ИБМХ
институт биомедицинской химии

Computer-Aided Prediction of Biological Activity for Finding Safety and Potent Medicines

Vladimir Poroikov, Prof. Dr.

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
http://www.ibmc.msk.ru

Outline

- **Chemical compounds & biological activity**
- **Computational approaches to prediction of biological activity.**
- **PASS: Prediction of Activity Spectra for Substances**
- **PharmaExpert: Tool for analysis of PASS predictions**
- **GUSAR: General Unrestrained Structure-Activity Relationships**
- **Summary**

International Year of CHEMISTRY 2011

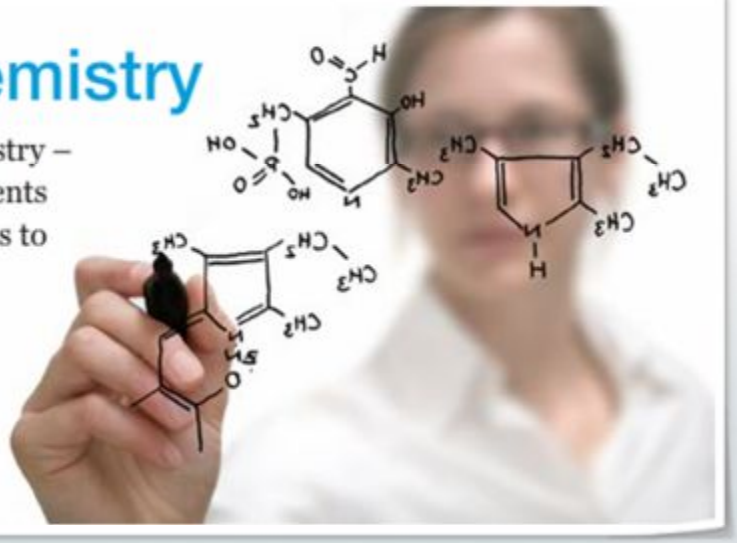
United Nations Educational, Scientific and Cultural Organization

International Union of Pure and Applied Chemistry

Partners for the International Year of Chemistry 2011

Celebrate Chemistry

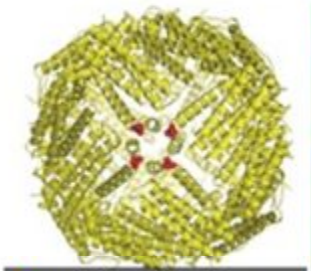
The International Year of Chemistry – 2011 will celebrate the achievements of chemistry and its contributions to the well-being of humankind.



From Ideas to Activities

View all Activities View all Features

You can participate in the IYC 2011 in many different ways. Here are just a few ideas and sample activities of earlier projects. What are you going to do? Think and start planning...



Bioinorganic Chem

Chemistry in Action

Sketch or Screen

Get Involved

Learn More

The IYC 2011 will be a year-long celebration in which anyone can participate. You can coordinate an activity, engage in a project, or simply share an idea. Join in now and become part of something special.

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IYC2011 Global Partners

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Events

View all

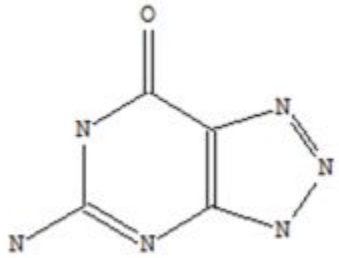
Apr 25, 2011	French Brazilian Meeting on Polymers in Florianopolis
Apr 26-29, 2011	Conference on Functional Polymeric Materials & Composites in Stellenbosch, South Africa

News

View all

Apr 4, 2011	Make plans to participate in the 43rd IUPAC World Congress in Puerto Rico
Apr 1, 2011	On the United Nation's World Water Day, 22 March 2011, UNESCO and IUPAC launched

1



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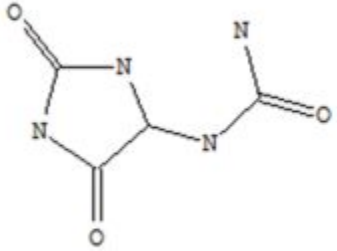

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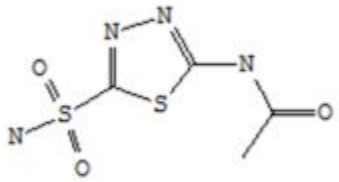

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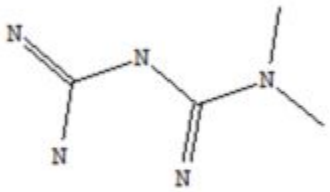

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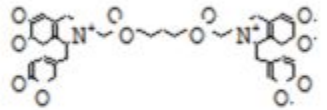

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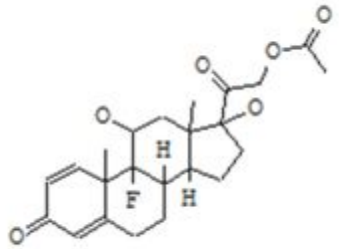

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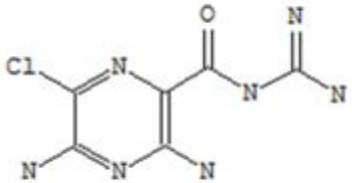

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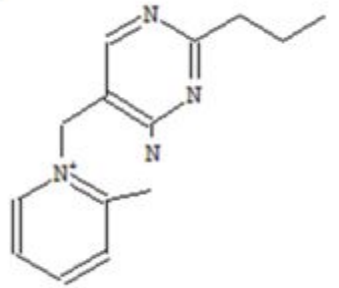

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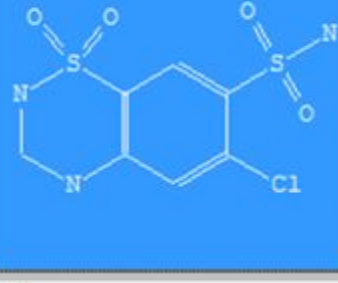

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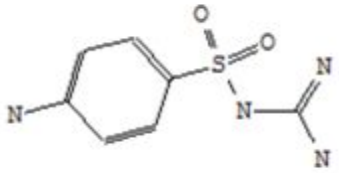

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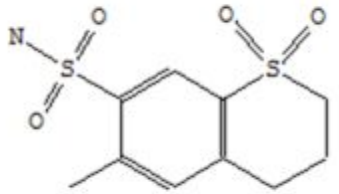

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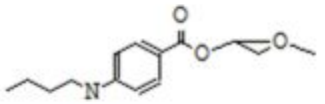

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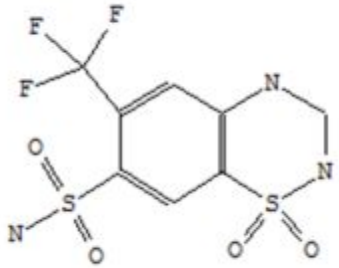

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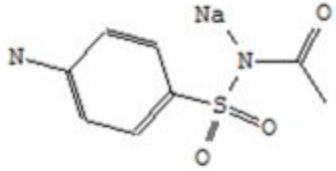

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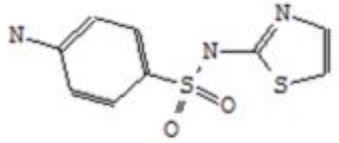

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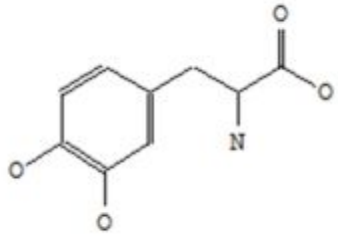

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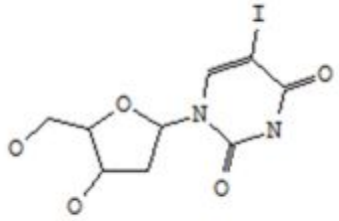

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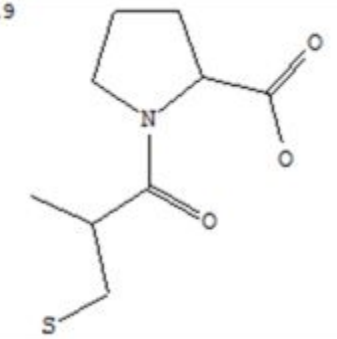

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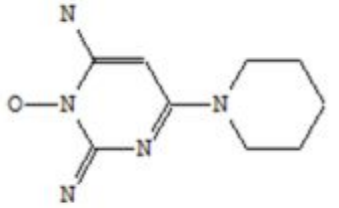
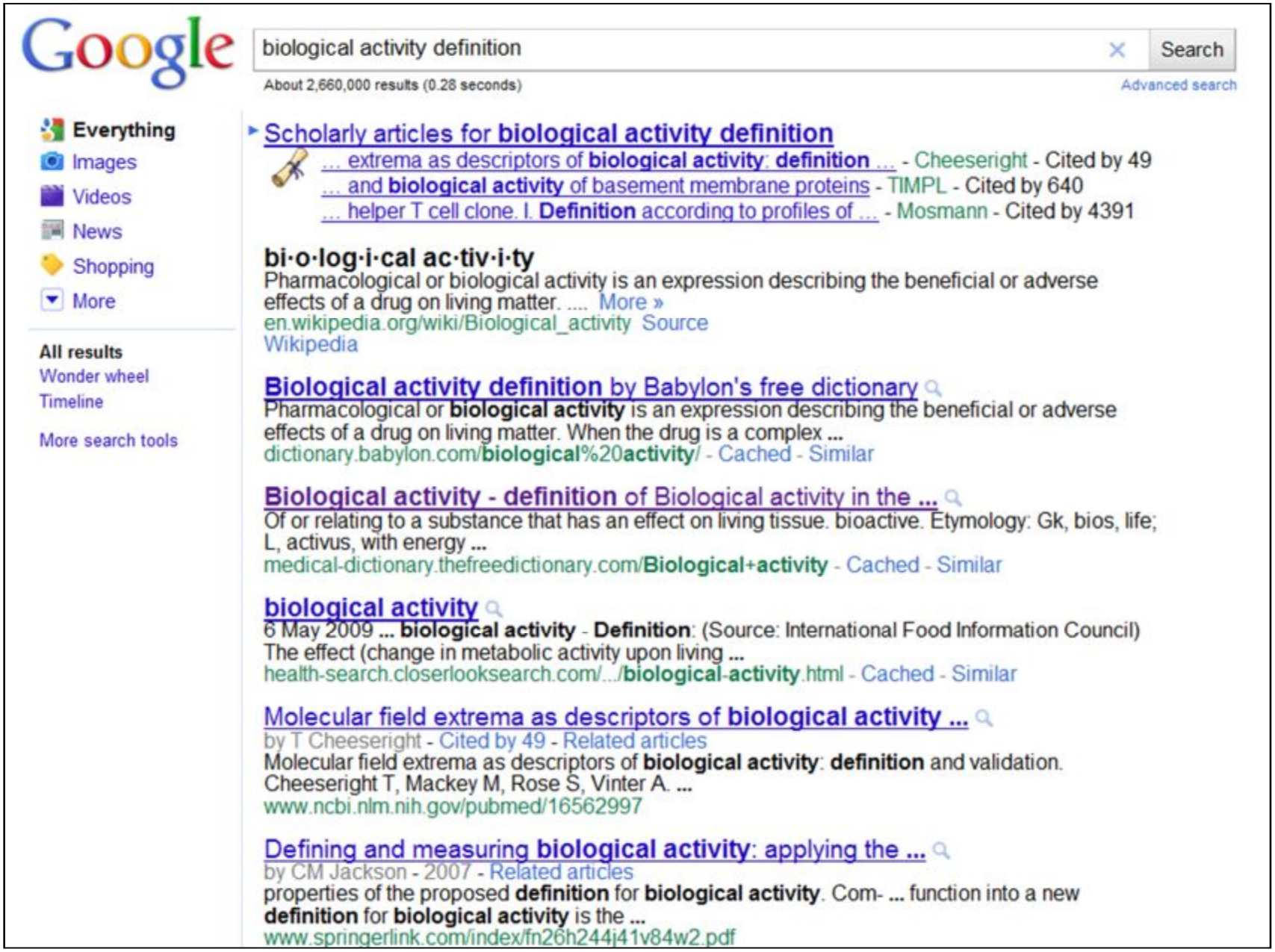


Biological Activity: Finding Definition



Biological Activity: Some Definitions

bioactive

Etymology: Gk, *bios*, life; L, *activus*, with energy

having an effect on or causing a reaction in living tissue.

Mosby's Medical Dictionary, 8th edition. © 2009, Elsevier.

bioactive [bi″o-ak´tiv]

having an effect on or eliciting a response from living tissue.

Miller-Keane Encyclopedia and Dictionary of Medicine, Nursing, and Allied Health, Seventh Edition. © 2003 by Saunders, an imprint of Elsevier, Inc.

bioactive

having an effect on or eliciting a response from living tissue.

bioactive food components

constituents in foods or dietary supplements, other than those needed to meet basic nutritional needs, that are responsible for changes in health status.

Saunders Comprehensive Veterinary Dictionary, 3 ed. © 2007 Elsevier, Inc.

In pharmacology, **biological activity** or **pharmacological activity** describes the beneficial or adverse effects of a drug on living matter. When a drug is a complex chemical mixture, this activity is exerted by the substance's active ingredient or pharmacophore but can be modified by the other constituents.

US 20100286088A1

(19) **United States**

(12) **Patent Application Publication**
Stevens et al.

(10) **Pub. No.: US 2010/0286088 A1**
(43) **Pub. Date: Nov. 11, 2010**

(54) **3-SUBSTITUTED-4-OXO-3,4-DIHYDRO-IMIDAZO[5,1-D][1,2,3,5-TETRAZINE-8-CARBOXYLIC ACID AMIDES AND THEIR USE**

(86) PCT No.: **PCT/GB08/04140**
§ 371 (c)(1),
(2), (4) Date: **Jun. 16, 2010**

Related U.S. Application Data

(60) Provisional application No. 61/014,520, filed on Dec. 18, 2007.

Publication Classification

(75) Inventors: **Malcolm Francis Graham Stevens**, Leicestershire (GB); **David Cousin**, Nottinghamshire (GB); **Sharon Jennings**, Leicestershire

(57) **ABSTRACT**

The present invention pertains generally to the field of therapeutic compounds, and more specifically to certain 3-substituted-4-oxo-3,4-dihydro-imidazo[5,1-d][1,2,3,5]tetrazine-8-carboxylic acid amide (collectively referred to herein as 3TM compounds). The present invention also pertains to pharmaceutical compositions comprising such compounds,

(12) **按照专利合作条约所公布的国际申请**

(19) **世界知识产权组织**
国 际 局

(43) **国际公布日**
2009 年3 月26 日 (26.03.2009)

PCT

(10) **国际公布号**
WO 2009/036656 A1

(51) **国际专利分类号:**
C07D 311/16 (2006.01) *A61P 35/00* (2006.01)
A61K 31/37 (2006.01) *A61P 27/02* (2006.01)

(21) **国际申请号:** PCT/CN2008/070118

(22) **国际申请日:** 2008 年1 月16 日 (16.01.2008)

(25) **申请语言:** 中文

(26) **公布语言:** 中文

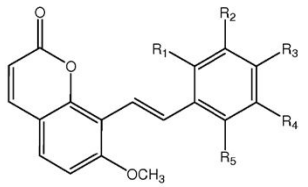
(30) **优先权:**
200710131803.0
2007 年9 月18 日 (18.09.2007) CN

(71) **申请人** (对除美国外的所有指定国): **南京中瑞药业有限公司(NANJING ZHONGRUI MEDICINE CO., LTD)** [CN/CN]; 中国江苏省南京市前半山园12

(72)
(75)
(74)
(81)

(54) **Title:** COUMARIN DERIVATIVES, PREPARATION PROCESSES AND USES THEREOF

(54) **发明名称:** 一种香豆素衍生物及其制备方法和用途



式I

(57) **Abstract:** Coumarin derivatives represented by general formula (I), their preparation methods, and their uses as angiogenesis inhibitors for the treatment of tumor and angio-retina diseases. This type of compounds is obtained by modification based on the structure of osthol. Vascular endothelial cell growth inhibiting experiments show that compounds of formula (I) have obvious EVC-304 cell multiplication inhibiting activity. Compared with combretastatin A-4 (CA4), the inhibiting activity of formula (I) is stronger and 1.5-4.0 times the activity of CA4.

