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институт биомедицинской химии

Computer-Aided Approaches to Virtual Screening and Rational Design of Multitargeted Drugs

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Outline

- Biological activity: many faces of the entity
- Identification of the most promising targets
  - Net2Drug
- Identification of the most promising lead compounds
  - PASS
  - PharmaExpert
  - GUSAR
- Examples of applications
- Summary

Due to biological activity, chemical compound may be used as a medicine for treatment of certain disease.

Due to biological activity, chemical compound may cause adverse or toxic effects in human.

Depending on the Dose and Route of Administration, the Substance May Be either Drug or Poison

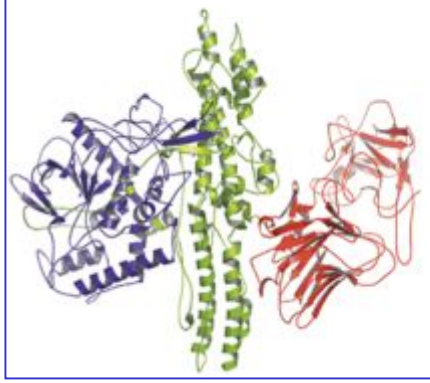
Botox

If Botox was not exactly a household word before the last presidential campaign, it became one during it. For a brief period of time, the campaign's leitmotiv was whether one of the candidates was being injected with Botox to erase the frown lines from his well-lived-in face. He denied using it, but the publicity put this nonsurgical wrinkle eraser on the map.

Botox is the trade-marked name of Allergan's purified protein--botulinum toxin Type A--derived from the anaerobic bacterium *Clostridium botulinum*. According to the company, Botox has been approved in more than 75 countries to treat 20 different neurological disorders. In addition to its cosmetic application, the toxin has been used in the U.S. for about 15 years for a range of therapeutic applications, including th treatment of crossed eyes and excessive sweating.

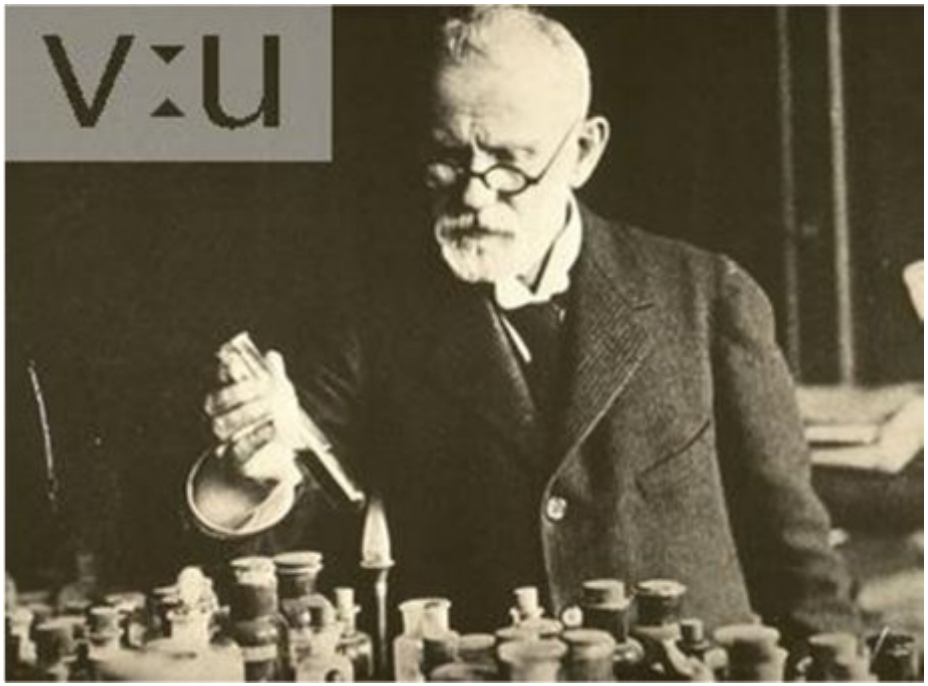
Allergan spokeswoman Caroline Van Hove notes that Botox "ranks as the number one minimally invasive cosmetic procedure in the U.S., according to recent statistics from the American Society of Plastic Surgeons." But its therapeutic uses outweigh the cosmetic, accounting for a 60% of Allergan's worldwide sales of $705 million in 2004.

Type A is one of seven distinct botulinum toxins (identified by A-G) produced by different strains of the bacterium. Each toxin type produces different immunologic response and is made by a different manufacturing process. In the U.K. and Europe, Ipsen markets a Type A toxin as Dysport that differs slightly from Botox. The only Type B toxin available is made by Solstice Neurosciences and is sold as Myobloc/Neuroblo No other antigenic toxins are available for therapeutic use.



Beginning of XX Century: “Magic bullet” concept

During the XX century the dominant paradigm in creation of new drugs was based on suggestion about selectivity of action on a certain molecular target that should lead to the normalization of pathological process.



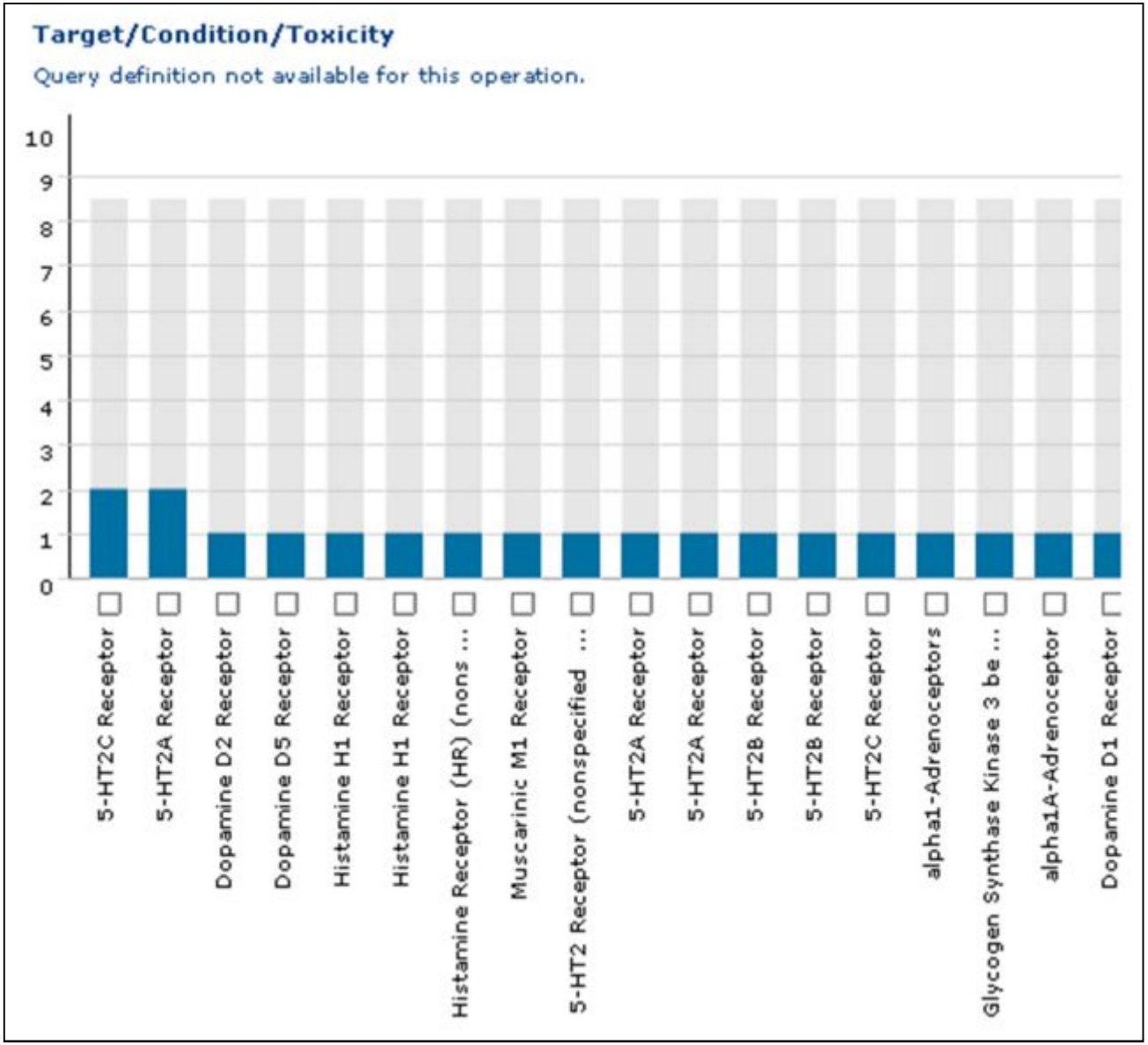
Paul Ehrlich (14 March 1854 – 20 August 1915) was a German scientist in the fields of hematology, immunology, and chemotherapy, and Nobel laureate. He is noted for curing syphilis and for his research in autoimmunity, calling it "*horror autotoxicus*". He coined the term chemotherapy and popularized the concept of a magic bullet.

Beginning of XXI Century: Multitargeting Reality

For example, "... popular statins, prescribed to decrease pathologically elevated cholesterol levels, interfere with cholesterol biosynthesis at the C_5 level (hydroxymethyl glutarate), and therefore interfere with the biosynthesis of farnesyl residues, cholic acids, sexual hormones and corticosteroids; it is really surprising that these drugs do not produce more severe side effects. Olanzapine, a successful neuroleptic and one of the top-selling drugs, acts as a highly unspecific, nanomolar antagonist of at least ten different neurotransmitter receptors.

Kubinyi H. *Nat. Rev. Drug Discov.*, 2003, 2: 665.

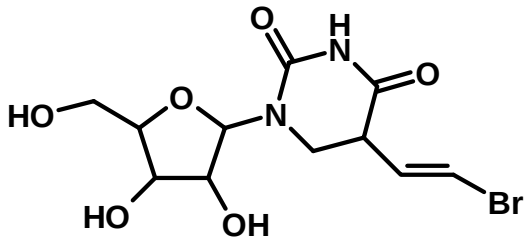
Pharmacological targets of Olanzapine ($IC_{50}<10^{-7}$)



Source: Thomson Reuters Integrity

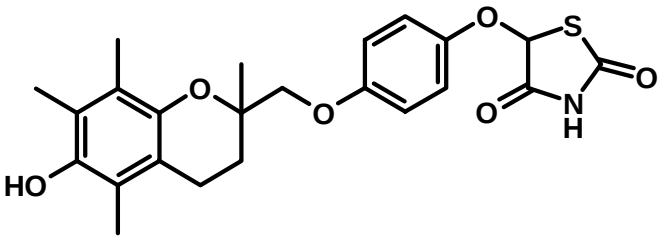
Examples of Adverse and Toxic Effects Due to the Multitargeted Drug Action

Structure → Biological Activity → Drug/Chemical



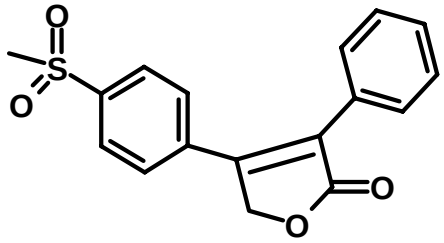
Antiviral,
Antitumor,
Neurotoxicity

Sorivudine



Antidiabetic,
Hepatotoxicity

Troglitazone



Antiarthritic,
Antiinflammatory,
COX-2 inhibitor,
Heart attack

Vioxx

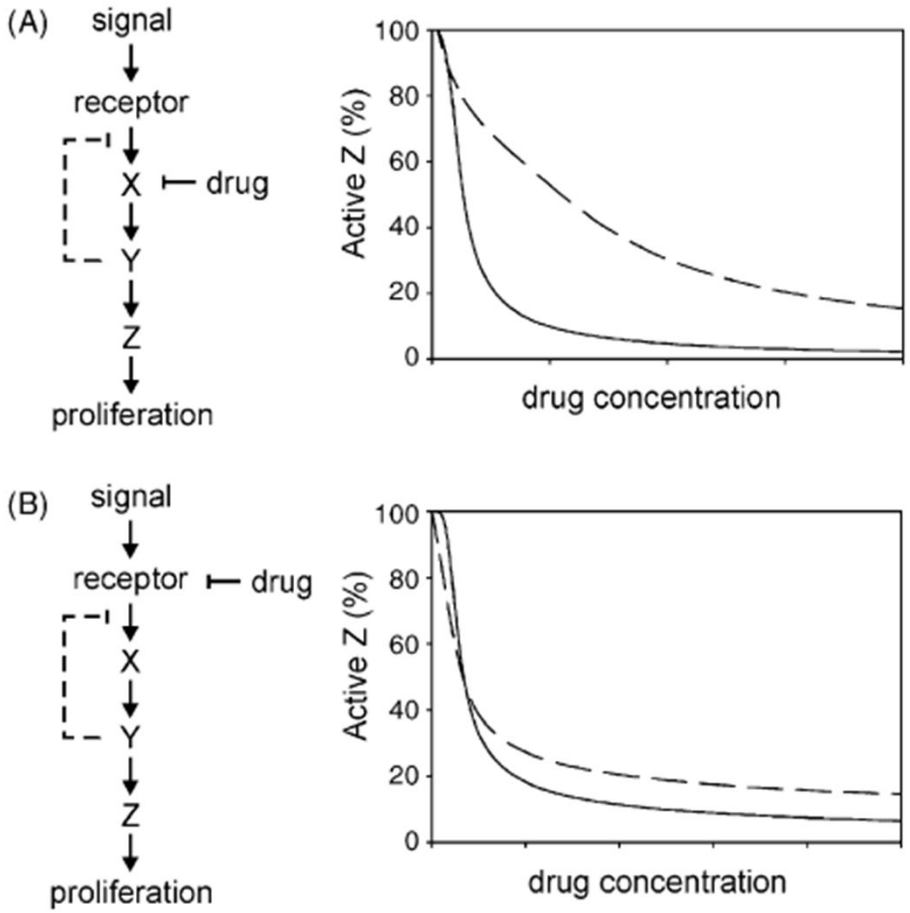
If some positive outcomes could be found in the multitargeted drugs action?

Needs for Multi-Targeted (Anticancer) Agents

- **In order to optimize the efficacy of single target therapy, we should be able to identify in each patient the oncogene to which the tumor is addicted, if any, but this is at present unrealistic.**
- **In many tumors, cross-talks between different signalling networks have been identified and inhibition of a single pathway might not be sufficient to hamper tumor progression.**
- **Almost invariably patients treated with single target agents acquire pharmacological resistance and undergo relapse, often due to the activation of alternative signalling pathways.**

Petrelli A. et al. Cur. Med. Chem., 2006, 15, 422.

Simple Case of Negative Feedback



Hornberg J.J. et al. BioSystems 83 (2006) 81–90.

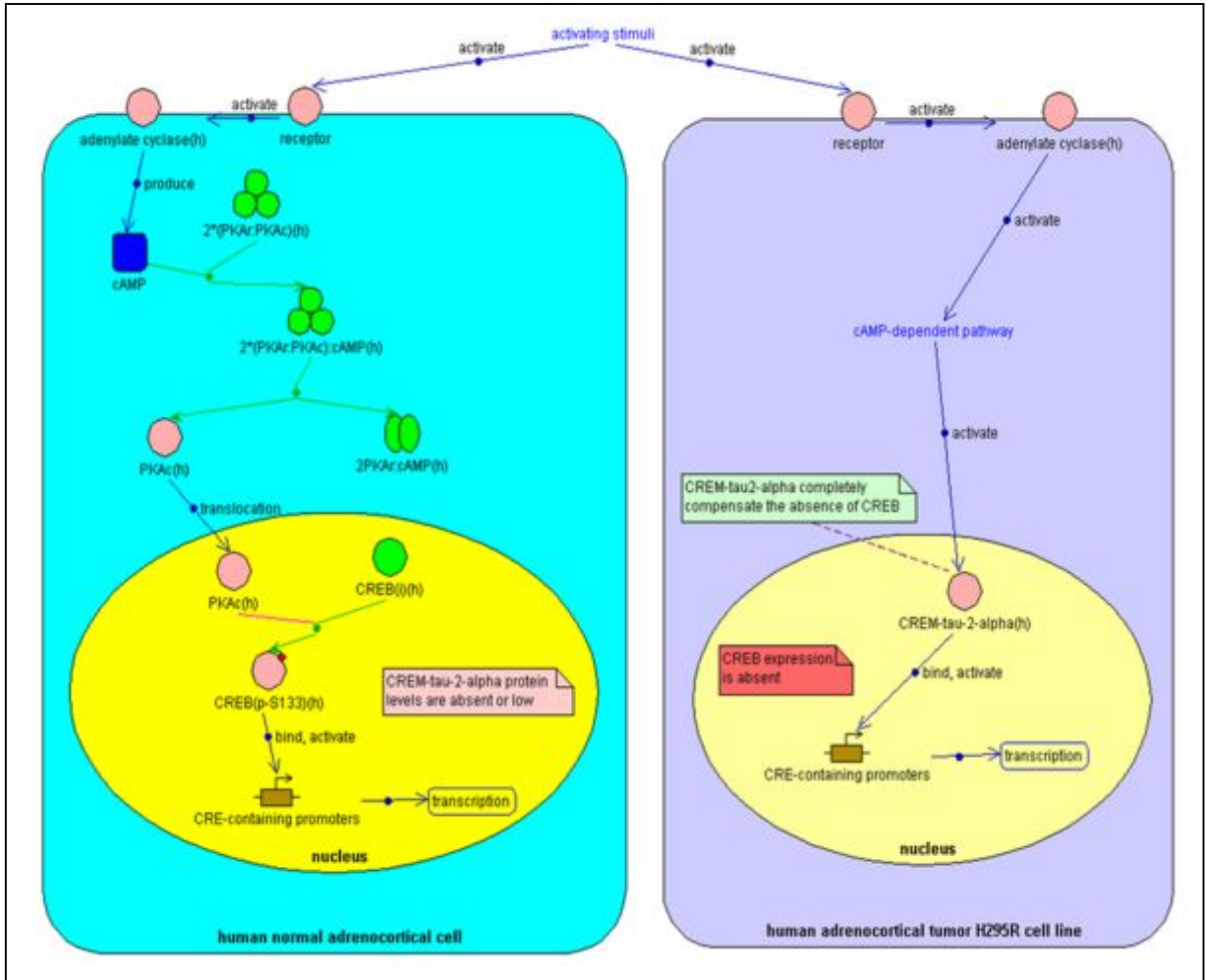
0021-972X/00/$03.00/0
The Journal of Clinical Endocrinology & Metabolism

Vol. 85, No. 1
Printed in U.S.A.

