

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

Vladimir Poroikov

**Department for Bioinformatics,
Institute of Biomedical Chemistry of Rus. Acad. Med. Sci.,
Pogodinskaya Street, 10, Moscow, 119121, Russia
E-mail: vladimir.poroikov@ibmc.msk.ru**

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**
- **Finding of multi-targeted pharmaceutical agents among the available samples or rational design *de novo*?**
- **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

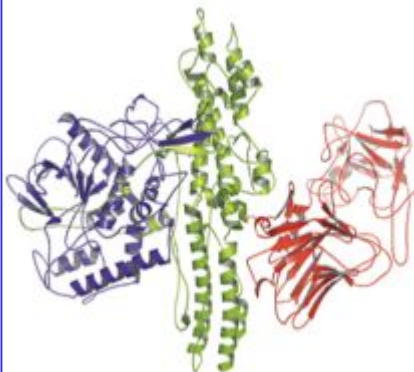
Botox

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 the treatment of crossed eyes and excessive sweating.

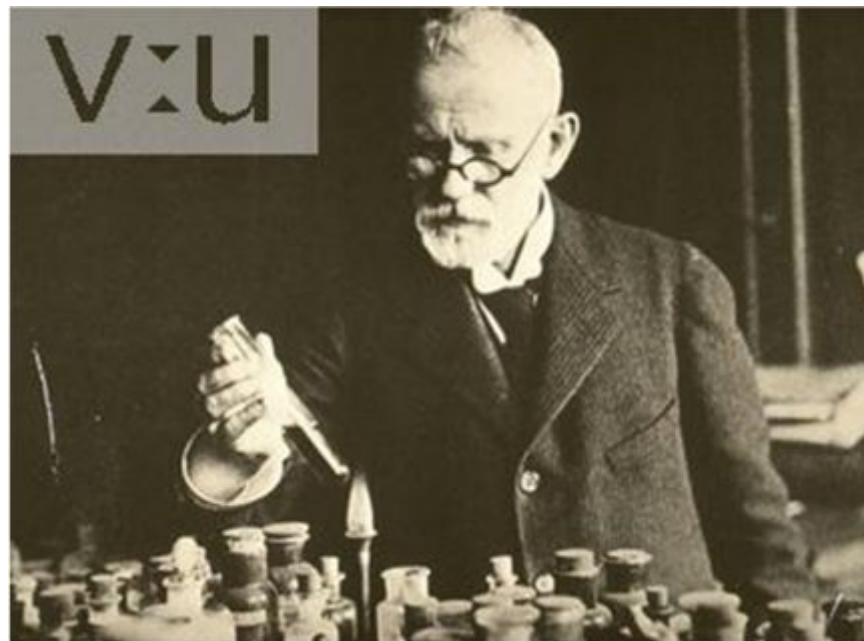
Allergan spokeswoman Caroline Van Hove notes that Botox "ranks as the number one minimally invasive cosmetic procedure in the U.S., according to recent statistics from the American Society of Plastic Surgeons." But its therapeutic uses outweigh the cosmetic, accounting for a 60% of Allergan's worldwide 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 Erlich, 1854-1915.

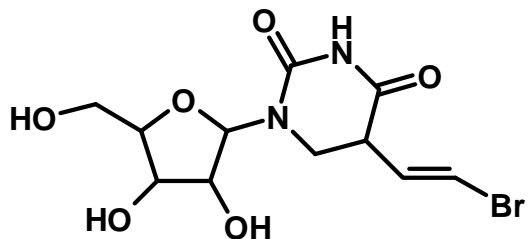
Beginning of XXI Century: Multitargeting Reality

For example, "... popular **statins**, prescribed to decrease pathologically elevated cholesterol levels, interfere with cholesterol biosynthesis at the C₅ 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.

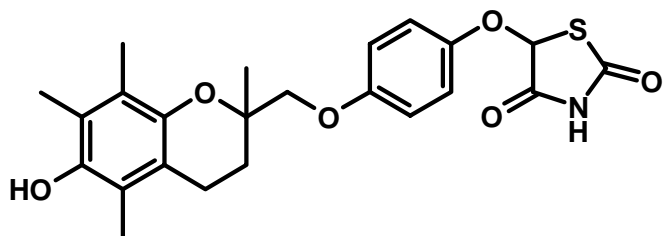
Examples of Adverse and Toxic Effects Due to the Multitargeted Drug Action

Structure → Biological Activity → Drug/Chemical



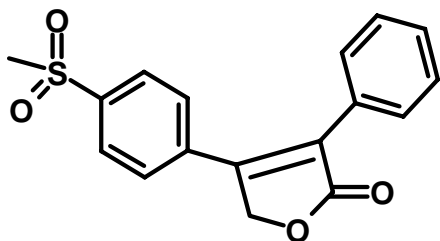
Antiviral,
Antitumor,
Neurotoxicity

Sorivudine



Antidiabetic,
Hepatotoxicity

Troglitazone



Antiarthritic,
Antiinflammatory,
COX-2 inhibitor,
Heart attack

Vioxx

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

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



update | discussion forum

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

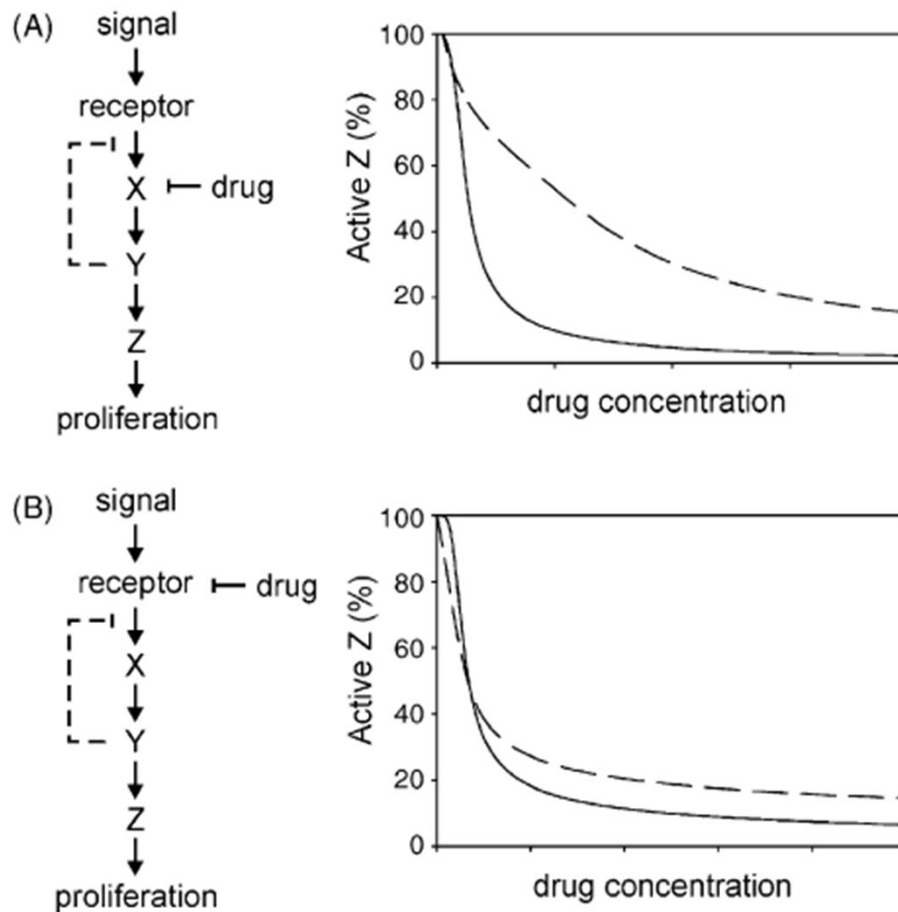
“In conclusion, the preparation of dual- or multiple-ligands on an almost rational basis is now conceivable and it can be expected that many of these molecules will yield drugs of superior clinical value compared with monotarget formulations”.

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

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.**

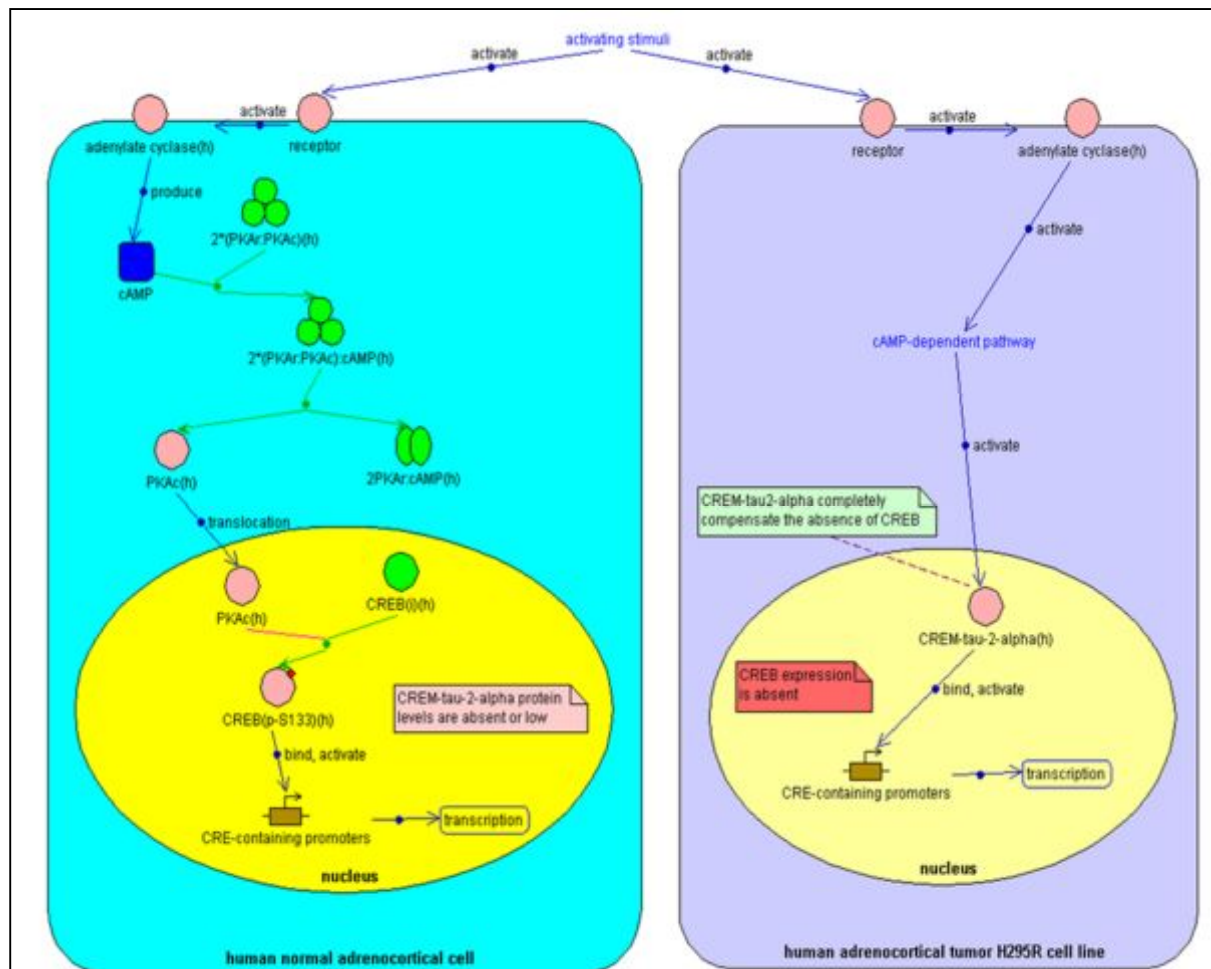
Simple Case of Negative Feedback



Loss of Expression of the Ubiquitous Transcription Factor cAMP Response Element-Binding Protein (CREB) and Compensatory Overexpression of the Activator CREM τ 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



Designed Multiple Ligands. An Emerging Drug Discovery Paradigm

Richard Morphy* and Zoran Rankovic

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 highly selective ligands. The physicochemical properties of designed multiple ligands were found to be less than those for preclinical compounds in general. These properties are controlled by the superfamily of targets 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}

Received 23rd March 2009

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DOI: 10.1039/b905821b

Opinion

The availability of interaction data has increased substantially in a total of 4767 unique interactions. On average every drug is currently connected to the network theory to the analysis of drug–target interactions. This implicitly on data comple-

Novel paradigms for drug discovery: computational multitarget screening

Ekachai Jenwitheesuk^{1,2}, Jeremy A. Horst^{1,3}, Kasey L. Rivas⁴, Wesley C. Van Voorhies^{1,3} and Ram Samudrala^{1,3}

nature
biotechnology

Synergistic drug combinations tend to improve therapeutically relevant selectivity

Joseph Lehar^{1–3}, Andrew S. Krueger², William Avery¹, Adrian M. Heilbut¹, Lisa M. Johansen¹, E. Roydon Price¹, Richard I. Rickles¹, Glenn F. Short III¹, Jane F. Staunton¹, Xiaowei Jin¹, Margaret S.