(57) **摘要:**

(12) **THE PATENT COOPERATION TREATY (PCT)**

(10) **International Publication Number**
WO 2007/131764 A2

(19) **United States**
Patent Application Publicatio
insky et al.

ROCYCLIC COMPOUNDS FOR THE GITION OF INTEGRINS AND USE EOF

(5

(12) **INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)**

(19) **World Intellectual Property Organization**
International Bureau

(43) **International Publication Date**
3 July 2008 (03.07.2008)

PCT

(10) **International Publication Number**
WO 2008/077548 A1

(51) **International Patent Classification:**
C07D 239/47 (2006.01) *A61K 31/505* (2006.01)
C07D 405/12 (2006.01) *A61P 35/00* (2006.01)
C07F 7/08 (2006.01)

(21) **International Application Number:**
PCT/EP2007/011161

(22) **International Filing Date:**
19 December 2007 (19.12.2007)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
06026650.9 22 December 2006 (22.12.2006) EP

(71) **Applicant** (*for all designated States except US*): **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse

(74) **Agent: SCHREINER, Siegfried**; Roche Di
GmbH, Patent Department (TR-E), Postfach 11 5
Penzberg (DE).

(81) **Designated States** (*unless otherwise indicated, kind of national protection available*): AE, AG,
AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC
ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU
IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA,
LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, M
MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG,
PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC,
ZM, ZW.

(84) **Designated States** (*unless otherwise indicated, kind of regional protection available*): ARIPO (

(12) **INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)**

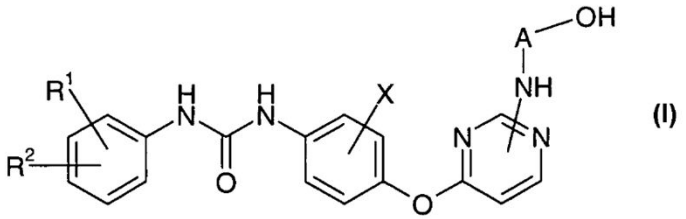
(19) **World Intellectual Property Organization**
International Bureau

(43) **International Publication Date**
18 September 2008 (18.09.2008)

PCT

(10) **International Publication Number**
WO 2008/112408 A1

(54) **Title:** PYRIMIDYL DERIVATIVES AS PROTEIN KINASE INHIBITORS



(I)

(57) **Abstract:** Objects of the present invention are the compounds of formula (I), their pharmaceutically acceptable salts, enantiomeric forms, diastereoisomers and racemates, the preparation of the above compounds, medicaments containing them and their manufacture, as well as the use of the above compounds in the control or prevention of illnesses such as cancer.

(22) **International Filing Date:**
16 April 2010 (16.04.2010)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
61/214,327 22 April 2009 (22.04.2009) US

(71) **Applicants** (*for all designated States except US*): **PRESIDENT AND FELLOWS OF HARVARD COLLEGE** [US/US]; 17 Quincy Street, Cambridge, MA 02138 (US). **CHILDREN'S MEDICAL CENTER CORPORA-**

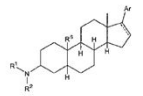
02140 (US). **CZAKÓ, Barbara** [H
Avenue, Apt. 16N, Cambridge, MA 02
László [HU/US]; 700 Huron Avenu
bridge, MA 02138 (US). **MAMMOT**
636 Washington Street, Apt. 2, Bro
(US). **INGBER, Donald, E.** [US/US
Street, Boston, MA 02116 (US).

(74) **Agent: BAKER, C., Hunter**; Wolf, (
P.C., 600 Atlantic Avenue, Boston
(US).

(81) **Designated States** (*unless otherwise kind of national protection available*):
AO, AT, AU, AZ, BA, BB, BG, BH,

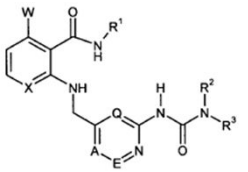
[Cont

(54) **Title**: ANGIOGENESIS INHIBITORS



(I)

(57) **Abstract**: Compounds of Struc
pharmaceutically acceptable salts th
inhibitors of angiogenesis:



(I),

combinations c
A at least one c
of angiogenesis inhibitors of general formula (I) and as compound B at least one compound from the group of histone deacetylase inhibitors (HDAC) of general formula (II) and their use for the treatment of different diseases resulting by persistent angiogenesis, are described.

(54) **Title:** SPIRO SUBSTITUTED COMPOUNDS AS ANGIOGENESIS INHIBITORS

(19) 世界知的所有権機関
国際事務局

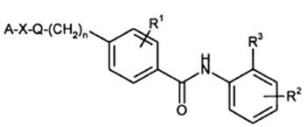
(43) 国際公開日
2 月 17 日(17.02.2011)

PCT

(10) 国際公開番号
WO 2011/019065 A1

分類:
00 (2006.01) *A61P 35/00* (2006.01)

番９８号 大日本住友製薬株式会社内 Osaka
(JP). 佐藤 英史(SATO, Hideshi) [JP/JP]; 〒5540022
丁目１番９８
Osaka (JP).



(II),

(54) **Title:** NEW HETEROCYCLIC COMPOUNDS FOR THE INHIBITION OF INTEGRINS AND USE THEREOF

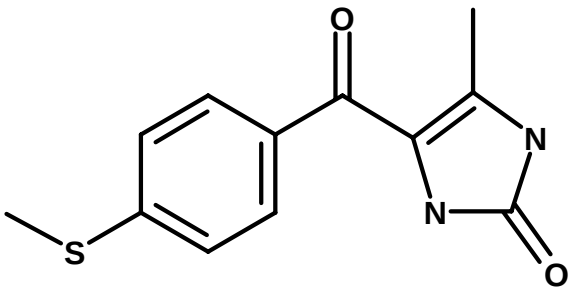
(57) **Abstract:** The present invention is related to a compound of formula (I), wherein A is a radical selected from the group comprising aromatic heterocyclic 5-membered ring systems; Ar is a radical selected from the group comprising optionally substituted 5- and 6-membered aromatic ring systems, whereby the ring system contains 0, 1, 2 or 3 heteroatoms selected from the group comprising N, O and S; Z is a radical individually and independently selected from the group $(CH_2)_n$-E-$(CH_2)_m$-L-$(CH_2)_k$ and $(CH_2)_m$-L-$(CH_2)_k$, wherein E is a radical which is either absent or present, whereby if E is present, E is selected from the group comprising O, S, NH, NR^a, CO, SO, SO_2, acetylene and substituted ethylene; L is a radical which is either absent or present, whereby if L is present, L is individually and independently selected from the group comprising O, S, NH, NR^b, CO, SO, SO_2, substituted ethylene and acetylene; and k, m and n are individually and independently O, 1, 2 or 3; ψ is a radical of formula (II), wherein Q is a radical selected from the group comprising a direct bond, Cl-C4alkyl, C=O, C=S, O, S, CR^cR^b, NR^d-NR^b, N=N, CR^d=N, N=CR^d, (C=O)-O, 0-(C=O), SO_2, NR^a, (C=O)-NR^c, NR^a-(C=O)-NR^b, NR^c-(C=O), 0-(C=0)-NR^c, NR^c-(C=0)-0, NR^c-(C=S), (C=S)-NR^c, NR^c-(C=S)-NR^d, NR^c-SO_2 and SO_2-NR^c. R1, R^a, R^b, R^c and R^d are radicals which are individually and independently selected from

種類の国内保
AT, AU, AZ, BA,
CH, CL, CN, CO,
C, EE, EG, ES, FI,
ID, ID, IL, IN, IS,
LA, LC, LK, LR,
, MK, MN, MW,
OM, PE, PG, PH,
SK, SL, SM, ST,
UA, UG, US, UZ,

Biological Activity: Positive Aspects

Among the different properties of chemical compounds biological activity plays a particular role, because it can provide the reason for their medical applications.

Structure → Biological Activity → Drug Name



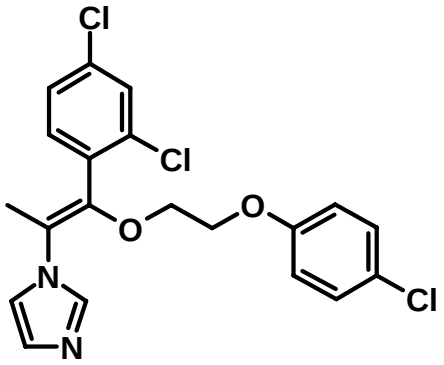
Cardiotonic

Enoximone

Biological Activity: Positive Aspects

Among the different properties of chemical compounds biological activity plays a particular role, because it can provide the reason for their medical applications.

Structure → Biological Activity → Drug Name



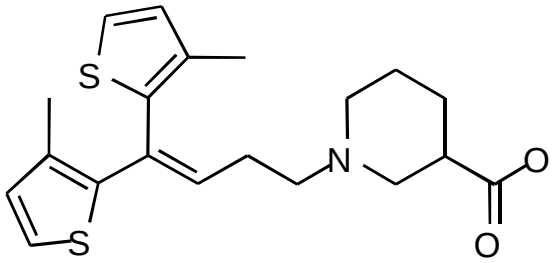
Antifungal

Omoconasole

Biological Activity: Positive Aspects

Among the different properties of chemical compounds biological activity plays a particular role, because it can provide the reason for their medical applications.

Structure → Biological Activity → Drug Name



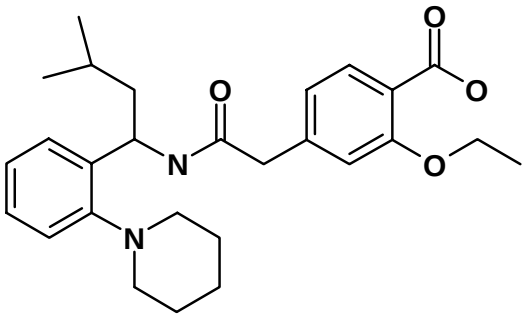
Antiepileptic,
Anxiolytic

Tiagabine

Biological Activity: Positive Aspects

Among the different properties of chemical compounds biological activity plays a particular role, because it can provide the reason for their medical applications.

Structure → Biological Activity → Drug Name



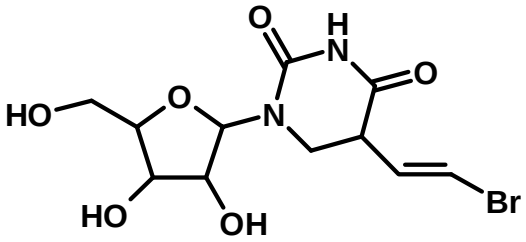
Antidiabetic, Insulin Secretagogues

Repaglinide

Biological Activity: Negative Aspects

On the other hand, due to its biological activity, chemical compound may have some adverse and toxic actions prevented its use in medical practice.

Structure ⟶ Biological Activity ⟶ Drug/Chemical



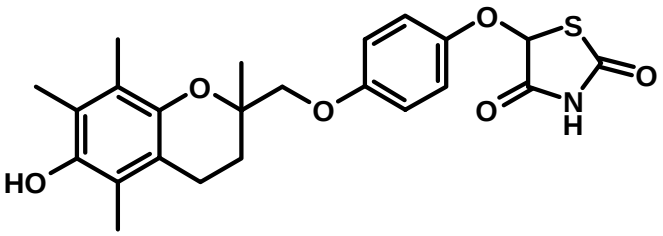
Antiviral,
Antitumor,
Neurotoxicity

Sorivudine

Biological Activity: Negative Aspects

On the other hand, due to its biological activity, chemical compound may have some adverse and toxic actions prevented its use in medical practice.

Structure ⟶ Biological Activity ⟶ Drug/Chemical



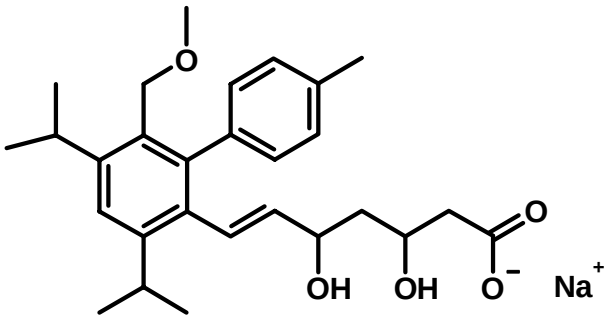
Antidiabetic, Hepatotoxicity

Troglitazone

Biological Activity: Negative Aspects

On the other hand, due to its biological activity, chemical compound may have some adverse and toxic actions prevented its use in medical practice.

Structure ⟶ Biological Activity ⟶ Drug/Chemical



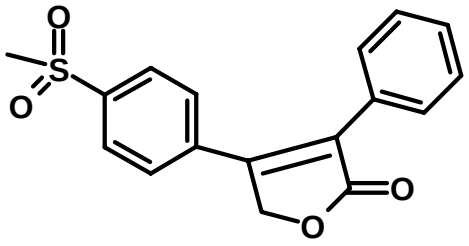
Anticholesterolemic, Baycol

Rhabdomyolysis

Biological Activity: Negative Aspects

On the other hand, due to its biological activity, chemical compound may have some adverse and toxic actions prevented its use in medical practice.

Structure ⟶ Biological Activity ⟶ Drug/Chemical



Antiarthritic,
Antiinflammatory,
COX-2 inhibitor,
Heart attack

Vioxx

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

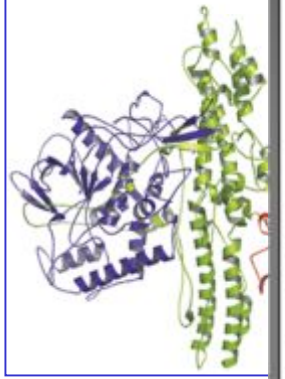
Botox

If Botox was not exactl
campaign's leitmotiv w
denied using it, but the

Botox is the trade-mark
botulinum. According t
addition to its cosmetic
treatment of crossed ey

Allergan spokeswoman
according to recent stat
60% of Allergan's worl

Type A is one of seven
different immunologic
Dysport that differs slig
No other antigenic toxi



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$212 Million Compensation for Wrinkle-Smoothing Botox Injection

Submitted by Davell Wilkins on Sat, 04/30/2011 - 13:52 **Health** **TNM** **Allergan**

ALLERGAN

The jury of Virginia 6 retweet U. S. District Court has ordered the Allergan Inc. to pay $212 million to a man who has claimed that injections of wrinkle-smoothing Botox left him with brain damage. Afterwards, on Thursday, the company has claimed that the 67-years old-man, Douglas M. Ray, was granted with an amount of $12 million as compensatory damages and $200 million as punitive damages.

The Botox is a purified form of the poison botulinum and given as an injection to smooth the wrinkles further, it is licensed to treat the muscular stiffness of the fingers and arms.

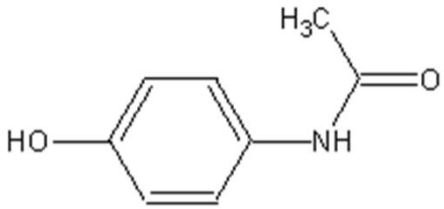
Internet and Web2.0

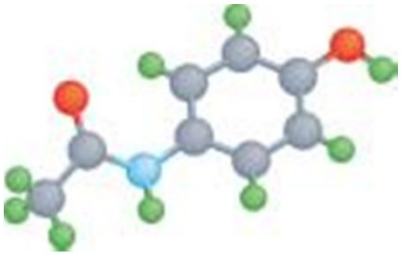
Sohu.com Inc. Revenue Increases
Twitter for Social Networking and Broadcasting
Wal-Mart Online Services Trial
New Study Enquires the Parents' Fear of Cyber Dangers
Justice Department Approves ITA Deal with Google

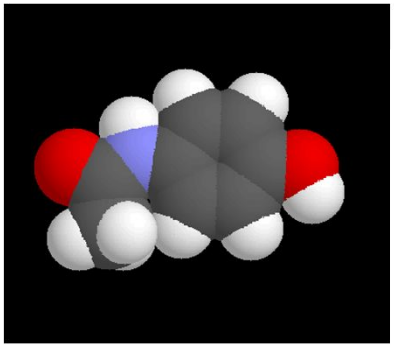
more

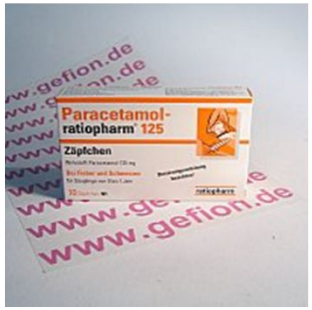
Nobody has the comprehensive information about biological activity profile for any pharmaceutical.