Loss of Expression of the Ubiquitous Transcription Factor cAMP Response Element-Binding Protein (CREB) and Compensatory Overexpression of the Activator CREMτ in the Human Adrenocortical Cancer Cell Line H295R*

LIONEL GROUSSIN, JEAN FRANCIS MASSIAS, XAVIER BERTAGNA, AND JÉRÔME BERTHERAT

Groupe d'Etude en Physiopathologie Endocrinienne, Centre National de la Recherche Scientifique, UPR1524, Institut Cochin de Génétique Moléculaire, Université René Descartes-Paris V, 75014 Paris, France



Multitargeted Drugs: The End of The "One-Target-One Disease Philosophy?"

DDT Vol. 9, No. 19 October 2004

The *Discussion Forum* provides a medium for airing your views on any issues related to the pharmaceutical industry and obtaining feedback and discussion on these views from others in the field. You can discuss issues that get you hot under the collar, practical problems at the bench, recently published literature, or just something bizarre or humorous that you wish to share. Publication of letters in this section is subject to editorial discretion and company-promotional letters will be rejected immediately. Furthermore, the views provided are those of the authors and are not intended to represent the views of the companies they work for. Moreover, these views do not reflect those of Elsevier, *Drug Discovery Today* or its editorial team. Please submit all letters to Steve Carney, Editor, *Drug Discovery Today*, e-mail: S.Carney@elsevier.com

Multitargeted drugs: the end of the 'one-target-one-disease' philosophy?

In a recent issue of *Drug Discovery Today*, Morphy *et al.* [1] discuss the opportunities and advantages associated with the design of ligands that act on two (or more) specific targets in an article entitled 'From magic bullets to designed multiple ligands'.

Several highly specific drugs that have only one target have clearly proven the usefulness of monotarget medicine. inhibitors and one protease inhibitor is administered, in the treatment of infection, where the β-lactamase inhibitor clavulanic acid is used in conjunction with amoxicillin, and in the treatment of Parkinson's disease, where L-4-dihydroxyphenylalanine (DOPA) is concomitantly administered with DOPA-decarboxylase and catechol-O-methyltransferase inhibitors. The risk with combination therapies is that the use of multiple drugs introduces problems with pharmacokinetics, toxicity and patient compliance. To circumvent these difficulties, and after authors use the term pharmacophores to define functional or structural elements that possess biological activity. However, this does not correspond to the official definition [6]: 'A pharmacophore is the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target structure and to trigger (or to block) its biological response.' A pharmacophore does not represent a real molecule or an actual association of functional groups, but is a purely abstract concept that encompasses the common molecular interactions of a group of compounds with their target structure. Pharmacophores are not 'pieces of molecules', and for this reason a truly rational computer-generation of DM ligands should not be based on the interactions of structural elements, but rather the comparison and association of true pharmacophores.

The second approach (screening approach) to DM ligands is based on the screening of large libraries for the two relevant bioassays. The substantial screening of a large number of compounds, which therefore have a

"In conclusion, the preparation of dual- or multiple-ligands on an almost rational basis is now conceivable and it can be expected that many of these molecules will yield drugs of superior clinical value compared with monotarget formulations".

Wermuth C. *Drug Disc. Today*, 2004, 9.

Journal of
Medicinal
Chemistry

Volume 48, Number 21 October 20, 2005

Perspective

Designed Multiple Ligands. An Emerging Drug Discovery Paradigm

Richard Morphy* and Zoran Rankovic

J. Med. Chem. **2006,** *49,* 4961−4970

The Physicochemical Challenges of Designing Multiple Ligands

Richard Morphy* and Zoran Rankovic

Medicinal Chemistry Department, Organon Laboratories, Newhouse, Lanarkshire, ML1 5SH, U.K.

Received March 16, 2006

Compounds designed to bind more than one target can provide a therapeutic benefit relative to hi
selective ligands. The physicochemical properties of designed multiple ligands were found to be le
than those for preclinical compounds in general. These properties are controlled by the superfami
the targets belong and the lead discovery strategy that was followed. The properties for peptide
coupled receptor (GPCR) ligands were the least favorable for oral delivery, whereas transporter,
GPCR, and oxidase ligands were the most druglike. The lead discovery strategy, framework com

The topology of drug–target interaction networks: implicit dependence on drug properties and target families†‡

Jordi Mestres,*[a] Elisabet Gregori-Puigjané,[a] Sergi Valverde[bc] and Ricard V. Solé[bd]

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Analysis of multiple compound–protein interactions reveals novel bioactive molecules

Hiroaki Yabuuchi[1,2], Satoshi Niijima[1,2], Hiromu Takematsu[2], Tomomi Ida[1], Takatsugu Hirokawa[3], Takafumi Hara[4], Teppei Ogawa[1], Yohsuke Minowa[1], Gozoh Tsujimoto[4] and Yasushi Okuno[1,*]

Cell

tems Biosciences for Drug Discovery, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan, [2] Laboratory of Membrane

Opinion

Novel paradigms for drug discovery: computational multitarget screening

Ekachai Jenwitheesuk[1,2], Jeremy A. Horst[1,3], Kasey L. Rivas[4], Wesley C. Van Voorhi
and Ram Samudrala[1,3]

The availability of interac
increased substantially in
a total of 4767 unique int
average every drug is curr
network theory to the ana
drug–target interactions.
implicitly on data comple

Botanical Drugs, Synergy, and Network Pharmacology: Forth and Back to Intelligent Mixtures

Author Jörg Gertsch
Affiliation Institute of Biochemistry and Molecular Medicine, University of Bern, Bern, Switzerland

Key words
© polypharmacology
© network pharmacology

Abstract
For centuries the science of pharmacognosy has over monosubstances, mixtures of bioactive compounds in botanical drugs allegedly exert synergistic therapeutic effects. Despite evolutionary

nature
biotechnology

Synergistic drug combinations tend to improve therapeutically relevant selectivity

Joseph Lehár[1–3], Andrew S Krueger[2], William Avery[1], Adrian M Heilbut[1], Lisa M Johansen[1], E Roydon Price[1], Richard J Rickles[1], Glenn F Short III[1], Jane E Staunton[1], Xiaowei Jin[1], Margaret S

Drug combina
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Journal of
Medicinal
Chemistry
Article

J. Med. Chem. **2010,** *55,* 36
DOI: 10.1021/jm

Bivalent β-Carbolines as Potential Multitarget Anti-Alzheimer Agents

[†] Kai-Uwe Schmidtke,[‡] Friedemann Gaube,[‡] Dirk Schepmann,[§] Bernhard Wünsch,[§] Jörg Heilm
ann,[†] and Thomas Winckler*[,‡]

rmazie, Lehrstuhl für Pharmazeutische/Medizinische Chemie, Friedrich-Schiller-Universität Jena, Germany,
rmazie, Lehrstuhl für Pharmazeutische Biologie, Friedrich-Schiller-Universität Jena, Semmelweisstrasse 10, D-
tut für Pharmazeutische und Medizinische Chemie der Westfälischen Wilhelms-Universität Münster, Germany,
harmazeutische Biologie, Universität Regensburg, Germany

y 4, 2010

eimer's disease (AD) is a prevalent neurodegenerative disorder with multifactorial causes
ires multitargeted treatment. Inhibitors of acetylcholinesterase (AChE) and butyrylcholineste
hE) improve cholinergic signaling in the central nervous system and thus AChE inhibitors are

Multi-Target QPDR Classification Model for Human Breast and Colon Cancer-Related Proteins using Star Graph Topological Indices

CRISTIAN ROBERT MUNTEANU,[1] ALEXANDRE L. MAGALHÃES,[1] EUGENIO URIARTE,[2] HUMBERTO GONZÁLEZ-DÍAZ,[2,*]

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[2] *Unit of Bioinformatics & Connectivity Analysis (UBICA), Institute of industrial Pharmacy, and*

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- Biological activity: many faces of the entity
- **Identification of the most promising targets**
  - **Net2Drug**
- Identification of the most promising lead compounds
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  - **PharmaExpert**
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How Many Drug Targets are There?

(Overington J.P et al. *Nat. Rev. Drug Discov.*, 2006, 5: 993-996)

Table 1 | **Molecular targets of FDA-approved drugs**

Class of drug target	Species	Number of molecular targets
Targets of approved drugs	Pathogen and human	324
Human genome targets of approved drugs	Human	266
Targets of approved small-molecule drugs	Pathogen and human	248
Targets of approved small-molecule drugs	Human	207
Targets of approved oral small-molecule drugs	Pathogen and human	227
Targets of approved oral small-molecule drugs	Human	186
Targets of approved therapeutic antibodies	Human	15
Targets of approved biologicals	Pathogen and human	76

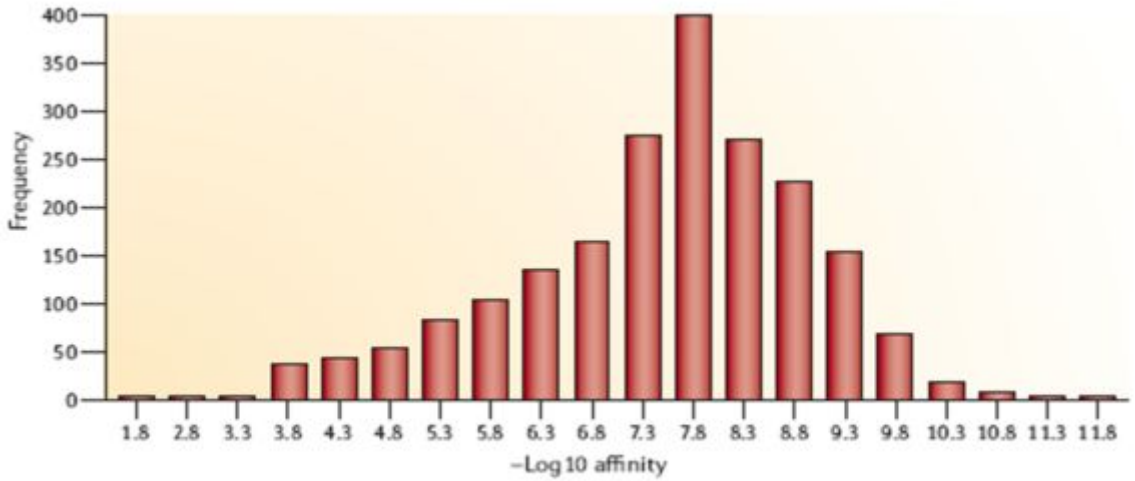
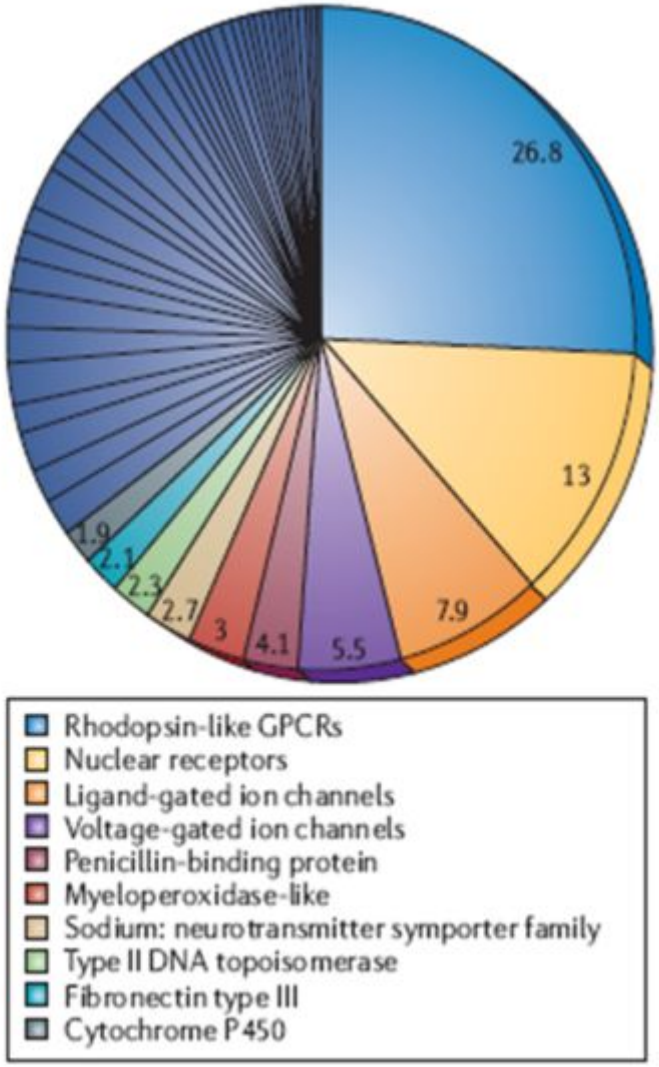
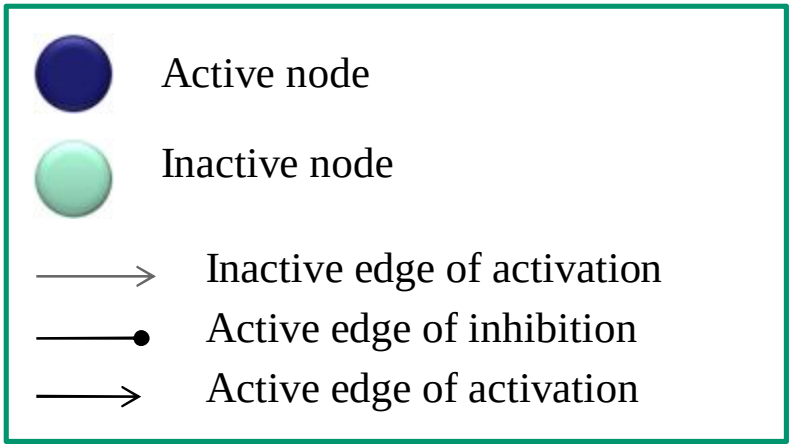
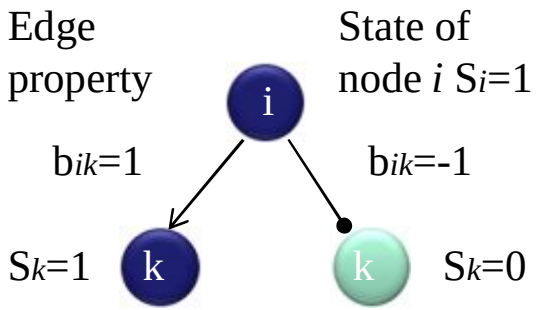