Drug combinations can limit the utility of a single drug and 94,110 drug combinations were generally more

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,*}

¹REQUIMTE/Faculty of Science, Chemistry Department, University of Porto 4169-007, Portugal, muntisa@gmail.com, almagalh@fc.up.pt

²Unit of Bioinformatics & Connectivity Analysis (UBICA), Institute of Industrial Pharmacy, and

Analysis of multiple compound–protein interactions reveals novel bioactive molecules

Hiroaki Yabuuchi^{1,5}, Satoshi Nijima^{1,5}, Hiromu Takematsu², Tomomi Ida¹, Takatsugu Hirokawa², Takafumi Hara⁴, Teppel Ogawa¹, Yohsuke Minowa¹, Gozoh Tsujimoto⁶ and Yasushi Okuno^{1,3*}

Cell

Items Bioscience for Drug Discovery, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan, ²Laboratory of Membrane Biology, Graduate School of Biosciences, Kyoto University, Kyoto, Japan, ³Chemical Protein Research Center, National Institute of Advanced Industrial Science and Technology, Tsukuba, Japan, ⁴Department of Cell Biology, Faculty of Science, Kyoto University, Kyoto, Japan, ⁵Department of Cell Biology, Faculty of Science, Kyoto University, Kyoto, Japan, ⁶Department of Cell Biology, Faculty of Science, Kyoto University, Kyoto, Japan

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

Author: Jing 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

J. Med. Chem. 2010, 53, 36

DOI: 10.1021/jm

Journal
Medicinal
Chemistry
Article

Bivalent β -Carbolines as Potential Multitarget Anti-Alzheimer Agents

¹Kai-Uwe Schmidtke,²Friedemann Gaube,³Dirk Schepmann,⁵Bernhard Wünsch,⁵Jörg Heilmann,¹and Thomas Winckler^{*,2}

¹Lehrstuhl für Pharmazeutische/ Medizinische Chemie, Friedrich-Schiller-Universität Jena, Germany, ²Lehrstuhl für Pharmazeutische Biologie, Friedrich-Schiller-Universität Jena, Semmelweisstrasse 10, D-07747 Jena, Germany, ³Lehrstuhl für Pharmazeutische und Medizinische Chemie der Westfälischen Wilhelms-Universität Münster, Germany, ⁴Lehrstuhl für Pharmazeutische Biologie, Universität Regensburg, Germany

July 4, 2010

Alzheimer's disease (AD) is a prevalent neurodegenerative disorder with multifactorial causes. The disease is characterized by a progressive loss of cognitive functions and requires multitargeted treatment. Inhibitors of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) improve cholinergic signaling in the central nervous system and thus AChE inhibitors are considered to be important for the treatment of AD. In addition, many other signaling pathways are involved in the pathogenesis of AD, including amyloid precursor protein and other signaling events.

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

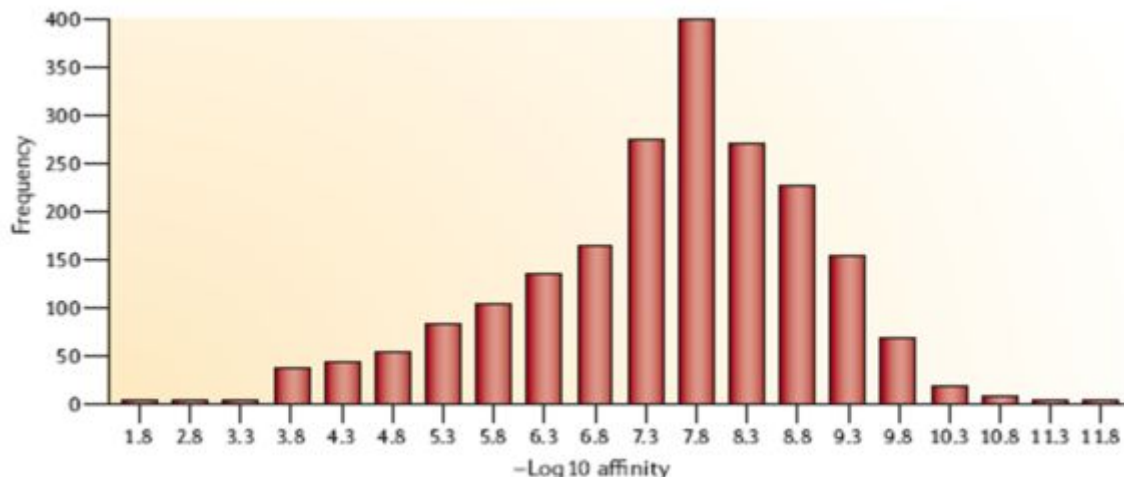
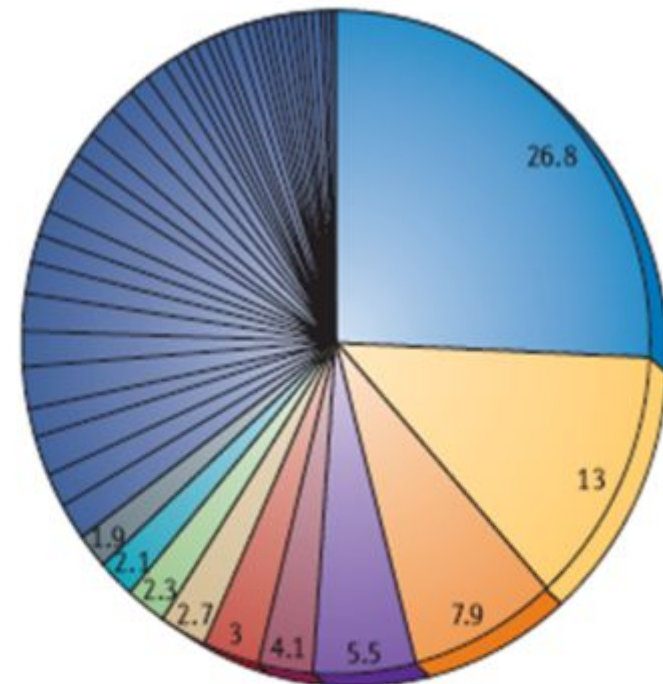
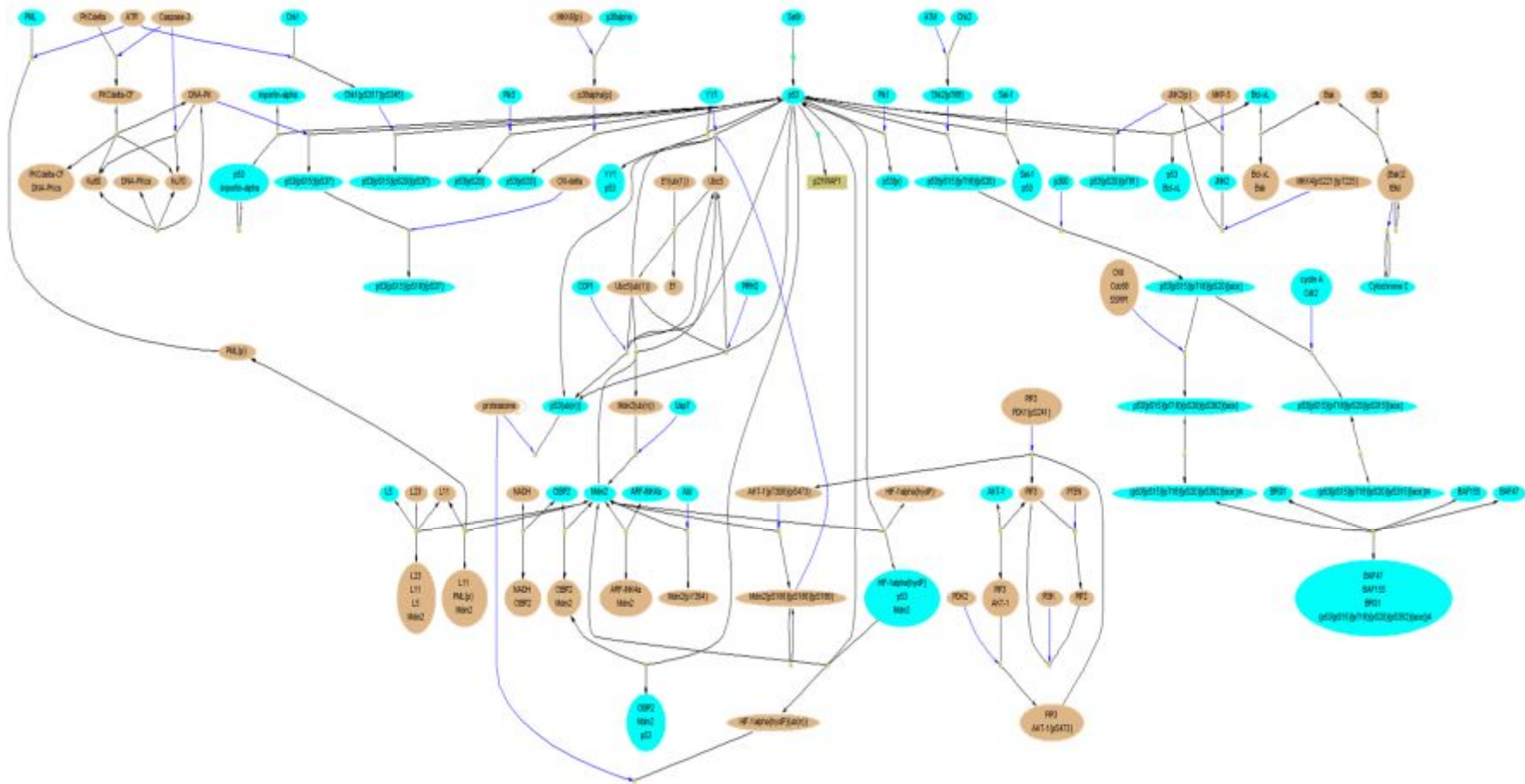


Figure 2 | Frequency distribution for small-molecule drug potencies.

- Rhodopsin-like GPCRs
- Nuclear receptors
- Ligand-gated ion channels
- Voltage-gated ion channels
- Penicillin-binding protein
- Myeloperoxidase-like
- Sodium: neurotransmitter symporter family
- Type II DNA topoisomerase
- Fibronectin type III
- Cytochrome P450

Search for New Targets in P53 Pathway Using Names of Known Targets as a Query



TRANSPATH Database (<http://www.biobase.de>)

***In silico* method for identification of promising anticancer drug targets[†]**

O.N. Koborova^{a*}, D.A. Filimonov^a, A.V. Zakharov^a, A.A. Lagunin^a, S.M. Ivanov^a,
A. Kel^b and V.V. Poroikov^a

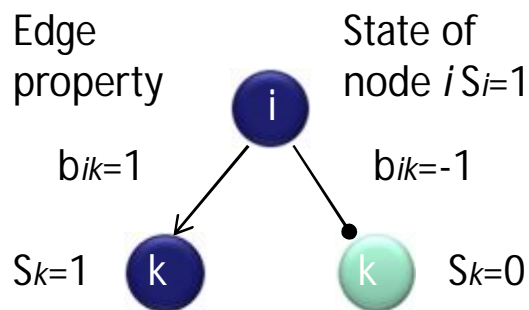
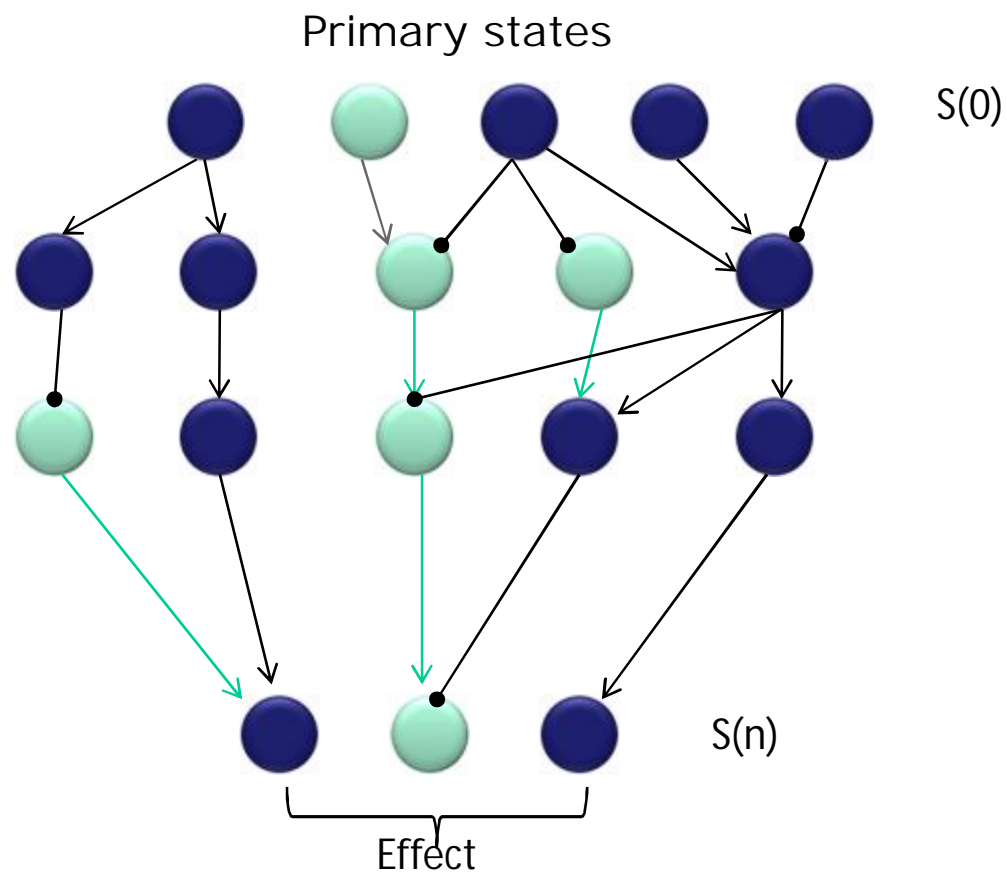
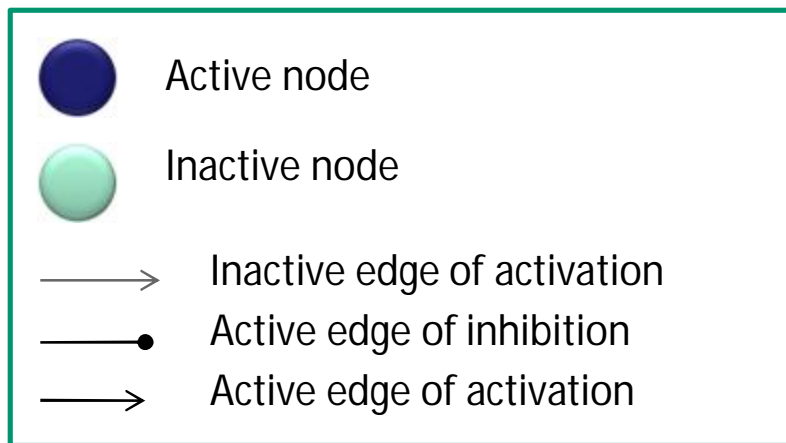
^a*Institute of Biomedical Chemistry of Russian Academy of Medical Sciences, Moscow, Russia;*