Acetaminophen (Paracetamol): Launched in 1900



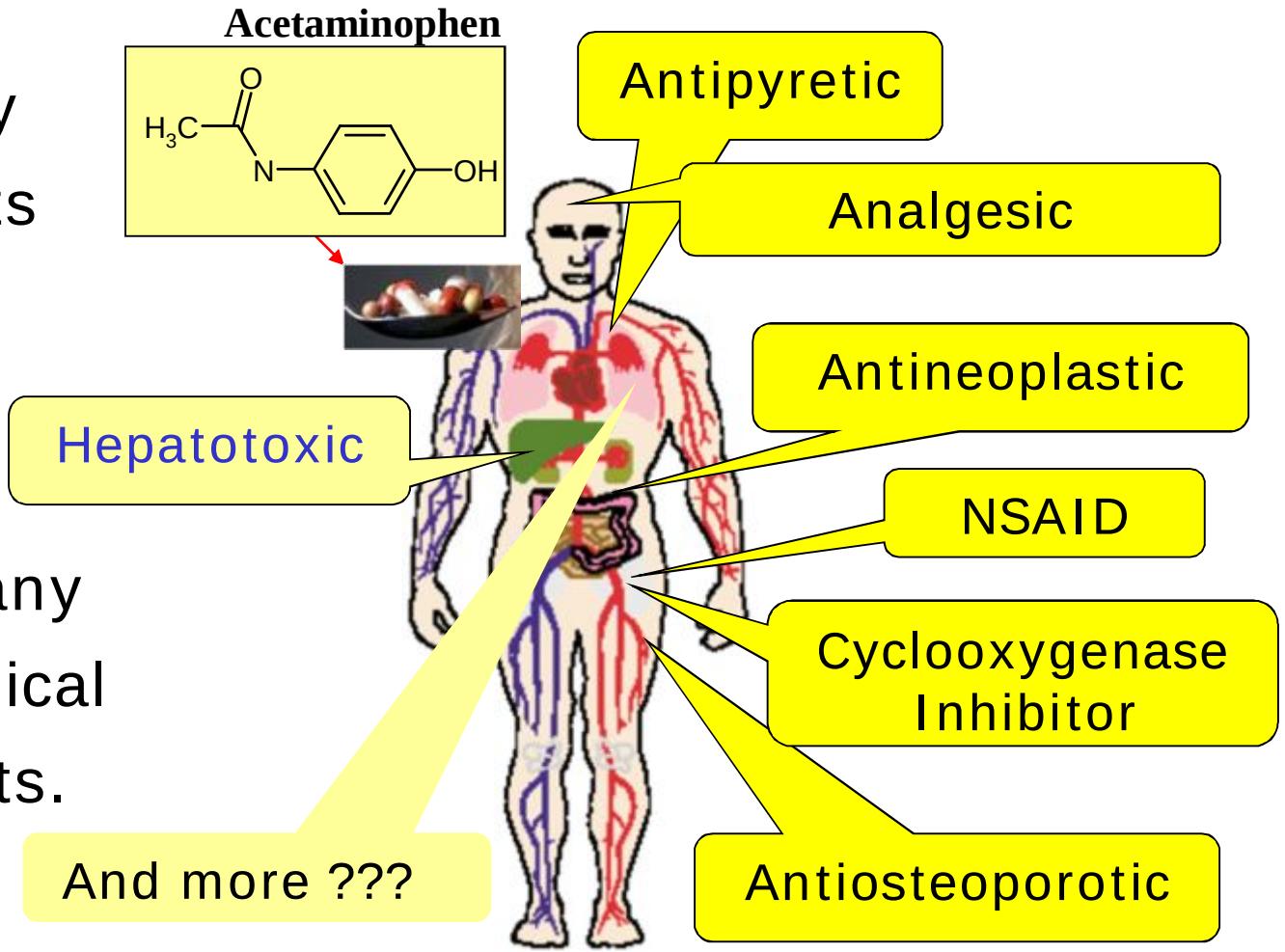




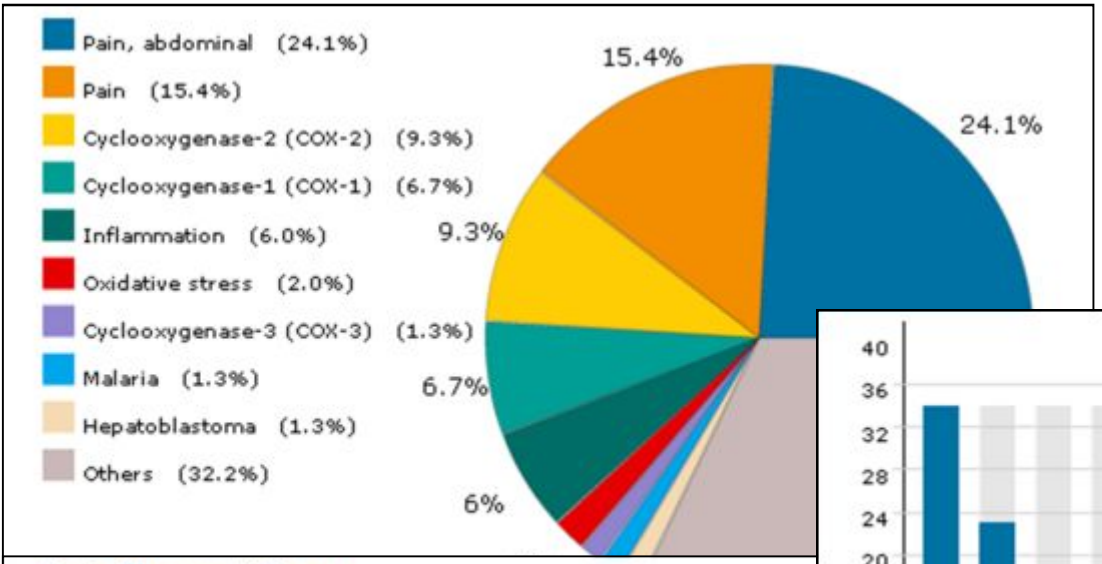


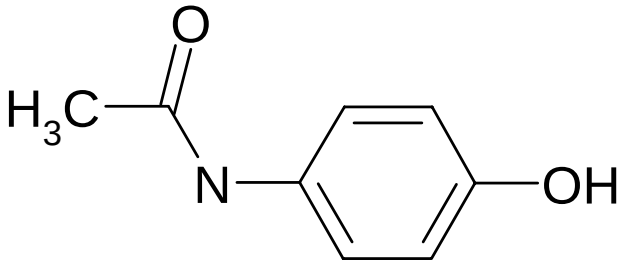
Drug Interaction with a Human Organism

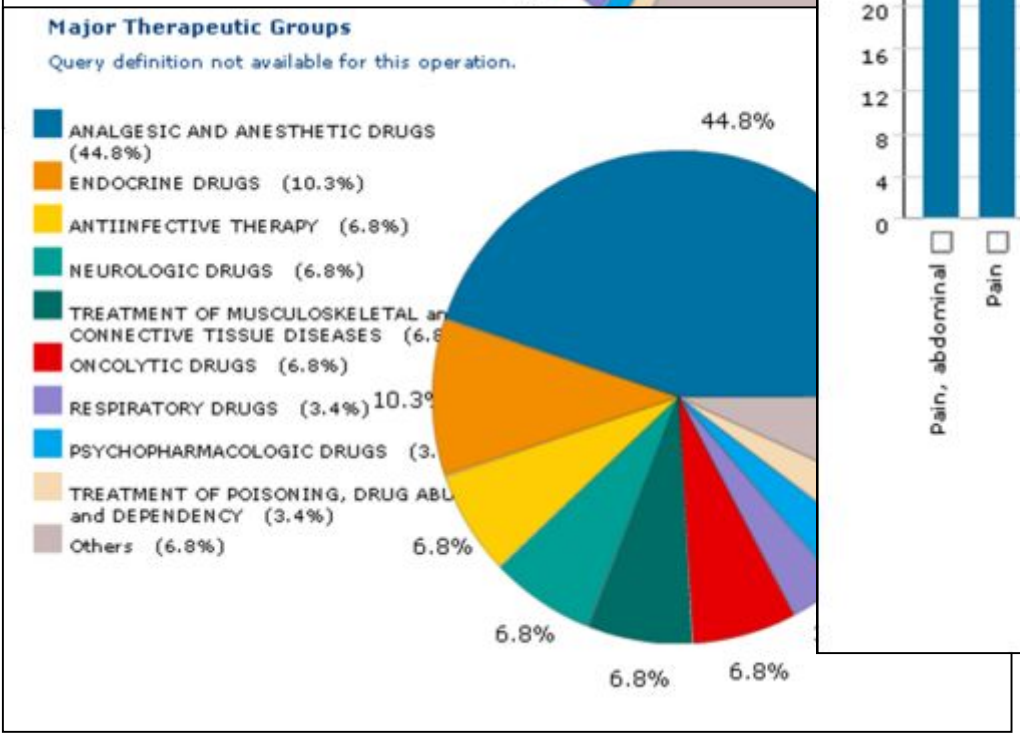
Typically, any drug interacts with many targets, that might be a cause for many pharmacological & toxic effects.

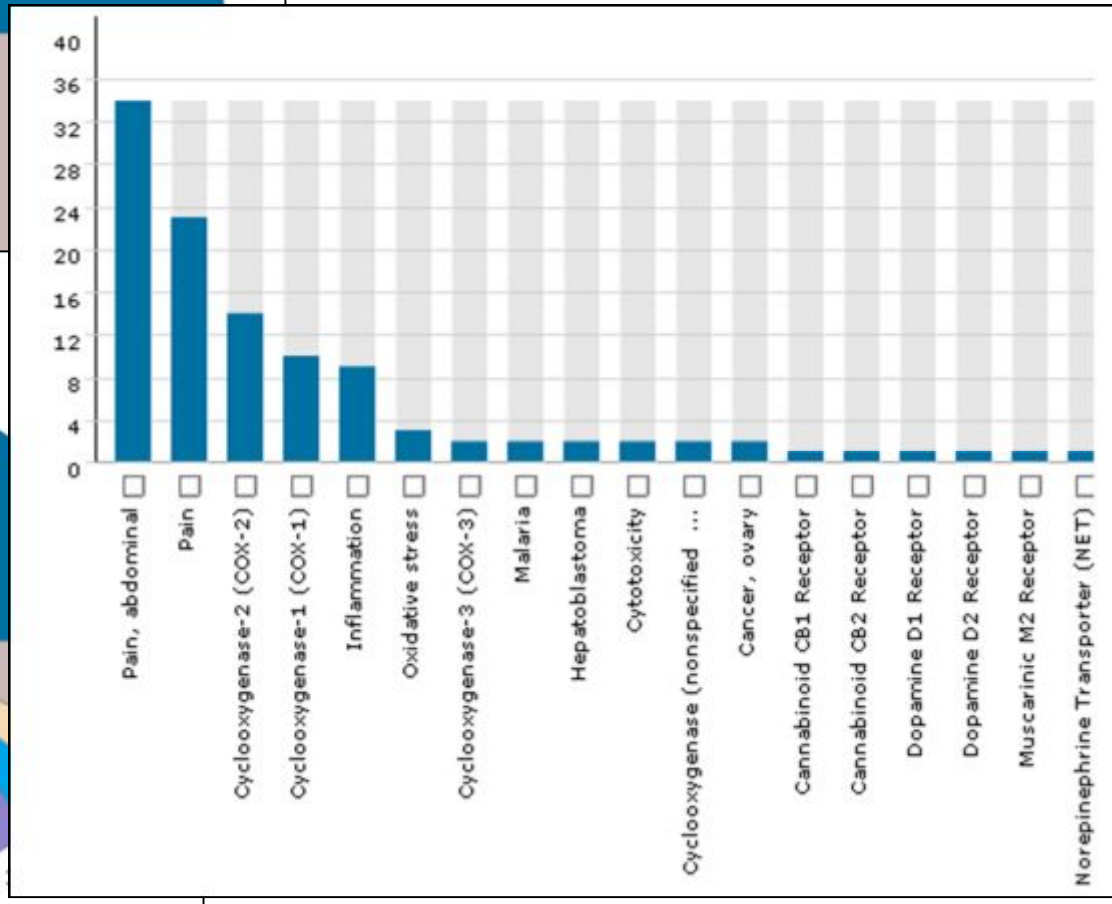


Pharmacological Studies of Acetaminophen









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

How to estimate the biological activity of chemical compounds at the early stages of research?

The cost of experimental testing of millions chemical compounds versus thousands targets is rising multiplicatively.

1 target 2 targets 3 targets ...

!

Samples of chemical compounds may be not available at these stages.

Computer prediction is the “Method of the Choice”.

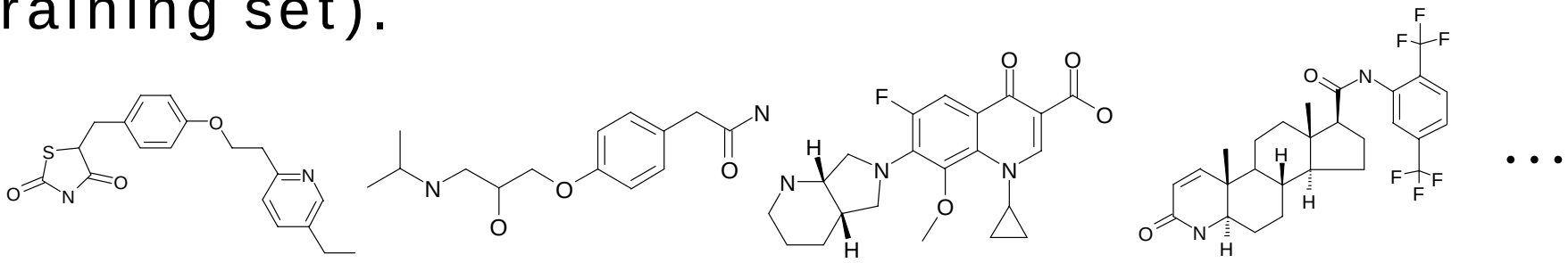
Outline

- Chemical compounds & biological activity
- **Computational approaches to prediction of biological activity.**
- PASS: Prediction of Activity Spectra for Substances
- PharmaExpert: Tool for analysis of PASS predictions
- GUSAR: General Unrestrained Structure-Activity Relationships
- Summary

Ligand-based approaches to prediction of biological activity

Prerequisites:

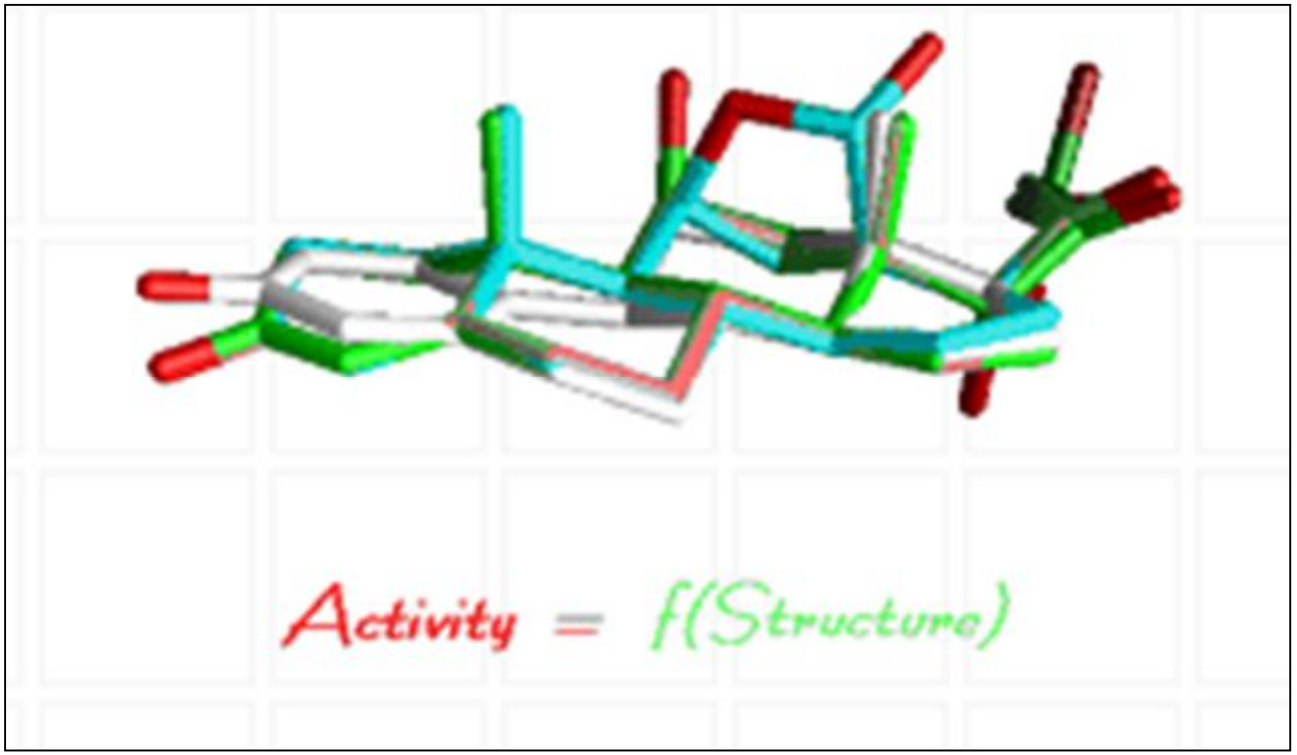
Set of ligands with known biological activity (training set).



