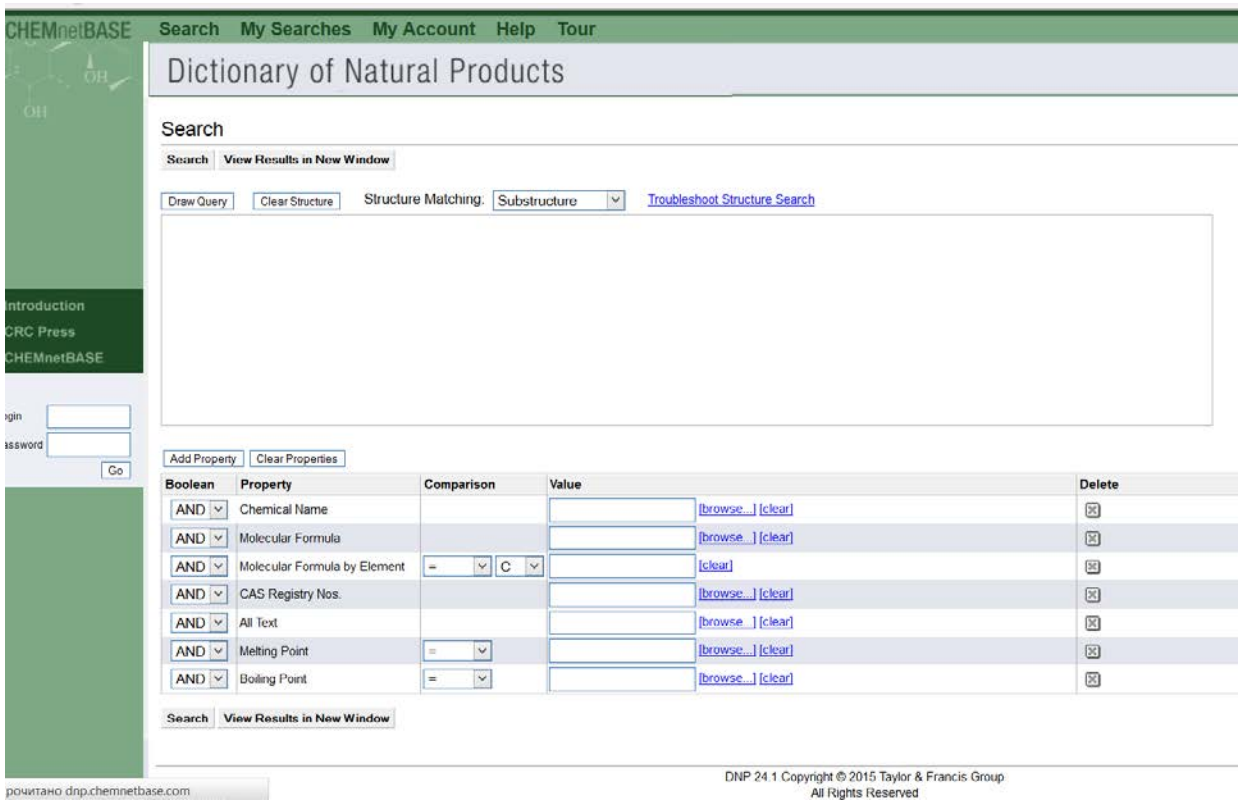
Alexey Lagunin, Dmitry Filimonov and Vladimir Poroikov*

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 to additive/synergistic or antagonistic effects. Rational design of more safe and potent pharmaceuticals requires an estimation of probable multiple actions of natural products. Our software PASS can perform such estimation. It predicts with reasonable accuracy over 3500 pharmacotherapeutic effects, mechanisms of action, interaction with the metabolic system, and specific toxicity for drug-like molecules on the basis of their structural formulae. We analyzed PASS predictions utilizing PharmaExpert, which performs selection of compounds with multiple mechanisms of action, analysis of activity-activity relationships and drug-drug interactions. The paper describes an

Sources of information about natural products: Dictionary of Natural Products

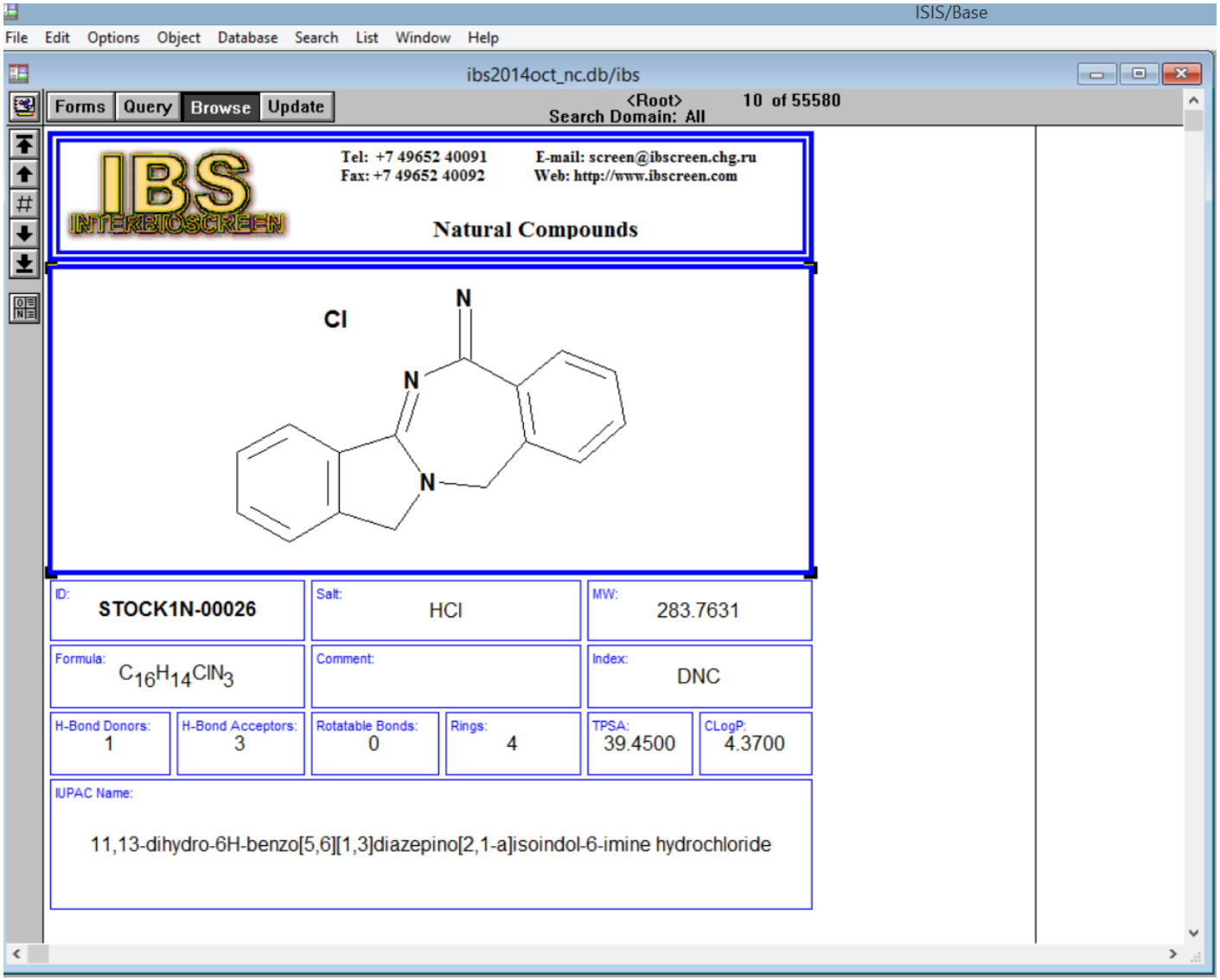




Chemical, physical, and biological data on more than 259,859 compounds contained in over 68,000 entries.

http://dnp.chemnetbase.com/

Sources of information about natural products: InterBioScreen Natural Compounds database



Over 55 000 natural compounds available in stock.

Sources of information about natural products: our Ayurvedic Medicines database

✓ **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.**

✓ **Content:**
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. ➡ **http://way2drug.com/plants**

Reference set of synthetic molecules: ChemBridge DVS

dvs_u_db.db/TEMP

Forms | Query | Browse | Update

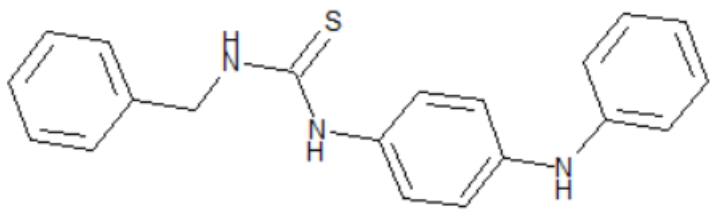
<Root> 25000 of 50000
Search Domain: All

ChemBridge Corporation

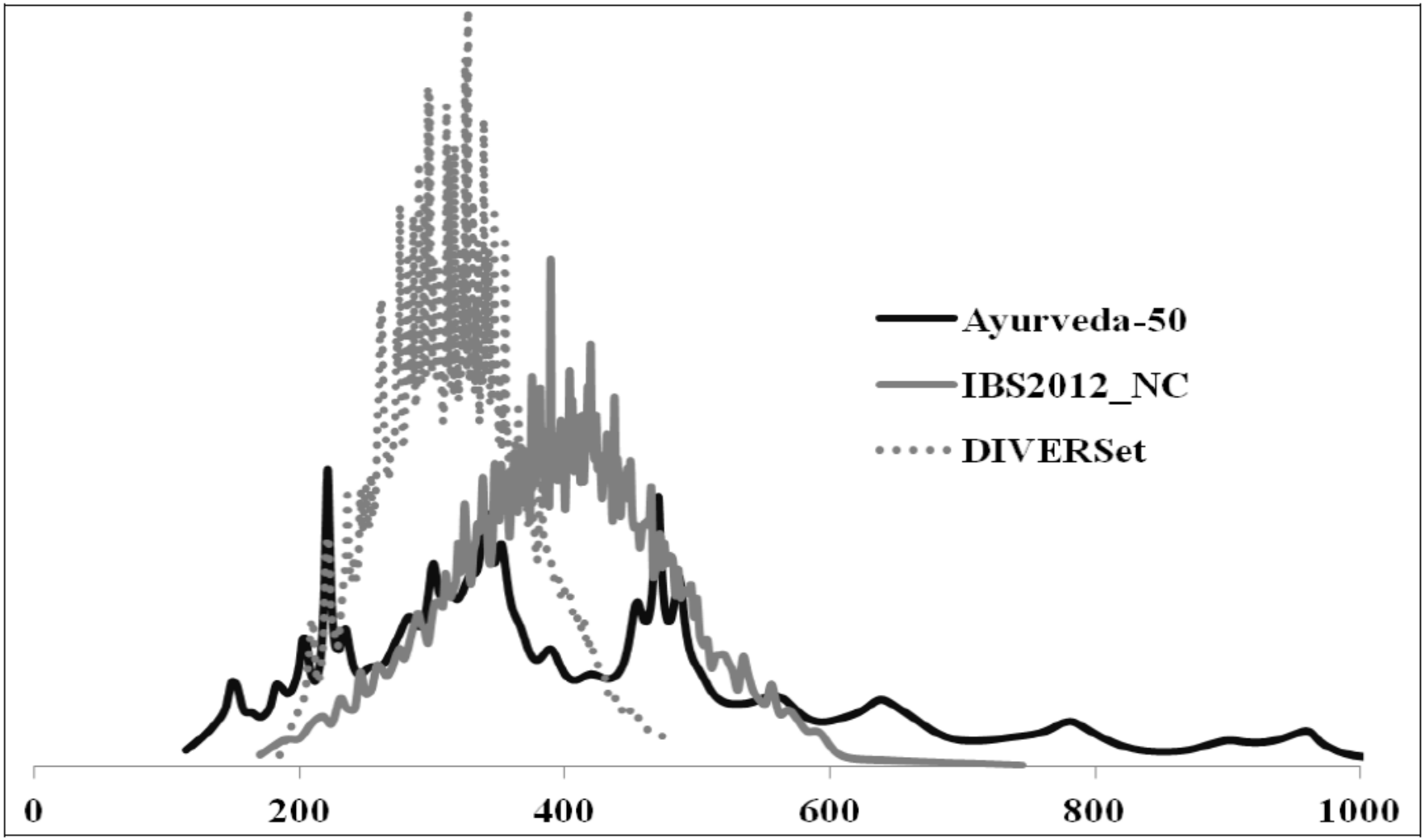
16981 Via Tazon, Suite G, San Diego, CA. 92127, USA
Phone: (858)451-7400; Fax: (858)451-7401
e-mail: sales@chembridge.com; web: www.chembridge.com