^b*BIOBASE GmbH, Wolfenbüttel, Germany*

(Received 7 July 2009; in final form 1 October 2009)

In recent years, the accumulation of the genomics, proteomics, transcriptomics data for topological and functional organization of regulatory networks in a cell has provided the possibility of identifying the potential targets involved in pathological processes and of selecting the most promising targets for future drug development. We propose an approach for anticancer drug target identification, which, using microarray data, allows discrete modelling of regulatory network behaviour. The effect of drugs inhibiting a particular protein or a combination of proteins in a regulatory network is analysed by simulation of a blockade of single nodes or their combinations. The method was applied to the four groups of breast cancer, HER2/neu-positive breast carcinomas, ductal carcinoma, invasive ductal carcinoma and/or a nodal metastasis, and to generalized breast cancer. As a result, some promising specific molecular targets and their combinations were identified. Inhibitors of some identified targets are known as potential drugs for therapy of malignant diseases; for some other targets we identified hits in the commercially available sample databases.

Dichotomic Modeling of Regulatory Networks in NetFlowEx program

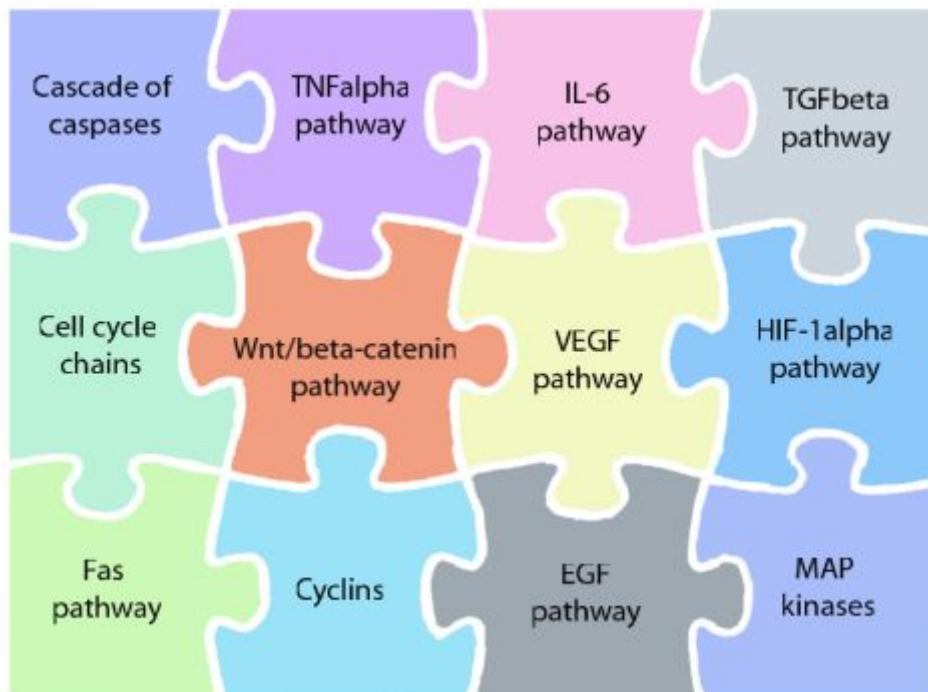


$$F_i(S_1, S_2, \dots, S_n) = \Theta(a_i + \sum_k S_k b_{ki})$$

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.

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			
	Cyclin B:CDK1 (G2/M phase)	SYK	N/A	SRC	N/A
Induction of apoptosis	Cytochrome C	SYK	N/A	N/A	N/A
		BCL-2			
	Caspase-3	N/A	N/A	RAF-1, GRB-2, PKC, RACK1	Alpha5 Beta1 Fibronectin receptor, Fibronectin
Induction of apoptosis	Caspase-3	MKK4, PI3K, MKK6, P38ALPHA, CRKL, HPK1			
		N/A	N/A	VEGF-A, VEGFR-2, HIF-1ALPHA	N/A

Known Functions of Novel Identified Targets

- **RACK1** has a role in protecting cancer cells from apoptosis by regulating the degradation of BimEL, which together with CIS could play an important role of drug resistance in chemotherapy.
- H-Ras-specific activation of Rac-**MKK3/6**-p38 pathway has a role in invasion and migration of breast epithelial cells.
- **CrkL** plays a specific role in integrin-induced migration as a downstream mediator of Src by activating small G proteins at focal adhesions.
- Growth factor-independent survival occurs during monocytic differentiation by caspase-mediated processing of **HPK1** towards HPK1-N.

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

PASS: Prediction of Activity Spectra for Substances

PASS - D:\AUREUS\Data Sets\Top 200 Drugs 2009.sdf

File Base Predict View Options Help

D:\PASS 2010\PASS10.SAR

D:\AUREUS\Data Sets\Top 200 Drugs 2009.sdf

5x5 4x4 3x3 2x2 GRAPH TEXT MNA

Activity Description

Purinergic P2Y12 antagonist

Substance that binds to purinergic P2Y12 receptor and prevents its stimulation.

SAR Base Information

Substances	266697
Descriptors	69734
Activity Types	5825
Selected Activity Types	4130
Average IEP	4.477, %
Prediction	<input checked="" type="checkbox"/> Enabled

Purinergic P2Y12 antagonist

Chart General Effects Mechanisms Toxicity Metabolism Genes Transporters

About PASS

PASS Prediction of Activity Spectra for Substances

Version 10.1 *Professional*

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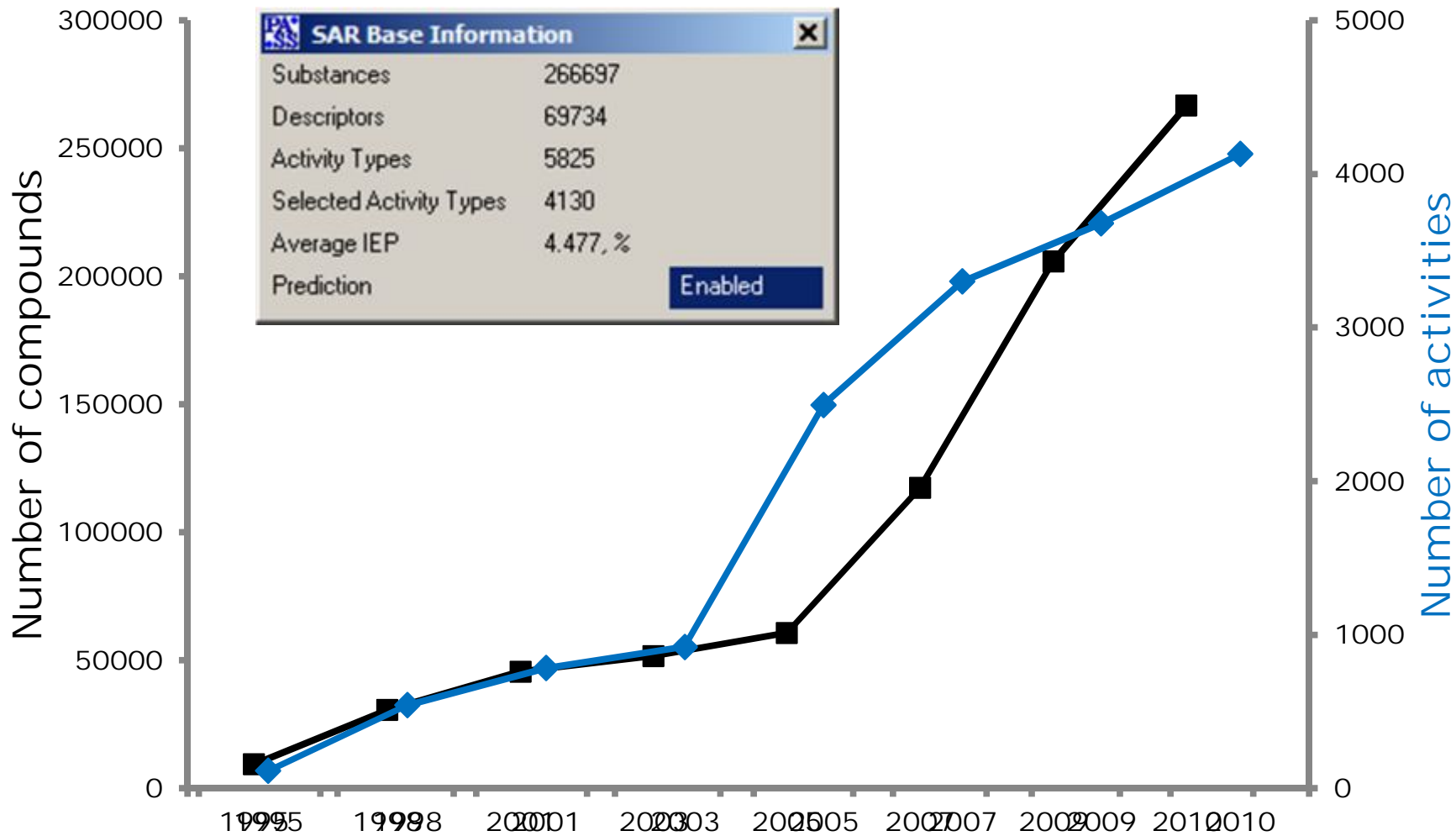
V. Poroikov, D. Filimonov & Associates

<http://www.ibmc.msk.ru/PASS>

- 53 of 501 Possible Pharmacological Effects
- 69 of 3295 Possible Molecular Mechanisms
- 4 of 57 Possible Side Effects and Toxicity
- 16 of 199 Possible Metabolism-Related Actions
- 3 of 29 Possible Gene Expression Regulation
- 1 of 49 Possible Transporters-Related Actions

29/154 0.868 0.001 Purinergic P2Y12 antagonist

PASS Training Set



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?