IC_{50} (μM):	**0.1**	**12**	**87**	**0.03**	**. . .**
Activity:	**Active**	**Inactive**	**Inactive**	**Active**	**. . .**

Methods:

(Quantitative) Structure-Activity Relationships (Q)SAR, Pharmacophore model.



http://www.qsar.org/

$$A = A_0 + k_1*D_1 + k_2*D_2 + k_3*D_3 + k_4*D_4 + k_5*D_5 + \ldots$$ (Free-Wilson)

$$\log 1/C = a*\pi + b*\pi^2 + c*\sigma + d*E_s + \text{const}$$ (Hansch)

MLR, ANN, SVM, etc.

Similarity principle: “Me-too-compounds” design

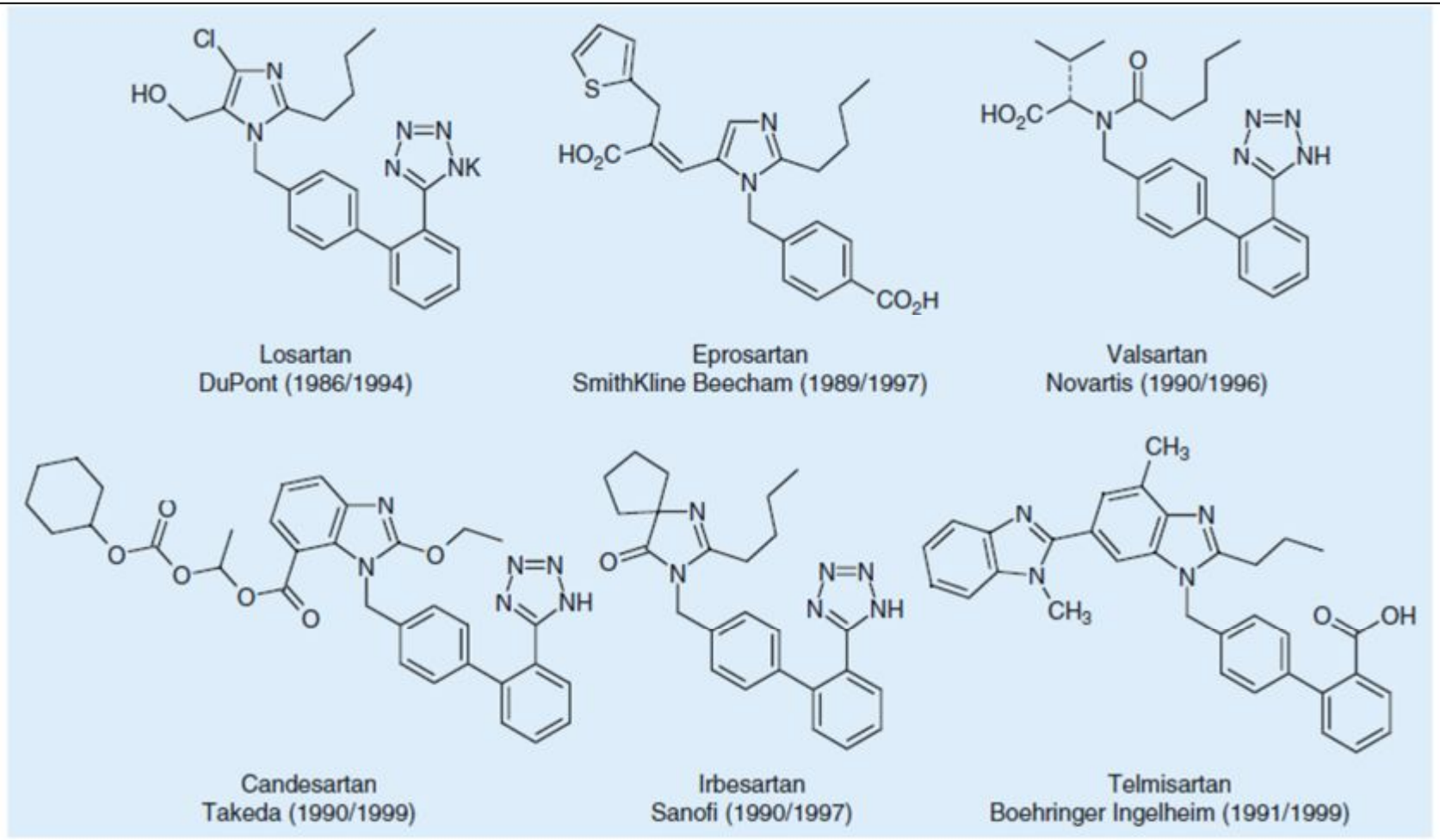


FIGURE 6.1 Angiotensin AT1 receptor antagonists derived from losartan. Despite their structural similarity of the structures, it can be assumed that the corresponding discoveries were made independently. The first year under parentheses is the basic patent year, the second one is the year of the first launch.

Wermuth C. *The Practice of Medicinal Chemistry*, 3rd edition, 2008, p.126.

Similarity-based prediction of biological activity

Tanimoto Coefficient of similarity for Molecules A and B:

$$Sab = \frac{c}{a + b - c}$$

Where:

a = bits set to 1 in A,

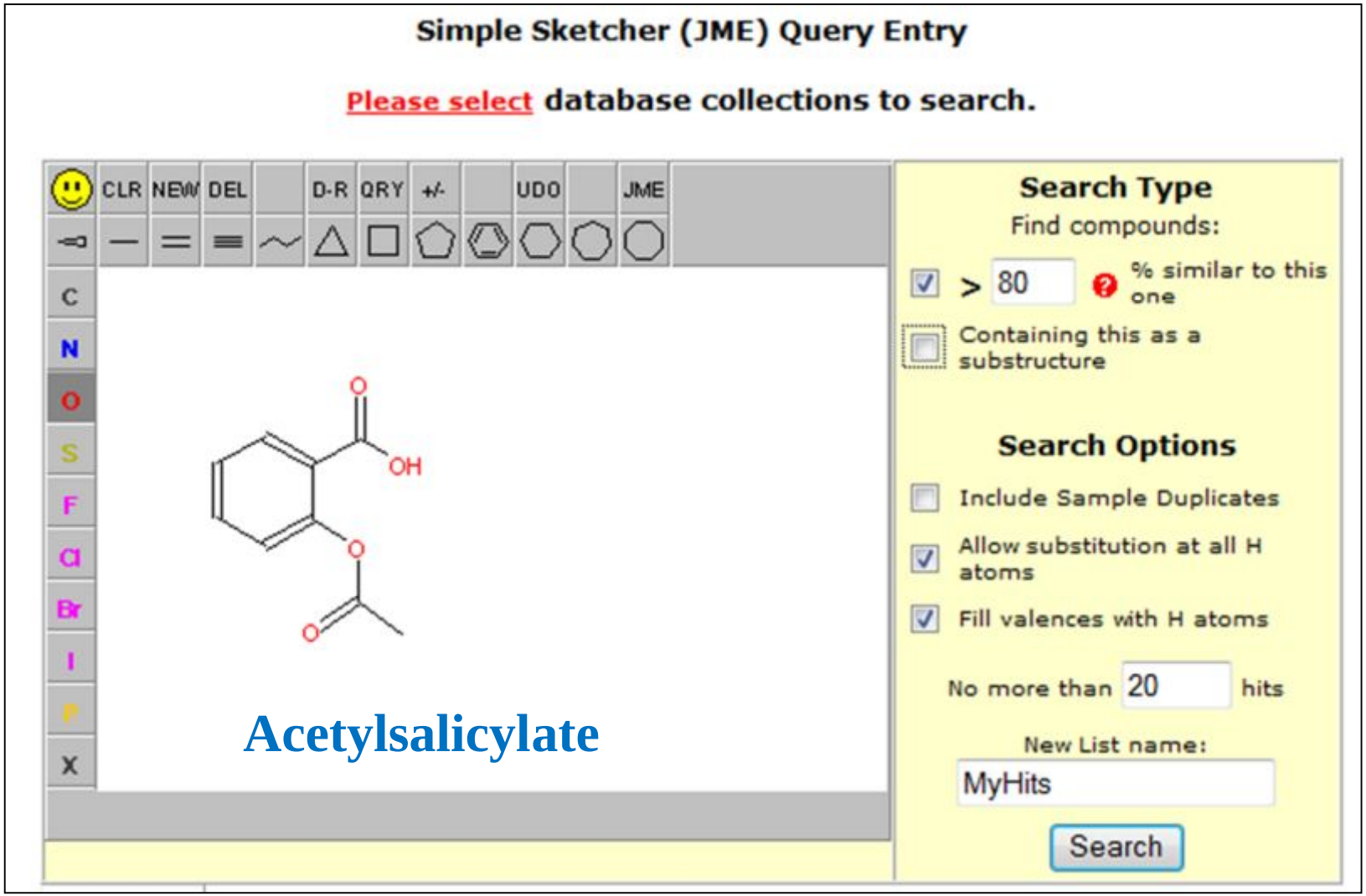
b = bits set to 1 in B,

c = number of 1 bits common to both

Range is 0 to 1.

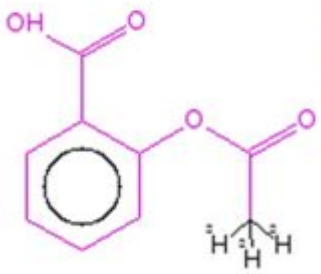
Value of 1 does not mean the molecules are identical.

Similarity search in ChemNavigator Library



Some results of similarity search for Acetylsalicylate

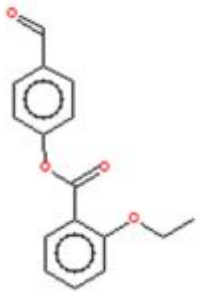
#1: CNC-315394159



Structure ID:	**180927362**
Collection:	Archived Compounds
Matched by:	Similarity: 99%
Major MW:	183.18
cLogP:	1.38
Min Purity:	90
Shipping Window:	30 Days

TC=99%

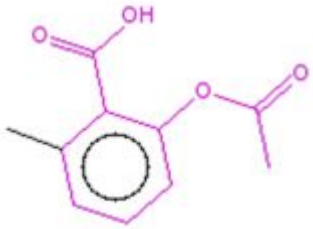
#4: CNC-310472239



Structure ID:	**69154582**
Collection:	Virtual Custom Chemistry
Matched by:	Similarity: 86%
Major MW:	270.28
cLogP:	3.72
Min Purity:	92
Shipping Window:	60 Days

TC=86%

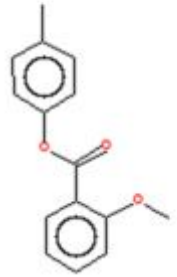
#2: CNC-315419843



Structure ID:	**79937939**
Collection:	Archived Compounds
Matched by:	Similarity: 87%
Major MW:	194.19
cLogP:	1.86
Min Purity:	90
Shipping Window:	30 Days

TC=87%

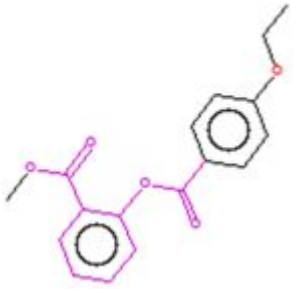
#5: CNC-308281405



Structure ID:	**36090778**
Collection:	Aldrich Market Select Screening Compounds
Matched by:	Similarity: 84%
Major MW:	242.27
cLogP:	4.12
Min Purity:	92
Shipping Window:	14 Days

TC=84%

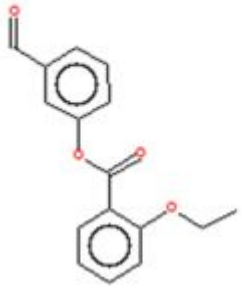
#3: CNC-310472181



Structure ID:	**69154554**
Collection:	Virtual Custom Chemistry
Matched by:	Similarity: 86%
Major MW:	300.31
cLogP:	4.15
Min Purity:	92
Shipping Window:	60 Days

TC=86%

#6: CNC-310472240



Structure ID:	**69154583**
Collection:	Virtual Custom Chemistry
Matched by:	Similarity: 84%
Major MW:	270.28
cLogP:	3.72
Min Purity:	92
Shipping Window:	60 Days

TC=84%

Do Structurally Similar Mo

Yvonne C. Martin,*,† James L. Kofron,

Global Pharmaceutical Research and Devel

Received April 12, 2002

To design diverse combinatori
collection, computational che
already chosen for the combin
this report shows that for I
screening assays, there is only
to an active is itself active. Al
screening and docking to three
compounds occurs not only be
similarity calculations but al
the target macromolecule in
probabilistic nature of library

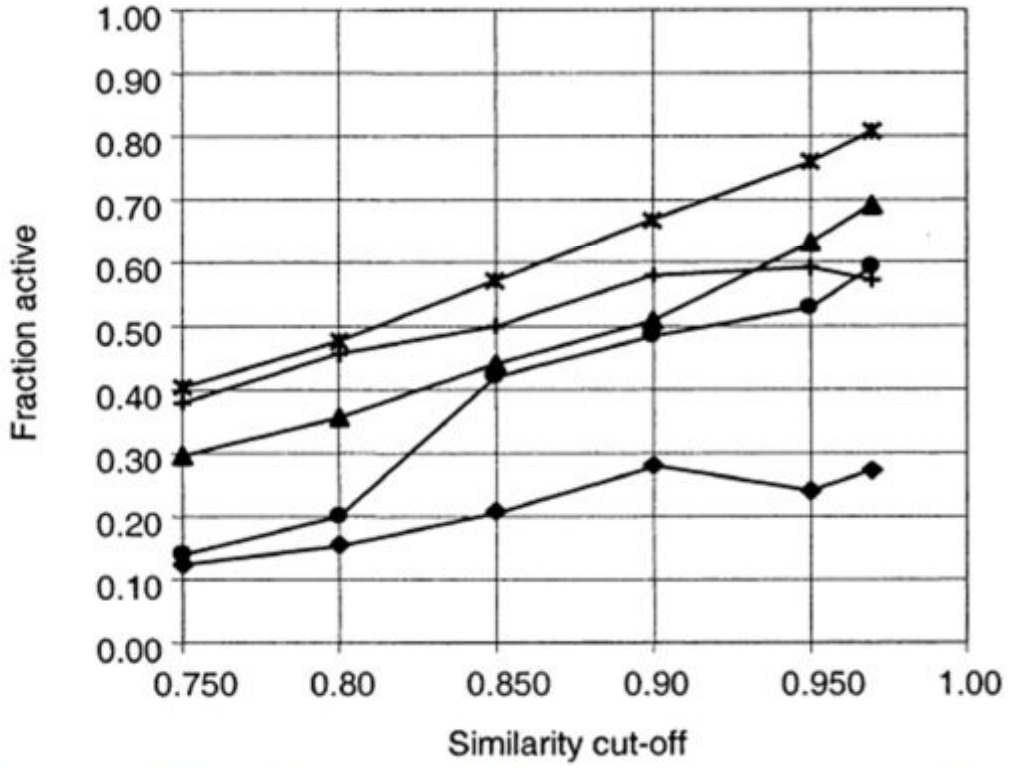


Figure 4. For five selected assays, a comparison of the fraction of similars to a potent active that are themselves active as a function of the similarity threshold used for the searching.