Program: **Diverset™**

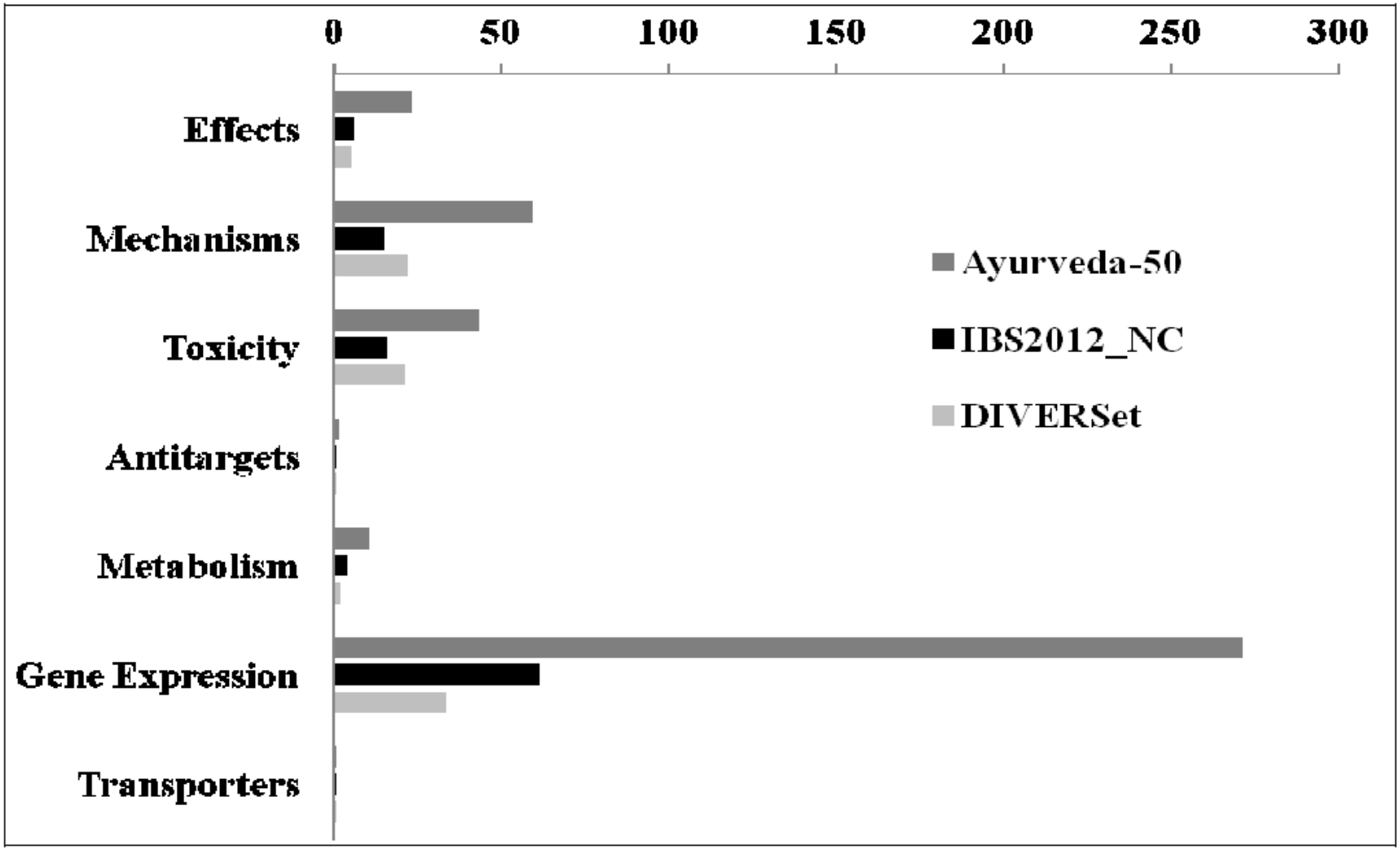
ID	7643138
Formula	$C_{20}H_{19}N_3S$
MW	333.46
RB	5
cLogP	4.13
tPSA	36.09
Hacc	0
Hdon	3
LogSw	-4.40
Supplier	ChemBridge