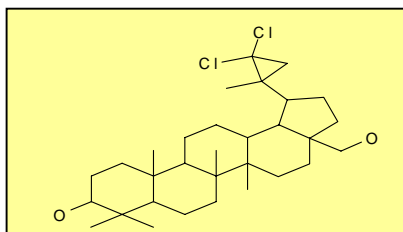
Structure of new compound



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

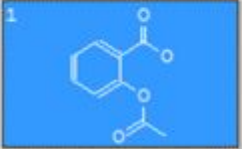
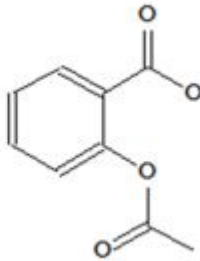


Structural Formula of Acetylsalicylate

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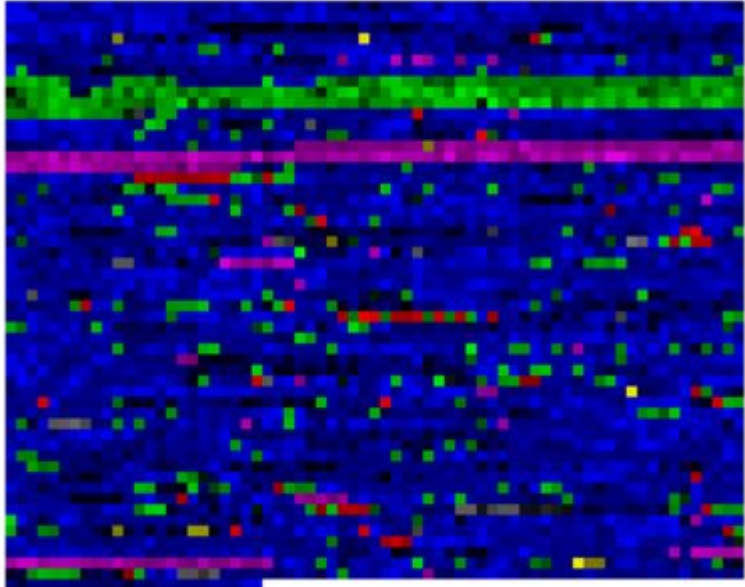
GRAPH | TEXT | MNA

1

No Selected Activity

Chart | General | Effects | Mechanisms | Toxicity | Metabolism | Genes | Transporters



25 Substructure Descriptors; 0 new.
There are 62 known activities.
Drug-Likeness: 0.554

1217 of 3750 Possible Activities
160 of 417 Possible Pharmacological Effects
937 of 3036 Possible Molecular Mechanisms
40 of 55 Possible Side Effects and Toxicity
75 of 196 Possible Metabolism-Related Actions
3 of 11 Possible Gene Expression Regulation
2 of 35 Possible Transporters-Related Actions

1/1

MOL File of Acetylsalicylate

C:\ACTUAL\DATABASES\TEST-MOLECULES\acetylsalicylate.mol

GRAPH TEXT MNA

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5 7 1 0 0 0 0
3 4 2 0 0 0 0
7 8 2 0 0 0 0
7 9 1 0 0 0 0
4 5 1 0 0 0 0
4 10 1 0 0 0 0
2 3 1 0 0 0 0
10 11 1 0 0 0 0
5 6 2 0 0 0 0
11 12 2 0 0 0 0
6 1 1 0 0 0 0
11 13 1 0 0 0 0
M END

```

No Selected Activity

Chart General Effects Mechanisms Toxicity Metabolism Genes Transporters

25 Substructure Descriptors: 0 new.
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160 of 417 Possible Pharmacological Effects
937 of 3036 Possible Molecular Mechanisms
40 of 55 Possible Side Effects and Toxicity
75 of 196 Possible Metabolism-Related Actions
3 of 11 Possible Gene Expression Regulation
2 of 35 Possible Transporters-Related Actions

1/1

MNA Descriptors of Acetylsalicylate

C:\ACTUAL\DATABASES\TEST-MOLECULES\acetylsalicylate.mol

GRAPH | TEXT | MNA