...”there is only a 30% chance that a compound that is > 0.85 (Tanimoto) similar to an active is itself active”.

Similarity & Dissimilarity terms have sense only in relation to the particular biological activity

“The concept of diversity only makes sense within a frame of reference. Within such a frame of reference **- in the case of medicinal chemistry, the biological assay** - a particular attribute carries far greater weight than any other. The difference may be light years on the relevant axis, but mere millimeters on all other axes. If this key axis (unit of measurement = light years) were missing from the frame of reference (equivalent to the comparative examination of the diversity of chemical structures irrespective of their effect in biological tests {= structural diversity}) and one were to zoom in sufficiently on the picture, then differences of mere millimeters may erroneously appear relevant”.

Roth H.-J. *Cur. Opin. Chem. Biol*., 2005, 9: 293–295.

Structural similarity might be a reason for rejection of patent application

Go to MPEP - Table of Contents

browse before

2144.09 Close Structural Similarity Between Chemical Compounds (Homologs, Analogues, Isomers) [R-6] - 2100 Patentability

2144.09 Close Structural Similarity Between Chemical Compounds (Homologs, Analogues, Isomers) [R-6]

>

I. < REJECTION BASED ON CLOSE STRUCTURAL SIMILARITY IS FOUNDED ON THE EXPECTATION THAT COMPOUNDS SIMILAR IN STRUCTURE WILL HAVE SIMILAR PROPERTIES

A *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (discussed in more detail below) and *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991) (discussed below and in MPEP § 2144) for an extensive review of the case law pertaining to obviousness based on close structural similarity of chemical compounds. See also MPEP § 2144.08, paragraph II.A.4.(c).

>

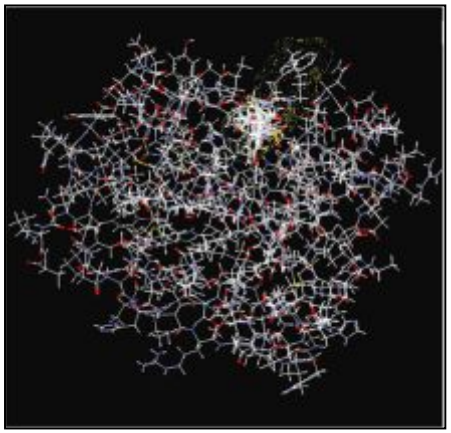
II. < HOMOLOGY AND ISOMERISM ARE FACTS WHICH MUST BE CONSIDERED WITH ALL OTHER RELEVANT FACTS IN DETERMINING OBVIOUSNESS

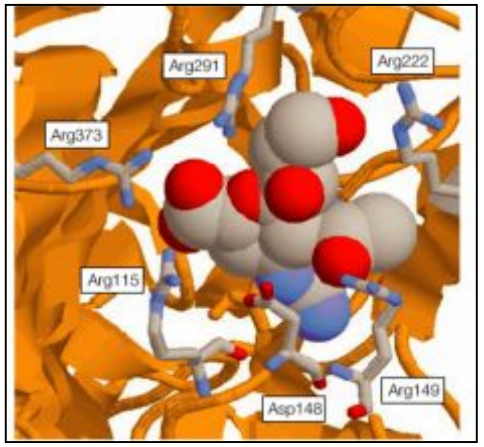
Compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH_2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977). See also *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (stereoisomers *prima facie* obvious).

Target-based approaches to prediction of biological activity

Prerequisites:

- ✓ Data about 3D structure of target macromolecule (X-ray, NMR, Modeling).
- ✓ Data about 3D structure of active site (binding site).





Methods:

- ✓ Docking and estimation of binding energy (scoring function).
- ✓ Active site mapping and *de novo* design.

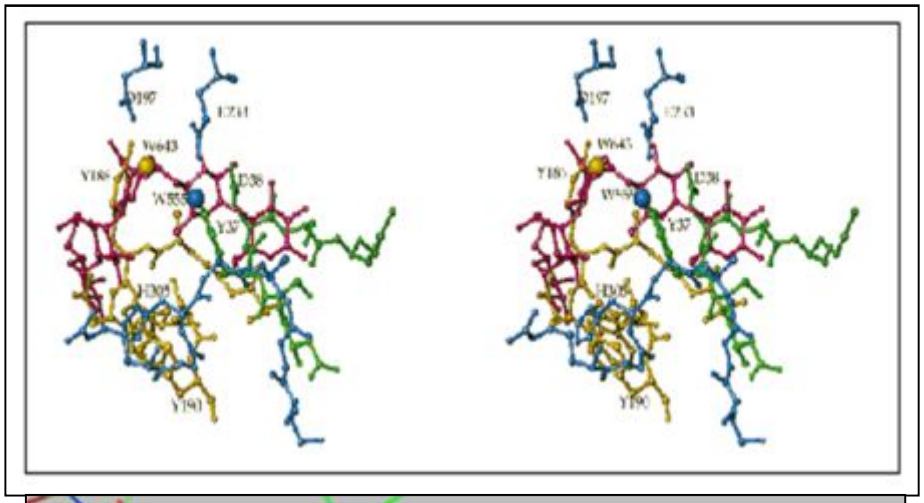
Molecular mechanics

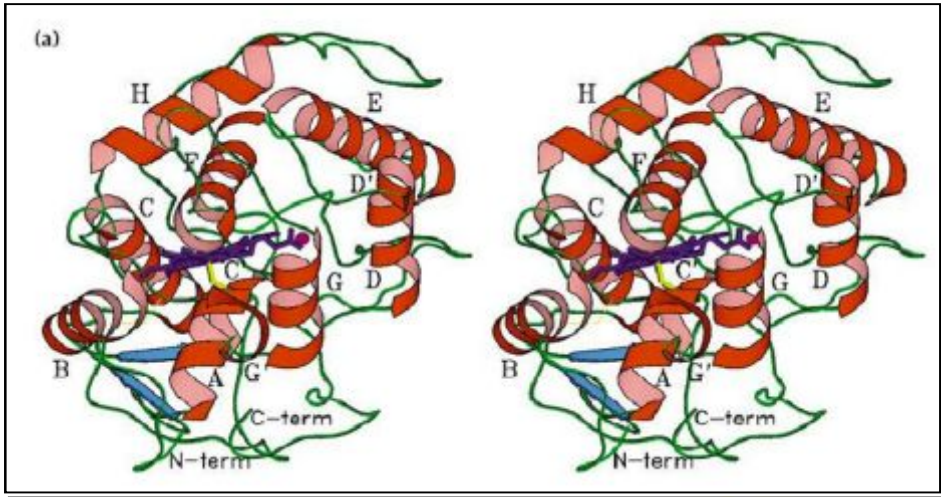
Description of molecules by “force fields”

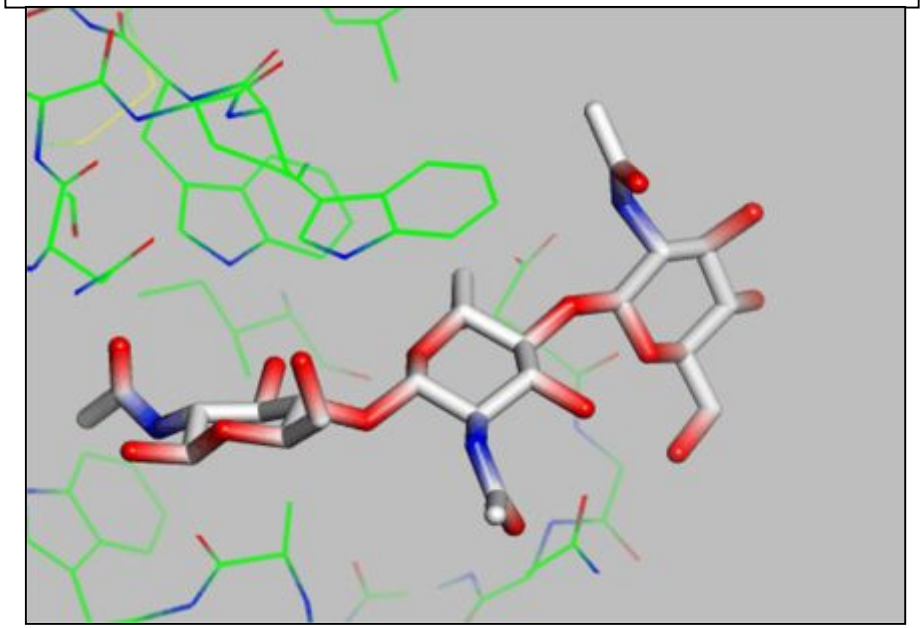
- *Atom types*
- *Bond types*
- *Relative positions of atoms*
- *General energy is the sum of components:*

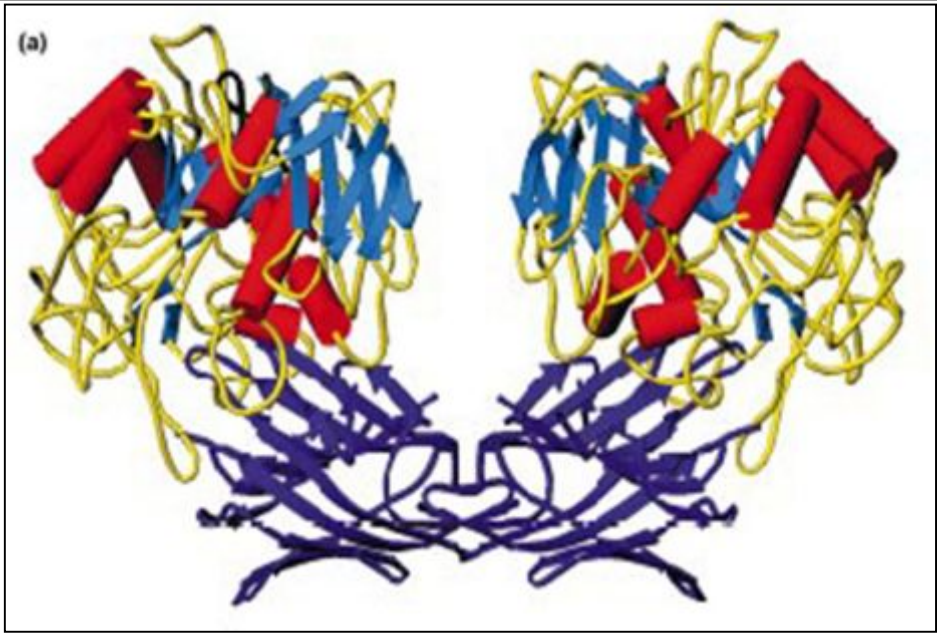
$$E_{\text{total}} = E_{\text{stretch}} + E_{\text{bend}} + E_{\text{torsion}} + E_{\text{vdw}} + E_{\text{electrostatic}} + \cdots$$

Visualization techniques









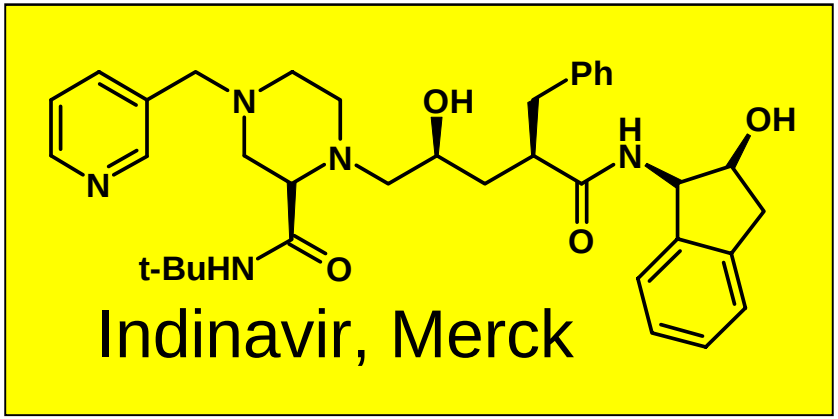
Target-Based Drug Design

Problems:

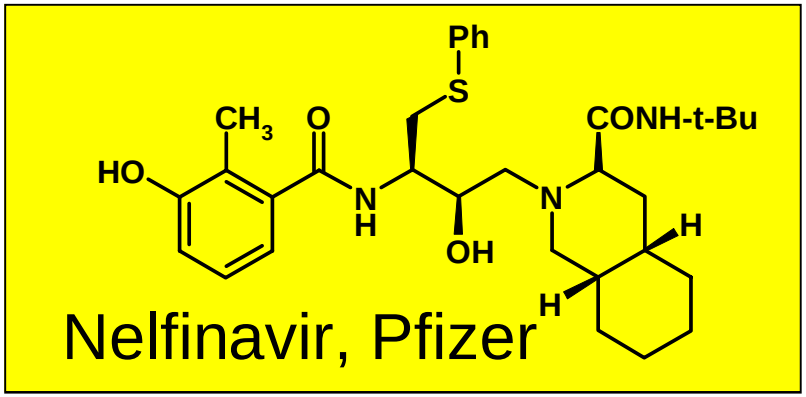
- ✓ 3D structure of the target is necessary.
- ✓ 3D structure in crystal vs. 3D structure in solution.
- ✓ Approximation of energy binding estimates.
- ✓ Approximation of 3D conformation of flexible ligands.

Examples of drugs developed on the basis of target-based drug design

HIV-1 protease inhibitors

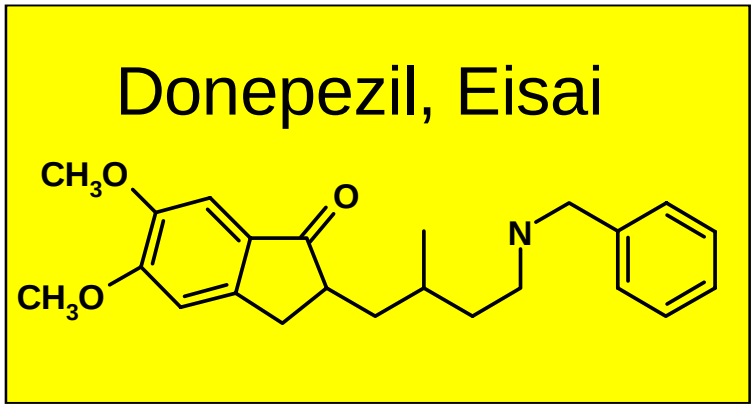


Indinavir, Merck

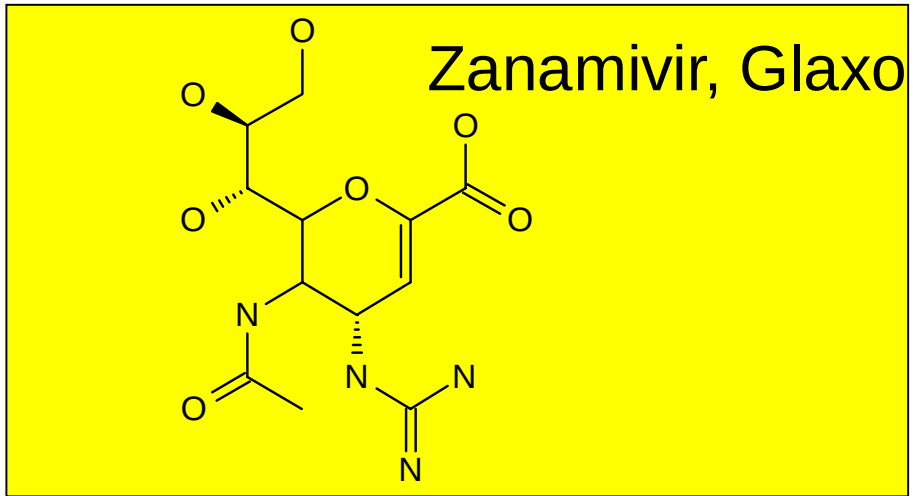


Nelfinavir, Pfizer

Alzheimer disease treatment (AChE inhibitor)