Comparison of three chemical libraries: distribution by molecular weights

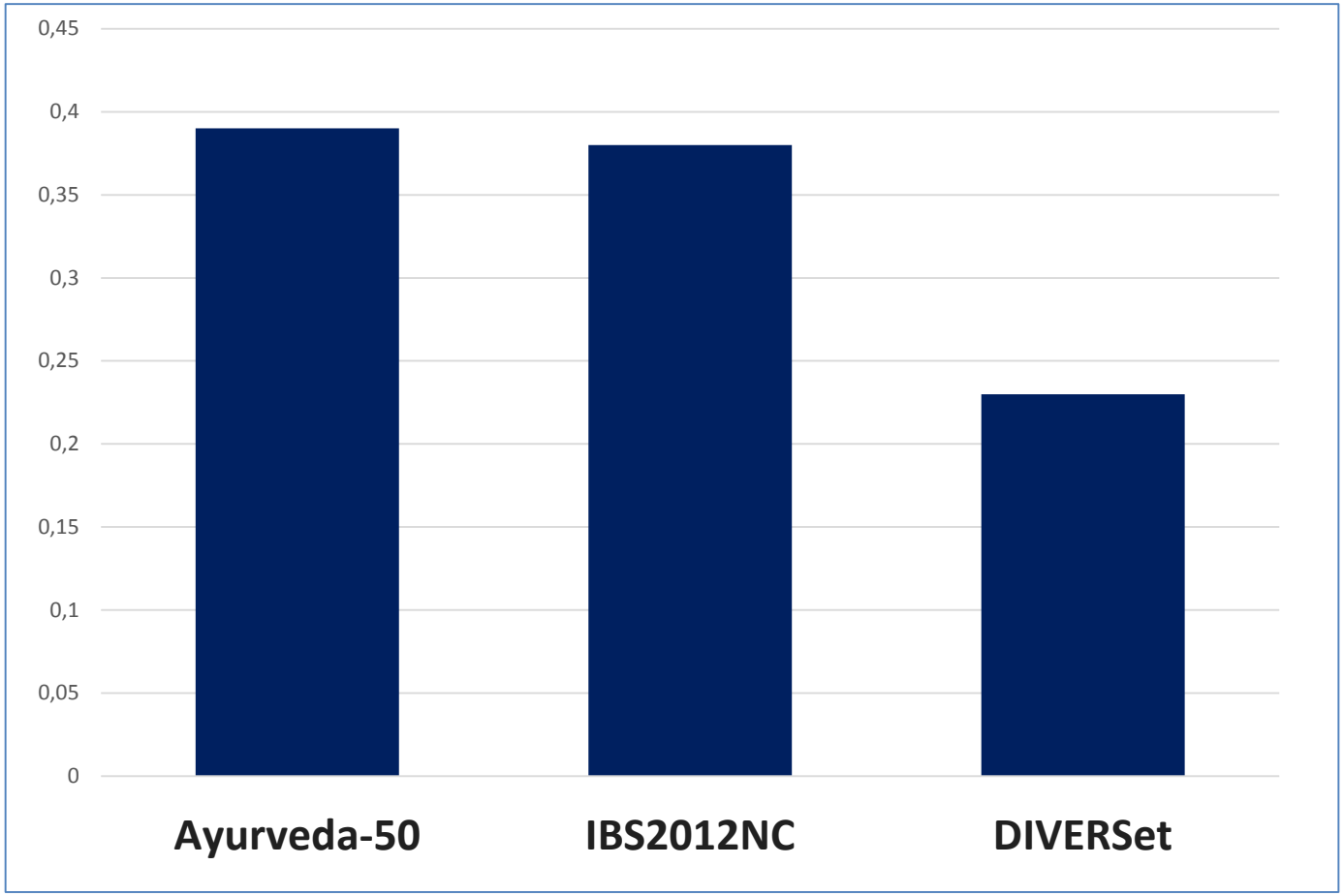


Comparison of three chemical libraries: average number of biological activities*



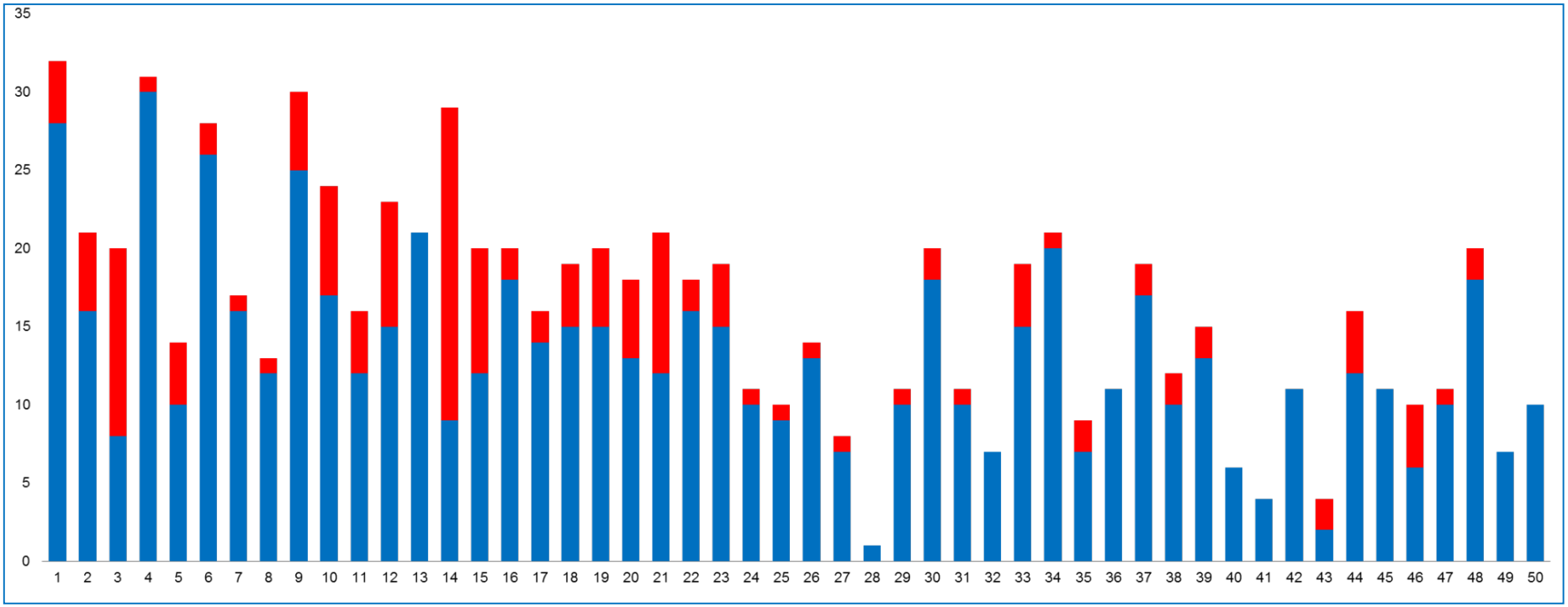
*Predicted by PASS for one structure.

Comparison of three chemical libraries: pharmacological potential (PP)*



*PP = Number of predicted effects / Number of predicted mechanisms

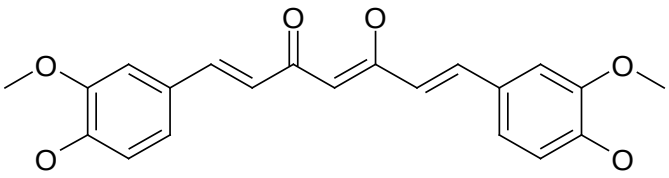
Comparison of predicted and known activities for phytoconsituents from fifty TIM medicinal plants



Blue – predicted; red – not predicted

Druzhilovskiy D., Rudik A., Ivanov S., Lagunin A., Filimonov D., Dinesh Gawande, Rajesh Kumar Goel, Vladimir Poroikov. (2012). Computer-aided analysis of hidden potential in traditional Indian medicine Ayurveda. Abstr. 19th EuroQSAR Symposium, Vienna, Austria, August 26-30, p. 128.

Exploited and Hidden Pharmacological Potential of Curcumin



Mol. Nutr. Food Res. 2008, 52, 000 – 000 DOI 10.1002/mnfr.200700354

Review

Multi-targeted therapy by curcumin: how spicy is it?

Ajay Goel[1], Sonia Jhurani[2] and Bharat B. Aggarwal[2]

[1] Gastrointestinal Cancer Research Laboratory, Department of Internal Medicine, Charles A. Sammons Cancer Center and Baylor Research Institute, Baylor University Medical Center, Dallas, TX, USA
[2] Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA

Although traditional medicines have been used for thousands of years, for most such medicines neither the active component nor their molecular targets have been very well identified. Curcumin, a yellow component of turmeric or curry powder, however, is an exception. Although inhibitors of cyclooxygenase-2, HER2, tumor necrosis factor, EGFR, Bcr-abl, proteosome, and vascular endothelial cell growth factor have been approved for human use by the United States Food and Drug Administration (FDA), curcumin as a single agent can down-regulate all these targets. Curcumin can also activate apoptosis, down-regulate cell survival gene products, and up-regulate p53, p21, and p27. Although curcumin is poorly absorbed after ingestion, multiple studies have suggested that even low levels of physiologically achievable concentrations of curcumin may be sufficient for its chemopreventive and chemotherapeutic activity. Thus, curcumin regulates multiple targets (multitargeted therapy), which is needed for treatment of most diseases, and it is inexpensive and has been found to be safe in human clinical trials. The present article reviews the key molecular mechanisms of curcumin action and compares this to some of the single-targeted therapies currently available for human cancer.

Keywords: Cancer / Curcumin / Cyclooxygenases / Multi-targeted therapy / Tumor necrosis factor

Received: September 7, 2007; revised: Ocober 12, 2007; accepted: October 21, 2007

The Targets of Curcumin

Hongyu Zhou[1], Christopher S. Beevers[1] and Shile Huang[*,1,2]

[1]Department of Biochemistry and Molecular Biology and [2]Feist-Weiller Cancer Center, Louisiana State University Health Sciences Center, 1501 Kings Highway, Shreveport, LA 71130-3932, USA

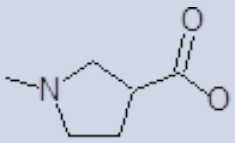
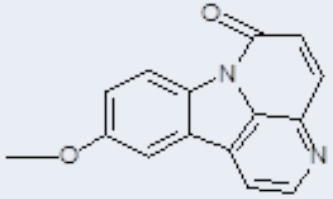
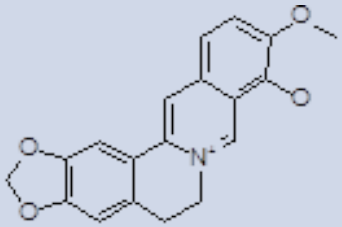
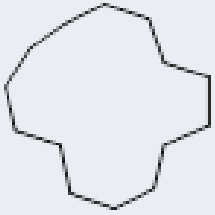
Abstract: Curcumin (diferuloylmethane), an orange-yellow component of turmeric or curry powder, is a polyphenol natural product isolated from the rhizome of the plant *Curcuma longa*. For centuries, curcumin has been used in some medicinal preparation or used as a food-coloring agent. In recent years, extensive *in vitro* and *in vivo* studies suggested curcumin has anticancer, antiviral, antiarthritic, anti-amyloid, antioxidant, and anti-inflammatory properties. The underlying mechanisms of these effects are diverse and appear to involve the regulation of various molecular targets, including transcription factors (such as nuclear factor-κB), growth factors (such as vascular endothelial cell growth factor), inflammatory cytokines (such as tumor necrosis factor, interleukin 1 and interleukin 6), protein kinases (such as mammalian target of rapamycin, mitogen-activated protein kinases, and Akt) and other enzymes (such as cyclooxygenase 2 and 5 lipoxygenase). Thus, due to its efficacy and regulation of multiple targets, as well as its safety for human use, curcumin has received considerable interest as a potential therapeutic agent for the prevention and/or treatment of various malignant diseases, arthritis, allergies, Alzheimer's disease, and other inflammatory illnesses. This review summarizes various *in vitro* and *in vivo* pharmacological aspects of curcumin as well as the underlying action mechanisms. The recently identified molecular targets and signaling pathways modulated by curcumin are also discussed here.

Keywords: Curcumin, molecular targets, transcription factors, growth factors, inflammatory cytokines, protein kinases, enzymes.