```

HC
HO
CHHHC
CHCC
CCCC
CCCC
CCCO
OHC
OC
OCC
C(C(CC-H)C(CC-H)-H(C))
C(C(CC-H)C(CC-C)-H(C))
C(C(CC-H)C(CC-C)-O(C-C))
C(C(CC-H)C(CC-O)-H(C))
C(C(CC-H)C(CC-O)-C(C-O-O))
-H(C(CC-H))
-H(C(H-H-H-C))
-H(O(H-C))
-C(C(CC-C)-O(H-C)-O(C))
-C(H(-C)H(-C)H(-C)-C(-C-O-O))
-C(C(H-H-H-C)-O(C-C)-O(C))
-O(C(CC-O)-C(-C-O-O))
-O(H(-O)-C(C-O-O))
-O(-C(C-O-O))
-O(-C(-C-O-O))
  
```

No Selected Activity

Chart | General | Effects | Mechanisms | Toxicity | Metabolism | Genes | Transporters

25 Substructure Descriptors; 0 new.
There are 62 known activities.
Drug-Likeness: 0.554

1217 of 3750 Possible Activities
160 of 417 Possible Pharmacological Effects
937 of 3036 Possible Molecular Mechanisms
40 of 55 Possible Side Effects and Toxicity
75 of 196 Possible Metabolism-Related Actions
3 of 11 Possible Gene Expression Regulation
2 of 35 Possible Transporters-Related Actions

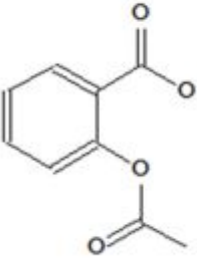
1/1

Biological Activity Predicted for Acetylsalicylate

C:\ACTUAL\DATABASES\TEST-MOLECULES\acetylsalicylate.mol

GRAPH | TEXT | MNA

1



No Selected Activity

Chart General | Effects | Mechanisms | Toxicity | Metabolism | Genes | Transporters

1217 of 3750 Possible Activities at Pa > 0.300

0.956	0.003	Fibrinolytic
0.935	0.013	Transferase stimulant
0.924	0.003	Prolyl aminopeptidase inhibitor
0.921	0.004	Antiseborrheic
0.917	0.005	Alkylglycerophosphocholine hydrolase inhibitor
0.912	0.005	Chlordecone reductase inhibitor
0.909	0.003	Dehydro-L-gulonate decarboxylase inhibitor
0.907	0.003	Arginine 2-monooxygenase inhibitor
0.910	0.009	Methylenetetrahydrofolate reductase (NADPH) inhibitor
0.904	0.005	Glucose oxidase inhibitor
0.905	0.009	Retinal oxidase inhibitor
0.897	0.003	Antiinflammatory, pancreatic
0.896	0.003	Glutathione thioesterase inhibitor
0.897	0.004	Monodehydroascorbate reductase (NADH) inhibitor
0.900	0.009	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
0.895	0.004	Phosphatidylethanolamine N-methyltransferase inhibitor
0.893	0.006	Sugar-phosphatase inhibitor
0.889	0.003	Phosphatidylcholine-retinol O-acyltransferase inhibitor
0.888	0.003	NADPH-cytochrome-c2 reductase inhibitor
0.888	0.004	Dextranase inhibitor
0.888	0.004	Arylsulfate sulfotransferase inhibitor
0.884	0.005	Arylacetonitrilase inhibitor
0.879	0.002	Glycerol dehydratase inhibitor
0.879	0.003	Antipyretic

25 Substructure Descriptors; 0 new.
 There are 62 known activities.
 Drug-Likeness: 0.554

1217 of 3750 Possible Activities
 160 of 417 Possible Pharmacological Effects
 937 of 3036 Possible Molecular Mechanisms
 40 of 55 Possible Side Effects and Toxicity
 75 of 196 Possible Metabolism-Related Actions
 3 of 11 Possible Gene Expression Regulation
 2 of 35 Possible Transporters-Related Actions

1/1

Online Biological Activity Prediction with PASS

The screenshot displays the PHARMAEXPERT website. At the top left is the logo "PHARMAEXPERT PREDICTIVE SERVICES". A navigation menu includes "Home", "Definition", "Products", "Services", "FAQ", and "Contacts". The main banner features the text "PASS online" in large blue letters, with the tagline "Better solutions for your research and development" and "It is easy to use" below it. A "GO" button is positioned to the right of the banner. Below the banner, there is a section titled "Get more information about biological potential of your compounds." and another section titled "News" with a date "29 Mar" and a snippet of text: "In silico finding of multitargeted pharmacological agents. Oral presentation of Vladimir Poroikov 'Computer-aided approaches to virtual screening and rational design of multitargeted drugs' at the 2nd Conference in Computational".

<http://pharmaexpert.ru/passonline>

Input of the Structural Formula (Clopidogrel)

PASS PREDICTION

Please, enter your structure

Attach MOL file

Обзор...

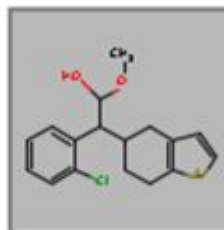
Get Prediction

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 I Net Predictions

European Journal of Medicinal Chemistry 44 (2009) 2015–2084

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: <http://www.elsevier.com/locate/ejmecb>

Original article

Synthesis and in vitro trichomonocidal, giardicidal and amebicidal activity of *N*-acetamide(sulfonamide)-2-methyl-4-nitro-1*H*-imidazoles^{1,2}

Emanuel Hernández-Núñez^a, Hugo Tlahuext^b, Rosa Moo-Puc^c, Héctor Torres-Gómez^a, Reyna Reyes-Martínez^d, Roberto Cedillo-Rivera^c, Carlos Nava-Zuazo^a, Gabriel Navarrete-Vazquez^{1,2*}

^aFacultad de Farmacia, Universidad Autónoma del Estado de Morelos, Cuernavaca, Morelos 62209, Mexico
^bCentro de Investigaciones Químicas, Universidad Autónoma del Estado de Morelos, Cuernavaca, Morelos 62209, Mexico
^cUnidad Interdisciplinaria de Investigación MBMx, IMSS-Facultad de Medicina, IMAIC, Mérida, Yucatán 97000, Mexico

OMICS - A Journal of Integrative Biology
Volume 9, Number 2, 2005
© Mary Ann Liebert, Inc.

**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 JUNIOR¹

Available online at www.sciencedirect.com

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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,*}

^aDepartment of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar 143 005, India
^bDepartment of Applied Chemistry, Guru Nanak Dev University, Amritsar 143 005, India

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Experimental Parasitology 106 (2004) 67–74

www.elsevier.com/locate/yexpr

Experimental Parasitology

In vitro activity of the β -carboline alkaloids harmame, 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

^aLaboratoire de Parasitologie, Hygiène et Zoologie Faculté de Pharmacie, 27 Bd. Jean Moulin, 13385 Marseille cedex 05, France
^bLaboratoire de Pharmacognosie Faculté de Pharmacie, 27 Bd. Jean Moulin, 13385 Marseille cedex 05, France