Figure 2 | **Frequency distribution for small-molecule drug potencies.**

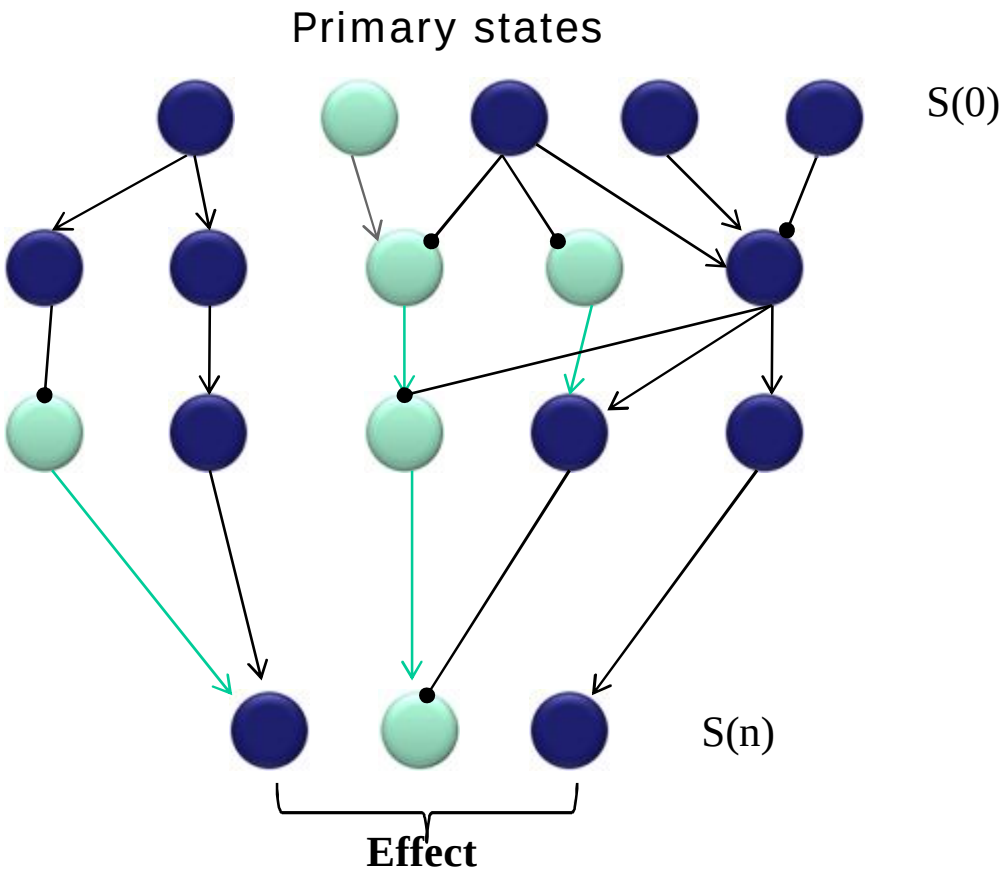


Dichotomic Modeling of Regulatory Networks in NetFlowEx program





$$Fi\ (S1, S2, \ldots, Sn) = \Theta(ai + \sum_k Skbki)$$



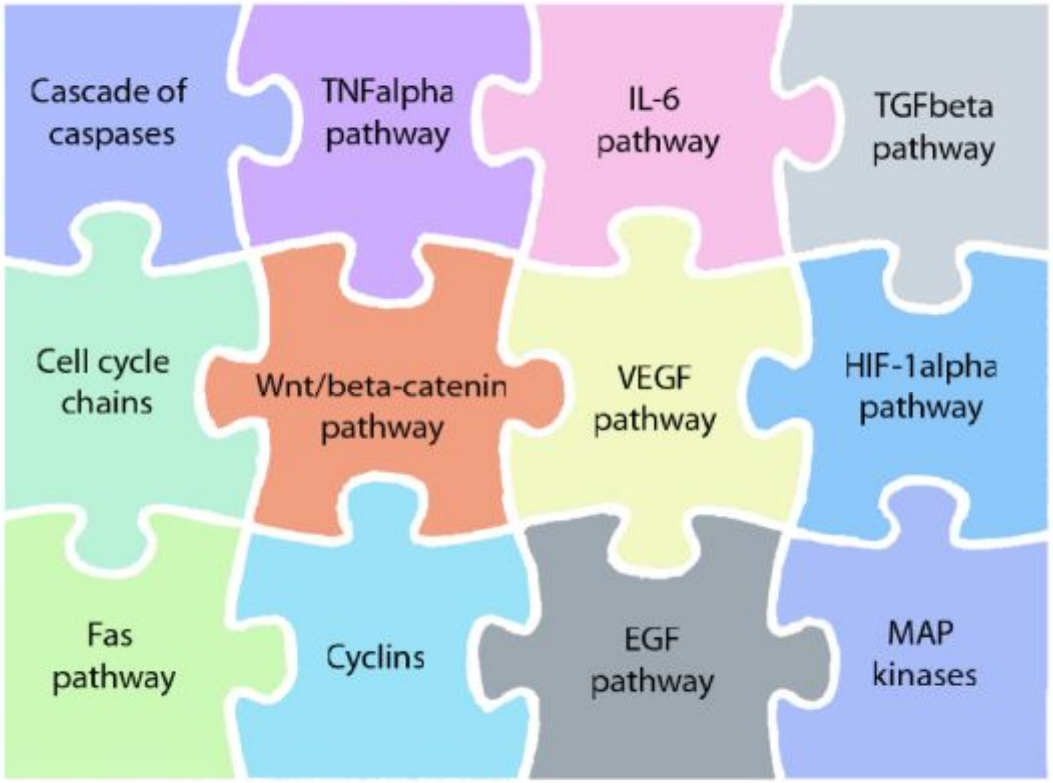
Koborova O.N. et al. *SAR and QSAR Environ. Res.*, 2009, 20, 755.

Input Data for Breast Cancer Modeling

Regulatory network

TRANSPATH® database

Fragment: 2336 edges and 1405 nodes



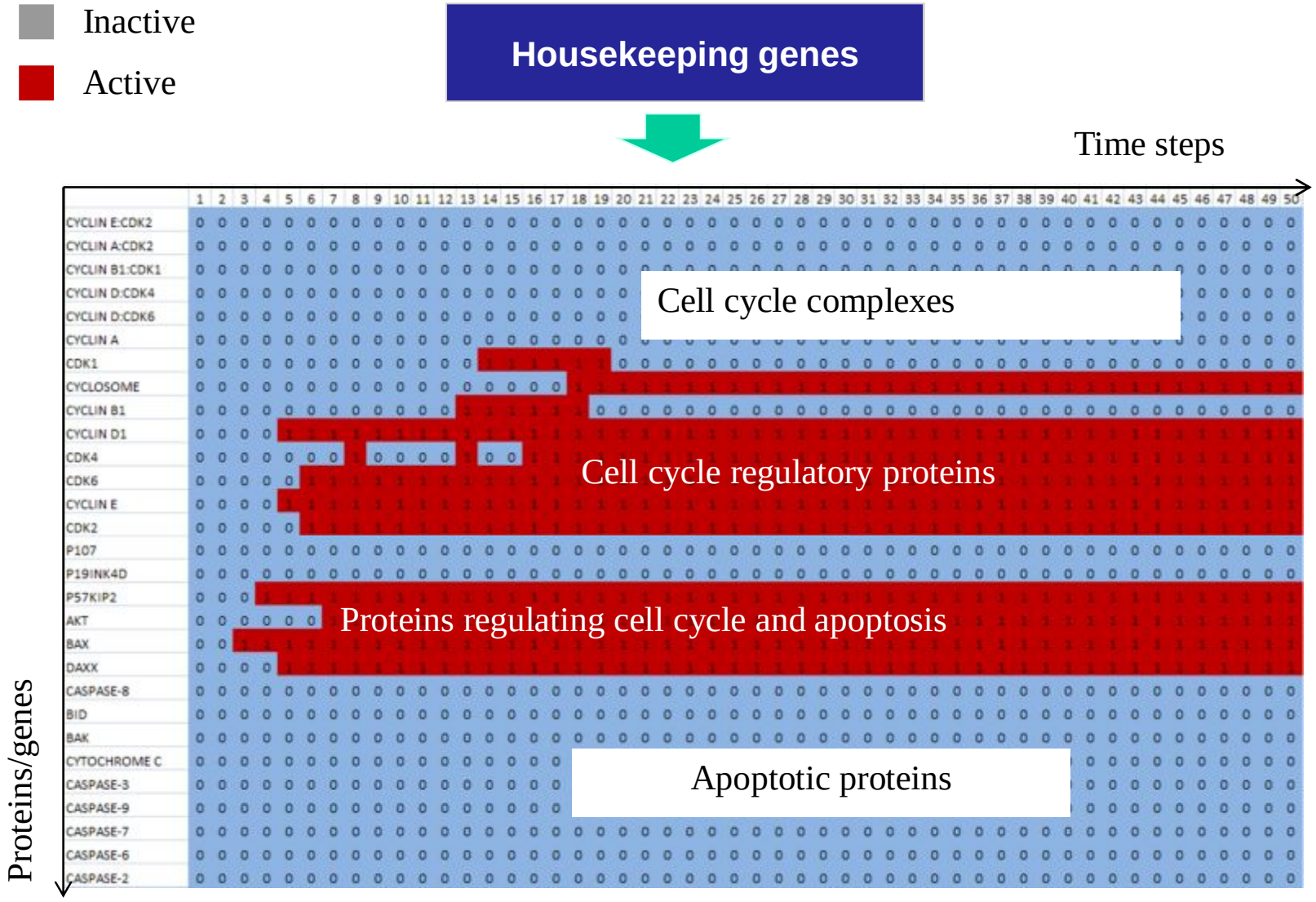
Microarray data for breast cancer

Cyclonet database

http://cyclonet.biouml.org

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

Simulation of normal cell processes

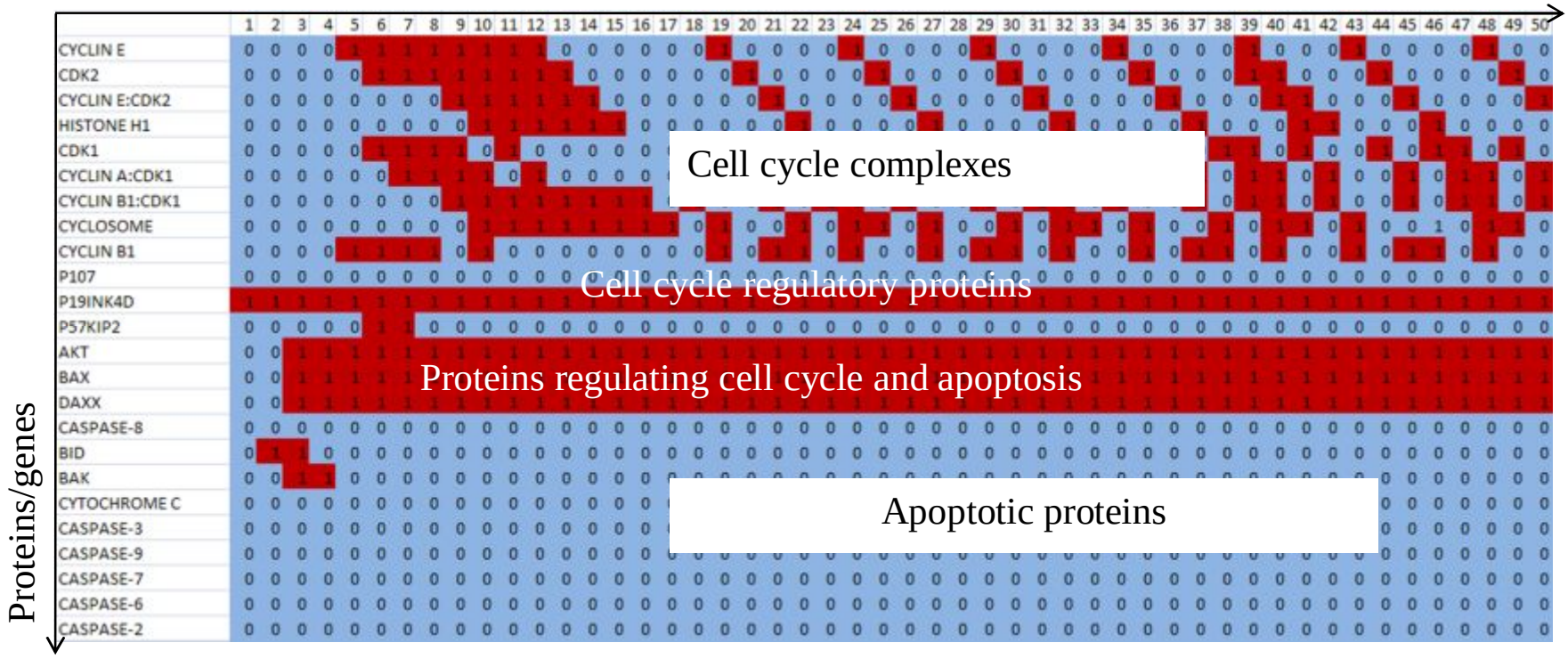


Simulation of pathological processes

Inactive

Active

Generalized breast cancer



Identified drug targets

Effect	Mechanism	HER2/neu positive breast carcinomas,	Ductal carcinoma	Invasive ductal carcinoma and/or a nodal metastasis	Generalized breast cancer
Cell cycle arrest	Cyclin D1:CDK4, Cyclin D1:CDK6 (G1 phase)	CYCD1, CYCLIN D1			
	Cyclin E:CDK2 (G1/S phase), Cyclin A:CDK2 (S phase)	CYCE, CYCLIN E, CDK2, PLK1, AKT-1			
		SYK	N/A	SRC	N/A
	Cyclin B:CDK1 (G2/M phase)	SYK	N/A	N/A	N/A
Induction of apoptosis	Cytochrome C	BCL-2			
		N/A	N/A	RAF-1, GRB-2, PKC, RACK1	Alpha5 Beta1 Fibronectin receptor, Fibronectin
	Caspase-3	MKK4, PI3K, MKK6, P38ALPHA, CRKL, HPK1			
		N/A	N/A	VEGF-A, VEGFR-2, HIF-1ALPHA	N/A

Some Double and Triple Targets' Combinations Identified For Breast Cancer

No	Number of compounds	Activity type	Activity type	Activity type
1	4	Bcl2 antagonist	Cyclin-dependent kinase 2 inhibitor	
2	10	Bcl2 antagonist	Myc inhibitor	
3	10	Bcl2 antagonist	Phosphatidylinositol 3-kinase beta inhibitor	
4	3	Cyclin-dependent kinase 2 inhibitor	Myc inhibitor	
5	7	Hypoxia inducible factor 1 alpha inhibitor	Myc inhibitor	
6	10	Hypoxia inducible factor 1 alpha inhibitor	Phosphatidylinositol 3-kinase beta inhibitor	
7	10	Myc inhibitor	Phosphatidylinositol 3-kinase inhibitor	
8	10	Bcl2 antagonist	Myc inhibitor	Phosphatidylinositol 3-kinase beta inhibitor