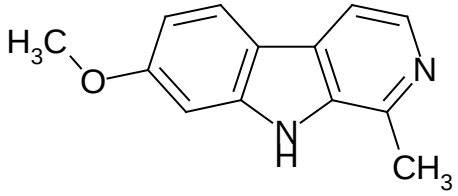
PASS Prediction

0,948 0,001 Preneoplastic conditions treatment	Goel A. et al., 2008
0,939 0,004 Mucositis treatment	Banasch A. et al., 2006
0,937 0,003 Feruloyl esterase inhibitor	
0,934 0,003 Ulcer gastric	
0,924 0,005 Retinal oxidase inhibitor	
0,898 0,002 Beta-carotene 15,15'-monooxygenase inhibitor	
0,900 0,009 Aspulvinone dimethylallyltransferase inhibitor	
0,892 0,003 CYP1A inhibitor	Patel R., et al., 2007
0,893 0,005 Sneezing	
0,897 0,012 NADH dehydrogenase (ubiquinone) inhibitor	
0,891 0,014 Membrane integrity agonist	
0,864 0,003 Monophenol monooxygenase inhibitor	Panich U. et al., 2010
0,864 0,005 Non mutagenic, Salmonella	
0,855 0,005 Ulcer peptic	
0,860 0,012 Antacid	
0,843 0,002 Histone acetyltransferase inhibitor	Israel M. et al., 2011
0,841 0,004 Antiinflammatory, intestinal	Goel A. et al., 2008
0,855 0,003 Antieczematic	Alhusin M. et al., 2011
0,832 0,002 Leukotriene C4 antagonist	Yoon J-H. et al., 2005
0,834 0,005 Linoleate diol synthase inhibitor	
0,828 0,002 CYP1A1 inhibitor	
0,829 0,004 Reductant	
0,831 0,010 Gluconate 2-dehydrogenase (acceptor) inhibitor	
0,822 0,003 CYP1A inducer	
0,834 0,015 Chlordecone reductase inhibitor	
0,840 0,023 Ubiquinol-cytochrome-c-reductase inhibitor	
0,819 0,003 Choleretic	Deters M. et al., 2003
0,816 0,002 GST P1-1 substrate	
0,814 0,002 Vanillyl-alcohol oxidase inhibitor	
0,813 0,002 GST P substrate	
0,820 0,010 HIF1A expression inhibitor	Choi H. et al., 2006
0,809 0,002 CYP1A1 inducer	
0,805 0,004 Apoptotic	
0,796 0,004 Antimutagenic	Biswas J. et al, 2010
0,821 0,032 Subarachnoid hemorrhage	
0,796 0,014 GST A substrate	
0,823 0,041 Porphyria	
0,784 0,003 Steroid N-acetylglucosaminyltransferase inhibitor	
0,779 0,007 Antihypercholesterolemic	Deters M. et al., 2003
0,774 0,003 Leukotriene C antagonist	Yoon J-H. et al., 2005
0,771 0,005 UDP-glucuronosyltransferase substrate	
0,770 0,005 Apoptosis agonist	Goel A. et al., 2008
0,757 0,003 Free radical scavenger	Hatcher H. et al., 2008
0,761 0,010 Hypercholesterolemic	
0,746 0,008 Caspase 3 stimulant	Karmakar S. et al., 2007
0,742 0,004 Carminative	
0,741 0,004 MAP kinase stimulant	Suh HW et al., 2007
0,746 0,017 Mucomembranous protector	
0,731 0,004 Glutathione S transferase substrate	
0,744 0,020 CYP2 substrate	
0,732 0,016 Fibrinolytic	Ameye L.G. et al., 2006
0,728 0,018 Aldehyde oxidase inhibitor	
0,713 0,003 4-Coumarate-CoA ligase inhibitor	
0,714 0,010 CYP2D6 substrate	
0,719 0,030 Membrane permeability inhibitor	Morin D. et al., 2001
0,737 0,004 Sweating	
0,717 0,016 Vasoprotector	
0,708 0,007 Chemopreventive	Goel A. et al., 2008
0,735 0,036 Glaucoma	
0,701 0,002 HIV-1 integrase inhibitor	Burke T. et al., 1995
0,743 0,045 Chorea	
0,721 0,023 Urine discoloration	
0,730 0,034 Toxic, vascular	
0,734 0,040 Hematotoxic	
0,702 0,010 Irritation	
0,697 0,007 Laryngospasm	
0,691 0,004 GST M substrate	
0,690 0,003 NOS2 expression inhibitor	Zheng M. et al., 2004
0,694 0,012 CYP2D substrate	
0,666 0,003 HIV-1 integrase (3'-Processing) inhibitor	
0,680 0,017 Fatty-acyl-CoA synthase inhibitor	Zhao J. et al., 2011
0,659 0,004 Antioxidant	Itokawa H. et al., 2008
0,671 0,018 Antiinflammatory	Itokawa H. et al., 2008
0,721 0,072 Phosphatidyl-N-methylethanolamine N-methyltransferase inhibitor	Goel A. et al., 2008
0,662 0,014 Caspase 9 stimulant	
0,653 0,005 Radioprotectant	Aravindan N. et al., 2008
0,648 0,002 HIV-1 integrase (Strand Transfer) inhibitor	
0,649 0,004 Peroxidase substrate	
0,700 0,058 CYP2I substrate	
0,645 0,004 Transcription factor NF kappa B inhibitor	Amoli MM. et al., 2006
0,683 0,042 Depression	
0,648 0,007 Antiulcerative	Goel A. et al., 2008
0,646 0,009 Vasodilator, renal	Ahn CM. et al., 2009
0,676 0,042 Urinary urge	
0,641 0,009 Hepatoprotectant	Somchit N., 2008
0,644 0,013 Cytoprotectant	Sood et al., 2011
0,652 0,022 Smooth muscle myosin light chain kinase inhibitor	
0,641 0,012 Anticarcinogenic	Corona-Rivera A. et al., 2007
0,647 0,019 Cytochrome P450 inhibitor	
0,636 0,009 Vasodilator, cerebral	
0,632 0,005 Chemoprotective	Goel A. et al., 2008
0,651 0,027 CYP2C8 inhibitor	
0,686 0,062 Myopathy	
0,623 0,003 Aryl sulfotransferase inhibitor	Vietri M. et al., 2003
0,622 0,005 Antineoplastic (multiple myeloma)	Goel A. et al., 2008
0,642 0,026 Skin necrosis	
0,646 0,030 Gastrointestinal hemorrhage	
0,668 0,056 Postural (orthostatic) hypotension	
0,612 0,007 CYP2E1 inducer	
0,646 0,051 15-Oxoprostaglandin 13-reductase inhibitor	
0,610 0,019 Conjunctivitis	
0,594 0,004 Transcription factor inhibitor	Thaloor D. et al., 1999
0,595 0,006 Thyrotropin receptor antagonist	
0,662 0,074 Hypomania	
0,587 0,004 3-Demethylubiquinone-9 3-O-methyltransferase inhibitor	Liu Z. et al., 2008
0,615 0,033 Fibrosis, interstitial	
0,636 0,050 Parkinsonism	
0,609 0,030 2-Hydroxyquinoline 8-monooxygenase inhibitor	
0,637 0,061 Antiseborrheic	
0,573 0,003 TNF expression inhibitor	Goel A. et al., 2008
0,575 0,051 HMOX1 expression enhancer	Pugazhenthi S. et al., 2007
0,575 0,013 Proliferative diseases treatment	Anand P. et al., 2008
0,573 0,012 Pyruvate decarboxylase inhibitor	Fujiwara H. et al., 2008
0,578 0,039 Sensitization	
0,571 0,013 Plastoquinol-plastocyanin reductase inhibitor	
0,592 0,036 Tachycardia, supraventricular	
0,565 0,010 Antineoplastic (cervical cancer)	Goel A. et al., 2008
0,564 0,010 Antimycobacterial	Changtam C. et al., 2010
0,574 0,020 Radioprotector	Goel A. et al., 2010
0,562 0,009 GABA aminotransferase inhibitor	
0,608 0,055 Shivering	
0,559 0,007 Antineoplastic (colorectal cancer)	Goel A. et al., 2008
0,579 0,028 Trans-acenaphthene-1,2-diol dehydrogenase inhibitor	
0,599 0,049 Protoporphyrinogen oxidase inhibitor	
0,610 0,061 Ulcer, aphthous	
0,558 0,010 UGT2B4 substrate	
0,571 0,024 Antipruritic, allergic	Graf J., 2000

In silico mining several medicinal plants with desirable pleiotropic (anticonvulsant, antidepressant, and nootropic) effects

No	Plant	Structure	Name	PASS predictions
1	*Achyranthes aspera*		3-Pyrrolidine-carboxylic acid; N-Me	0.547 0.098 Nootropic 0.593 0.024 Anticonvulsant 0.281 0.069 Antidepressant
2	*Aerva lanata*		6H-Indolo(3,2,1-de)(1,5)naphthyridin-6-one, 10-methoxy-	0.687 0.041 Nootropic 0.285 0.138 Anticonvulsant 0.205 0.111 Antidepressant
3	*Berberis vulgaris*		Lambertine	0.386 0.231 Nootropic 0.326 0.109 Anticonvulsant 0.469 0.026 Antidepressant
4	*Glycyrrhiza glabra*		Cyclotetradecane	0.544 0.100 Nootropic 0.406 0.067 Anticonvulsant 0.218 0.102 Antidepressant
. . .	. . .	. . .	. . .	. . .

Predicted biological activities for major phytocomponents of Passiflora Incarnata: Harmine



0.674 0.045 Nootropic

0.698 0.004 5 Hydroxytryptamine 3A antagonist
0.557 0.081 Nerve growth factor agonist
0.469 0.031 Cyclic AMP phosphodiesterase inhibitor
0.499 0.091 Calcium channel (voltage-sensitive) activator
0.437 0.072 Cyclic AMP agonist
0.367 0.030 Calcium channel activator

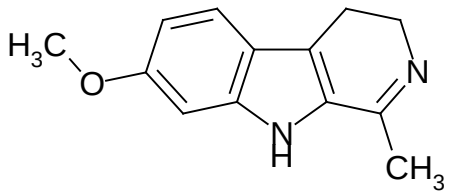
0.116 0.336 Anticonvulsant

0.698 0.004 5 Hydroxytryptamine 3A antagonist
0.629 0.005 Cyclic AMP antagonist
0.438 0.038 Calmodulin antagonist
0.374 0.010 Benzodiazepine agonist partial

0.253 0.083 Antidepressant

0.745 0.023 5 Hydroxytryptamine release stimulant
0.698 0.004 5 Hydroxytryptamine 3A antagonist
0.557 0.081 Nerve growth factor agonist
0.414 0.046 5 Hydroxytryptamine 7 antagonist
0.351 0.039 Imidazoline receptor agonist

Predicted biological activities for major phytocomponents of Passiflora Incarnata: Harmaline



0.704 0.036 Nootropic

0.478 0.052 5 Hydroxytryptamine 3A antagonist

0.443 0.039 Cyclic AMP phosphodiesterase inhibitor

0.269 0.150 Anticonvulsant

0.478 0.052 5 Hydroxytryptamine 3A antagonist

0.440 0.037 Calmodulin antagonist

0.424 0.126 Cyclic AMP antagonist

0.394 0.062 5 Hydroxytryptamine 7 antagonist

0.344 0.048 Antidepressant

0.745 0.023 5 Hydroxytryptamine release stimulant

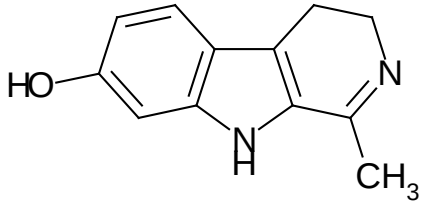
0.478 0.052 5 Hydroxytryptamine 3A antagonist

0.388 0.005 MAO inhibitor

0.409 0.027 Imidazoline receptor agonist

0.394 0.062 5 Hydroxytryptamine 7 antagonist

Predicted biological activities for major phytocomponents of Passiflora Incarnata: Harmalol



0.672 0.046 Nootropic

0.662 0.005 5 Hydroxytryptamine 3A antagonist

0.568 0.044 Calcium channel (voltage-sensitive) activator

0.409 0.050 Cyclic AMP phosphodiesterase inhibitor

0.330 0.034 Adrenaline release stimulant

0.245 0.170 Anticonvulsant

0.662 0.005 5 Hydroxytryptamine 3 antagonist

0.409 0.050 Cyclic AMP phosphodiesterase inhibitor

0.431 0.116 Cyclic AMP antagonist

0.425 0.048 Calmodulin antagonist

0.209 0.108 Antidepressant

0.844 0.011 5 Hydroxytryptamine release stimulant

0.662 0.005 5 Hydroxytryptamine 3 antagonist

0.387 0.005 MAO inhibitor

0.400 0.056 5 Hydroxytryptamine 7 antagonist

Revealing Medicinal Plants That Are Useful for the Comprehensive Management of Epilepsy and Associated Comorbidities through *In Silico* Mining of Their Phytochemical Diversity

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Key words
- *Passiflora incarnata*
- Passifloraceae
- epilepsy
- PASS
- PharmaExpert
- depression
- memory deficit

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Abstract

In silico techniques in drug discovery may rationalise and speed up the identification of lead molecules from nature. Drug discovery from medicinal plants has mostly been confined to indications in accordance with their ethnical use only. However, the availability of multiple phytoconstituents in medicinal plants suggests that these may be much more useful beyond their traditional uses and in the management of chronic diseases, along with their comorbidities. In this study, the computer programmes PASS and PharmaExpert were used to reveal the medicinal plants useful in the comprehensive management of epilepsy and associated psychiatric disorders based on the pleiotropic effects predicted for their phytoconstituents. *In silico* analysis revealed that seven of 50 medicinal plants from traditional Indian medicine possessed the desired pleiotropic effect, i.e., anticonvulsant, antidepressant, and nootropic activities. The majority of phytoconstituents from *Passiflora incarnata* were concurrently predicted to have the desired pleiotropic effects. Therefore, *P. incarnata* was pharmacologically validated using the pentylenetetrazole kindling mouse model. Behavioural and neurochemical evaluations confirmed the ameliorative role of *P. incarnata* in epilepsy and the associated depression and memory deficit. The pharmacological findings from this study propose that PASS and PharmaExpert may serve as good tools for the optimisation of the selection of plants based on their phytoconstituents for the treatment of different ailments, even beyond their traditional use.