European Journal of Medicinal Chemistry 44 (2009) 2469–2487

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: <http://www.elsevier.com/locate/ejmecb>

Original article

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

Yohann Benhabane^b, Carole Di Giorgio^{a,*}, Gérard Boyer^b, Anne-Sophie Sabatier^a, Diane Allegro^c, Vincent Peyrot^c, Michel De Méo^a

^aLaboratoire de Biopharmacologie et Métabolisme Environnemental (SA 274, FR 3036 – ICCREVE), Université Aix-Marseille, Faculté de Pharmacie, 27 Bd Jean Moulin, 13385 Marseille Cedex 05, France
^bLaboratoire IRE, case 552, (ISE2 – UMR 6263) – Université Paul Cézanne, Faculté de Sciences, 13307 Marseille Cedex 20, France
^cCIRI2 (INSERM) – Université Aix-Marseille, Faculté de Pharmacie, 27 Bd Jean Moulin, 13385 Marseille Cedex 05, France

Ethnobotanical Leaflets

Volume 2008, Issue 1 2008 Article 29

Phytochemical Investigation and Pharmacological Studies of the Flowers of *Pithecellobium Dulce*

P. G. R. Chandran* S. Balaji[†]

PharmaExpert: Selection of Multitargeted Ligands

PharmaExpert

File Tools View Help

Pa > 0.100

Prediction & Interpretation - G:\work\Net2Drug>Last_report\twenty-structures-analogi-mol-2_PASS.SDF, 4/20

1 2 3 4 5 6 7

Save TXT Save SD Clipboard Exclude

Pa Pi Types of Activities Pa/Pi descending

Pa	Pi	Types of Activities
0.681	0.003	Myc inhibitor
0.323	0.005	Mcl-1 antagonist
0.331	0.140	Kinase inhibitor
0.162	0.022	Bcl2 antagonist
0.291	0.237	Interleukin alpha agonist
0.145	0.094	Bcl-xL inhibitor
0.255	0.215	Transforming growth factor agonist
0.110	0.087	Interleukin 2 antagonist

Pa Pi AutoID

Number of selected compounds:

AutoID 4: < DRUG_LIKENESS > 0.339; 52 Substructure descriptors, 2 new; 8 Possible activities.

Check non predicted activities Calculation

Effect Mechanisms Toxicity Metabolism Transport Gene Expression

Multitargeted actions

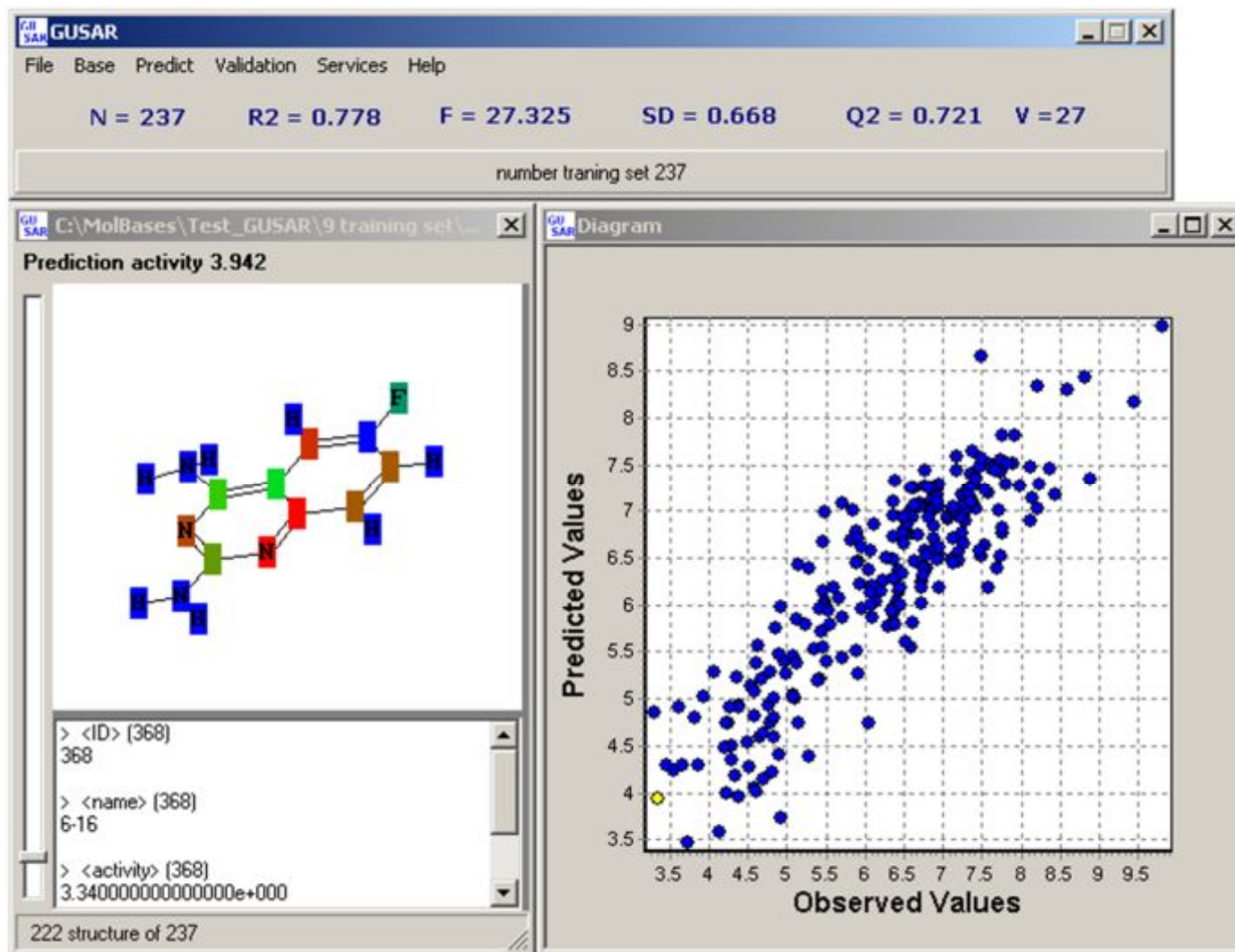
Effects

Number of targets: 3 Run Load Save

[N-acetylserylglucosylglucosylceramide N-acetylgalactosyltransferase inhibitor
 3 Beta-hydroxy-delta 5-steroid dehydrogenase inhibitor
 5 Lipoygenase inhibitor
 5 Alpha-reductase inhibitor
 ABCA1 expression enhancer
 Abl kinase inhibitor
 Acetylcholine nicotinic antagonist
 ADAM10 endopeptidase inhibitor
 Adenosine A3 receptor agonist
 Adenylate cyclase inhibitor
 ADP ribose polymerase 1 inhibitor
 ADP ribose polymerase inhibitor
 Aggrecanase inhibitor
 AICAR transaminase inhibitor
 Alkylphospholipid
 Aminopeptidase microsomal inhibitor
 Aminopeptidase N inhibitor
 AMPA receptor antagonist
 Androgen antagonist
 Aromatase inhibitor
 Aspartate carboxyltransferase inhibitor
 ATM kinase inhibitor
 ATPase (Vacuolar H+) inhibitor

No	Pa	Number	Activity type	Activity type
1	0.146	2	Bcl2 antagonist	Bcl-xL inhibitor
2	0.227	1	Bcl2 antagonist	Cyclin-dependent kinase 9 inhibitor
3	0.291	1	Bcl2 antagonist	Interleukin alpha agonist
4	0.121	3	Bcl2 antagonist	Interleukin 2 antagonist
5	0.364	3	Bcl2 antagonist	Kinase inhibitor
6	0.323	3	Bcl2 antagonist	Mcl-1 antagonist
7	0.706	3	Bcl2 antagonist	Myc inhibitor
8	0.255	1	Bcl2 antagonist	Transforming growth factor agonist
9	0.227	1	Bcl-xL inhibitor	Cyclin-dependent kinase 9 inhibitor
10	0.291	1	Bcl-xL inhibitor	Interleukin alpha agonist
11	0.110	2	Bcl-xL inhibitor	Interleukin 2 antagonist
12	0.331	2	Bcl-xL inhibitor	Kinase inhibitor
13	0.323	2	Bcl-xL inhibitor	Mcl-1 antagonist
14	0.681	2	Bcl-xL inhibitor	Myc inhibitor
15	0.255	1	Bcl-xL inhibitor	Transforming growth factor agonist
16	0.582	1	Cyclin-dependent kinase 2 inhibitor	Cyclin-dependent kinase 4 inhibitor
17	0.167	1	Cyclin-dependent kinase 2 inhibitor	Gelatinase inhibitor
18	0.303	1	Cyclin-dependent kinase 2 inhibitor	Guanylate cyclase stimulant
19	0.404	2	Cyclin-dependent kinase 2 inhibitor	Kinase inhibitor
20	0.676	2	Cyclin-dependent kinase 2 inhibitor	Myc inhibitor
21	0.284	1	Cyclin-dependent kinase 2 inhibitor	Neuropeptide antagonist
22	0.303	1	Cyclin-dependent kinase 4 inhibitor	Guanylate cyclase stimulant

GUSAR: General Unrestricted Structure-Activity Relationships



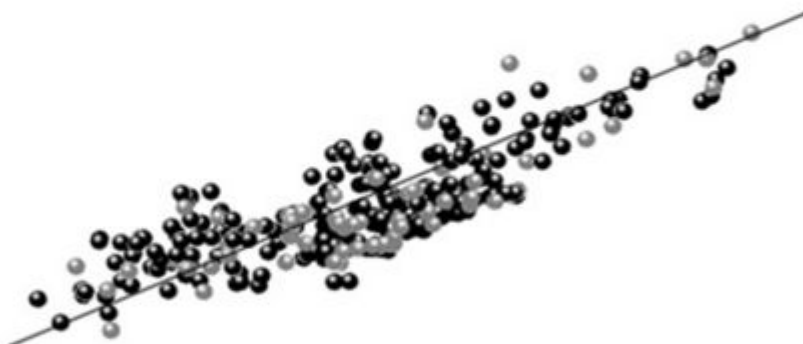
Multitargeted QSAR



RELIABLE QUANTITATIVE-STRUCTURE ACTIVITY
RELATIONSHIPS FOR YOUR CHEMICAL COMPOUNDS

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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.

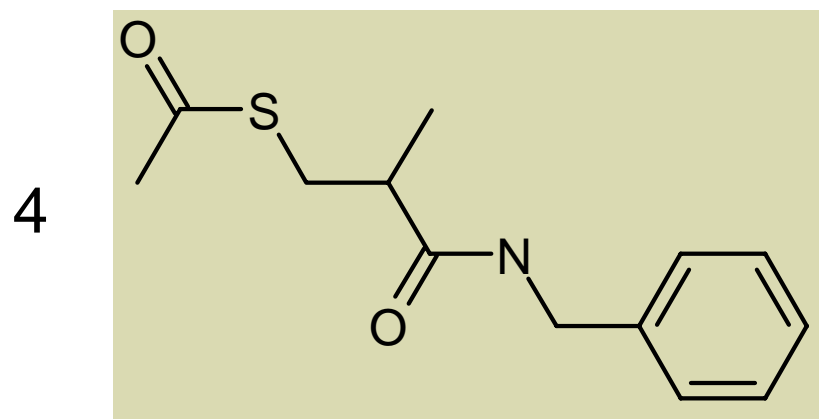
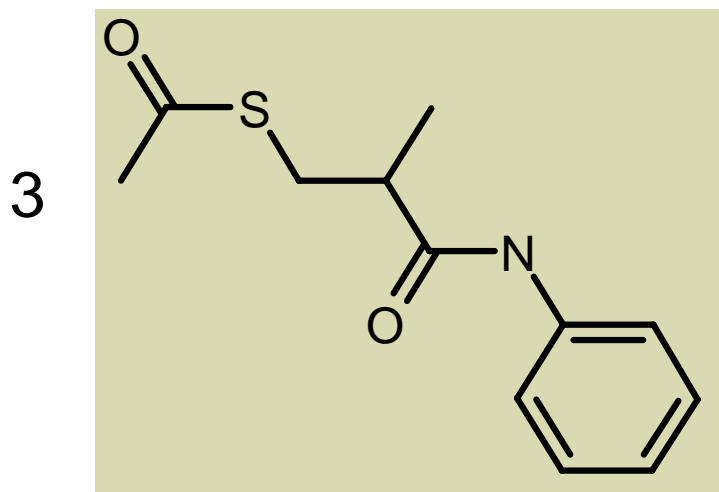
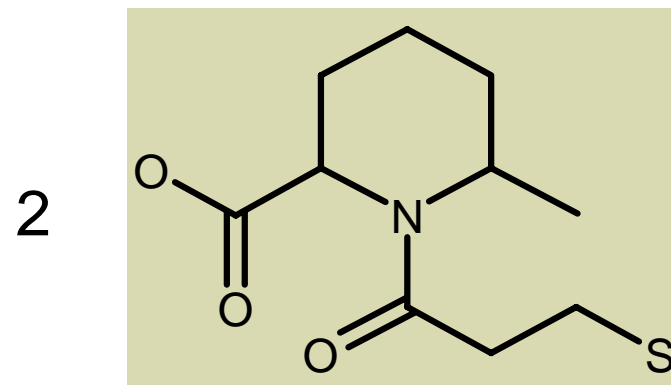
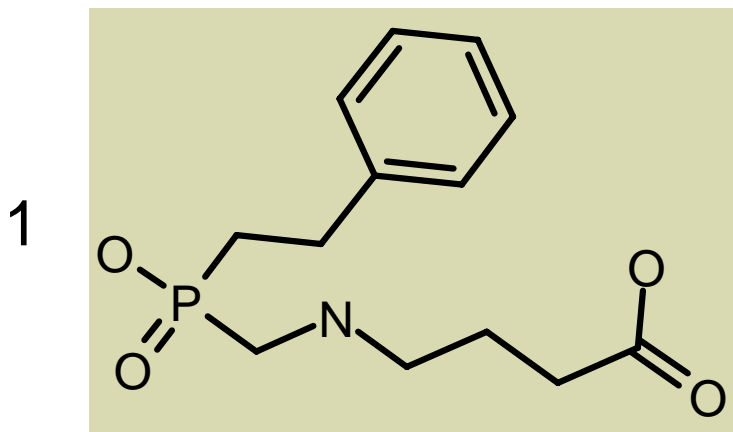


<http://pharmaexpert.ru/gusar>

Finding of New Antihypertensive Agents with Dual Mechanisms of Action

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

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.



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

Search for Multitargeted Agents in ChemNavigator Library

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

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

Hits for 23 double and 4 triple combinations of targets with $P_a > 50\%$ 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).

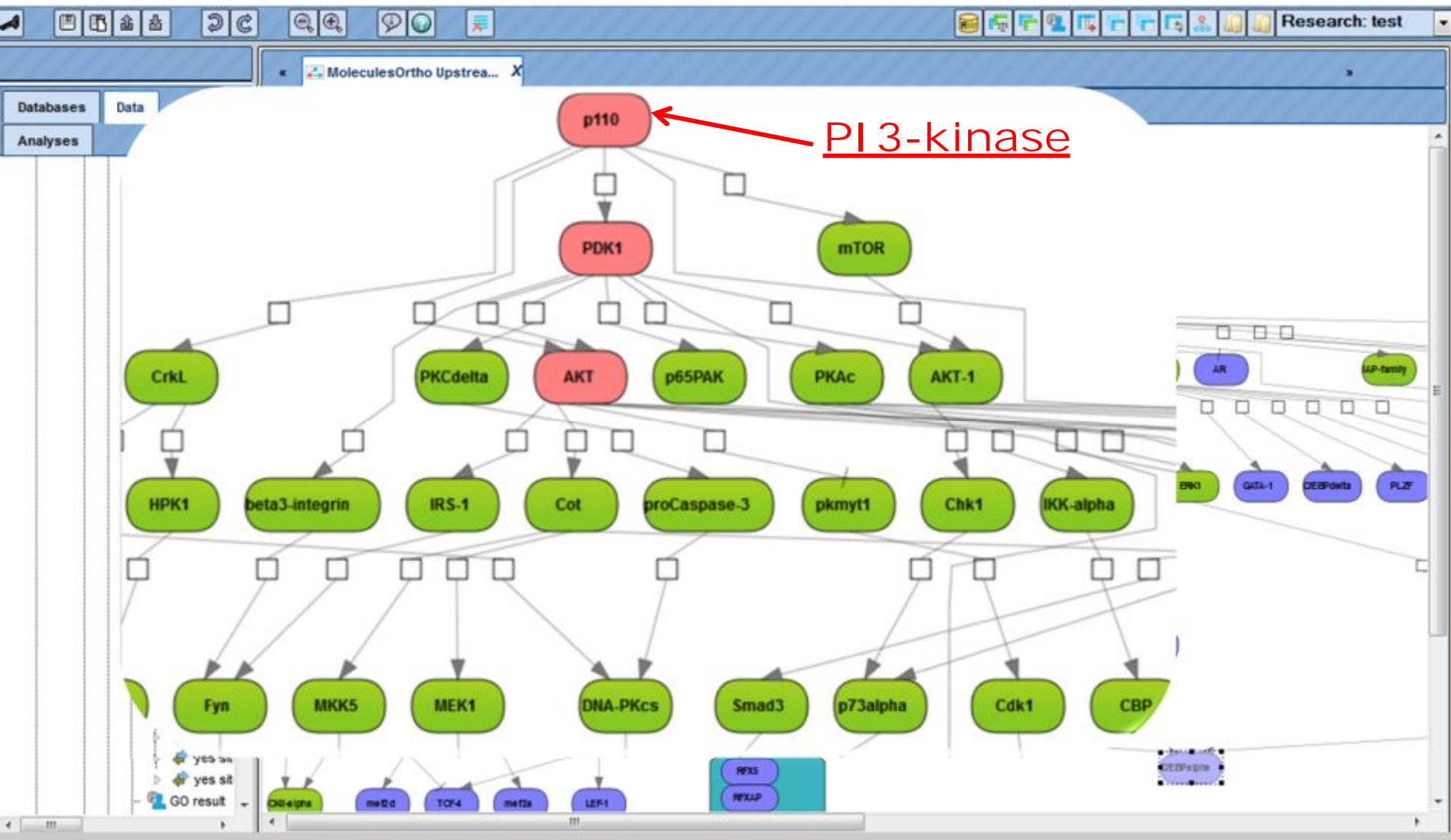
Results of Biological Testing in Cancer Cell Lines

Out of 16 soluble compounds only one (**Molecule I, CPI**) showed growth suppression in 3 different **breast cancer** cell lines - at 10 μM . Quite good killing of breast cancer cells, but still 1 μM 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.

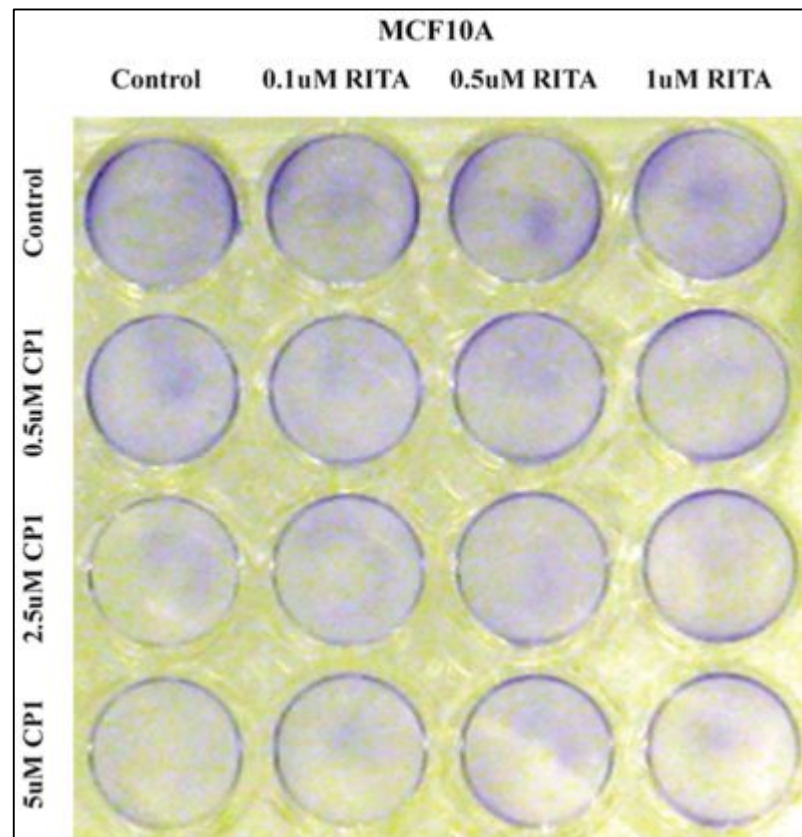
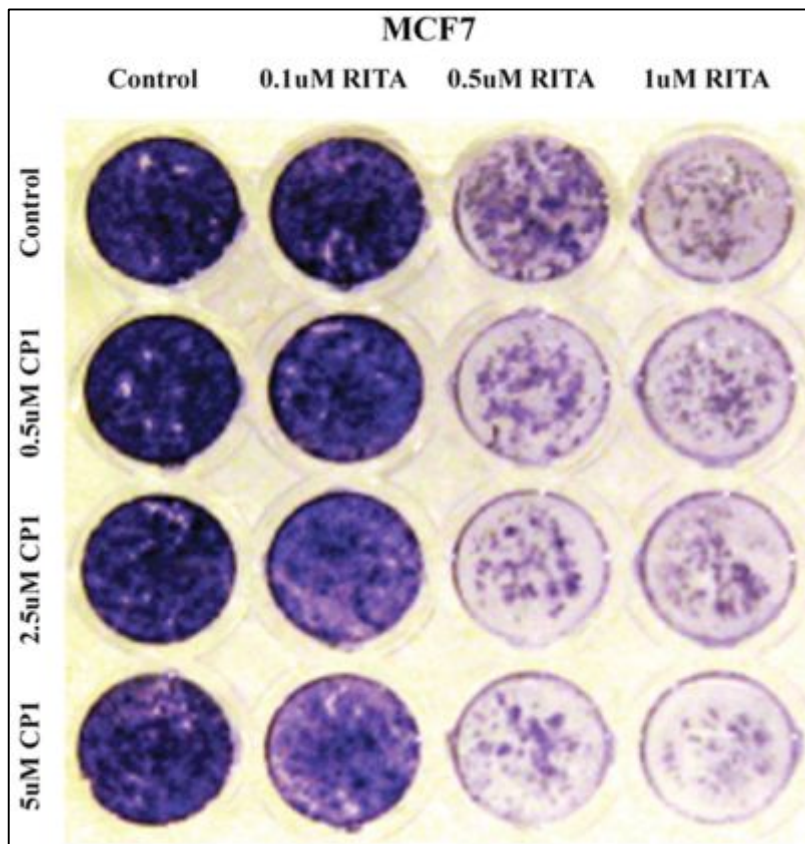
One more compound (**Molecule II**) could be interesting - but not in breast cancer. Out of panel of 7 different cancer lines it killed only **melanoma** cells. It kills only melanoma cells without any effects in other cell lines.