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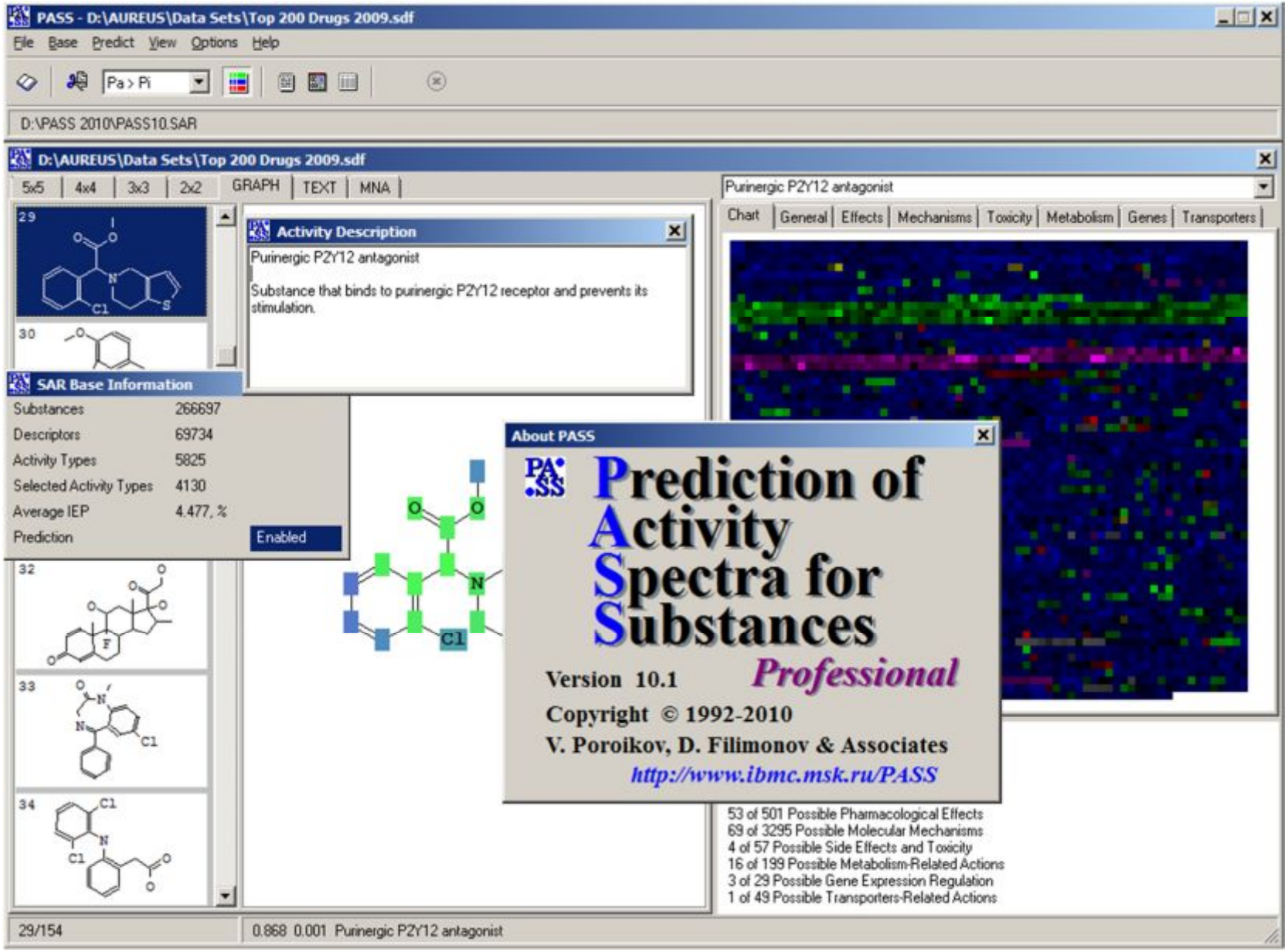
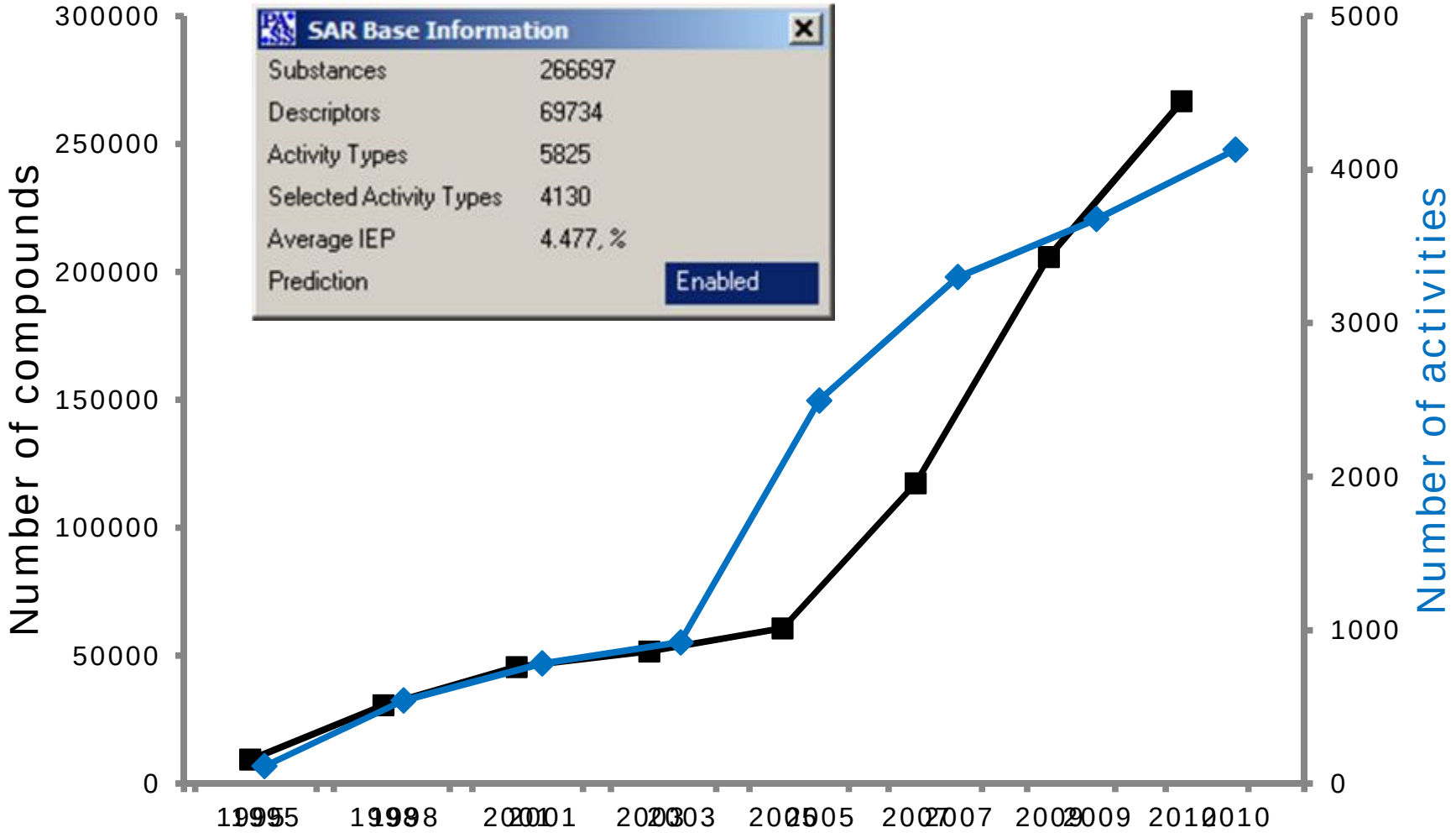
PASS: Prediction of Activity Spectra for Substances



PASS Training Set



The key persons in PASS development

РОССИЙСКАЯ ФЕДЕРАЦИЯ

СВИДЕТЕЛЬСТВО

об официальной регистрации программы для ЭВМ

№ 2006613275

PASS (Prediction of Activity Spectra for Substances)

Правообладатель(ли): ***Филимонов Дмитрий Алексеевич (RU), Поройков Владимир Васильевич (RU), Глориозова Татьяна Андреевна (RU), Лагунин Алексей Александрович (RU)***

Автор(ы): ***Филимонов Дмитрий Алексеевич, Поройков Владимир Васильевич, Глориозова Татьяна Андреевна, Лагунин Алексей Александрович (RU)***

Заявка № **2006612815**

Дата поступления **17 августа 2006 г.**

Зарегистрировано в Реестре программ для ЭВМ

15 сентября 2006 г.

Руководитель Федеральной службы по интеллектуальной собственности, патентам и товарным знакам

Б.П. Симонов

PASS Approach is Described in Detail:

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 Chemical Journal*, 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 & Fransis, 459-478.

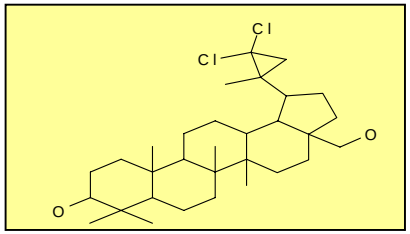
http://pharmaexpert.ru/passonline

How PASS Predicts Biological Activity Spectrum?

Structure of new compound

Estimating the probability that it has a particular biological activity

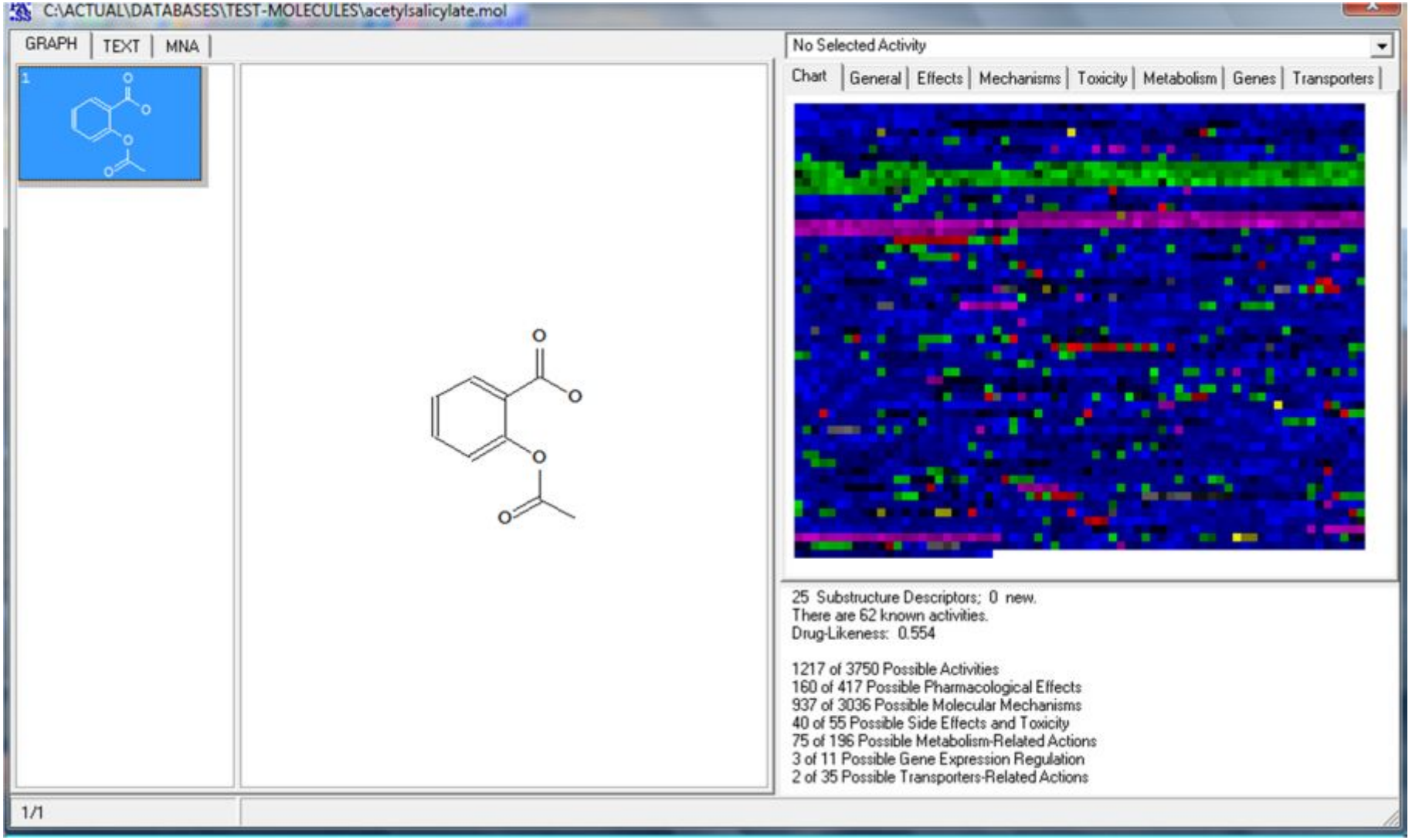
Predicted biological activity spectrum



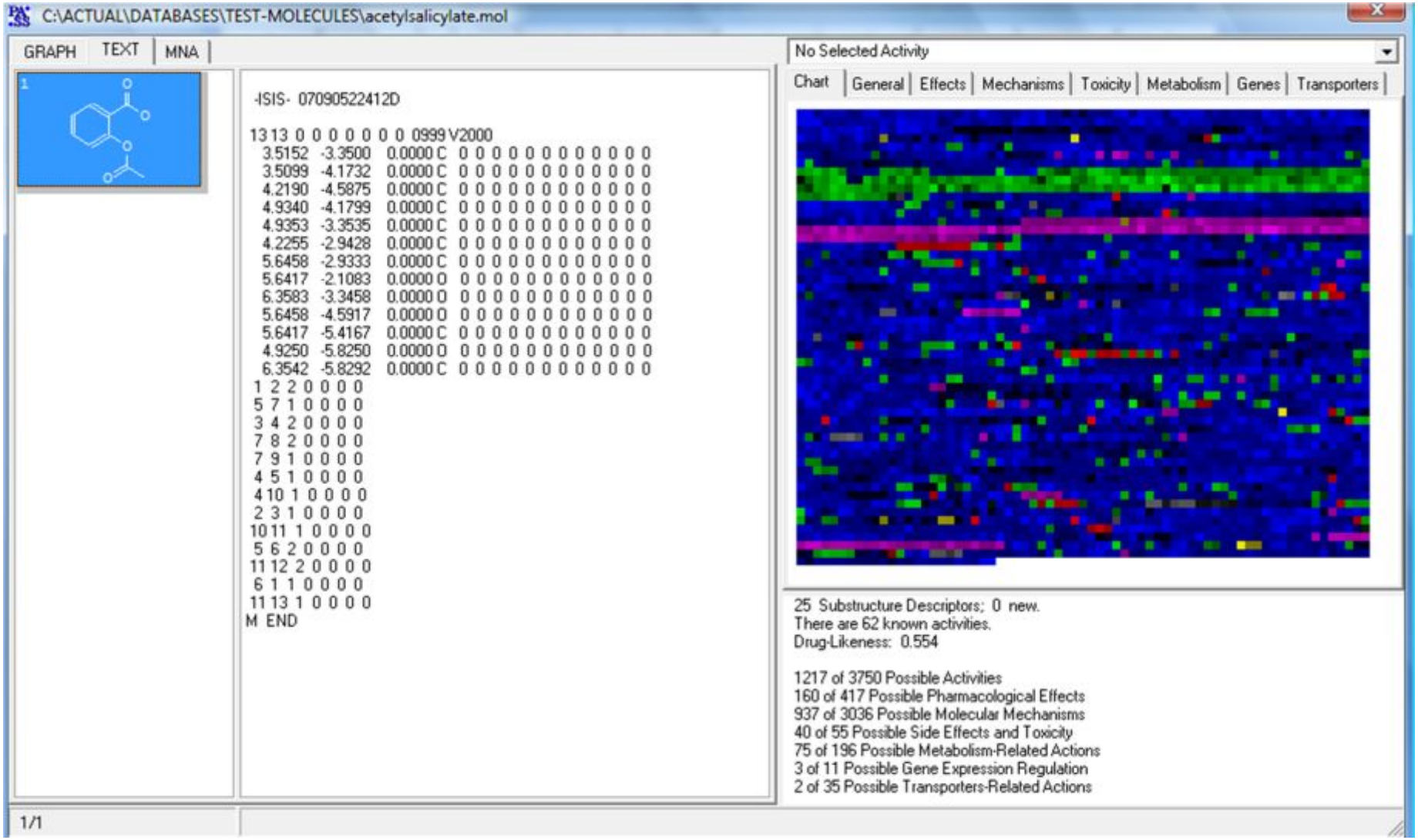
Anxiolytic
Sedative
5HT1A Inhibitor
Carcinogen