Abbreviations

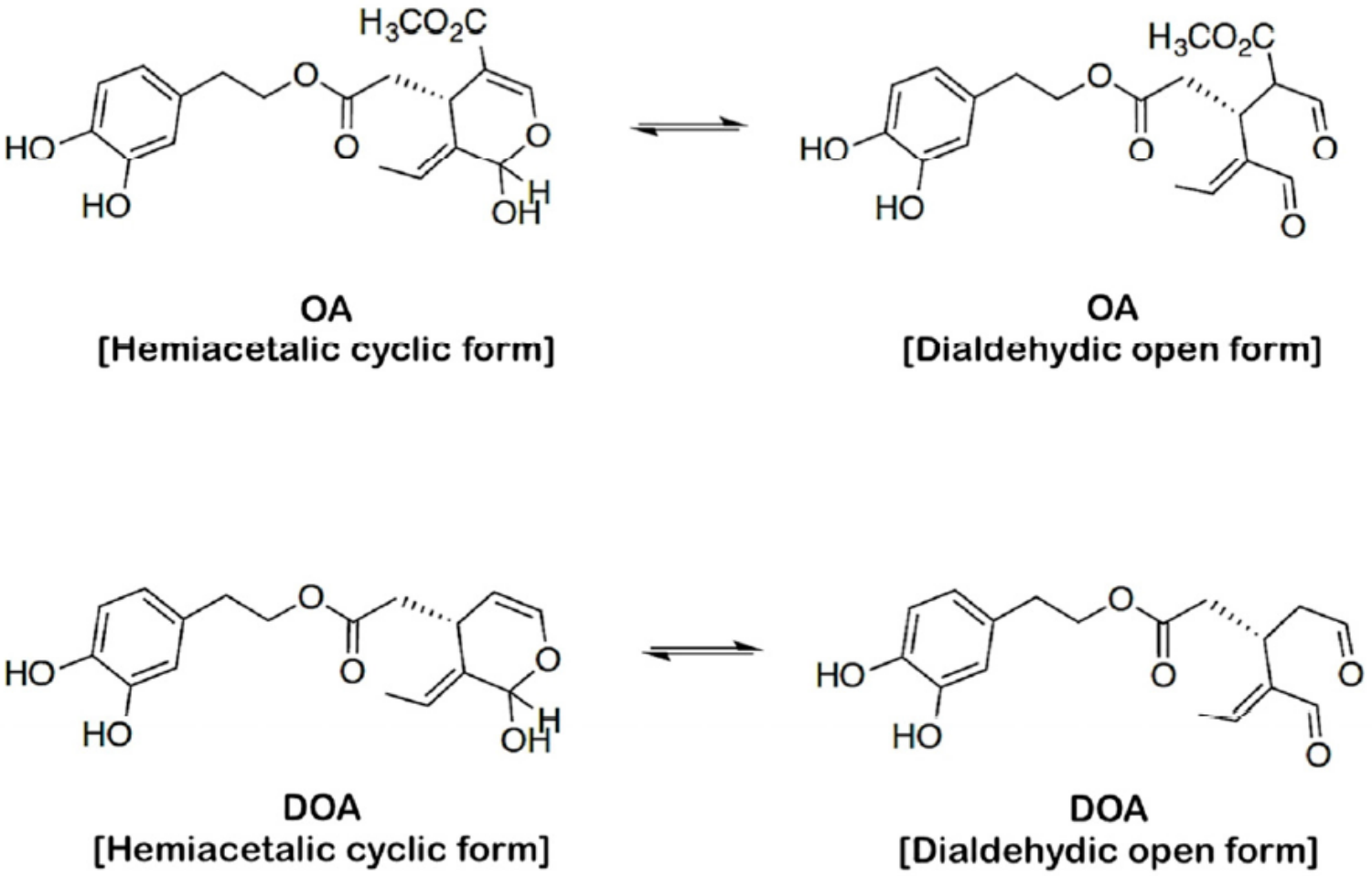
AChE:	acetylcholinesterase
AUC:	area under the curve
CPCSEA:	Committee for the Purpose of Control and Supervision of Experiments on Animals
DNP:	Dictionary of Natural Products
EPM:	elevated plus maze
FST:	forced swim test
LOO CV:	leave-one-out cross-validation
MNA:	multilevel neighbourhoods of atoms
MOA:	mechanisms of action
NO:	nitric oxide
Pa:	probability "to be active"
PASS:	prediction activity spectra of substance
Pi:	probability "to be inactive"
PIHE:	*Passiflora incarnata* hydroethanolic extract
PTZ:	pentylenetetrazole
PHT:	phenytoin
SFZ:	shock-free zone
TIM:	traditional Indian medicine
TST:	tail suspension test

Supporting information available online at http://www.thieme-connect/products

Introduction

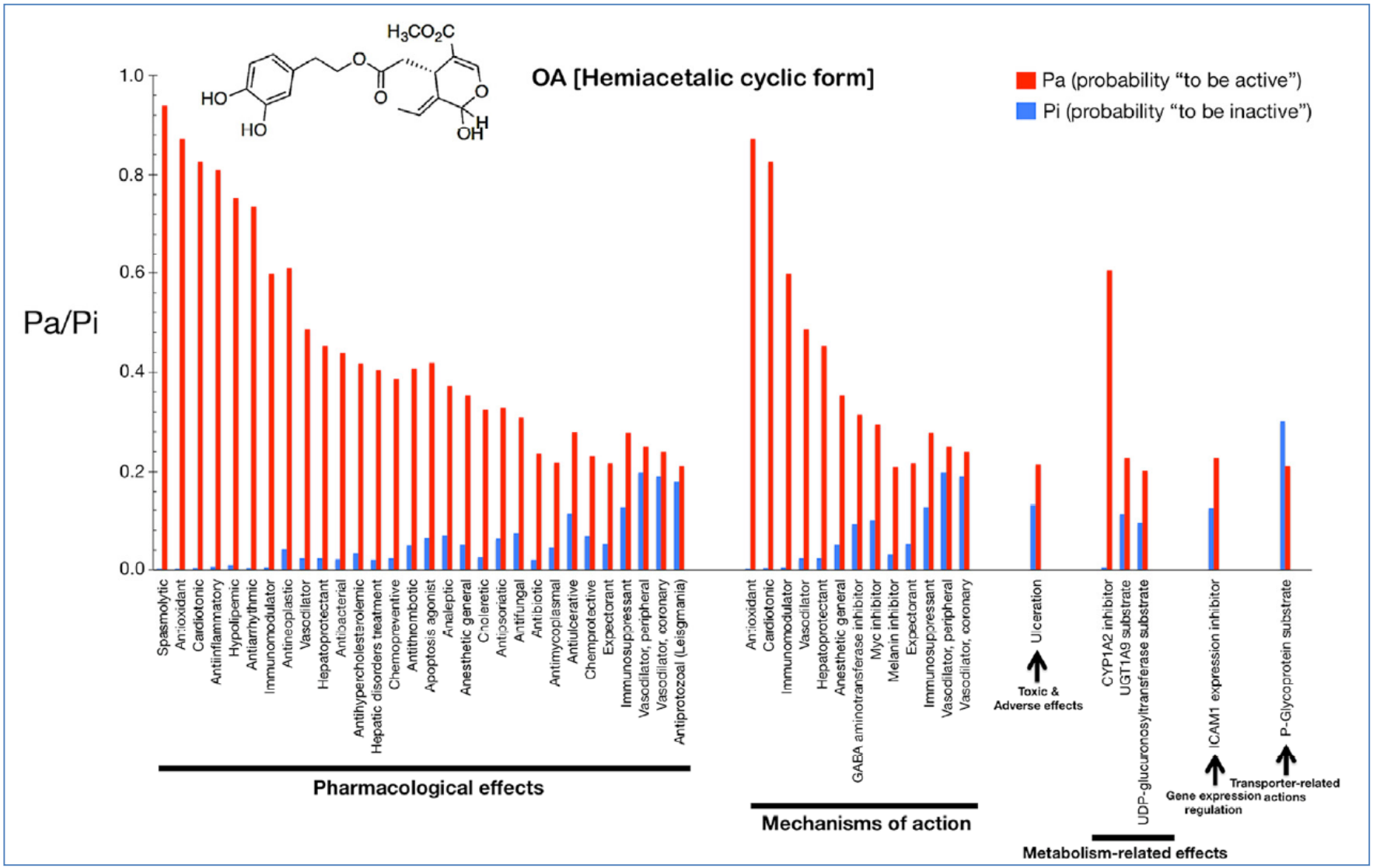
Medicinal plants have been used for the treatment of various ailments in different systems of traditional medicine and have also served as a source for many drugs in modern medicine [1, 2]. These plants have been explored either based on bioactivity-guided fractionation to identify bioactive principles for traditional activities of interest or based on the random exploration of the phytoconstituents without assigning any specific pharmacological activity [3, 4]. In any case, these explorations have led to enrichment of the phytochemical information about these medicinal

Computer-aided discovery of biological activity spectra for anti-aging and anti-cancer olive oil oleoproteins



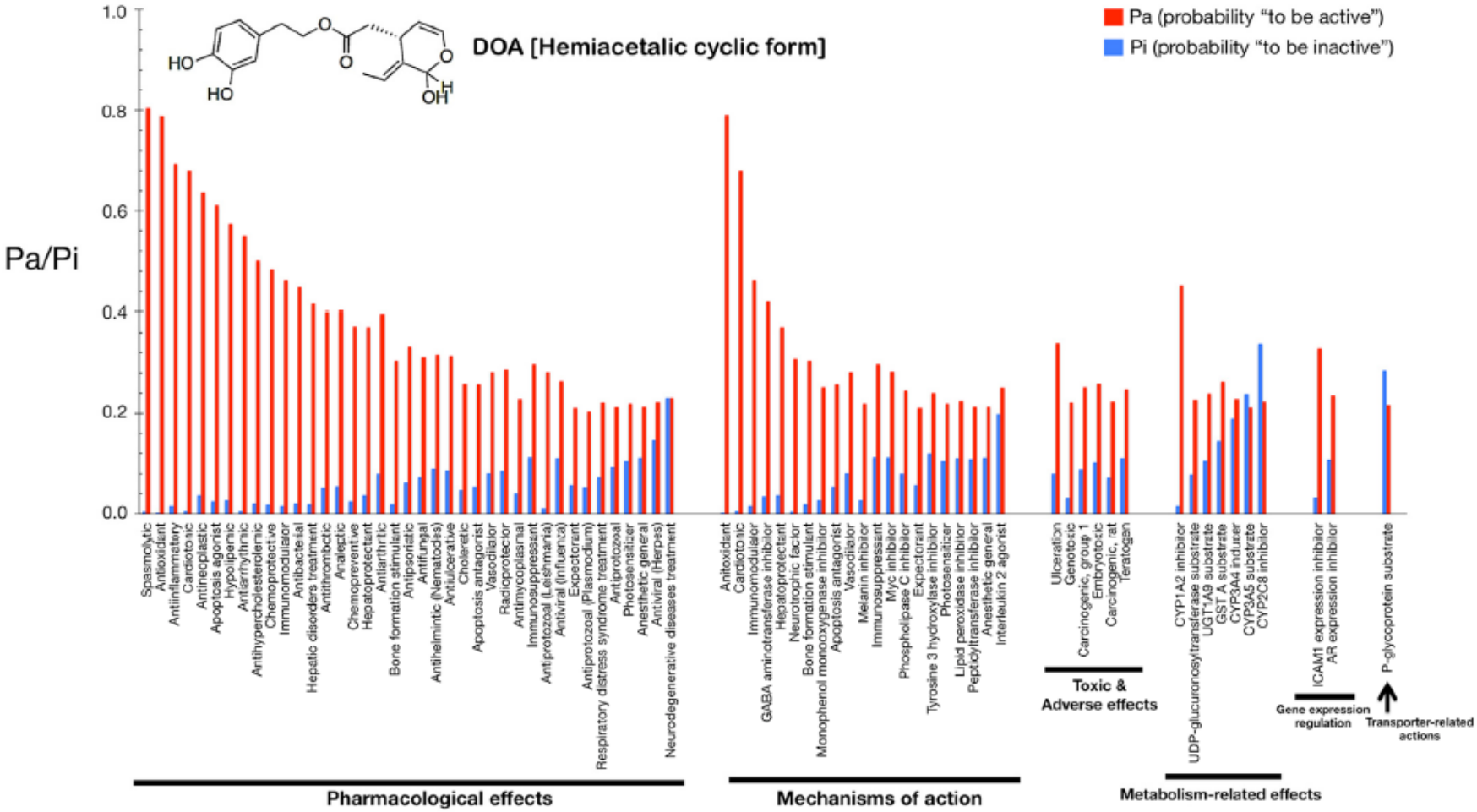
Corominas-Faja B. et al. *Aging*, 2014, 6: 731-741.