Galina Selivanova, Karolinska Institute, Sweden

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

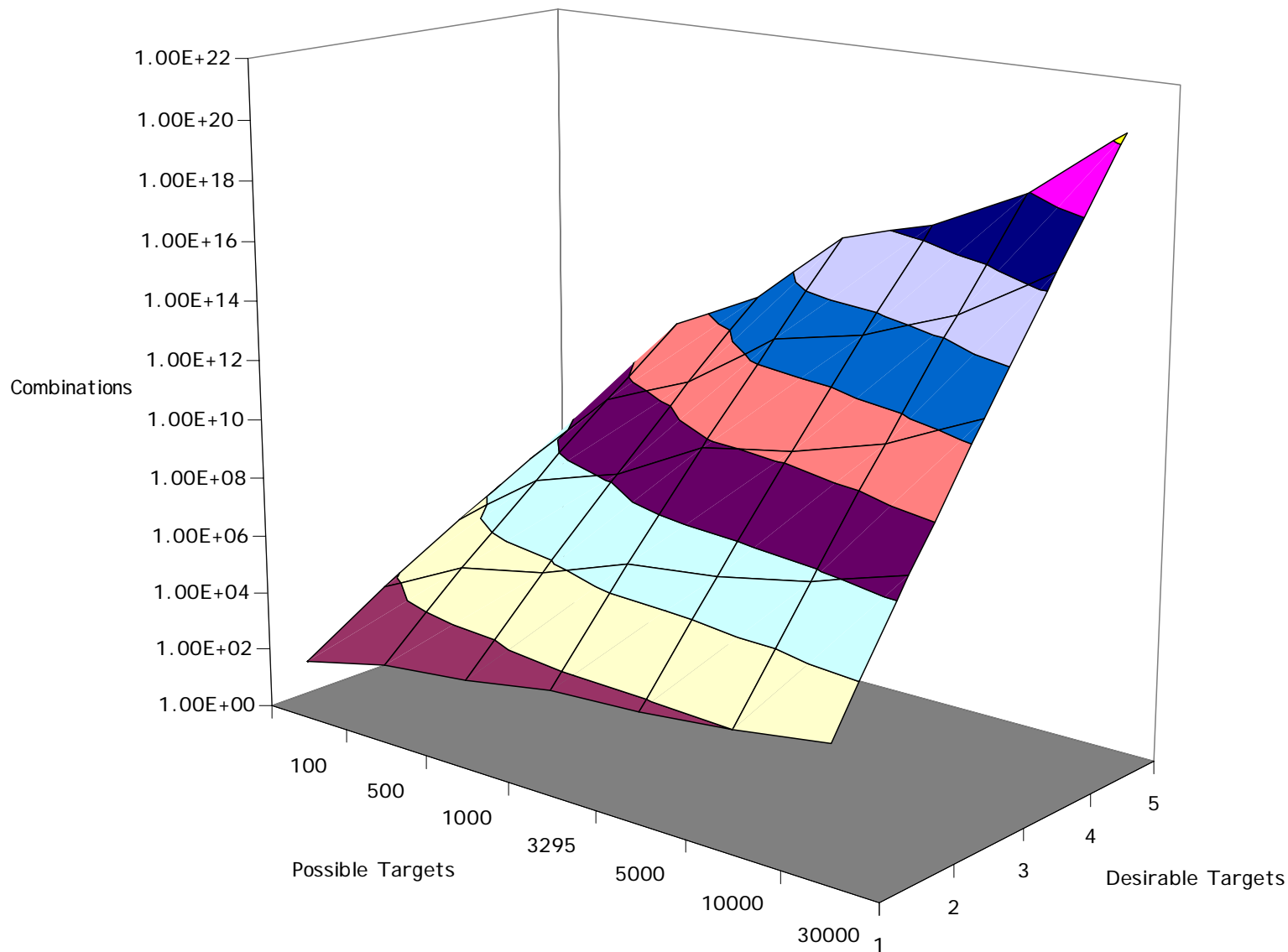


Synergistic effect was observed between CPI and Rita in several breast cancer cell lines, but not in non-transformed mammary epithelial cell line



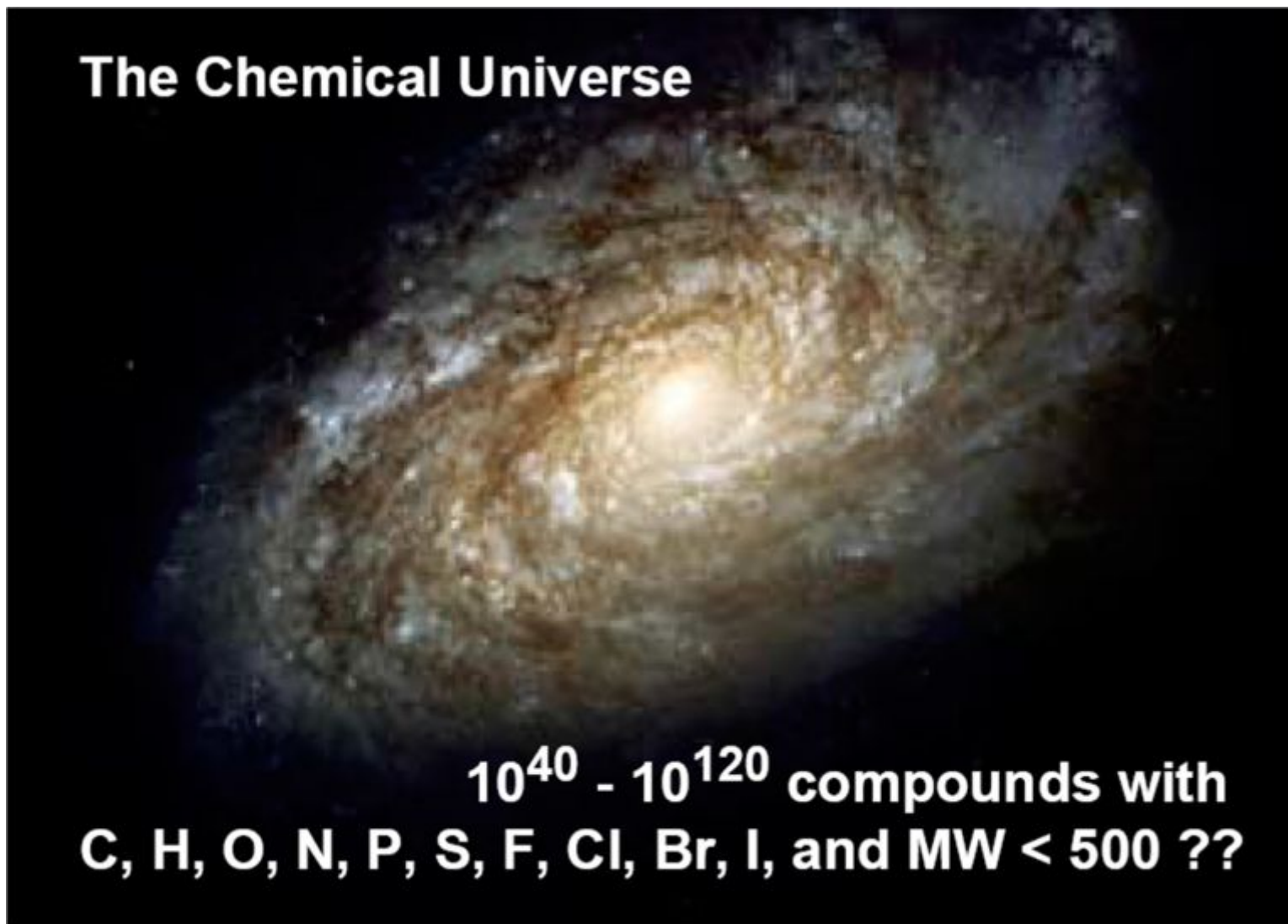
Galina Selivanova, Karolinska Institute, Sweden

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



Chemogenomics: Chemical Space (Estimated)

The Chemical Universe



**10^{40} - 10^{120} compounds with
C, H, O, N, P, S, F, Cl, Br, I, and MW < 500 ??**

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 P_a и P_i values are calculated.

Each atom is colored in accordance with the following:

Red	$:= 0.3 + 0.7 * P_i$	(negative impact on activity)
Green	$:= 0.3 + 0.7 * P_a$	(positive impact on activity)
Blue	$:= 1 - 0.7 * (P_i + P_a)$	(neutral impact on activity)

This can be interpreted in the following way:

If $P_a = 0$ and $P_i = 1$, then Red = 1, Green = 0.3, Blue = 0.3 – **bright red color**;

If $P_a = 1$ and $P_i = 0$, then Red = 0.3, Green = 1, и Blue = 0.3 – **bright green color**;

If $P_a = 0$ and $P_i = 0$, then Red = 0.3, Green = 0.3, Blue = 1 – **bright blue color**;

If $P_a = 0.33$ and $P_i = 0.33$, 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

PASS - C:\DATABASES\TEST-MOLECULES\sulphathiazole.sdf

File Base Predict View Options Help

C:\Program Files\PASS-ETC-AUG-2005\MNICKLAUS-AUG-2005\RunImage\PASS.SAR

C:\DATABASES\TEST-MOLECULES\sulphathiazole.sdf

Antibacterial

0.443 0.012

Activity Spectrum

Chart General Effects Mechanisms Toxicity

Dihydropterote synthase inhibitor
Iodide peroxidase inhibitor

139 of 2005 Possible Activities at Pa > Pi

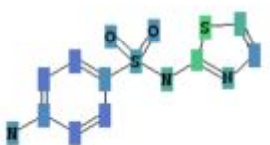
0.889	0.005	Antiobesity
0.835	0.005	Para amino benzoic acid antagonist
0.736	0.006	Dihydropterote synthase inhibitor
0.721	0.006	Antidiabetic
0.556	0.006	Antiprotozoal (Coccidial)
0.552	0.019	Prostaglandin E1 antagonist
0.509	0.026	Prostaglandin H2 antagonist
0.485	0.045	Potassium channel antagonist
0.453	0.013	Cyclooxygenase inhibitor
0.468	0.028	Antiprotozoal
0.443	0.012	Antibacterial
0.412	0.021	Diuretic inhibitor
0.408	0.024	Gingipain R inhibitor
0.421	0.053	Antiinfective
0.371	0.006	Hypoglycemic
0.328	0.015	Antineoplastic (breast cancer)
0.362	0.054	Antimycobacterial
0.351	0.047	Antituberculosic
0.325	0.023	Saluretic
0.345	0.052	Myelodysplastic syndrome treatment

> <id> (2)
2

32 Substructure Descriptors: 0 new.
There are 3 known activities.
Drug-Likeness: 0.156

139 of 2005 Possible Activities
35 of 224 Possible Pharmacological Effects

2 structure of 2



PASS - C:\DATABASES\TEST-MOLECULES\sulphathiazole.sdf

File Base Predict View Options Help

C:\Program Files\PASS-ETC-AUG-2005\MNICKLAUS-AUG-2005\RunImage\PASS.SAR

C:\DATABASES\TEST-MOLECULES\sulphathiazole.sdf

Endothelin receptor antagonist

0.158 0.019

Activity Spectrum

Chart General Effects Mechanisms Toxicity

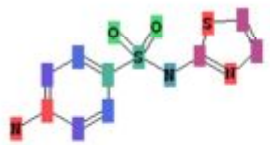
0.280	0.048	Ribonucleoside triphosphate reductase inhibitor
0.288	0.061	Channel-conductance-controlling ATPase inhibitor
0.254	0.029	Tubulin antagonist
0.269	0.061	Antiprotozoal (Trichomonas)
0.248	0.044	Thromboxane A2 antagonist
0.204	0.004	5-Hydroxytryptamine 6 antagonist
0.244	0.045	Lipoxygenase inhibitor
0.287	0.093	CYP2E2 substrate
0.246	0.060	Oligopeptidase B inhibitor
0.205	0.021	Thromboxane antagonist
0.235	0.059	Benzodiazepine inverse agonist
0.176	0.001	11-Beta-hydroxysteroid dehydrogenase 1 inhibitor
0.176	0.001	11-Beta-hydroxysteroid dehydrogenase inhibitor
0.264	0.100	Serine-phosphoethanolamine synthase inhibitor
0.241	0.083	Antithrombocytopenic
0.235	0.079	Poly(ADP-ribose) glycohydrolase inhibitor
0.216	0.066	Corticosteroid antagonist
0.154	0.008	Thyroid hormone antagonist
0.219	0.074	Granzyme A inhibitor
0.246	0.106	Carcinogenic
0.279	0.139	Antiulcerative
0.155	0.016	Beta tubulin antagonist
0.256	0.117	Carcinogenic, male mice
0.158	0.019	Endothelin receptor antagonist
0.237	0.107	(S)-3-hydroxyacid ester dehydrogenase inhibitor

> <id> (2)
2

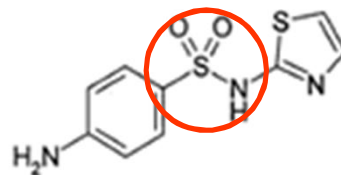
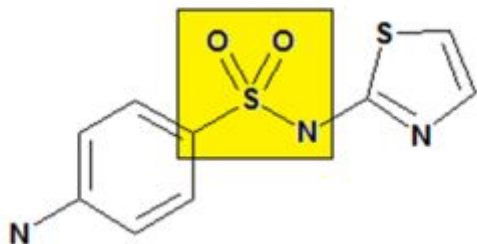
32 Substructure Descriptors: 0 new.
There are 3 known activities.
Drug-Likeness: 0.156

139 of 2005 Possible Activities
35 of 224 Possible Pharmacological Effects

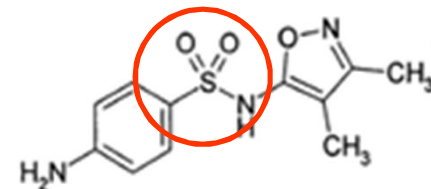
2 structure of 2



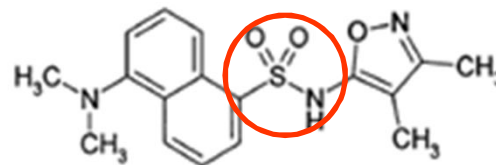
The fragment of sulfathiazole identified by PASS as having “positive” influence on ET_A antagonistic activity:



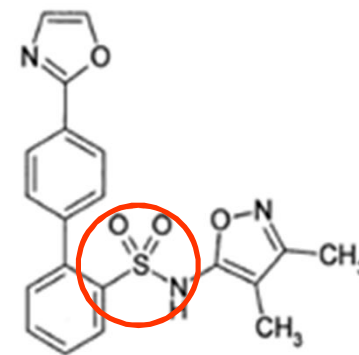
1 sulfathiazole
 ET_A IC_{50} = 69 μ M



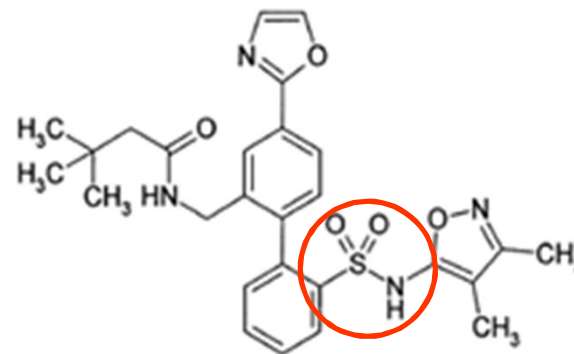
2 sulfisoxazole
 ET_A IC_{50} = 0.78 μ M



3 BMS-182874
 ET_A IC_{50} = 0.15 μ M

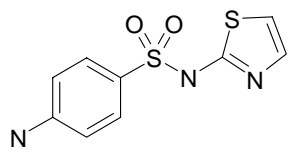
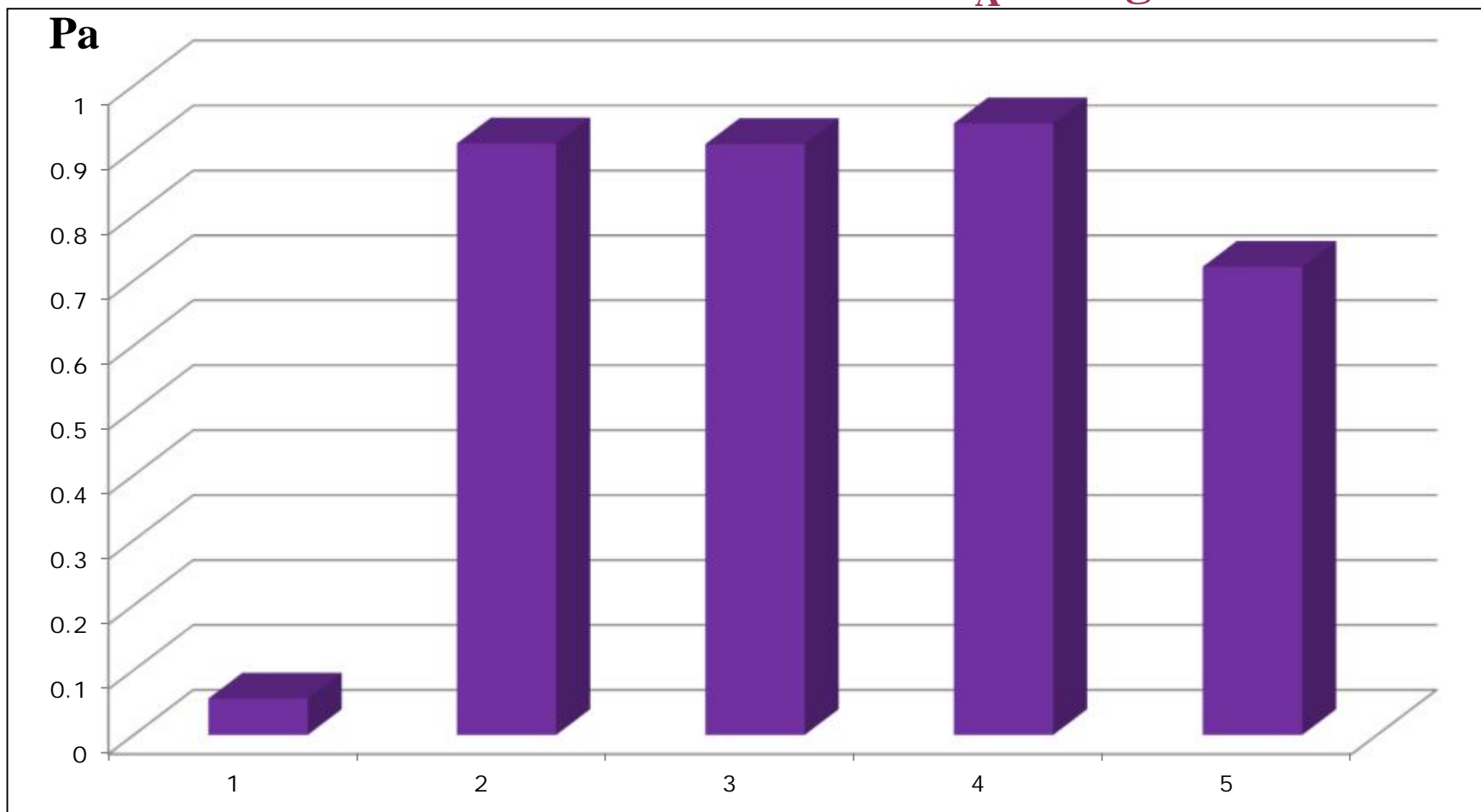


4 BMS-193884
 ET_A K_i = 1.4 nM

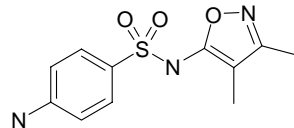


5 BMS-207940
 ET_A K_i = 0.010 nM

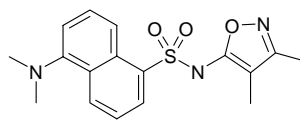
From Sulfathiazole to Potent ET_A Antagonist



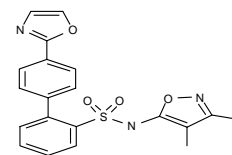
IC₅₀: 60 μM



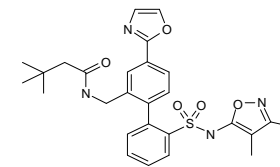
0.78 μM



0.15 μM



1.4 nM



0.01 nM

PASS Constructor: Structure Modification & Prediction “on the Fly”

PASS

File Base Predict View Options Help

No Pa limit 11737 Loading fragments for 0:00:00

constr

PASS Molecule Editor Selected fragments: Active Inactive **MNA-level 2** ANGIOTENSIN CONVERTING ENZYME INHIBITOR

Activity Name Pa Pi ND

ANGIOTENSIN CONVERTING ENZYME	0.151	0.283	
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History

Activity Name	Pa	Pi
ANGIOTENSIN CONVERTING ENZYME INHIBITOR	0.151	0.283