Pa	Pi	Action:
0.853	0.020	Anxiolytic
0.694	0.035	Sedative

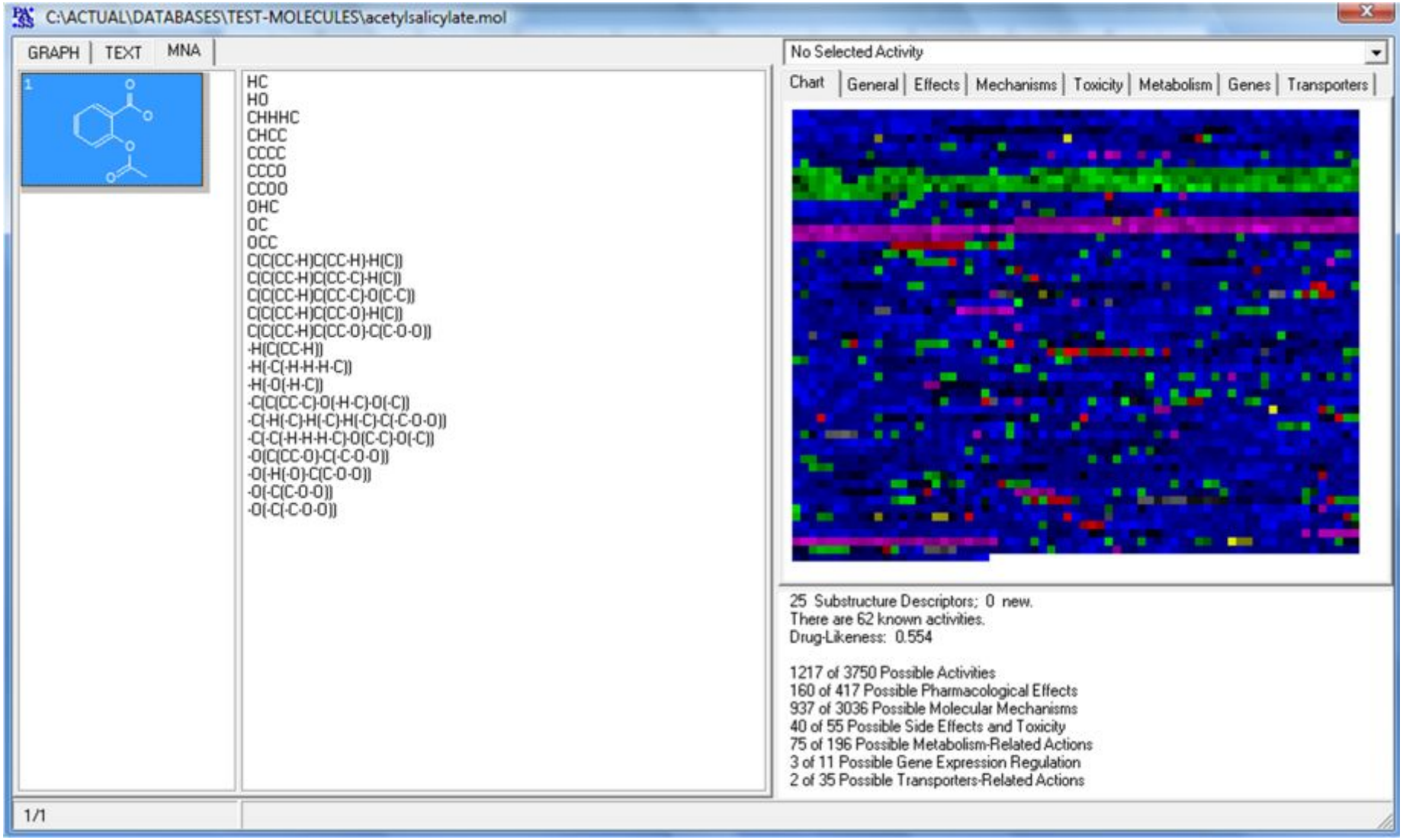
Structural Formula of Acetylsalicylate



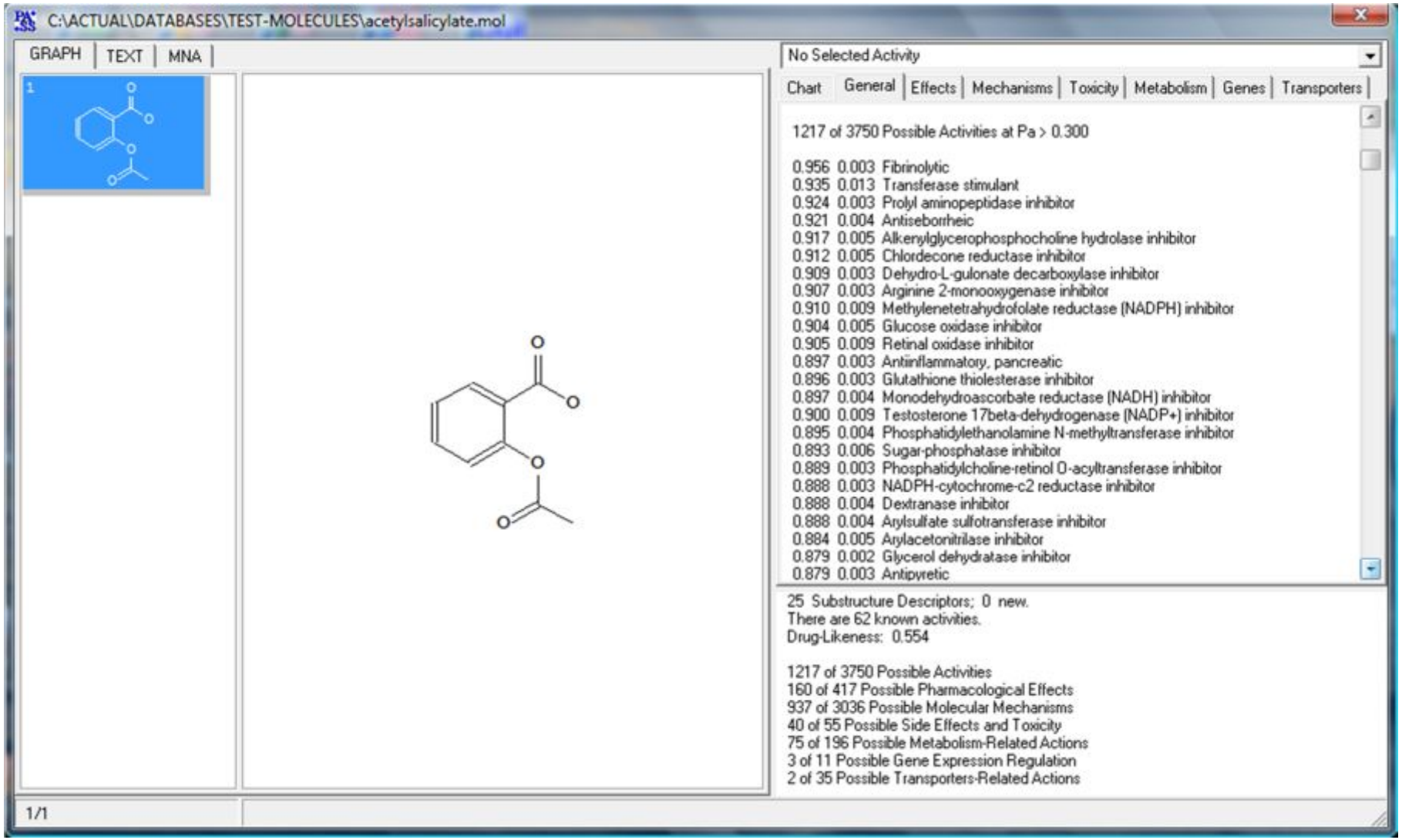
MOL File of Acetylsalicylate



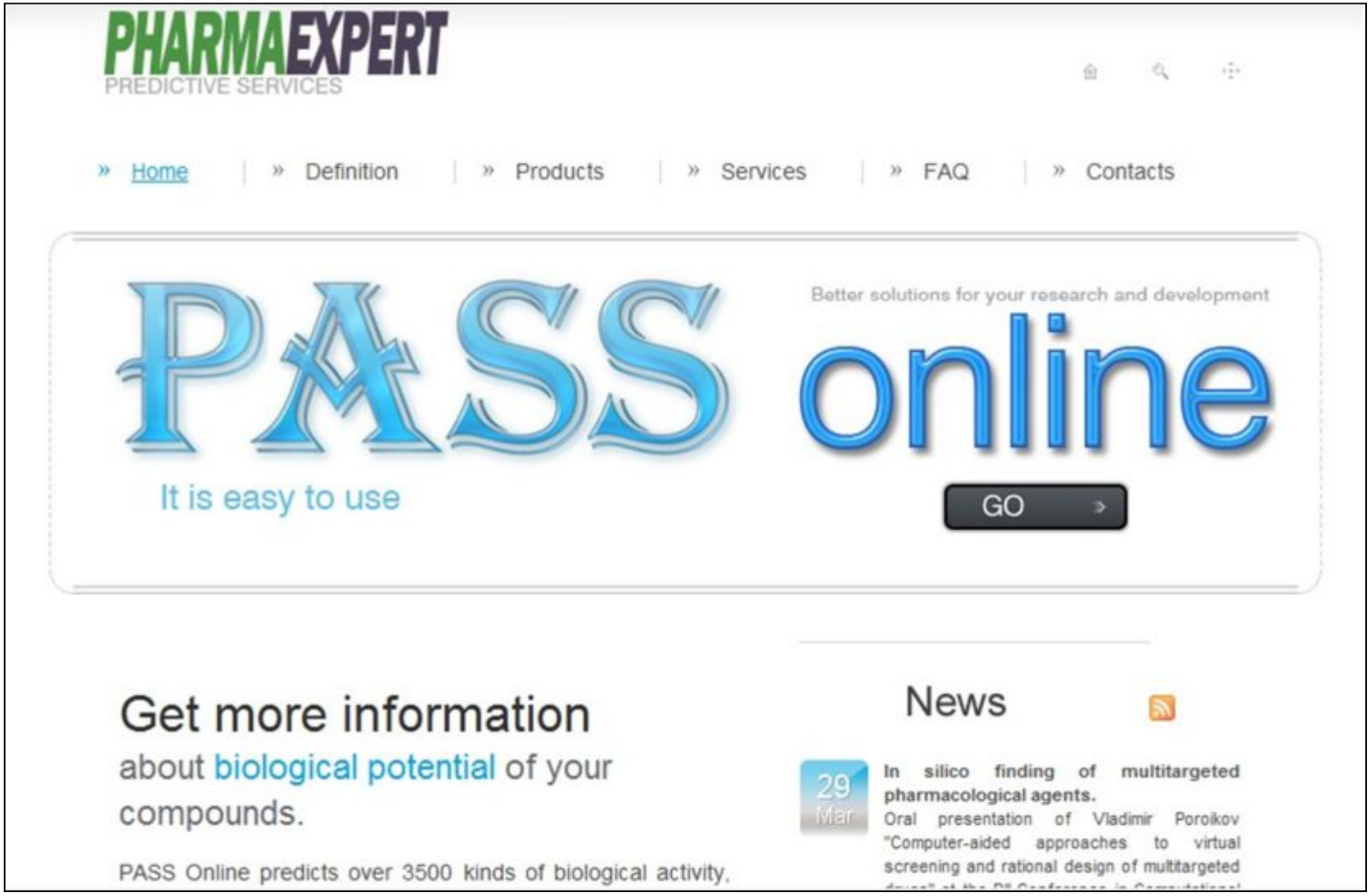
MNA Descriptors of Acetylsalicylate



Biological Activity Predicted for Acetylsalicylate



Online Biological Activity Prediction with PASS



http://pharmaexpert.ru/passonline

Input of the Structural Formula (Clopidogrel)

PASS PREDICTION

Please, enter your structure

Attach MOL file Обзор...

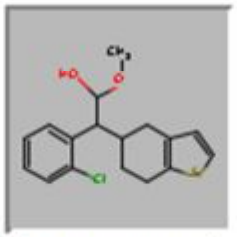
Get Prediction

To find out the information about MOL file, click here

OR

Use of Marvin Applet (http://www.chemaxon.com)

To run the **applet**, you need the Java x86 installed on your PC



Get Prediction

Results of Prediction for Clopidogrel

Results

All Pa>Pi Pa>30% Pa>70%

ok

Pa	Pi	Activity	
0,947	0,005	Neuroprotector	+
0,801	0,007	Antithrombotic	+
0,740	0,037	Amyotrophic lateral sclerosis treatment	
0,697	0,005	Platelet aggregation inhibitor	+
0,687	0,012	Acute neurologic disorders treatment	+
0,679	0,013	Atherosclerosis treatment	
0,625	0,009	Sleep disorders treatment	
0,597	0,010	Angiogenesis inhibitor	+
0,596	0,025	Analgesic	
0,667	0,099	Cardioprotectant	
0,634	0,082	Hepatotoxic	
0,605	0,075	Dopamine D4 agonist	
0,549	0,022	Antianginal	
0,536	0,032	Antipsoriatic	+
0,520	0,051	Antiarthritic	+
0,435	0,004	Platelet antagonist	+
0,423	0,009	Glutamate (mGluR1) antagonist	+
0,412	0,011	Glutamate (mGluR group I) antagonist	+
0,426	0,035	Monoamine uptake inhibitor	
0,410	0,030	Anticoagulant	+

. . .

Over Forty Publications with Independent Confirmation of PASS INet Predictions

European Journal of Medicinal Chemistry 44 (2009) 2075–2084

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

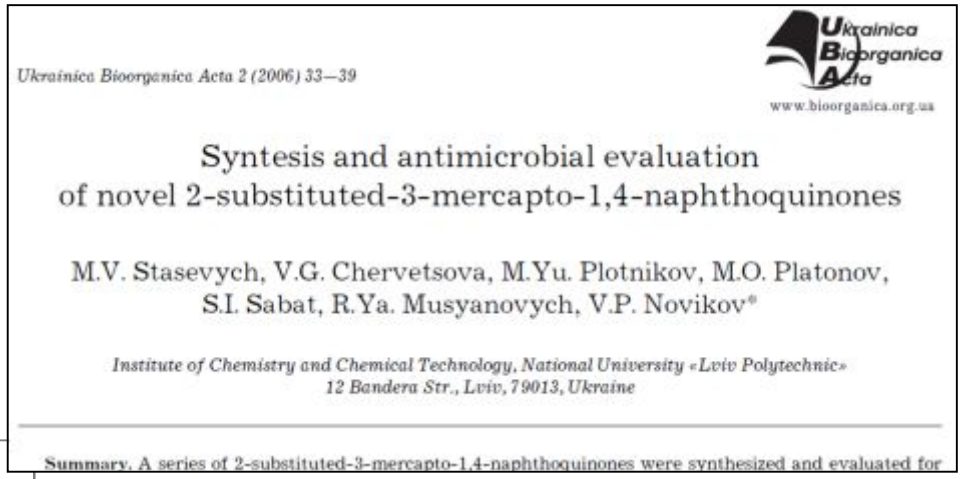
journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis and in vitro trichomonicidal, giardicidal and amebicidal activity of *N*-acetamide(sulfonamide)-2-methyl-4-nitro-1*H*-imidazoles☆

Emanuel Hernández-Núñez[a], Hugo Tlahuext[b], Rosa Moo-Puc[c], Héctor Torres-Gómez[a], Reyna Reyes-Martínez[b], Roberto Cedillo-Rivera[c], Carlos Nava-Zuazo[a], Gabriel Navarrete-Vazquez[a,*]

[a] Facultad de Farmacia, Universidad Autónoma del Estado de Morelos, Cuernavaca, Morelos 62209, Mexico
[b] Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Morelos, Cuernavaca, Morelos 62209, Mexico
[c] Unidad Interinstitucional de Investigación Médica, IMSS-Facultad de Medicina, UADY, Mérida, Yucatán 97000, Mexico



Ukrainica Bioorganica Acta 2 (2006) 33—39

Ukrainica Bioorganica Acta

www.bioorganica.org.ua

Syntesis and antimicrobial evaluation of novel 2-substituted-3-mercapto-1,4-naphthoquinones

M.V. Stasevych, V.G. Chervetsova, M.Yu. Plotnikov, M.O. Platonov, S.I. Sabat, R.Ya. Musyanovych, V.P. Novikov*

Institute of Chemistry and Chemical Technology, National University «Lviv Polytechnic»
12 Bandera Str., Lviv, 79013, Ukraine

Summary. A series of 2-substituted-3-mercapto-1,4-naphthoquinones were synthesized and evaluated for

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Bioorganic & Medicinal Chemistry Letters

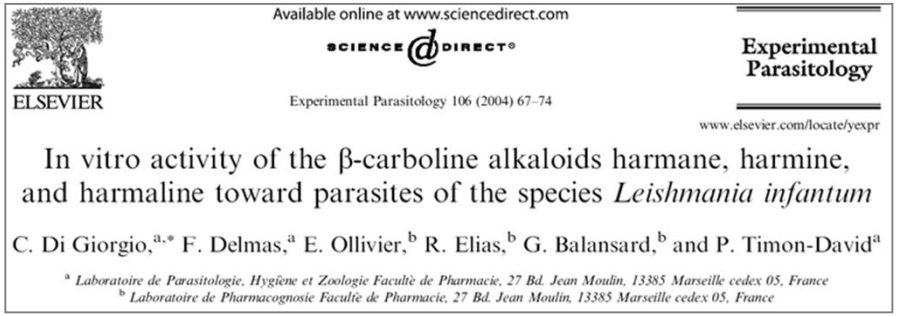
ELSEVIER

Bioorganic & Medicinal Chemistry Letters xxx (2005) xxx–xxx

Quinazolines revisited: search for novel anxiolytic and GABAergic agents

R. K Goel,[a,*] Vipan Kumar[b] and M. P. Mahajan[b,*]

[a]*Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar 143 005, India*
[b]*Department of Applied Chemistry, Guru Nanak Dev University, Amritsar 143 005, India*



Available online at www.sciencedirect.com

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Experimental Parasitology

ELSEVIER

Experimental Parasitology 106 (2004) 67–74

www.elsevier.com/locate/yexpr

In vitro activity of the β-carboline alkaloids harmane, harmine, and harmaline toward parasites of the species *Leishmania infantum*

C. Di Giorgio,[a,*] F. Delmas,[a] E. Ollivier,[b] R. Elias,[b] G. Balansard,[b] and P. Timon-David[a]

[a] *Laboratoire de Parasitologie, Hygiène et Zoologie Faculté de Pharmacie, 27 Bd. Jean Moulin, 13385 Marseille cedex 05, France*
[b] *Laboratoire de Pharmacognosie Faculté de Pharmacie, 27 Bd. Jean Moulin, 13385 Marseille cedex 05, France*