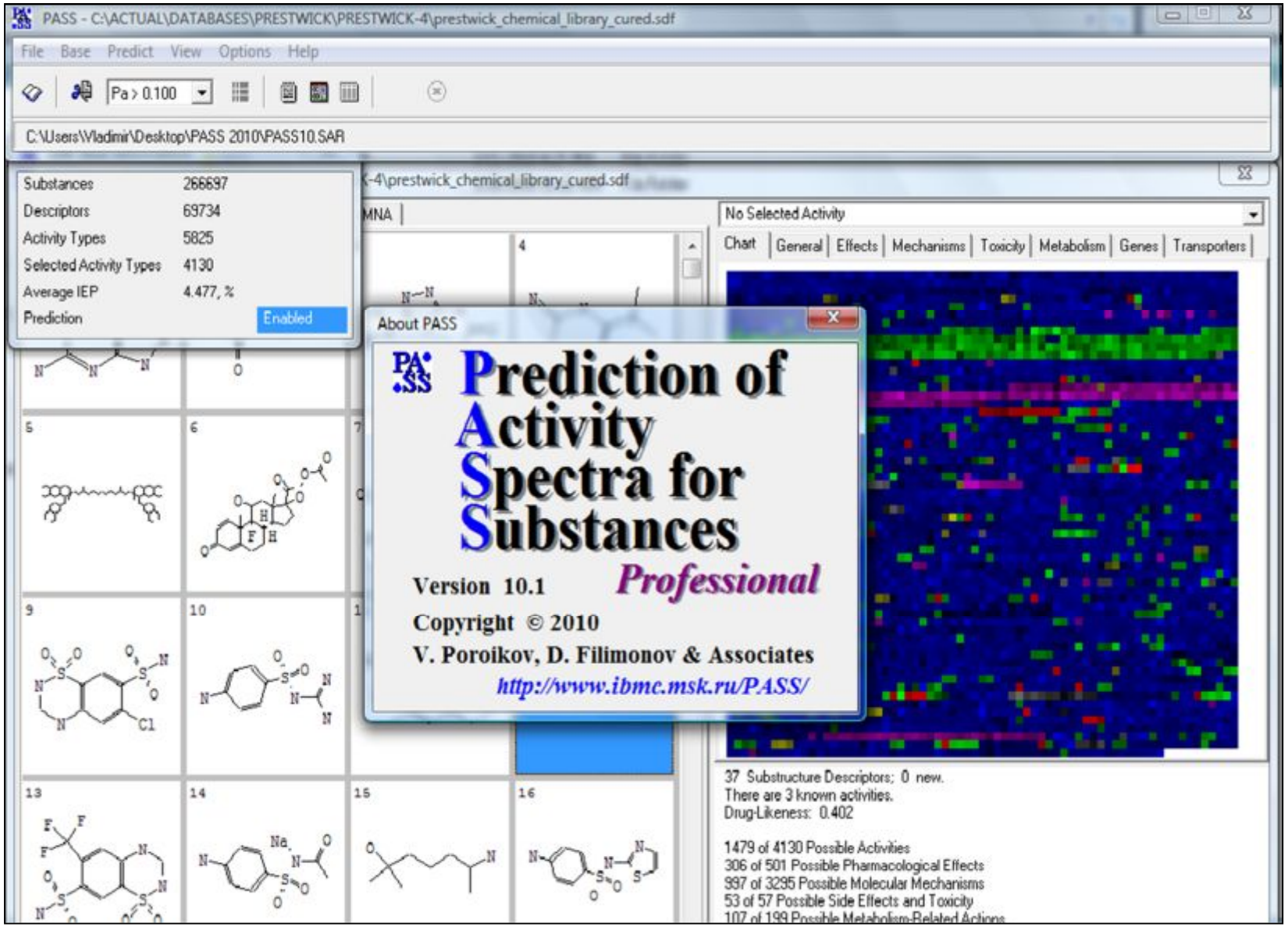
Flu A and B treatment (neuraminidase inhibitor)

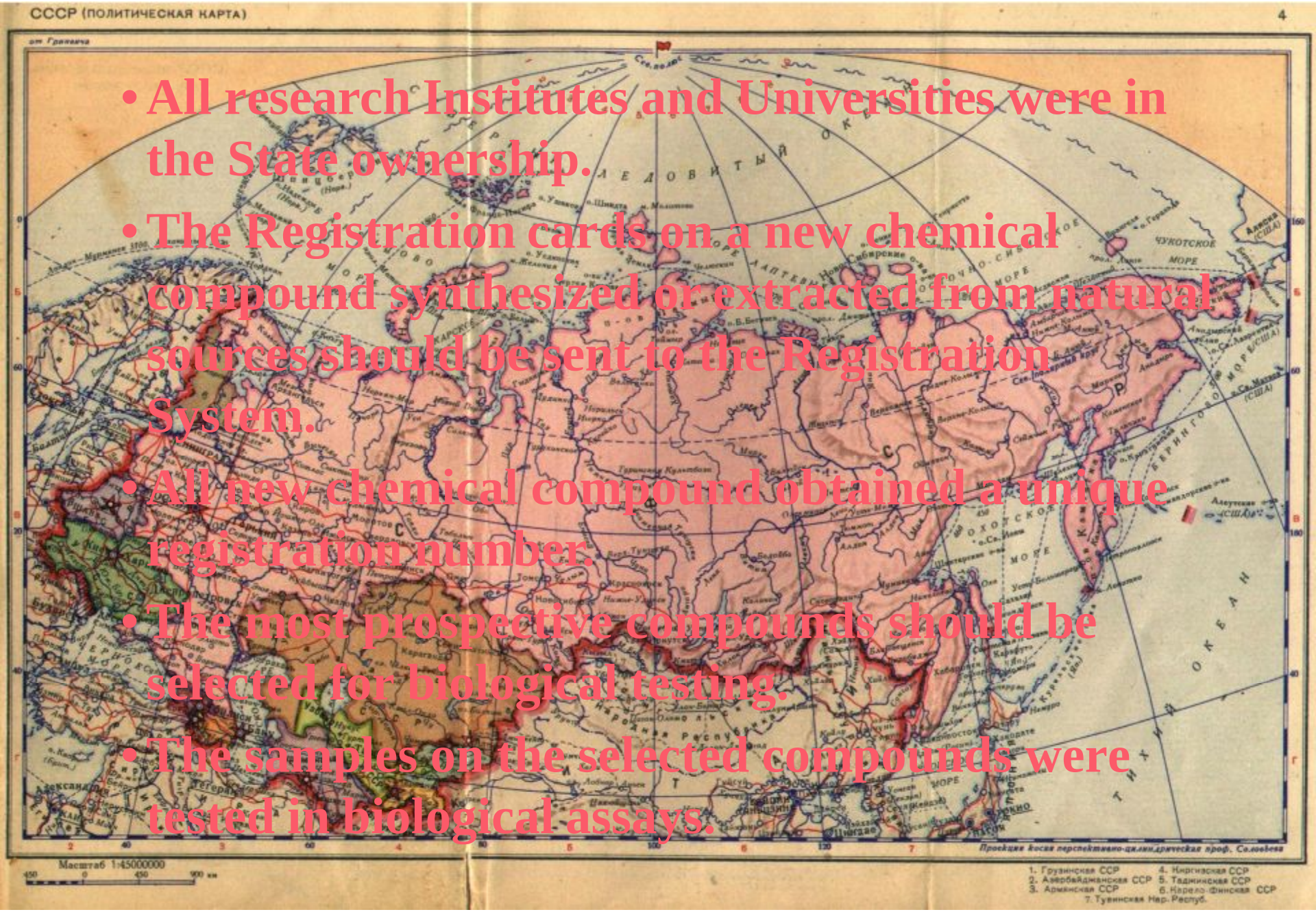


Outline

- Chemical compounds & biological activity
- Computational approaches to prediction of biological activity.
- **PASS: Prediction of Activity Spectra for Substances**
- PharmaExpert: Tool for analysis of PASS predictions
- GUSAR: General Unrestrained Structure-Activity Relationships
- Summary

PASS: Prediction of Activity Spectra for Substances




СССР (ПОЛИТИЧЕСКАЯ КАРТА)
4
• All research Institutes and Universities were in the State ownership.
• The Registration cards on a new chemical compound synthesized or extracted from natural sources should be sent to the Registration System.
• All new chemical compound obtained a unique registration number.
• The most prospective compounds should be selected for biological testing.
• The samples on the selected compounds were tested in biological assays.
Масштаб 1:45000000
1. Грузинская ССР
2. Азербайджанская ССР
3. Армянская ССР
4. Киргизская ССР
5. Таджикская ССР
6. Карело-Финская ССР
7. Тувинская Нар. Республ.

PASS History: Permanent Updating and Improvement

1972 Collection of the training set started (USSR National System of New Chemical Compounds Registration).

1976-1993 Early versions of different computer programs for biological activity spectra prediction (V.A. Avidon; V.E. Golender & A.B. Rosenblit)

1995 First publication about PASS software: 9,314 compounds; 114 activities, AP~76%.

1998 PASS C&T version 4.0: 30,537 compounds; 541 activities, AP~82%.

2005 PASS Pro 2005: ~60,000 compounds; ~2500 activities, AP~89%.

2009 PASS Professional version 9.1: ~205,000 compounds; 3750 activities, AP ~95%.

2011 PASS Pro 11.4: 250,407 compounds; 4444 activities, AP ~95%.

PASS 11.4 Characteristics

✓ Training Set	➢ 250,407 drugs, drug-candidates and pharmacological substances comprise the training set.
✓ Biological Activity	➢ 4444 biological activities can be predicted (Active vs. Inactive)
✓ Chemical Structure	➢ Multilevel Neighborhoods of Atoms (MNA) descriptors (Filimonov et al., 1999).
✓ Mathematical Algorithm	➢ Bayesian approach was selected by comparison of many different methods (Filimonov & Poroikov, 2008).
✓ Validation	➢ Average accuracy of prediction in LOO CV for the whole training set is ~95%; robustness was shown using principal compounds from MDDR database (Poroikov et al., 2000).

Filimonov D.A. et al. J. Chem. Inform. Computer Sci., 1999, 39, 666.
Poroikov V.V. et al. J. Chem. Inform. Computer Sci., 2000, 40, 1349.
Filimonov D.A., Poroikov V.V. In: Chemoinformatics Approaches to Virtual Screening. RSC Publ., 2008, p.182-216.

PASS Validation (Experiment Design)

18977 compounds with 124 activities were selected from MDDR.

The set of compounds was 50 times divided at random into two equal subsets.

The first subset was used as the training set, the second one as the evaluation subset and vice versa (100 experiments).

20, 40, 60, 80% of information (activity/structure data) were excluded from the training set.

Average accuracy of prediction (IAP) was calculated for each type of activity.

Robustness of Biological Activity Spectra Predicting by Computer Program PASS for Noncongeneric Sets of Chemical Compounds

V. V. Poroikov,*,† D. A. Filimonov,† Yu. V. Borodina,† A. A. Lagunin,† and A. Kos‡

Institute of Biomedical Chemistry RAMS, Pogodinskaya Str., 10, Moscow 119832, Russia, and AKos Consulting & Solutions GmbH, Rossligasse 2, CH-4125 Riehen, Switzerland

Received March 1, 2000

The computer system PASS provides simultaneous prediction of several hundreds of biological activity types for any drug-like compound. The prediction is based on the analysis of structure−activity relationships of the training set including more than 30000 known biologically active compounds. In this paper we investigate the influence on the accuracy of predicting the types of activity with PASS by (a) reduction of the number of structures in the training set and (b) reduction of the number of known activities in the training set. The compounds from the MDDR database are used to create heterogeneous training and evaluation sets. We demonstrate that predictions are robust despite the exclusion of up to 60% of information.

INTRODUCTION

Traditional QSAR and 3D molecular modeling are successful at predicting the biological activities for chemical structures, provided they work with small number of types of activity and usually stay in the same chemical series.[1−5] Similarity searching[6,7] and clustering methods[7,8] can be used to separate compounds into structural groups[9] and for the prediction of biological activities and compound selection.[10]

Table 1. Some Predicted Biological Activities for Cavinton[a]

no.	Pa	Pi	activity	expt
1	0.929	0.004	peripheral vasodilator	
2	0.900	0.000	multiple sclerosis treatment	
3	0.855	0.005	vasodilator	+
4	0.844	0.003	abortion inducer	+
5	0.812	0.001	antineoplastic enhancer	
6	0.760	0.006	coronary vasodilator	+
7	0.732	0.007	spasmogenic	

What is the Biological Activity Spectrum?

Biological Activity Spectrum is the “intrinsic” property of the compound that reflects all biological activities, which can be found in the compound’s interaction with biological entity.

Poroikov V.V., Filimonov D.A., Boudunova A.P. (1993). Automatic Documentation and Mathematical Linguistics. Allerton Press, Inc., 27 (3), 40.

Filimonov D.A., Poroikov V.V., et. al. (1995). Experimental and Clinical Pharmacology, 58, 56 (Rus).

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

Geronikaki A., Poroikov V., et al. (1999). *Quant. Struct.-Activ. Relationships*, 18, 16.

Poroikov V.V., Filimonov D.A., et al. (2000). *J. Chem. Inform. Comput. Sci.*, 40, 1349.

Lagunin A., Stepanchikova A., Filimonov D., Poroikov V. (2000). *Bioinformatics*, 16, 747.

Poroikov V., Filimonov D. et al. (2001). *SAR & QSAR in Environ. Res.*, 12, 327.

Anzali S., Barnickel G., Cezanne B., Krug M., Filimonov D., Poroikov V. (2001). *J. Med. Chem.*, 44, 2432.

Poroikov V.V., Filimonov D.A. (2002). *J. Comput. Aid. Molecul. Des.*, 16, 819.

Stepanchikova A.V., Lagunin A.A., Filimonov D.A., Poroikov V.V. (2003). *Current Med. Chem.*, 10, 225.

Poroikov V. and Filimonov D. In: *Predictive Toxicology*. Ed. by Christoph Helma. Taylor & Francis, 2005, p.459-478.

Poroikov V., Filimonov D., Lagunin A. et al. (2007). *SAR & QSAR in Environmental Research*., 18, 101-110.

This Definition Significantly Differs from Some Others:

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

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

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

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

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

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

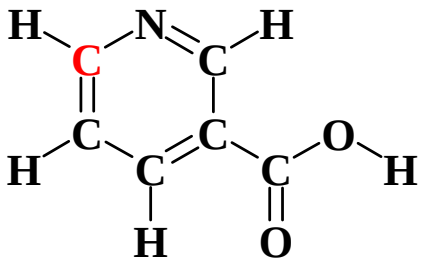
Information Included into PASS Activity Spectra (I)

- Anti-infective actions (e.g., Antileishmanial);
- Pharmacotherapeutic actions (e.g., Anxiolytic);
- Actions blocking a certain process (e.g., Apoptosis antagonist);
- Actions stimulated a certain process (e.g., Apoptosis agonist);
- Actions blocking activity of certain endogenous substance (e.g., Acetylcholine antagonist);
- Actions simulating activity of certain endogenous substance (e.g., Acetylcholine agonist);
- Action blocking a release of a certain endogenous substance (e.g., cytochrome C release inhibitor);
- Action stimulating a release of a certain endogenous substance (e.g., acetylcholine release stimulant);
- Action blocking an uptake of a certain endogenous substance (e.g., adenosine uptake inhibitor);
- Actions inhibiting a certain enzyme (e.g., 12 Lipoxygenase inhibitor);
- Actions stimulating action of a certain enzyme (e.g., ATPase stimulant);

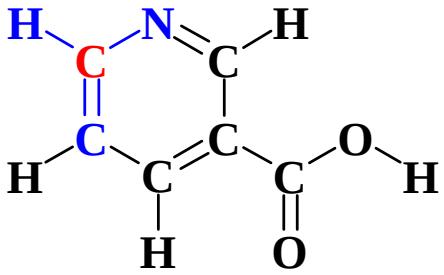
Information Included into PASS Activity Spectra (II)

- Actions blocking a certain receptor (e.g., 5 Hydroxytrypamine 1 agonist);
- Actions stimulating a certain receptor (e.g., 5 Hydroxytrypamine 1 antagonist);
- Actions blocking a certain channel (e.g., Chloride channel antagonist);
- Actions stimulating a certain channel (e.g., Calcium channel agonist);
- Actions blocking a certain transporter (e.g., GABA transporter 1 inhibitor);
- Actions that is a substrate of a certain metabolic enzyme (e.g., CYP3A4 substrate)
- Actions inhibiting a certain metabolic enzyme (e.g, CYP3A4 inhibitor)
- Actions inducing a certain metabolic enzyme (e.g., CYP3A4 inducer);
- Actions inhibiting a certain protein (e.g., Collagen inhibitor);
- Actions inhibiting an expression of a certain transcription factor (e.g., Transcription factor Rho inhibitor);
- Actions stimulating an expression of a certain transcription factor (e.g., TP53 expression enhancer);
- Actions that cause a certain adverse/toxic effect (e.g., Carcinogen).