Predicted biological activity spectra for oleoprotein aglycone



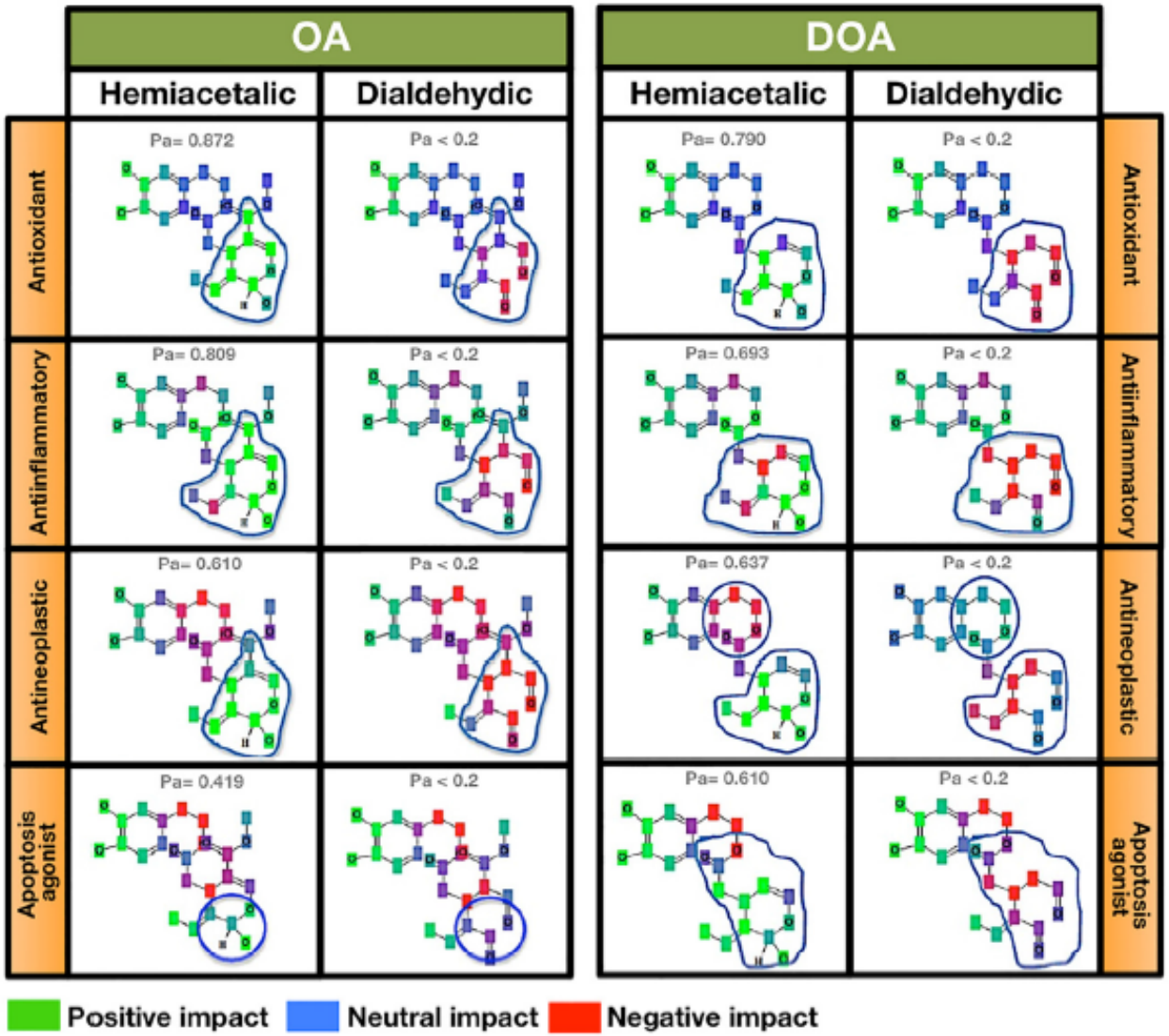
Corominas-Faja B. et al. *Aging*, 2014, 6: 731-741.

Predicted biological activity spectra for decarboxymetyl oleoprotein aglycone



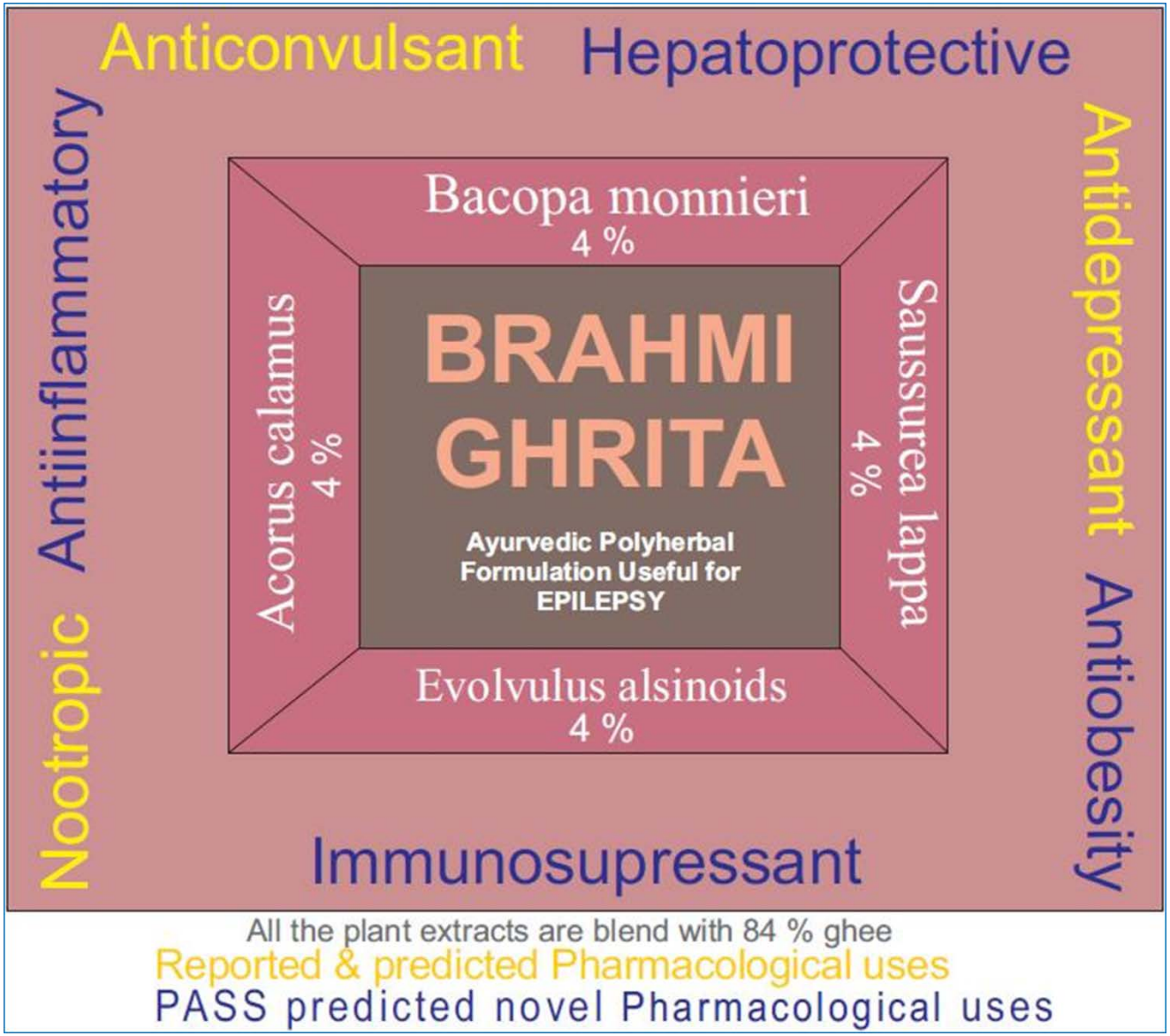
Corominas-Faja B. et al. *Aging*, 2014, 6: 731-741.

Contribution of particular atoms to anti-aging/anti-cancer activities of OA and DOA



Corominas-Faja B. et al. *Aging*, 2014, 6: 731-741.