European Journal of Medicinal Chemistry 44 (2009) 2459–2467

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

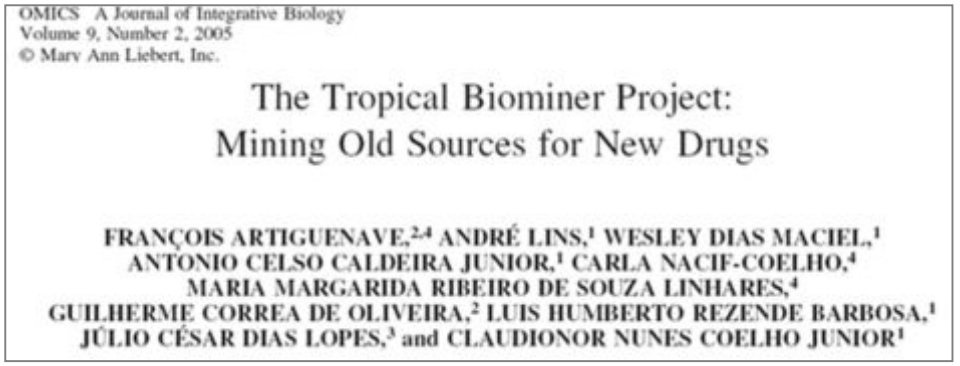
journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Photo-inducible cytotoxic and clastogenic activities of 3,6-di-substituted acridines obtained by acylation of proflavine

Yohann Benchabane[b], Carole Di Giorgio[a,*], Gérard Boyer[b], Anne-Sophie Sabatier[a], Diane Allegro[c], Vincent Peyrot[c], Michel De Méo[a]

[a] *Laboratoire de Biopharmacologie et Mutagenèse Environnementale (EA 3784, FR 3098 – ECCOREV), Université Aix-Marseille, Faculté de Pharmacie, 27 Bd Jean Moulin, 13385 Marseille, Cedex 05, France*
[b] *Laboratoire ITE, case 552, (UMR2 – UMR 6263) – Université Paul Cézanne, Faculté St Jérôme, 13397 Marseille, Cedex 20, France*
[c] *CRMO (IFR 88-ESR – Université Aix-Marseille, Faculté de Pharmacie, 27 Bd Jean Moulin, 13385 Marseille, Cedex 05, France*



OMICS A Journal of Integrative Biology
Volume 9, Number 2, 2005
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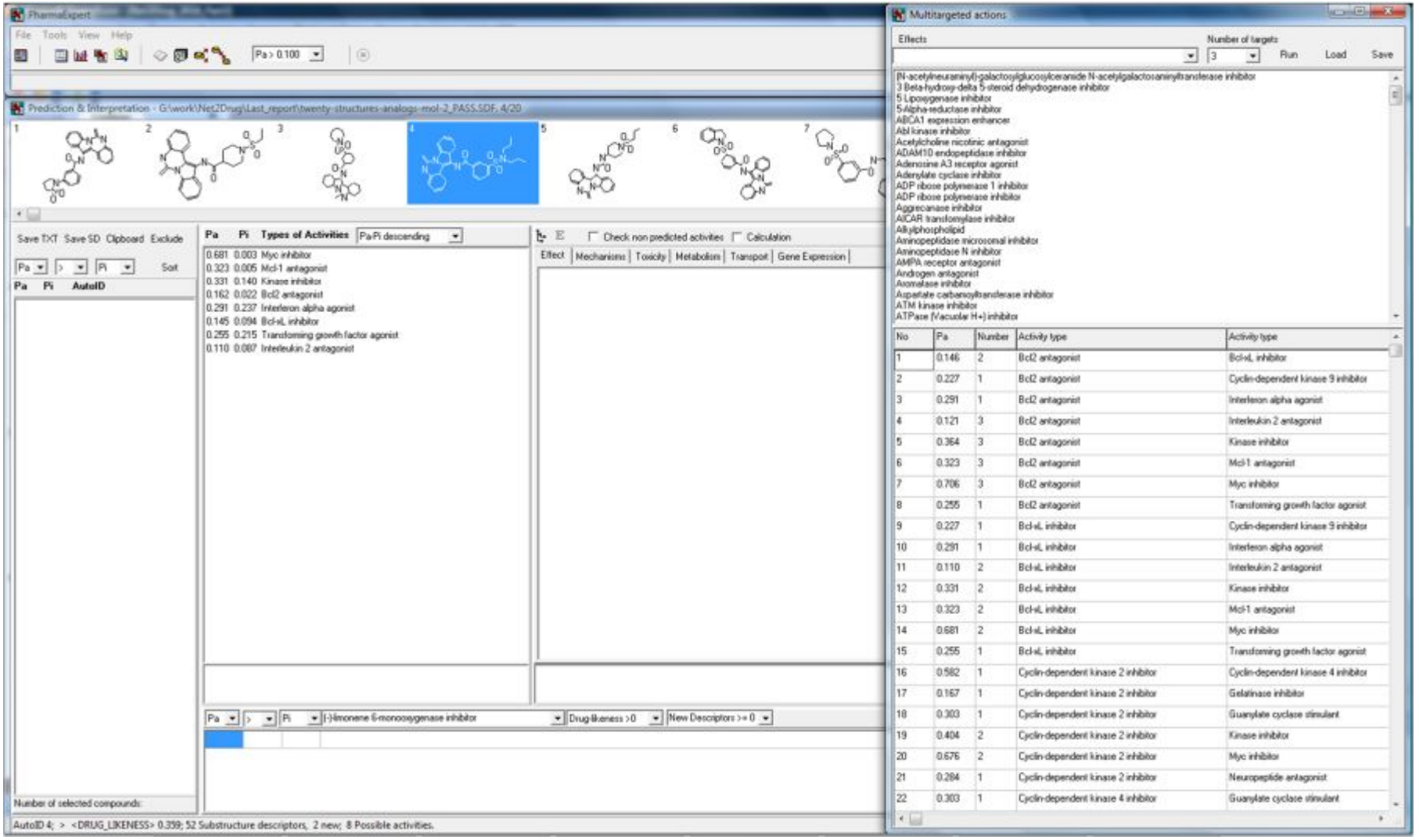
The Tropical Biominer Project: Mining Old Sources for New Drugs

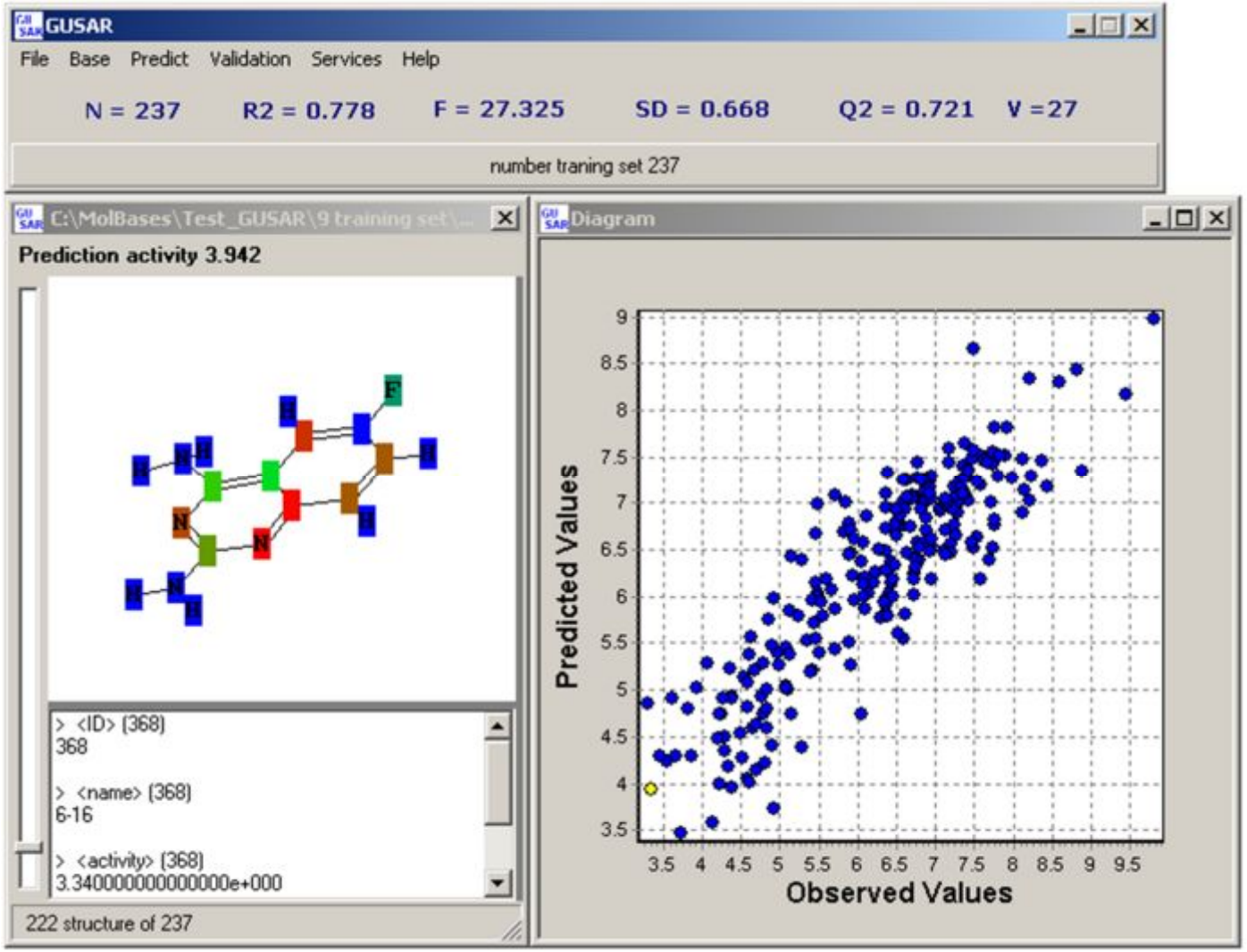
FRANÇOIS ARTIGUENAVE,[2,4] ANDRÉ LINS,[1] WESLEY DIAS MACIEL,[1] ANTONIO CELSO CALDEIRA JUNIOR,[1] CARLA NACIF-COELHO,[4] MARIA MARGARIDA RIBEIRO DE SOUZA LINHARES,[4] GUILHERME CORREA DE OLIVEIRA,[2] LUIS HUMBERTO REZENDE BARBOSA,[1] JÚLIO CÉSAR DIAS LOPES,[3] and CLAUDIONOR NUNES COELHO JUNIOR[1]

For review see: Geronikaki A. et al. *SAR & QSAR Environ. Res.*, 2008, 19, 27.

PharmaExpert: Selection of Multitargeted Ligands



GUSAR: General Unrestricted Structure-Activity Relationships



Filimonov D.A., et al. (2009). *SAR and QSAR Environ. Res.*, 20 (7-8), 679-709.

Multitargeted QSAR

GUSAR ONLINE

RELIABLE QUANTITATIVE-STRUCTURE ACTIVITY RELATIONSHIPS FOR YOUR CHEMICAL COMPOUNDS

WWW.PHARMAEXPERT.RU

GUSAR | QSAR METHOD | APPLICABILITY DOMAIN | CONSENSUS | REFERENCES

Acute Rat Toxicity | Antitargets | Environmental

SOLUTIONS
FOR YOUR RESEARCH

DRAW STRUCTURE

APPROACH TO YOUR QSAR MODELLING

GUSAR software was developed to create QSAR/QSPR models on the basis of the appropriate training sets represented as SDfile contained data about chemical structures and endpoint in quantitative terms.

Java

http://pharmaexpert.ru/gusar

Outline

- Biological activity: many faces of the entity
- **Identification of the most promising targets**
  - **Net2Drug**
- Identification of the most promising lead compounds
  - **PASS**
  - **PharmaExpert**
  - **GUSAR**
- **Examples of applications**
- Summary

Finding of New Antihypertensive Agents with Dual Mechanisms of Action

About 30 mechanism of antihypertensive action was available in PASS in 2001.

Prediction of Biological Activity Spectra were performed for ~180,000 compounds from ChemBridge и AsInEx databases.

Compounds with predicted dual mechanisms of antihypertensive action were identified.

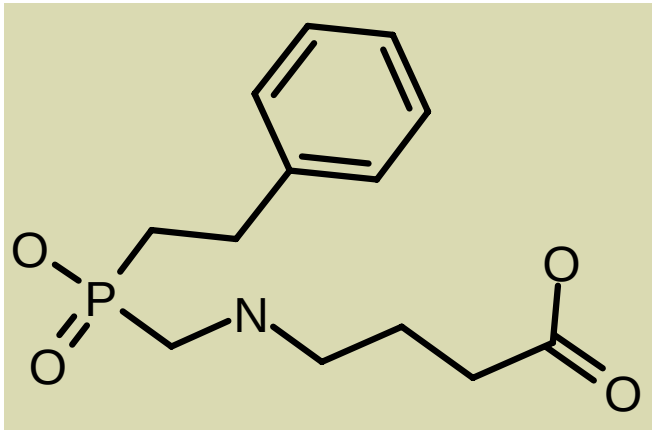
Four selected compounds were tested *in vitro* as inhibitors of ACE and NEP.

Some unknown combinations of the antihypertensive mechanisms were found.

Lagunin A.A. et al. J. Med. Chem., 2003, *46*, 3326.

All four studied compounds were shown to be the inhibitors of both ACE and NEP with IC_{50} in range 10^{-7} - 10^{-9} M.

1



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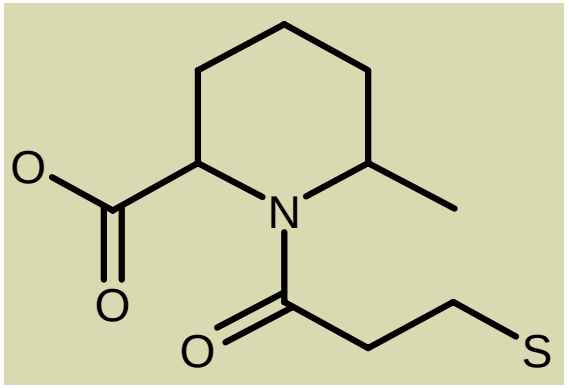

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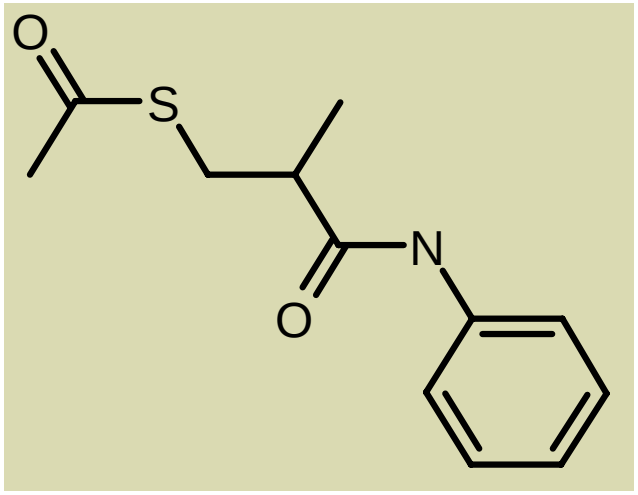

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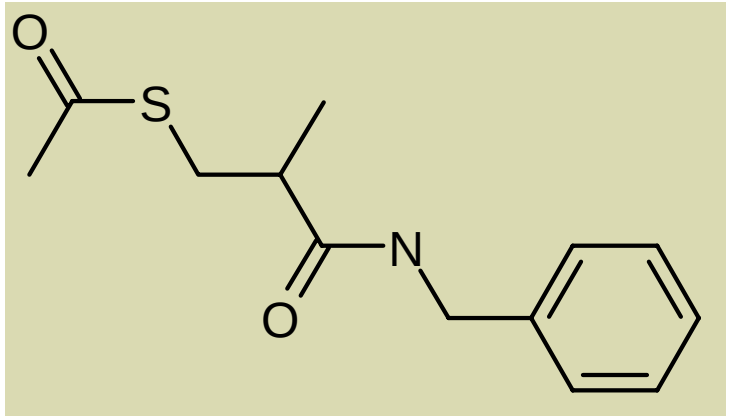

Lagunin A.A. et al. J. Med. Chem., 2003, *46*, 3326.

ChemNavigator Library: The Biggest Source of Commercially Available Samples

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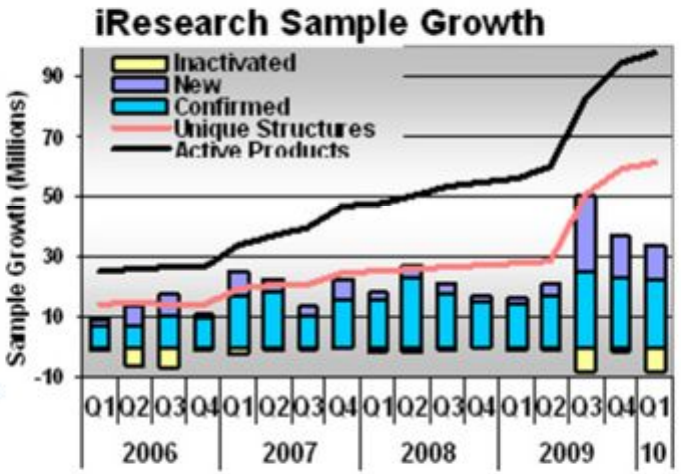
iResearch™ Library

The iResearch Library is ChemNavigator's up-to-date compilation of commercially accessible screening compounds from international chemistry suppliers. The database currently tracks over 91.5 million chemical samples. Database licenses include access to regular updates, sourcing information, and ChemNavigator's optional Chemistry Procurement Service. The database may be licensed on CD/DVD ROM or accessed through an on-line iResearch System subscription.