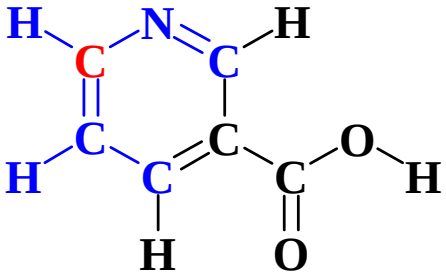
Multilevel Neighborhoods of Atoms (MNA) Descriptors



MNA / 0: C



MNA / 1: C(CN-H)



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

Filimonov D.A. et al. J. Chem. Inform. Computer Sci., 1999, 39, 666.

Prediction of Biological Activity Spectra

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

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

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

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

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

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

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

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.

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.

Stepanchikova A.V., Lagunin A.A., Filimonov D.A., Poroikov V.V. (2003). Prediction of biological activity spectra for substances: Evaluation on the diverse set of drugs-like structures. *Current Med. Chem*., 10 (3), 225-233.

Sadym A., Lagunin A., Filimonov D., Poroikov V. (2003). Prediction of biological activity spectra via Internet. *SAR and QSAR in Environmental Research*, 14 (5-6), 339-347.

http://pharmaexpert.ru/passonline

The Results of Prediction Are Presented by:

The list of activities which are probable for a particular compound with the estimates of Pa (probability to be active) and Pi (probability to be inactive) for each activity.

Pa and Pi are calculated independently: Pa + Pi ≠ 1.

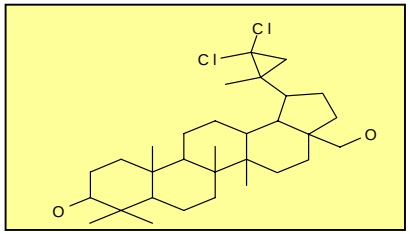
Pa (Pi) can be considered as the probability of the compound belonging to classes of active (inactive) compounds respectively, or as the probability of the first (second) kind of errors for the compound under prediction.

How PASS Predicts Biological Activity Spectrum?

Structure of new compound

Estimating the probability that it has a particular biological activity

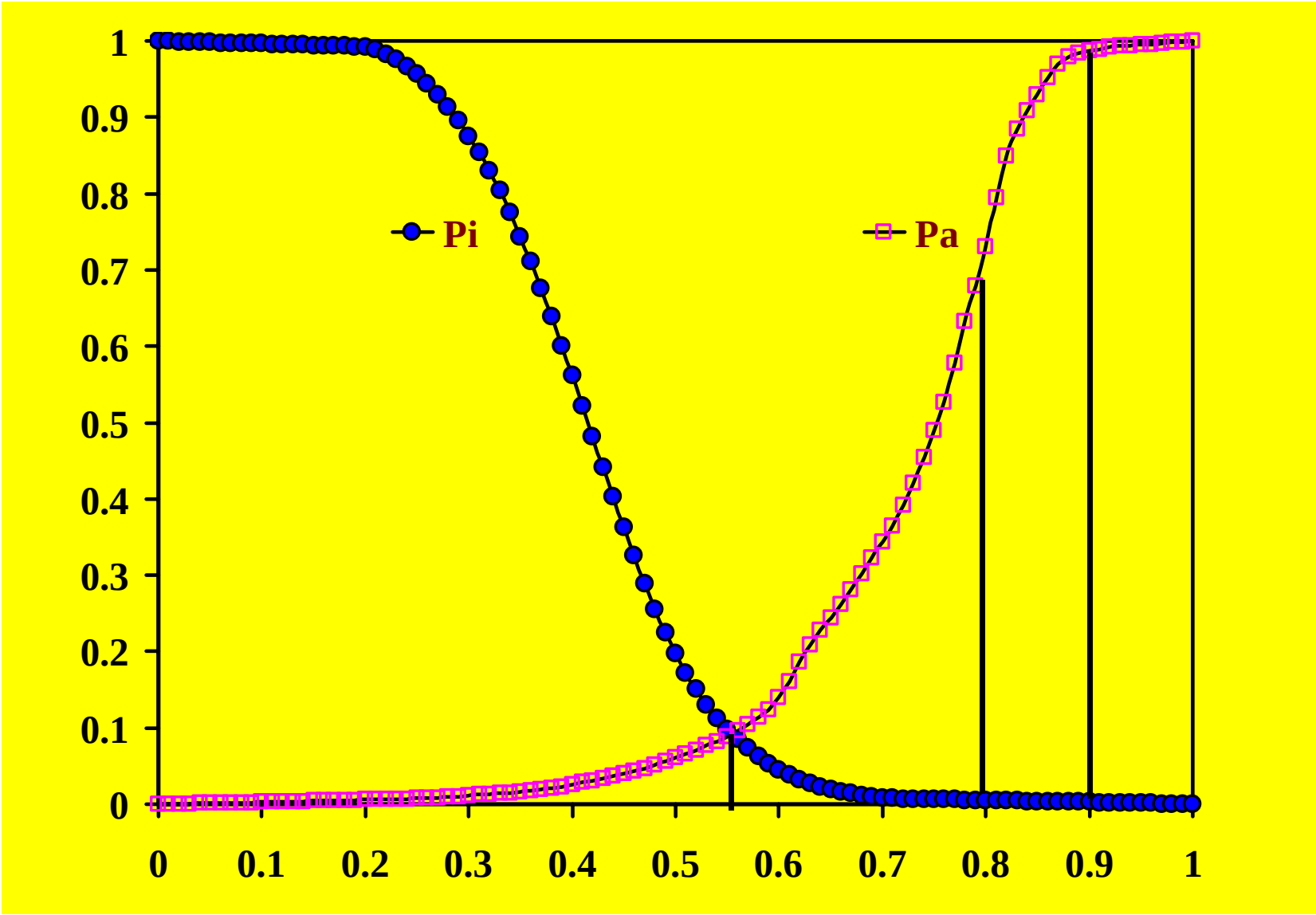
Predicted biological activity spectrum



Anxiolytic
Sedative
5HT1A Inhibitor
Carcinogen

Pa	Pi	Action:
0.853	0.020	Anxiolytic
0.694	0.035	Sedative

Initial Estimation Functions of Pa and Pi for Antihistaminic Activity

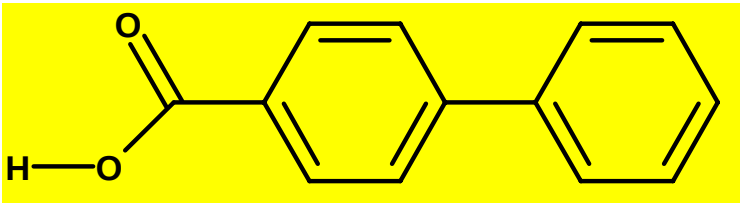


Example: Choosing the Antiinfective Compounds Without Carcinogenicity

- 4-Biphenylamine

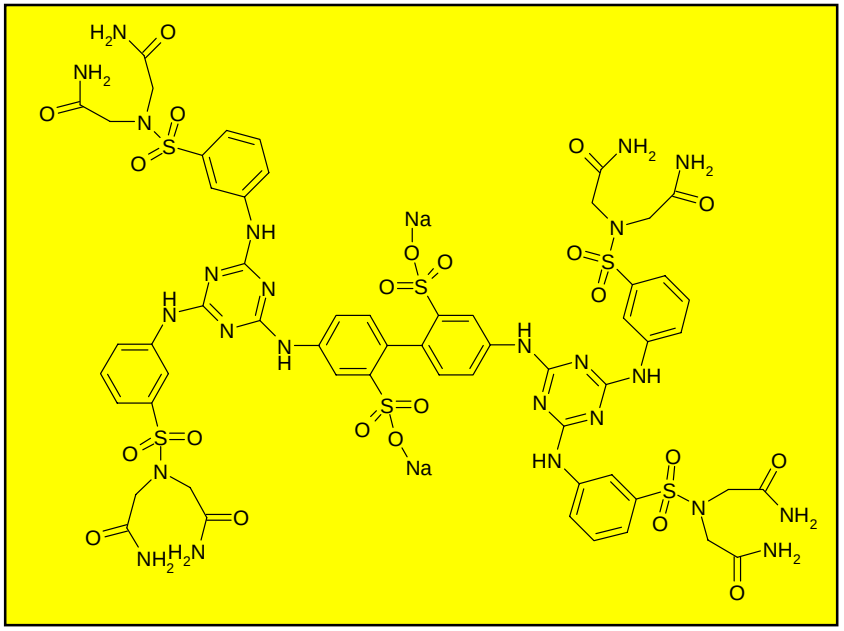
- Antiinfective
- (Pa = 0.559)
- Carcinogenic
- (Pa = 0.605)

- Derivative

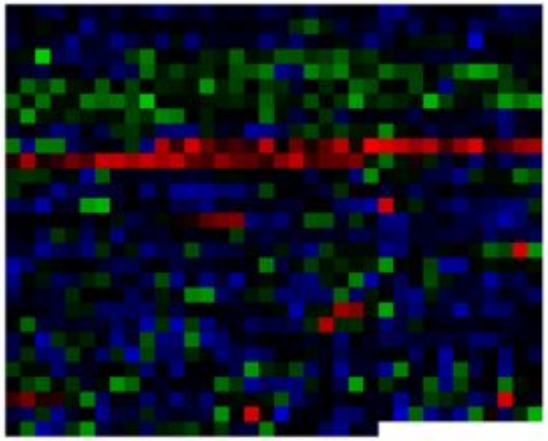


- Antiinfective
- (Pa = 0.550)
- No carcinogenic effect is predicted

Prediction for RFI-641 (Wyeth)



A. Nikitenko et al., ASDD-2005.



> <PASS.ACTIVITY.SPECTRUM>

0.929	0.008	Carcinogen, female rats, ezy
0.762	0.010	Carcinogen, female rats, smi
0.706	0.006	Carcinogen, female rats, lgi
0.743	0.056	Hematotoxic
0.707	0.020	Toxic
0.682	0.014	Teratogen
0.674	0.013	Anaphylatoxin receptor antagonist
0.675	0.028	Carcinogen, female mice, hmo
0.655	0.015	Embryotoxic
0.634	0.015	Angiogenesis inhibitor
0.629	0.025	Transactivat. transcript. prot. inhib.
0.615	0.045	Carcinogen, male rats, ezy
0.600	0.038	Carcinogen, male rats, kid
0.549	0.021	Carcinogen, female rats, liv
0.545	0.021	Carcinogen, male rats, liv
0.550	0.040	Carcinogen, female mice, sto
0.529	0.026	Antiprotozoal (Toxoplasma)
0.536	0.037	TNF alpha antagonist
0.508	0.020	Carcinogenic
0.517	0.030	Carcinogen, male rats
0.502	0.030	Carcinogen, female rats
0.501	0.042	Platelet aggregation stimulant
		. . .
0.304	0.107	Antiviral

Bisphenol **A**: Cause of Diabetes and Cadiovascular Disorders?

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Published online 16 September 2008 | Nature | doi:10.1038/news.2008.1110

Updated online: 16 September 2008

News

Bisphenol A linked to disease in humans

More studies of the controversial chemical are on the way.

Heidi Ledford

High levels of bisphenol A (BPA) — a chemical used in some containers for food and drink — may be associated with an increased risk of diabetes and cardiovascular disease in humans, a new study has found.

commented

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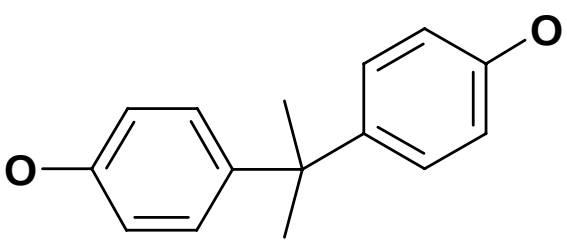
Lab disinfectant harms mouse fertility
18 June 2008

US panel has 'some concern' about effects of bisphenol A
09 August 2007

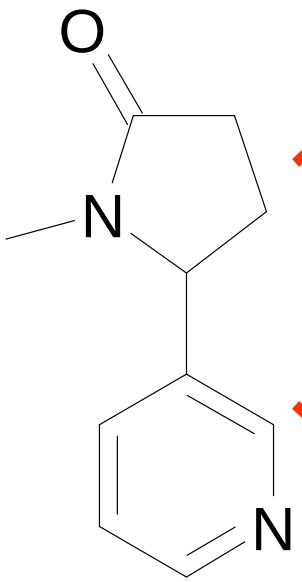
PASS prediction for Bisphenol **A**



0.757	0.004	Toxic, respiratory center
0.740	0.021	Hypercholesterolemic
0.744	0.050	Hematotoxic
0.704	**0.026**	**Hyperglycemic**
0.644	0.014	Carcinogenic, group 1
0.630	0.010	Carcinogenic, group 3
0.693	0.076	Neurotoxic
0.625	0.023	DNA damaging
0.611	0.009	Eye irritation, high
0.584	0.016	Spasmogenic
0.583	0.023	Emetic
0.608	**0.048**	**Cardiotoxic**
0.569	0.034	Thrombocytopoiesis inhibitor
0.547	0.014	Eye irritation, weak
0.519	0.012	Skin irritation, weak
0.574	0.092	Convulsant
0.559	0.082	Hepatotoxic
0.555	**0.109**	**Arrhythmogenic**
0.506	0.070	Nephrotoxic
0.513	**0.100**	**Torsades de pointes**

Cotinine: New Agent for Alzheimer Disease Treatment?

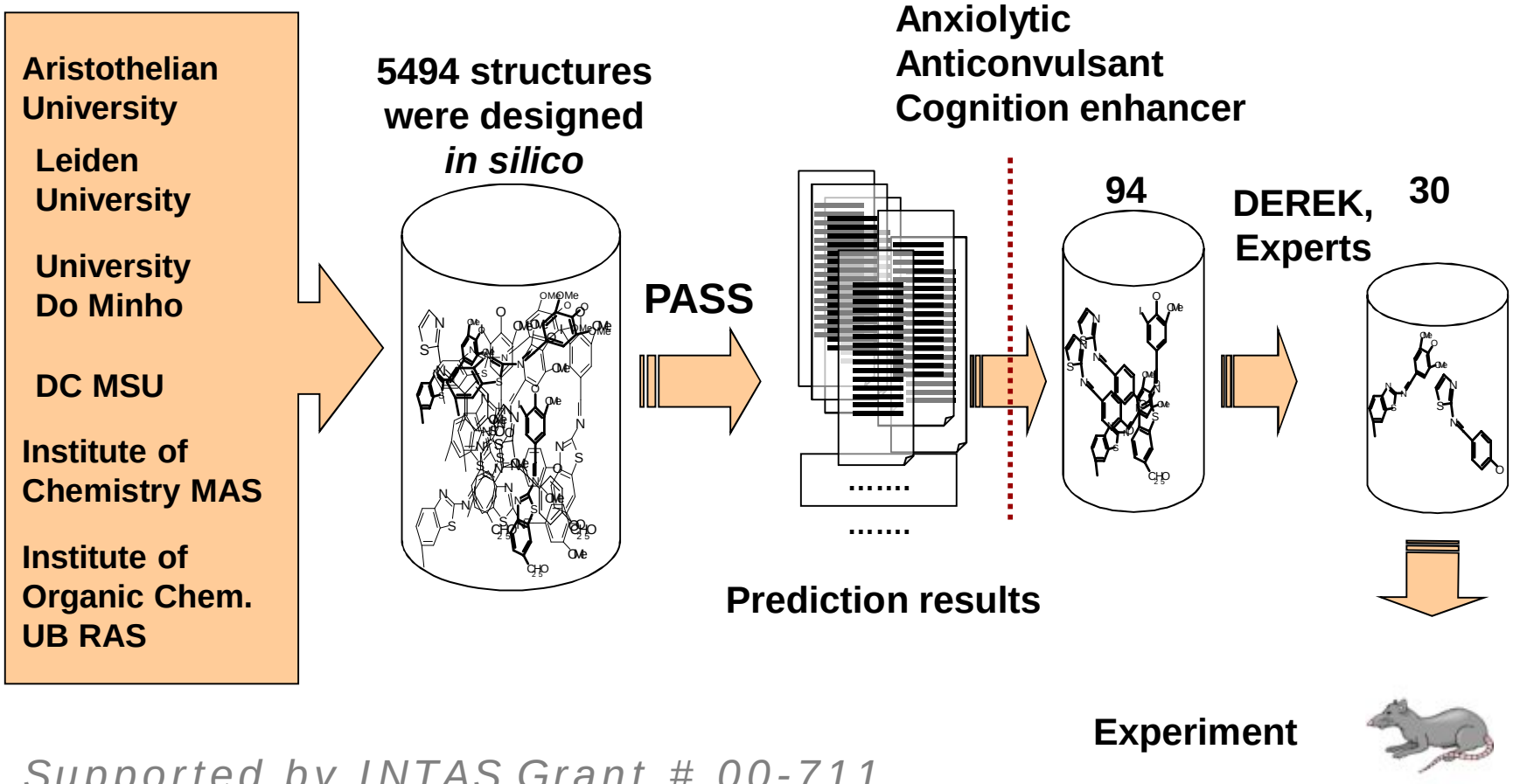
If Cotinine's Cognition Enhancing Effect Could Be Predicted by PASS?