Brahmi Ghrita: *Bacopa monnieri*, *Acorus calamus*, *Saussurea lappa* and *Evolvulus alsinoids*



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 substance has a wide spectrum of biological activities as evident from some new uses of many old drugs. PASS (Prediction of Activity Spectra for Substances) has been employed as a strong potential tool to predict the biological activity spectrum of synthetic substances for the discovery of new drugs. But the potential of PASS to predict the biological activity spectra of natural products is still

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

Introduction

Natural products (NPs) are used in folk medicine since many thousands year, due to their biological origin, better ADME/T (absorption, distribution, metabolism, and excretion/toxicity) characteristics and high chemical diversity. Presently, NPs are considered as a valuable source of lead structures for new pharmaceutical agents. Over 70% of New Chemical Entities (NCEs) introduced into medical practice from 1981–2006 were obtained on

European Journal of Pharmacology 704 (2013) 33–40

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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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Depression
Learning and memory deficit

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

Лагунин А.А.[1], Дружиловский Д.С.[1], Рудик А.В.[1], Филимонов Д.А.[1], Gawande D.[2], Suresh K[2], Goel R.[2], Поройков В.В.[1]

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[2] *Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala-147002, India, tel.: 91 (175) 304-62-54, fax: 91 (175)228-30-73, E-mail: goelrkpup@gmail.com*

Реферат

С целью изучения скрытого потенциала традиционной индийской медицины Аюрведа создан веб-ресурс по фитокомпонентам 50 лекарственных растений из (http://ayurveda.pharmaexpert.ru). В реляционную централизованную специализированную базу данных введена информация о 50 ийской медицине и входящих в их ости 288 фитокомпонентов. гической активности 946 ми биологической активности и ыборку компьютерной программы ированной обучающей выборки и о одному и кросс-валидация сь, что значения средней ошибки ачений, полученных при 5%, соответственно), что ализированной версии программы ы PASS получен прогноз спектров карственных растений ТИМ. С ализ результатов прогноза для ; для ряда растений проведено экстрактов из лекарственных акотерапевтические 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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[2] Department of Pharmaceutical Sciences and Drug Research, Punjabi University, 147002, India goelrkpup@gmail.com

[3] Russian National Research Medical University, department of Biochemistry of N Biological Faculty, 117997, Ostrovitianov str. 1, Moscow, Russia.

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 therapeut

NPR

REVIEW

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Cite this: *Nat. Prod. Rep.*, 2014, 31, 1585

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

Alexey A. Lagunin,*[ac] 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,[ac] Dmitry S. Druzhilovsky[a] and Vladimir V. Poroikov*[ac]

Covering: up to 2014

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 app-roaches.

Components of Way2Drug platform (I)

PASS Online

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.

GUSAR Online

GUSAR online presents: consensus prediction, applicability domain assessment, internal and external models validation and clearly interpretations of obtaining results (acute rodents toxicity, antitargets, etc.).

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.

Components of Way2Ddug platform (II)

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.

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.

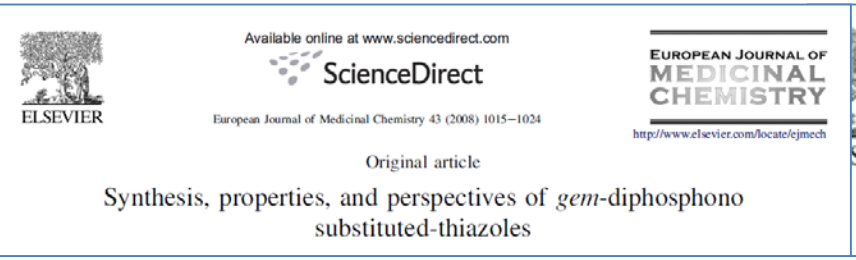
SOMP

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.

. . .

Way2Drug services are available online

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



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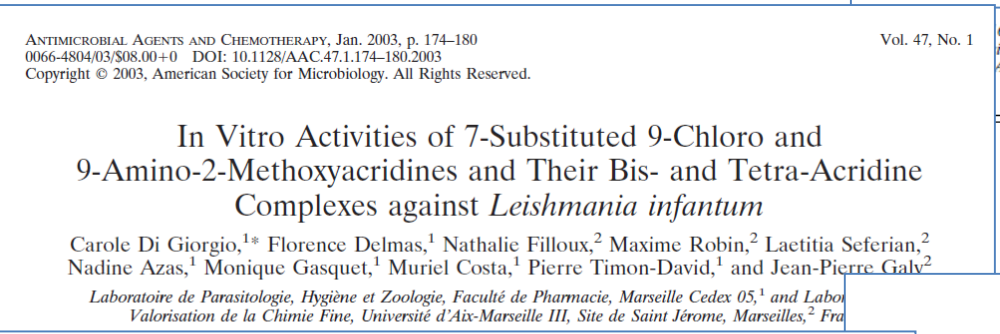

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0066-4804/03/$08.00+0 DOI: 10.1128/AAC.47.1.174–180.2003

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

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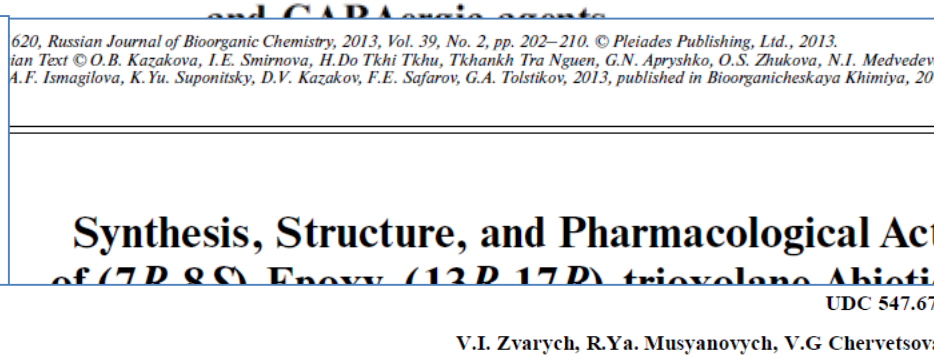
Valorisation de la Chimie Fine, Université d'Aix-Marseille III, Site de Saint Jérome, Marseilles,[2] Fra



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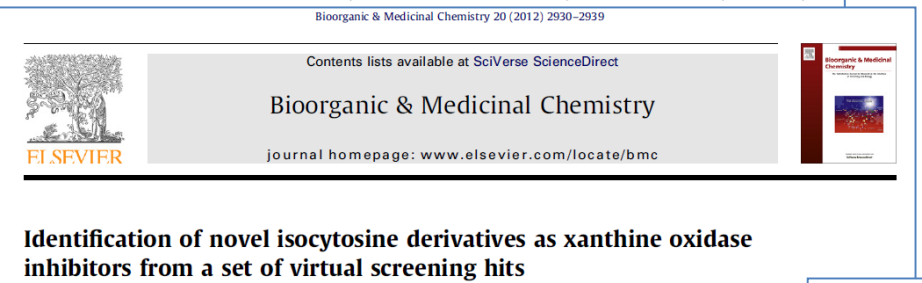
ian Text © O.B. Kazakova, I.E. Smirnova, H.Do Tkhi Tkhu, Tkhankh Tra Nguen, G.N. Apryshko, O.S. Zhukova, N.I. Medvedev
A.F. Ismagilova, K.Yu. Suponitsky, D.V. Kazakov, F.E. Safarov, G.A. Tolstikov, 2013, published in Bioorganicheskaya Khimiya, 20

Synthesis, Structure, and Pharmacological Act

of (7*R*,8*S*)-Epoxy-(13*R*,17*R*)-trioxolano-Abieti



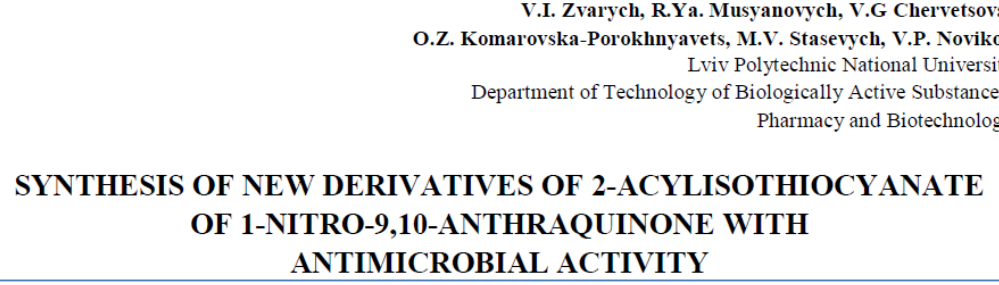
Bioorganic & Medicinal Chemistry 20 (2012) 2930–2939

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



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

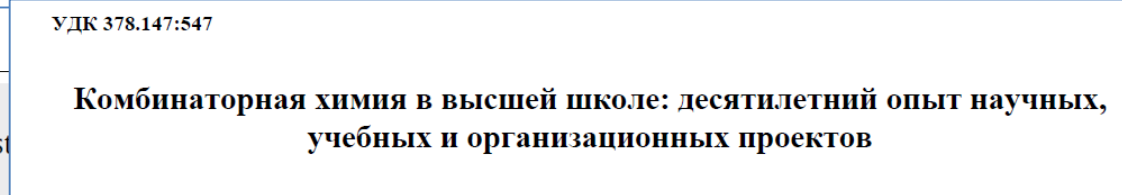
Pharmacy and Biotechnolog

SYNTHESIS OF NEW DERIVATIVES OF 2-ACYLISOTHIOCYANATE OF 1-NITRO-9,10-ANTHRAQUINONE WITH ANTIMICROBIAL ACTIVITY

European Journal of Medicinal Chemistry 45 (2010) 2606–2612

Contents lists available at ScienceDirect

European Journal of Medicinal Chemist



УДК 378.147:547

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

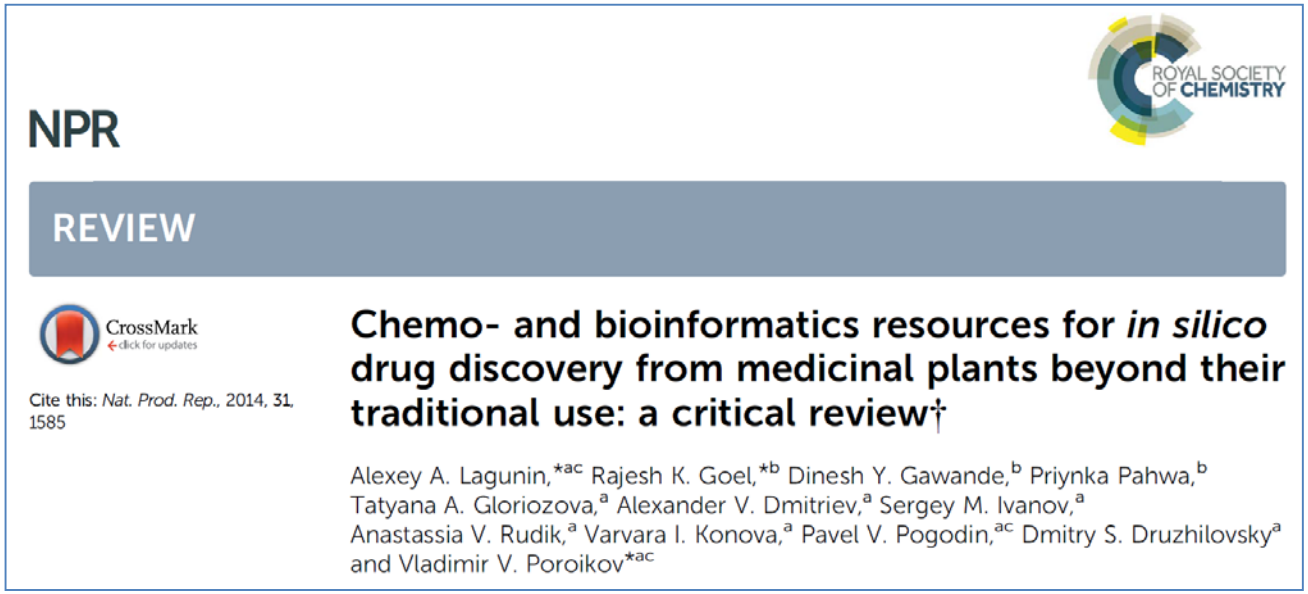
Somw publications with the experimental confirmation of prediction results for natural products

№	Natural product	Activity	Experimental confirmation
1	Spirosolenol from roots of *Solanum anguivi*	Antiinflammatory	*in vitro*
2	Phytocomponents of *Vitex negundo*	Antioxidant, antineoplastic	*in vitro*
3	Phytocomponents of *Ficus religiosa L. (Moraceae)*	Anticonvulsant GABA , Aminotransferase inhibitor	*in vitro*
4	Quercetin	Antiinflammatory, antibacterial	*in vitro*
5	Polyketides from marine-derived fungus *Ascochyta salicorniae*	Protein phosphatase inhibitor	*in vitro*

There is dozen publications where the authors used our web-services for prediction of the biological activity spectrum of natural products with the experimental confirmation of the prediction results.