Sample Growth

Over the past 3 years the number of chemical samples registered into the iResearch Library has grown to over 91.5 Million chemical samples.



Update Frequency

The iResearch Library is updated on a weekly basis. We process over 1 million sample record updates per month to provide our clients the most comprehensive and up-to-date view of chemistry for drug discovery.

iResearch Library Facts

Over **91.5** million chemical structures (over **55.3** million unique)

More than **301** chemistry suppliers represented

Broad diversity (more than **56000** unique ring systems)

Database represents current view of commercial compounds

Suppliers

Chemical suppliers, Looking to grow your chemistry business? Over 30 commercial pharmaceutical research organizations use the iResearch Library to identify chemistry for their research programs.

Read more about the ChemNavigator suppliers.

Finding of Multitargeted Anticancer Agents in ChemNavigator Library

PASS prediction of selected anticancer activities were executed for 24 mln chemical compounds from ChemNavigator library (http://chemnavigator.com).

About 335,000 chemical compounds were identified as probable anticancer hits at cutoff Pa > 50%.

Hits for 23 double and 4 triple combinations of targets with Pa>50% were found (~6,500 compounds).

Sixteen GUSAR models were applied for identification of probable mechanisms of action.

Net2Drug program was used for the analysis of double and triple nodes' blockade influence on the network behavior.

64 chemical compounds were selected on the basis of PASS predictions; 26 samples were purchased for anticancer testing in Karolinska Institute (Sweden).

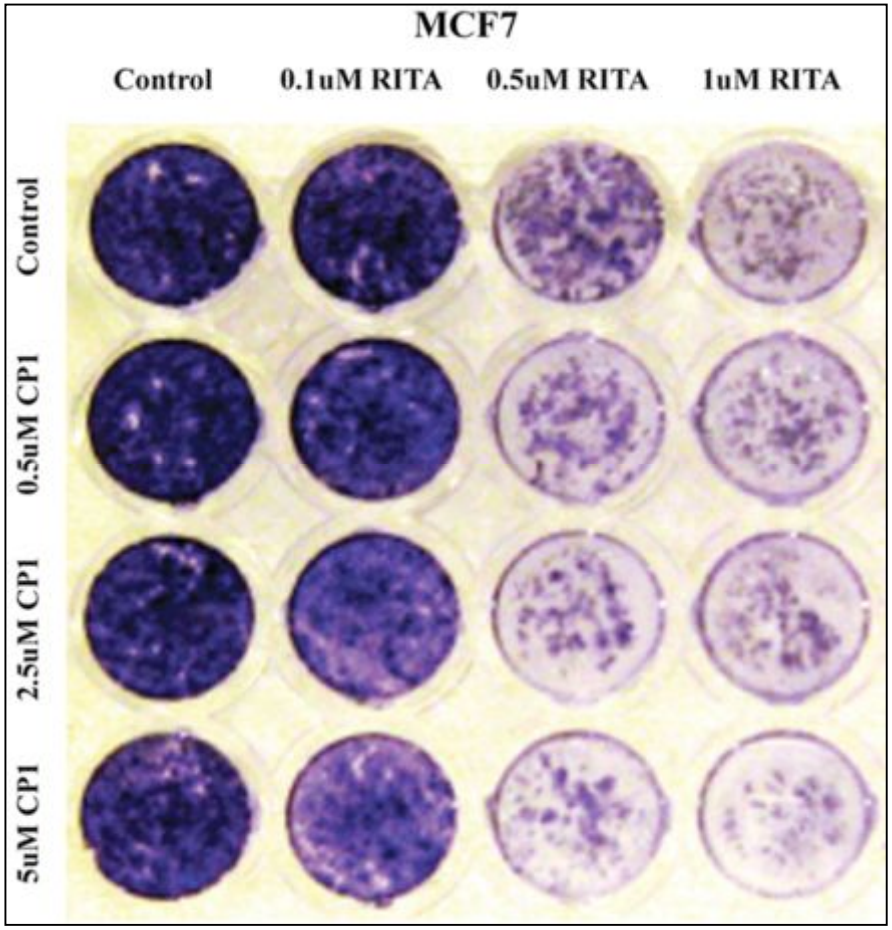
Results of Biological Testing in Cancer Cell Lines

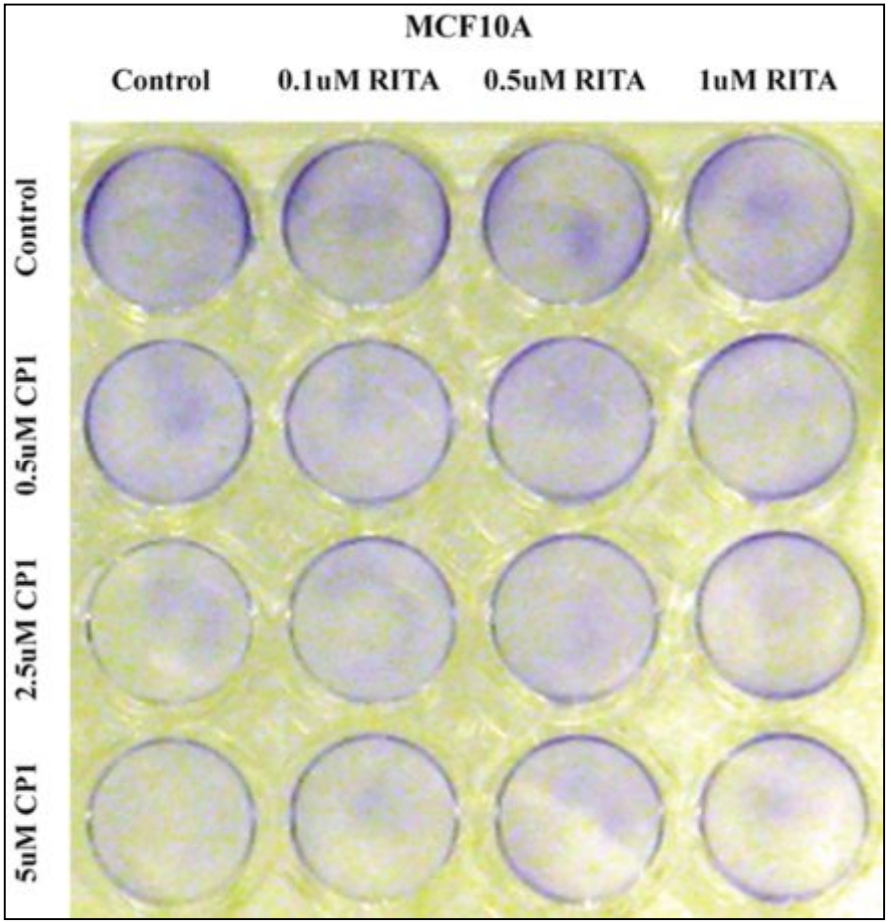
Out of 16 soluble compounds only one (Molecule I, CPI) showed growth suppression in 3 different breast cancer cell lines - at 10 uM. Quite good killing of breast cancer cells, but still 1 uM RITA was much better (it was used in parallel as a positive control). The effect appears to be p53-independent (kills p53-null colon cancer cells) and it does not affect the growth of non-transformed mammary epithelial cells.

One more compound (Molecule II) could be interesting - but not in breast cancer. Out of panel of 7 different cancer lines it killed only melanoma cells. It kills only melanoma cells without any effects in other cell lines.

Galina Selivanova, Karolinska Institute, Sweden

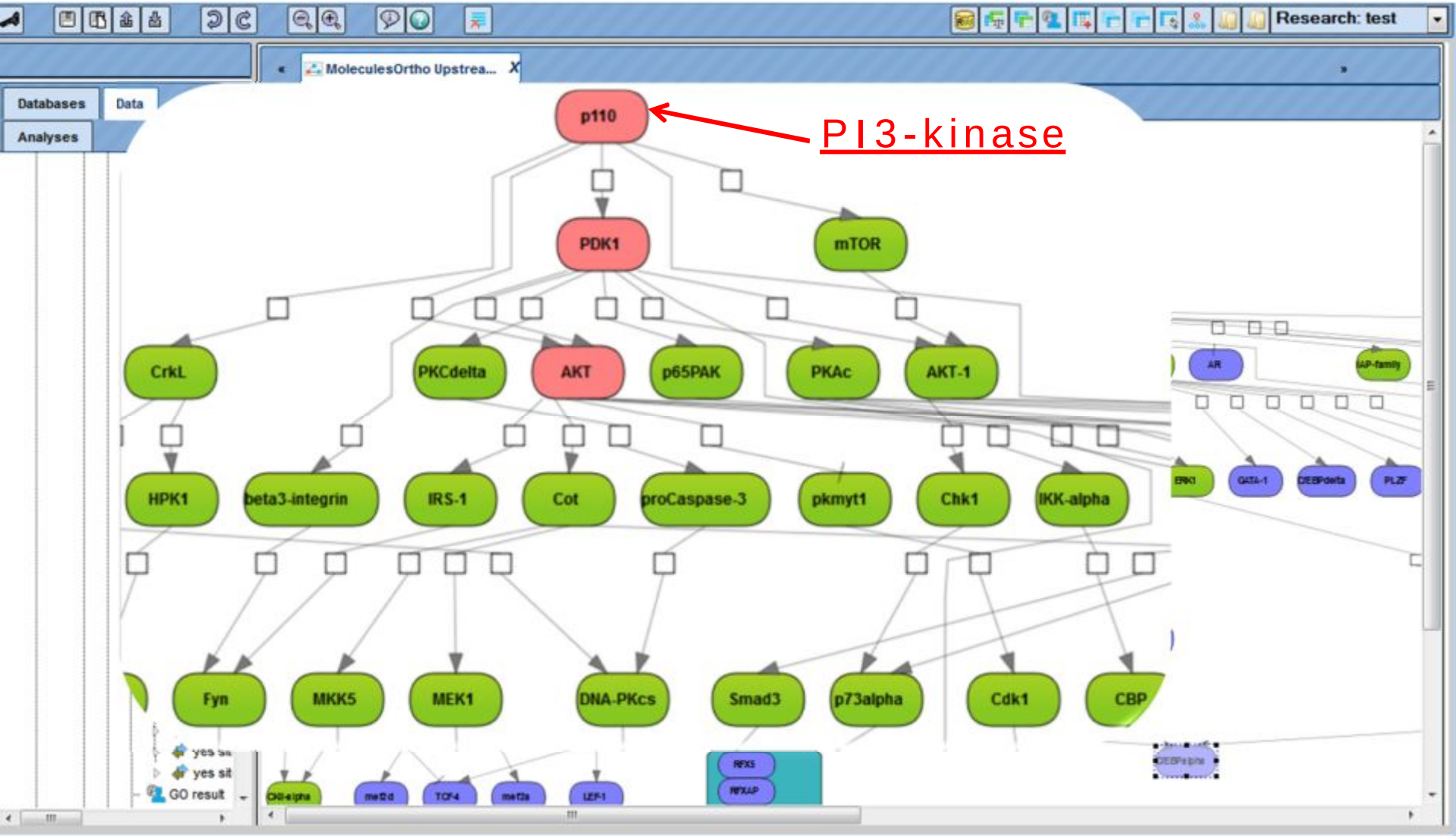
Synergistic effect was observed between CPI and Rita in several breast cancer cell lines, but not in non-transformed mammary epithelial cell line



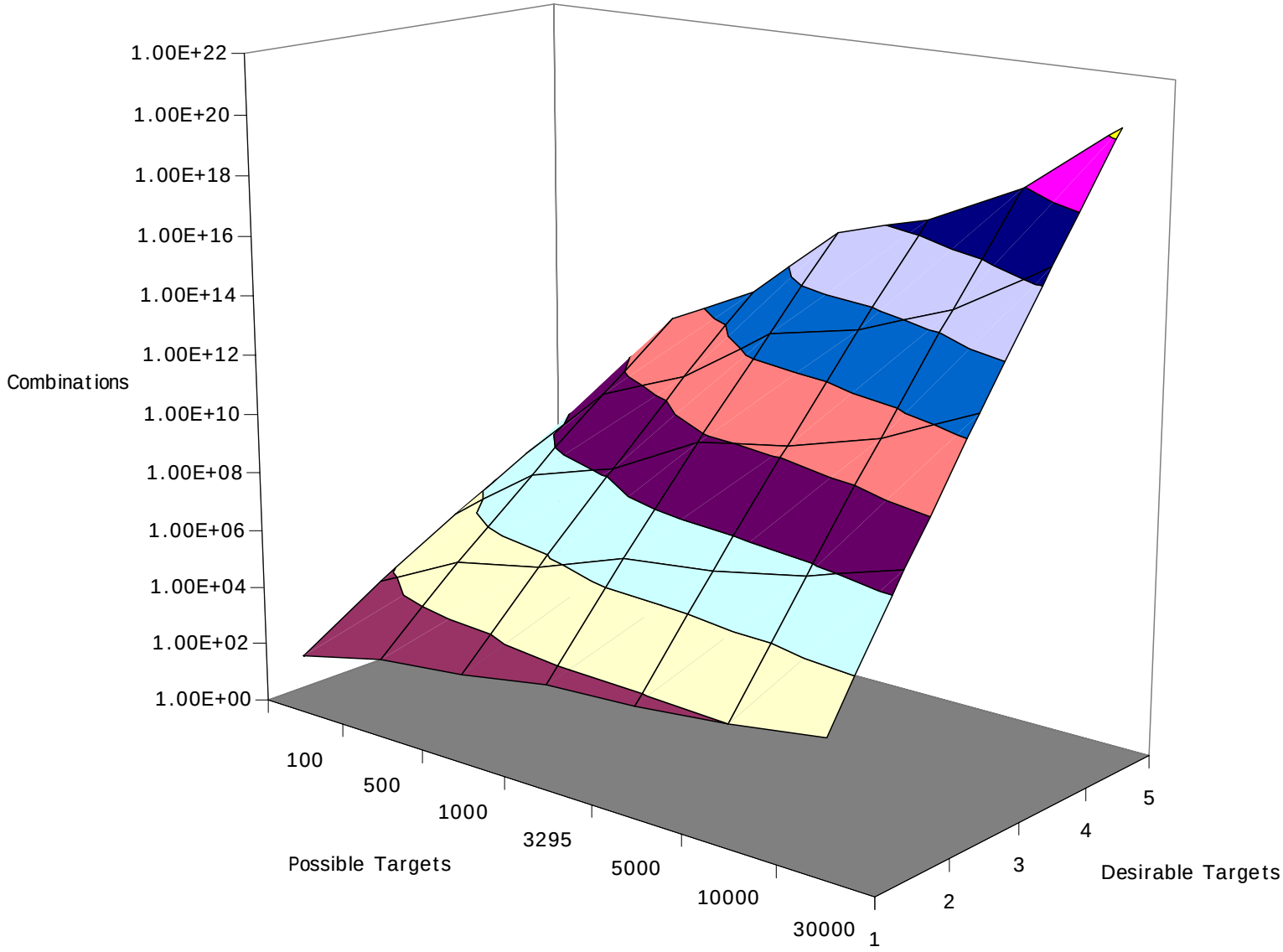


Galina Selivanova, Karolinska Institute, Sweden

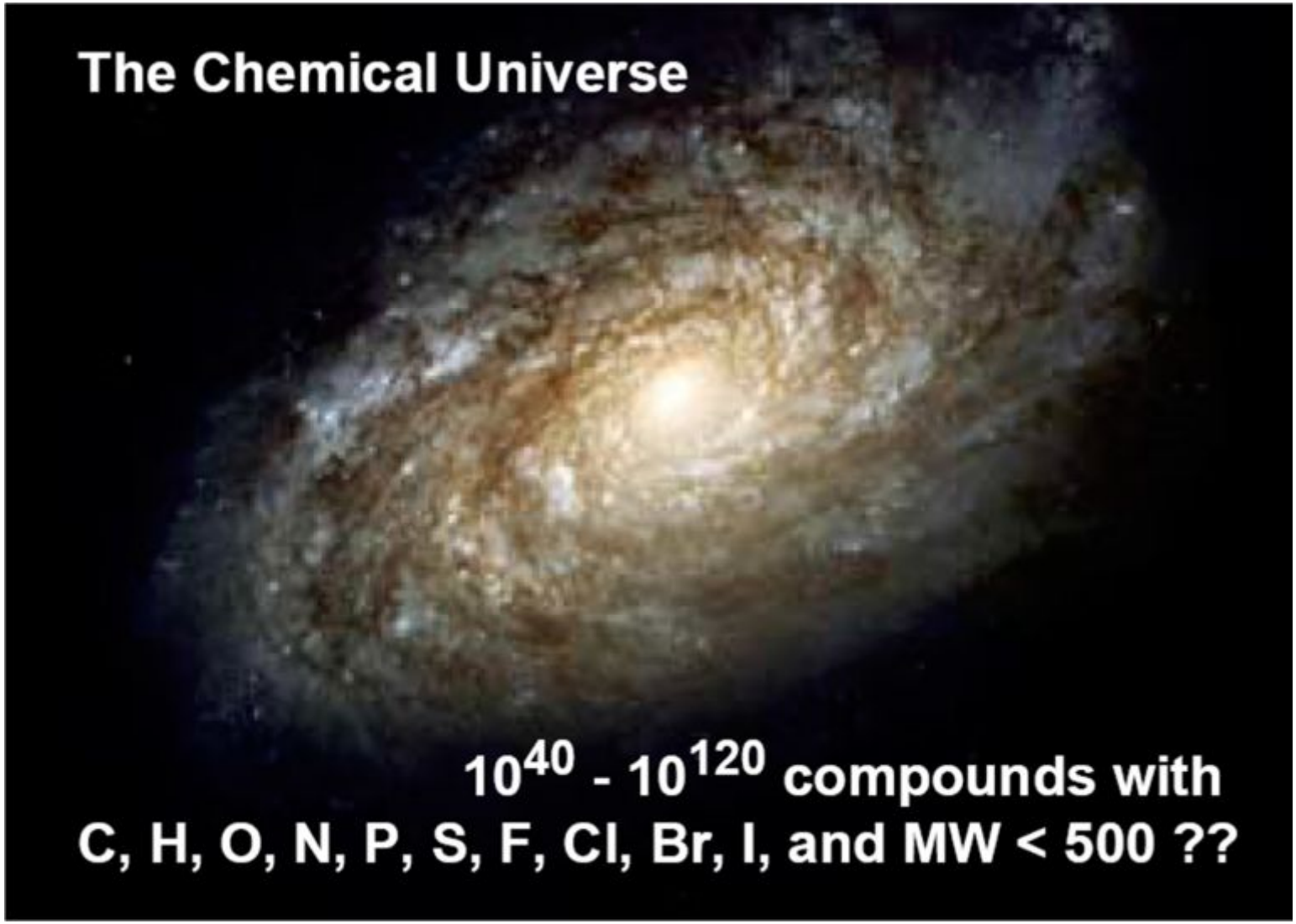
Molecular mechanisms of Rita action and potential target proteins for a complementary compound



Targets' Combinatorics: N!/((N-M)!M!)