Initial Structure

PASS

File Base Predict View Options Help

No Pa limit 11737 Loading fragments for 0:00:00

constr

PASS Molecule Editor Selected fragments: Active Inactive **MNA-level 2** ANGIOTENSIN CONVERTING ENZYME INHIBITOR

Activity Name Pa Pi ND

ANGIOTENSIN CONVERTING ENZYME	0.233	0.215	
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History

Activity Name	Pa	Pi
ANGIOTENSIN CONVERTING ENZYME INHIBITOR	0.233	0.215

Wednesday, March 24, 2010 3:29 PM

PRESENTATION FRAGMENT-BASED-... Poroikov-ACS-24-0... PASS Profconst_mar... PASS

Adding an “Active” Fragment: $P_a = 0.233 \rightarrow 0.304$

PASS

File Base Predict View Options Help

No Pa limit 11737 Loading fragments for 0:00:00

constr

PASS Molecule Editor Selected fragments: Active Inactive **MNA-level 2** ANGIOTENSIN CONVERTING ENZYME INHIBITOR

C O N H Other Templates 100% Help

7 1 Activity Name Pa Pi ND
ANGIOTENSIN CONVERTING ENZYME 0.233 0.215

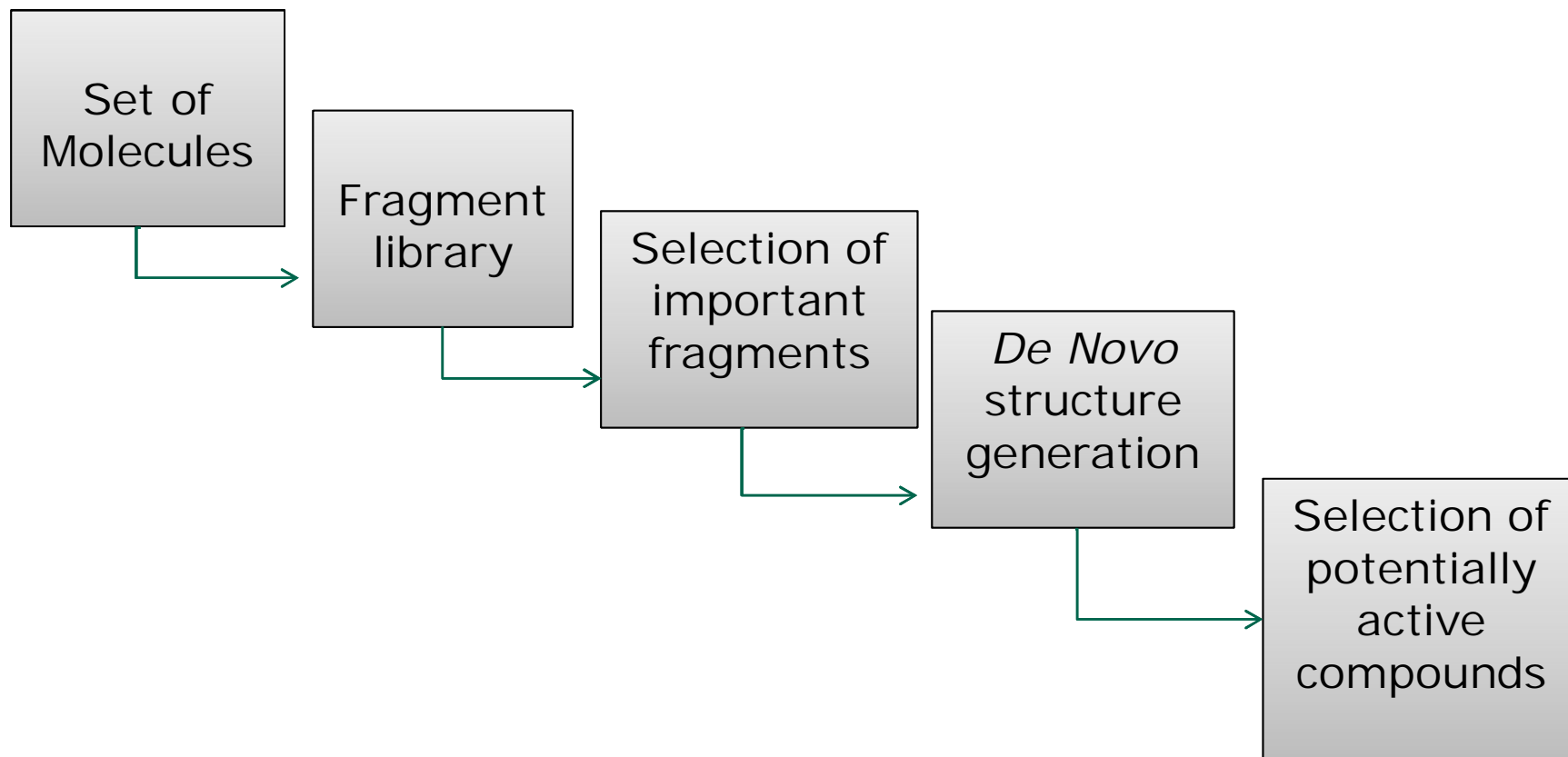
8 2 9 3 10 4 11 5 12 6

2 3 4 5

History
Activity Name Pa Pi
ANGIOTENSIN CONVERTING ENZYME 0.233 0.215

PRESENTATION FRAGMENT-BASED-... Poroikov-ACS-24-0... PASS Profconst_mar... PASS EN 3:25 PM

In silico generation of new molecules with the required biological activity using fragment libraries

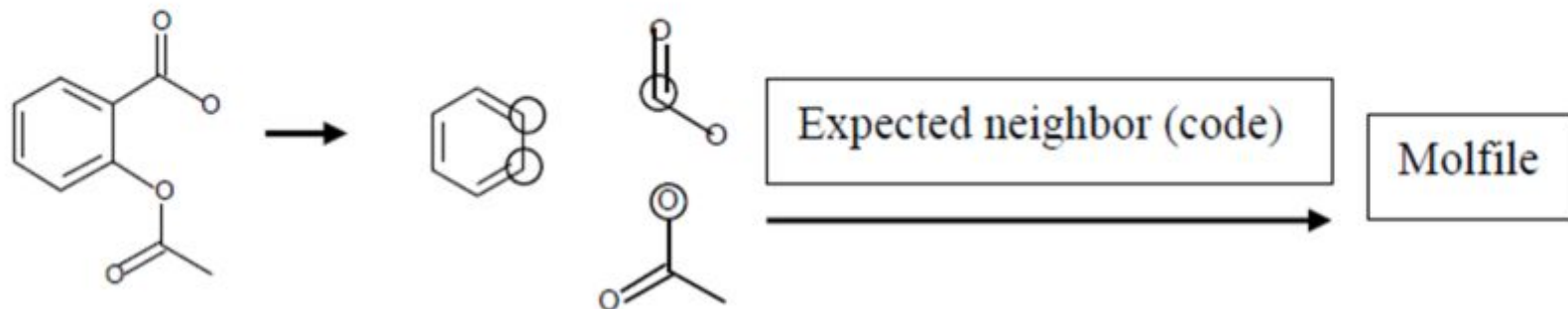


Example of Defragmentation of Acetylsalicylic Acid

The rules are presented below:

- The following bond types - C-N, N-N, N-O, C-C, S-S, C-O, as well as bonds between the ring atom and non-ring atom and bonds connecting two cycles can be split.
- Double and triple bonds cannot be broken.

The example of splitting of the acetylsalicylic acid structure (active pharmaceutical ingredient of Aspirin) is shown in figure 1.



Finding of New COX & LOX Inhibitors in Virtually Designed Chemical Library

J. Med. Chem. 2008, 51, 1601–1609

1601

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

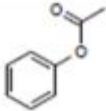

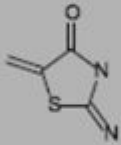
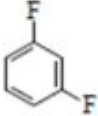
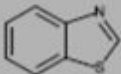

Athina A. Geronikaki,[†] Alexey A. Lagunin,^{*,‡} Dimitra I. Hadjipavlou-Litina,[†] Phaedra T. Eleftheriou,[†] Dmitrii A. Filimonov,[‡] Vladimir V. Poroikov,[‡] Intekhab Alam,[§] and Anil K. Saxena[§]

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

Received July 24, 2007

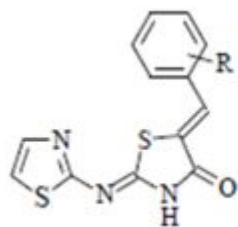
New anti-inflammatory agents possessing dual cyclooxygenase/lipoxygenase (COX/LOX) inhibition were discovered by computer-aided prediction of biological activity for 573 virtually designed chemical compounds. Prediction of biological activity was performed by PASS, and prediction results were analyzed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

Influence of Fragments on COX-1, COX-2 and LOX inhibition

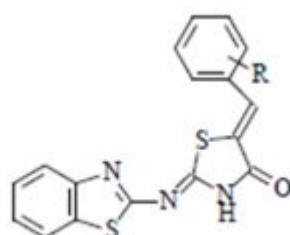
Fragment	Chemical name	Final C-values		
		COX-1	COX-2	LOX
 1	phenyl acetate	100	100	--
 2	fluor-benzene	100	100	84
 3	2-imino-5-methylidene-1,3-thiazolidin-4-one	100	96	100
 4	di-fluor-benzene	100	100	-33
 5	benzothiazole	89	100	69
 6	isobutane	88	58	96

...

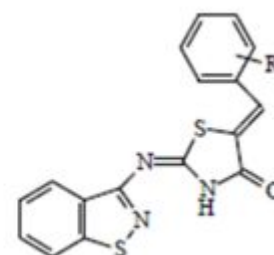
Experimental evaluation of LOX, COX-1, and COX-2 inhibition obtained for the set of benzothiazole- (BT), benzisothiazole-(BIT) and thiazole (TH) derivatives.



TH



BT



BIT

N	R	CPE ⁺ , %	COX-1 inhibition (IC ₅₀ , μM)		COX-2 inhibition %		LOX inhibition (IC ₅₀ , μM)	
			BT	TH**	BT	TH**	BT	TH**
1	2-NO ₂	-	>200	-	9.4		35.5	-
2	3-NO ₂	40.0	0.31	>200	32.0	12.1	42.0	89.1
3	4-NO ₂	57.0	0.51	141.3	8.0	4.51	50.1	251.2
4	2-Cl	71.8	0.018	>200	58.8	2.11	71.0	114.6
5	3-Cl	78.0	22.4	125.0	32.0	30.4	35.5	125.9
6	4-Cl	68.7	0.31	>200	20.0	6.2	50.0	120.0

**Fragment-based design, synthesis, biological evaluation and structure–
activity relationships of 2-benzo/benzisothiazolimino–5–arylidene–4–
thiazolidinones as cyclooxygenase/lipoxygenase inhibitors**

Phaedra Eleftheriou^b, Athina Geronikaki^{a*}, Dimitra Hadjipavlou-Litina^a, Paola Vicini^c,
Olga Filz^{d*}, Dmitry Filimonov^d, Vladimir Poroikov^d

ABSTRACT

One of the current strategies for the treatment of complex multifactorial diseases is based on the modulation of several targets. Taking into account up-to-date knowledge about the mechanism of inflammation, balanced inhibition of cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2) and lipoxygenase (LOX) could be proposed as a promising strategy for treatment of inflammation. Computational screening of chemical libraries can be used for identification of multi-target agents. Detection of fragments responsible for interaction with the binding site of target protein provides the basis for design of new molecules with increased affinity as well as for selective inhibition of one specific target. A new statistical method was proposed and applied to create a fragment library which is focused on the inhibition of COX-1, COX-2 and LOX enzymes. Using fragments, selected on the basis of both functional significance and chemical accessibility, novel potent inhibitors of cyclooxygenase-1, cyclooxygenase-2 and lipoxygenase were designed. Synthesis of compounds and *in vitro* and *in vivo* biological testing confirmed the results of computational experiments. The benzothiazolyl moiety, incorporated in the studied compounds, improved affinity to all three enzymes, leading to more potent inhibitors in comparison with previously tested thiazolyl derivatives.

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. However, the chance to find compounds active versus all combinations of multiple targets is rather small. Direct design is necessary in many cases.**

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