Lagunin A.A. et al. Nat. Prod. Rep., 2014, 31: 1585-1611.

More info about the computational resources:



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REVIEW

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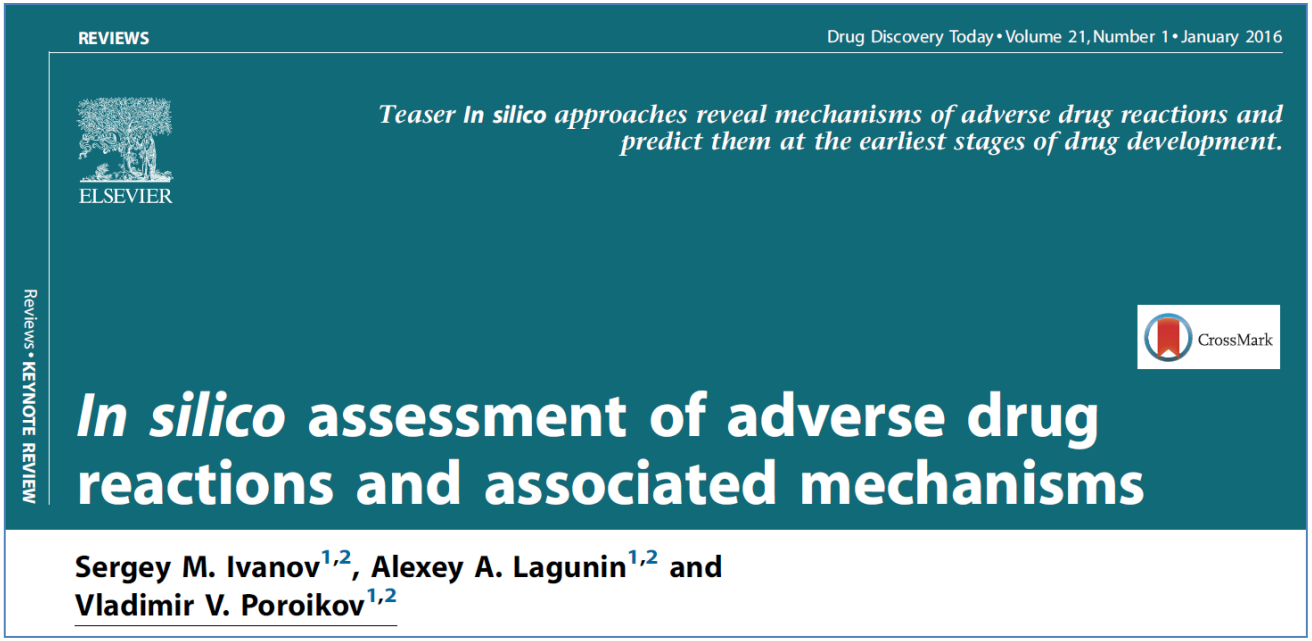
Cite this: *Nat. Prod. Rep.*, 2014, 31, 1585

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

Alexey A. Lagunin,*[ac] 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,[ac] Dmitry S. Druzhilovsky[a] and Vladimir V. Poroikov*[ac]



REVIEWS

Drug Discovery Today • Volume 21, Number 1 • January 2016

ELSEVIER

Teaser **In silico** *approaches reveal mechanisms of adverse drug reactions and predict them at the earliest stages of drug development.*

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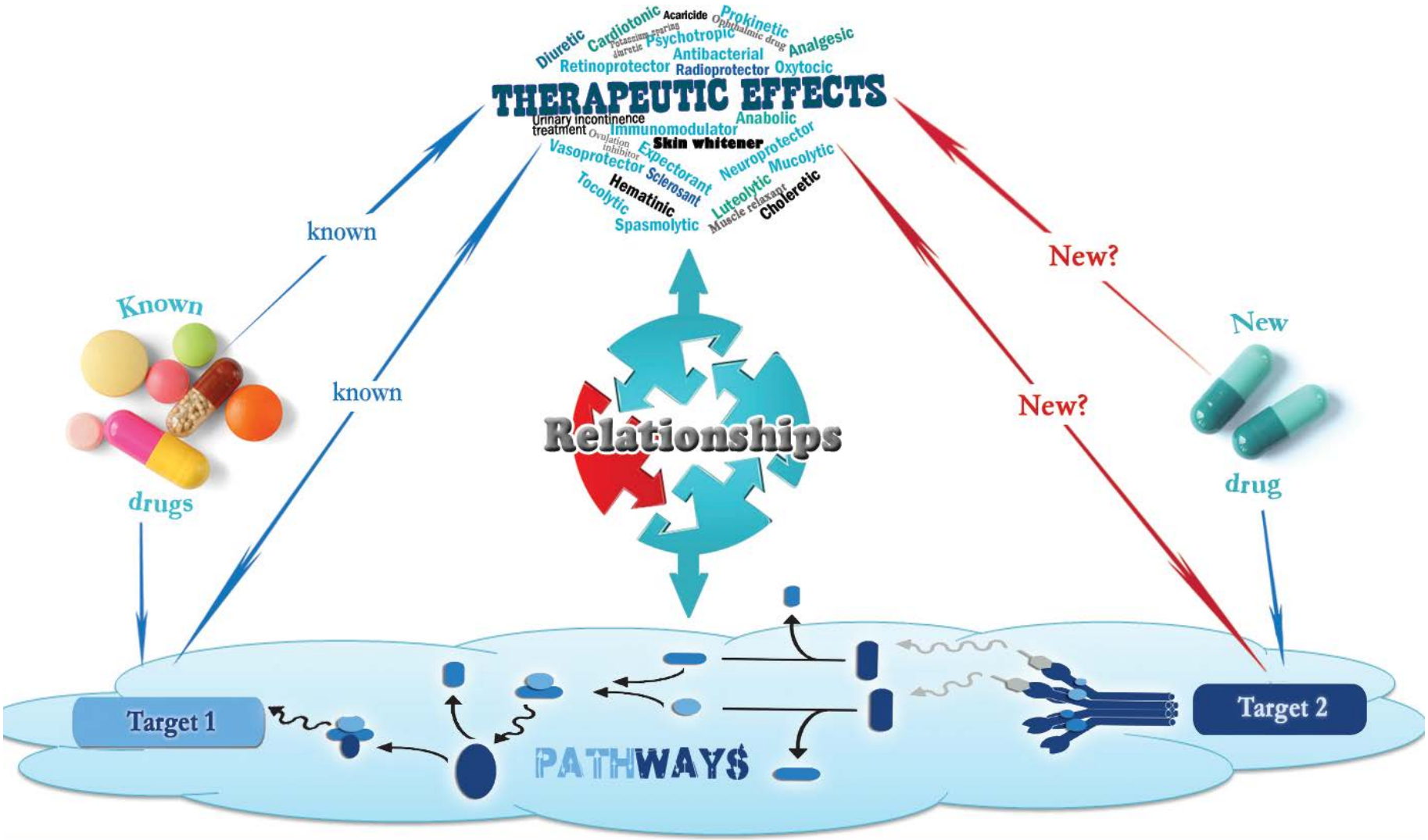
Reviews • KEYNOTE REVIEW

In silico assessment of adverse drug reactions and associated mechanisms

Sergey M. Ivanov[1,2], Alexey A. Lagunin[1,2] and Vladimir V. Poroikov[1,2]

General computer-aided approach to estimating the hidden pharmacotherapeutic potential of medicinal plants



Comparison of predictions with known effects of *Aloe vera* phytocomponents

No.	Known effects	Prediction by PASS and PharmExpert with the cutoff Pa>0.5					
		Effects	MOA	KEGG	NCI pathways	Reactome	Any approach
1	Antibacterial	+	+	+	+	+	+
2	Antifungal	+	+	+	+	+	+
3	Anti-inflammatory	+	+	+	+	+	+
4	Antimutagenic	+	-	-	-	-	+
5	Antioxidant	+	+	-	-	+	+
6	Antiprotozoal (Leishmania)	+	-	-	-	-	+
7	Antiulcerative	+	+	+	-	+	+
8	Cardioprotectant	+	-	+	+	+	+
9	Cytostatic	+	-	-	-	+	+
10	Cytotoxic	+	-	+	+	+	+
11	Hepatoprotectant	+	+	+	+	+	+
12	Hypoglycemic	-	+	+	+	+	+
13	Hypolipemic	-	+	+	-	+	+
14	Immunostimulant	-	-	+	+	+	+
15	Neurodegenerative diseases treatment	-	-	+	+	+	+
16	Wound-healing agent	-	+	+	+	+	+
	True Positives (TP)	**11**	**9**	**12**	**10**	**14**	**16**
	True Negatives (TN)	67	63	54	67	49	28
	False positives (FP)	39	43	52	39	57	78
	False negatives (FN)	5	7	4	6	2	0
	Sensitivity, TP/(TP+FN)	**0.69**	**0.56**	**0.75**	**0.63**	**0.88**	**1.00**
	Specificity, TN/(TN+FP)	0.63	0.59	0.51	0.63	0.46	0.26
	Precision, TP/(TP+FP)	0.22	0.17	0.19	0.20	0.20	0.17

Summary

- ✓ **Natural products is a valuable source for creating novel medicines because they are particularly designed by "Mother Nature" for interaction with biological systems, and due to their great chemical and pharmacological diversity.**
- ✓ **The hidden pharmacological potential of medicinal plants, their phytoconstituents and other natural products may be discovered using computer-aided analysis by PASS and PharmaExpert.**
- ✓ **Way2Drug containing many computational predictive resources may become a platform for different collaborative projects in the field of drug discovery.**

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Tatyana Gloriozova, M.Sc.

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Dmitry Druzhilovskiy, Ph.D.

Alexey Zakharov, Ph.D.

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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Institute for Health and Consumer Protection (IHCP)

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Biosergen

UBC

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Thank you for your kind attention!

We are open for collaboration.

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