Chemogenomics: Chemical Space (Estimated)



H. Kubinyi, 2004

Influence of Individual Atoms on a Particular Activity

For each atom in a molecule all MNA descriptors are generated. Using these descriptors for each particular activity Pa и Pi values are calculated. Each atom is colored in accordance with the following:

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

This can be interpreted in the following way:

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

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

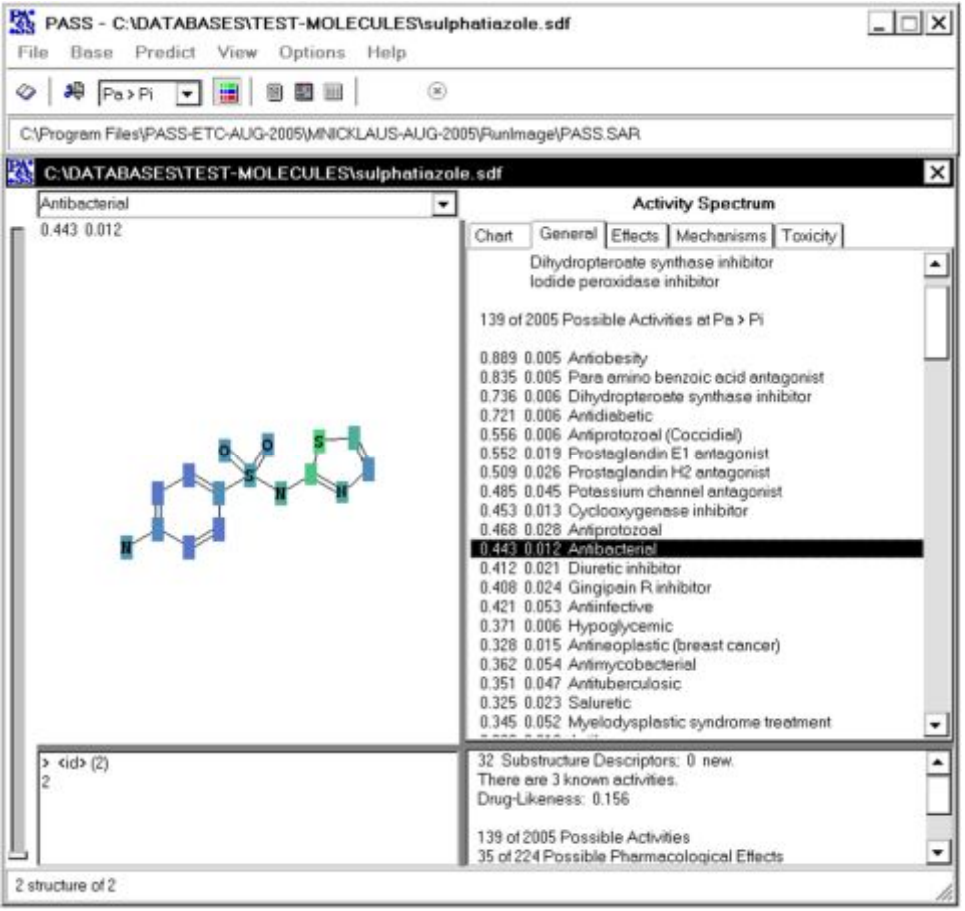
If Pa = 0 and Pi = 0, then Red = 0.3, Green = 0.3, Blue = 1 – bright blue color;

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

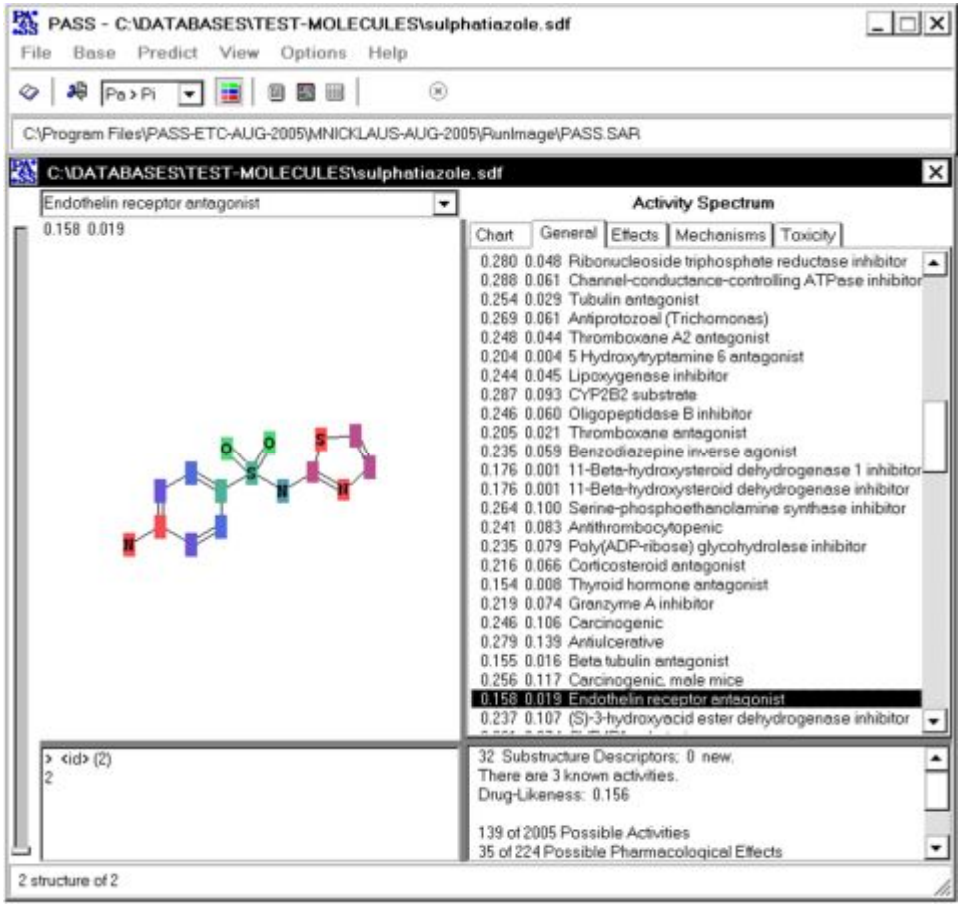
Example: sulfathiazole has antibacterial activity, and also it is a weak antagonist of ET_A receptors

PASS PREDICTIONS

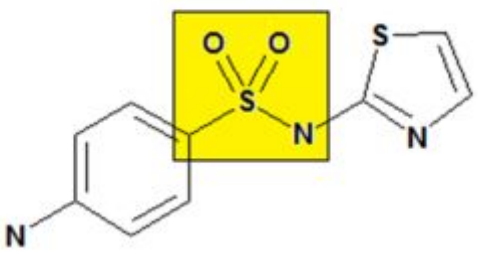
Antibacterial Activity

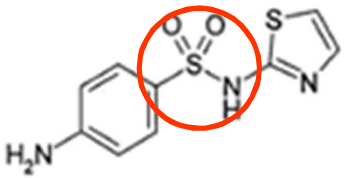


ET_A Receptor Antagonist

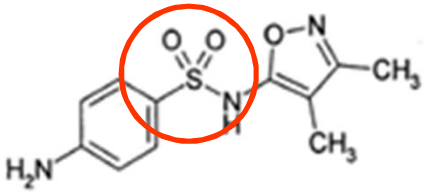


The fragment of sulfathiazole identified by PASS as having "positive" influence on ET_A antagonistic activity:

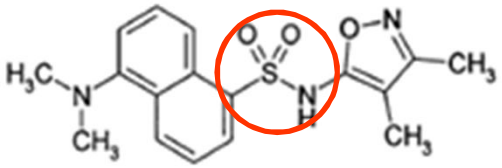




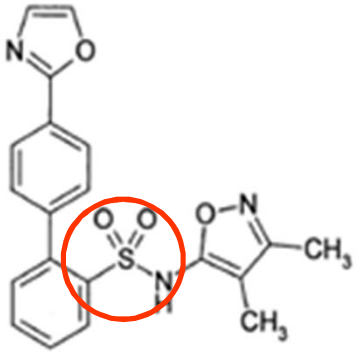
1 sulfathiazole
ET_A IC_{50} = 69 μM



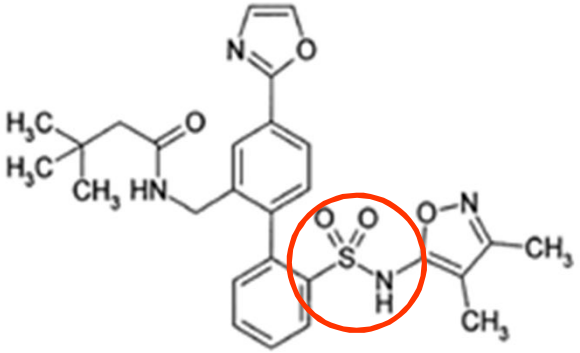
2 sulfisoxazole
ET_A IC_{50} = 0.78 μM



3 BMS-182874
ET_A IC_{50} = 0.15 μM



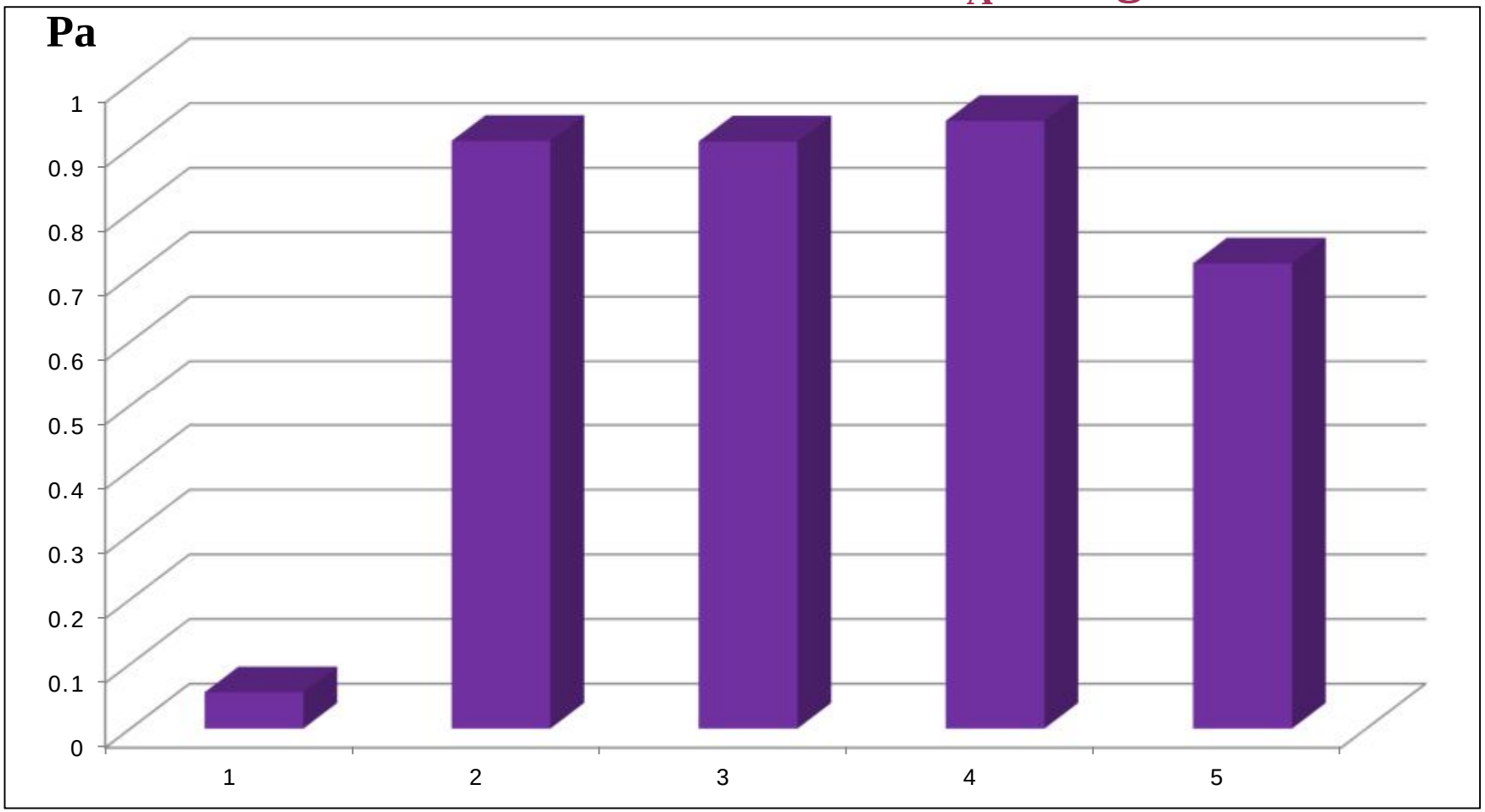
4 BMS-193884
ET_A Ki = 1.4 nM

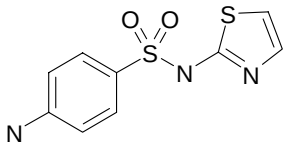


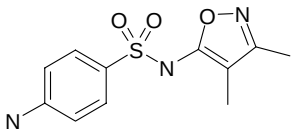
5 BMS-207940
ET_A Ki = 0.010 nM

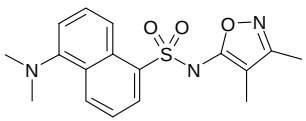
Wermuth C. J. Med. Chem., 2004, 47, 1303-1314.

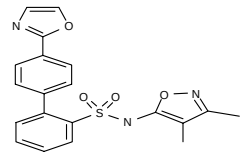
From Sulfathiazole to Potent ET_A Antagonist

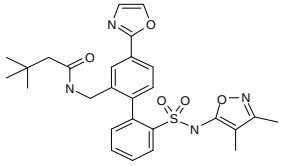












IC_{50}: **60 µM** **0.78 µM** **0.15 µM** **1.4 nM** **0.01 nM**

Afternoon session, 16:00-16:15

Olga Filz, IBMC

In silico fragment-based design of novel anti-inflammatory agents

Summary

1. **Multi-targeted agents may have advantages comparing to the ligands acting on a single target.**
2. **The most prospective targets and their combinations can be identified by different simulations of processes in regulatory pathways.**
3. **Compounds that likely have the targeted activities can be found by virtual screening in the databases of available samples.**
4. **In silico fragment-based design may be another prospective way of finding multitargeted ligands.**

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