17 of 501 Possible Pharmacological Effects at Pa > 0.500

Pa	Pi	
0.892	**0.005**	**Nootropic**
0.887	0.003	Sialagogue
0.889	0.005	Antineurotic
0.830	0.004	Psychostimulant
0.672	0.005	Respiratory analeptic
0.672	0.009	Antihypoxic
0.668	0.047	Kidney function stimulant
0.603	0.008	Analeptic
0.591	0.003	Antismoking
0.592	0.019	Vasodilator, cerebral
0.609	0.041	Digestive functional disorders treatment
0.554	**0.016**	**Cognition disorders treatment**
0.635	0.136	Immunomodulator (HIV)
0.553	0.067	Autism spectrum disorders treatment
0.516	0.069	Vasoprotector
0.544	0.113	Antineoplastic (non-small cell lung cancer)
0.510	0.174	Antiinflammatory, pancreatic

Significant Increase of the Fraction of "Actives" by Computer Prediction



Supported by INTAS Grant # 00-711.

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

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

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

School of Pharmacy, Department of Pharmaceutical Chemistry, Aristotle University of Thessaloniki, Thessaloniki, Greece, School of Pharmacy and Chemistry, Liverpool John Moores University, Liverpool, L3 3AF UK, Institute of Biomedical Chemistry, Russian Academy of Medicinal Science, Moscow, Russia, Institute of Pharmacology, Russian Academy of Medicinal Science, Moscow, Russia, and Institute of Chemistry, Moldavian Academy of Science, Kishinev, Moldova

Received November 3, 2003

To discover new cognition enhancers, a set of virtually designed synthesizable compounds from different chemical series was investigated using two computer-aided approaches. One of the approaches is prediction of biological activity spectra for substances (PASS) and the second is prediction of toxicity, mutagenicity, and carcinogenicity (DEREK). To increase the probability of finding new chemical entities, we investigated a heterogeneous set of highly diverse chemicals including different types of heterocycles: five-membered (thiophenes, thiazoles, imidazoles, oxazoles, pyrroles), six-membered (pyridines, pyrimidines), seven-membered (diazepines, triazepines), fused five+six-membered heterocycles (indoles, benzothiazoles, purines, indolizines, neutral, mesoionic, and cationic azolopyridines). A database including 5494 structures of compounds was created. On the basis of the PASS and DEREK prediction results, eight compounds with the highest probability of cognition-enhancing effect were selected. The cognition-enhancing activity testing showed that all of the selected compounds had a pronounced antiamnesic effect and were found to reduce significantly scopolamine-induced amnesia of passive avoidance reflex (PAR). The action of compounds at doses of 1 and 10 mg/kg caused a statistically significant increase in latent time of reflex and in the number of animals, which

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Bioorganic & Medicinal Chemistry 12 (2004) 6559–6568

Design, synthesis, computational and biological evaluation of new anxiolytics

Athina Geronikaki,[a,*] Eugeni Babaev,[b] John Dearden,[c] Wim Dehaen,[d] Dmitrii Filimonov,[e] Irina Galaeva,[f] Valentina Krajneva,[f] Alexey Lagunin,[e] Fliur Macaev,[g] Guenadiy Molodavkin,[f] Vladimir Poroikov,[e] Serghei Pogrebnoi,[g] Victor Saloutin,[h] Alla Stepanchikova,[e] Eugenia Stingaci,[g] Natalia Tkach,[b] Liudmila Vlad[g] and Tatiana Voronina[f]

[a]*School of Pharmacy, Department of Pharmaceutical Chemistry, Aristotelian University of Thessaloniki, Thessaloniki 54124, Greece*
[b]*Chemical Department of Moscow State University, Moscow 119899, Russia*
[c]*School of Pharmacy and Chemistry, Liverpool John Moores University, Liverpool L3 3AF, UK*
[d]*Leuven University, Leuven 3001, Belgium*
[e]*Institute of Biomedical Chemistry of Russian Academy of Medicinal Science, 119121 Moscow, Russia*
[f]*Institute of Pharmacology of Russian Academy of Medicinal Science, Moscow 125315, Russia*
[g]*Institute of Chemistry of Moldova Academy of Science, Chisinau MD-2028, Moldova*
[h]*Institute of Organic Chemistry of Urals Division of Russian Academy of Science, Ekaterinburg 620219, Russia*

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Available online 2 October 2004

DRUG REPOSITIONING: IDENTIFYING AND DEVELOPING NEW USES FOR EXISTING DRUGS

Ted T. Ashburn and Karl B. Thor

Biopharmaceutical companies attempting to increase productivity through novel discovery technologies have fallen short of achieving the desired results. Repositioning existing drugs f new indications could deliver the productivity increases that the industry n while shiftin the locus of production to biotechnology companies. More and more compa existing pharmacopoeia for repositioning candidates, and the number of re stories is increasing.

The biopharmaceutical industry has a problem: output has not kept pace with the enormous increases in pharma R&D spending (FIG. 1)[1]. This gap in productivity exists even though pharma companies have invested

Pharmaceuticals), which c extended-release niacin for l vance (Bristol-Myers Squib), w plus glyburide for diabetes; a

Drug News Perspect 22(2), March 2009

MEETING REPORT

DRUG REPOSITIONING SUMMIT: FINDING NEW ROUTES TO SUCCESS

Highlights from the Cambridge Healthtech Institute's Third Annual Drug Repositioning Summit, held October

INSIGHT

THE VALUE OF DRUG REPOSITIONING IN THE CURRENT PHARMACEUTICAL MARKET

REVIEWS

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

ELSEVIER

Reviews • KEYNOTE REVIEW

In silico repositioning of approved drugs for rare and neglected diseases

Sean Ekins[1,2,3,4], Antony J. Williams[5], Matthew D. Krasowski[6] and Joel S. Freundlich[7]

Sean Ekins
Sean Ekins is Principal

OPEN ACCESS Freely available online

PLoS COMPUTATIO

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

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

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

Abstract

The rise of multi-drug resistant (MDR) and extensively drug resistant (XDR) tuberculosis around the world, incl industrialized nations, poses a great threat to human health and defines a need to develop new, effective and ine anti-tubercular agents. Previously we developed a chemical systems biology approach to identify off-targets pharmaceuticals on a proteome-wide scale. In this paper we further demonstrate the value of this approach thr discovery that existing commercially available drugs, prescribed for the treatment of Parkinson's disease, have the to treat MDR and XDR tuberculosis. These drugs, entacapone and tolcapone, are predicted to bind to the enzyme InhA and

Invest New Drugs
DOI 10.1007/s10637-010-9422-6

PRECLINICAL STUDIES

A novel activity from an old compound: Manzamine A reduces the metastatic potential of AsPC-1 pancreatic cancer cells and sensitizes them to TRAIL-induced apoptosis

Esther A. Guzmán · Jacob D. Johnson · Patricia A. Linley · Sarath E. Gunasekera · Amy E. Wright

Received: 5 November 2009 / Accepted: 11 March 2010

Abstract *Purpose*: Pancreatic cancer is the fourth leading cause of cancer death in the United States, and new drugs to treat the disease are needed. Pancreatic cancer cells are highly metastatic and exhibit resistance to apoptosis. Small

Introduction

Pancreatic cancer is the fourth leading cause of cancer death in the United States, accounting for about ten percent

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

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

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

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

Computer-aided prediction of the biological activity spectra by the program PASS was applied to a set of 130 pharmaceuticals from the list of the Top 200 medicines. The known pharmacological effects were found in the predicted activity spectra in 93.2% of cases. Additionally, the probability of some supplementary effects was also predicted to be significant, including angiogenesis inhibition, bone formation stimulation, possible use in cognition disorders treatment, multiple sclerosis treatment, *etc.* These predictions, if confirmed experimentally, may become a cause for a new application of pharmaceuticals from the Top 200 list. Most of known side and toxic effects were also predicted by PASS. PASS predictions at earlier R&D stages may thus provide a basis for finding new "leads" among already launched drugs and may help direct more attention to those particular effects of pharmaceuticals in clinical use which become apparent only in a small part of the population and require additional precautions.

Keywords: Biological activity spectra; Top 200 medicines; Side effect; Toxicity; Computer-aided prediction; PASS

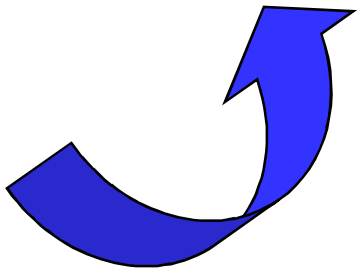
Finding New Activities for Old Drugs

Example: Top 200 Pharmaceuticals
(132 different drug-like substances):

Acetaminophen/Codeine
Albuterol; Albuterol Aerosol

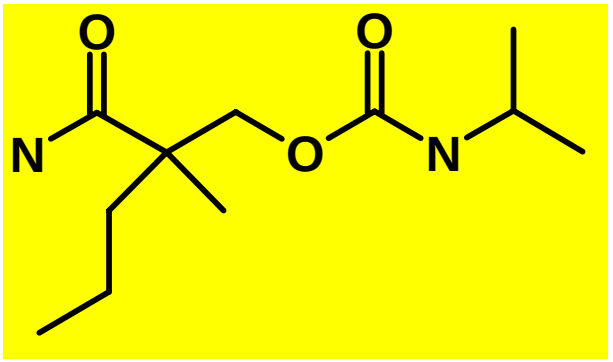
Alendronate; Fosamax
Allopurinol
Alprazolam
Amitriptyline
. . .
Verapamil
Warfarin; Coumadin
Zafirlukast; Accolate
Zolpidem; Ambien

93% of known pharmacological actions and 83% of known side effects & toxicity were predicted by PASS.



Poroikov V., Akimov D., Shabelnikova E., Filimonov D.
SAR & QSAR Environ. Res., 2001, 12 (4), 327-344.

New Activities Were Predicted in Many Cases, e.g. for Carisoprodol



Known Activity:

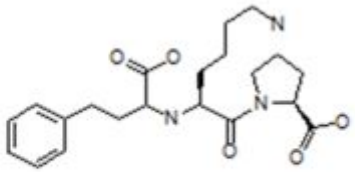
Skeletal muscle relaxant

Predicted Activities:

Angiogenesis inhibitor (Pa=0.569)

Multiple sclerosis treatment (Pa=0.549)

Results of prediction for Lisinopril



> <PASS.MNA.COUNT>
52

> <PASS.MNA.NEW.COUNT>
0

> <PASS.KNOWN.ACTIVITIES>
Angiotensin converting enzyme inhibitor
Antidiabetic
Antidiabetic symptomatic
Antihypertensive
Cardiotonic
Diuretic
Lysine carboxypeptidase inhibitor
Urologic disorders treatment
Vasodilator
Vasodilator, coronary
X-Trp aminopeptidase inhibitor

> <PASS.RESULT.COUNT>
20 of 1917 Possible Activities at Pa > 0.500

> <PASS.ACTIVITY.SPECTRUM>

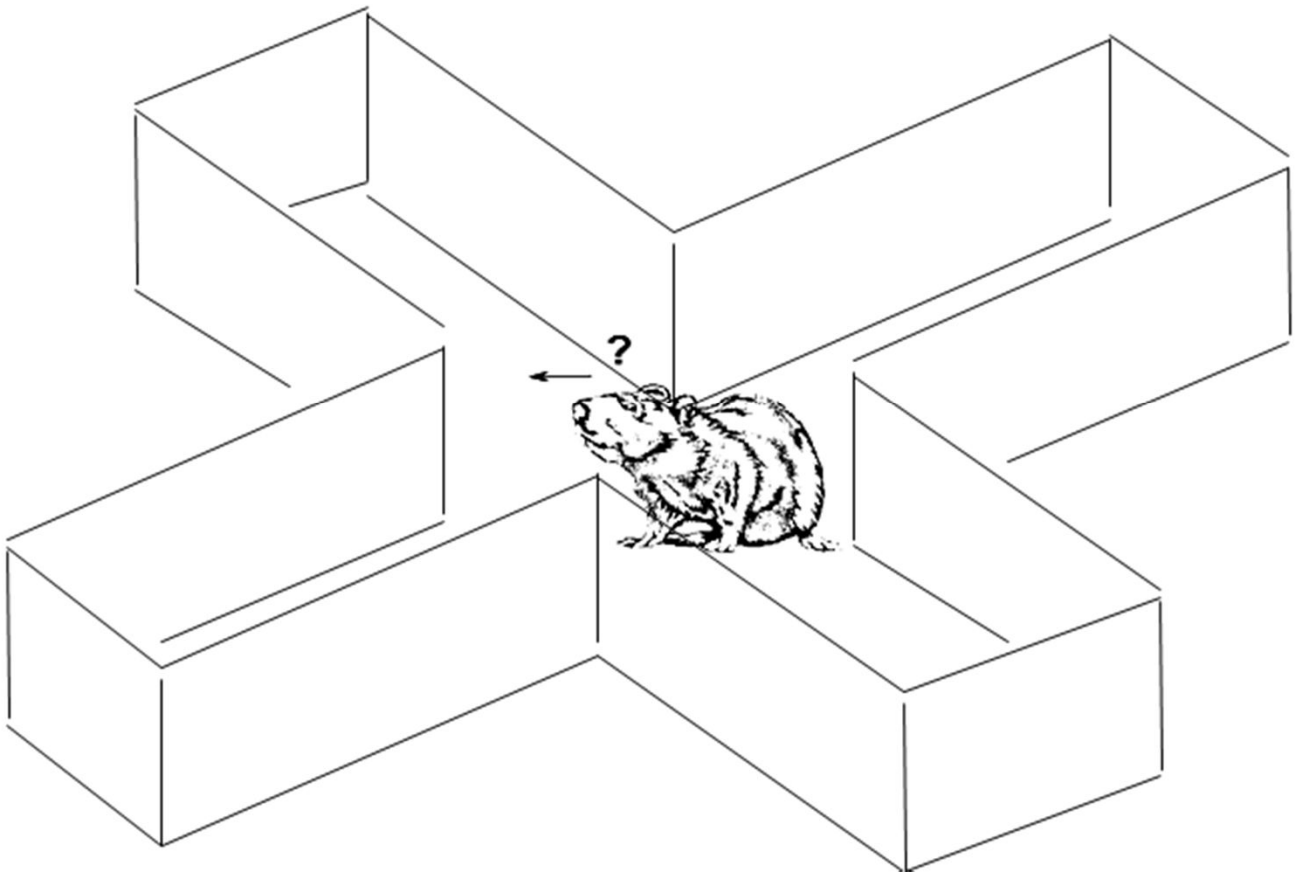
0.749	0.014	Interleukin agonist
0.746	0.028	Amyotrophic lateral sclerosis treatment
0.762	0.055	Fibrinogen receptor antagonist
0.638	0.006	Neurolysin inhibitor
0.632	0.023	Chemoprotective
0.631	0.037	Immunomodulator
0.660	0.072	Sickle-cell anemia treatment
0.632	0.049	Cardioprotectant
0.618	0.048	Nootropic
0.560	0.007	X-Pro dipeptidase inhibitor
0.626	0.075	Opioid dependency treatment
0.550	0.004	Angiotensin converting enzyme inhibitor
0.577	0.054	Multiple sclerosis treatment
0.533	0.012	Neurotrophic factor
0.520	0.008	Astacin inhibitor
0.526	0.025	Antihypertensive
0.525	0.029	Vasodilator, renal
0.535	0.040	Psychostimulant
0.543	0.071	Lipoprotein lipase inhibitor
0.500	0.037	Immunostimulant

Prediction of biological activity for some antihypertensive drugs

Name	Nootropic effect, %	A1, %	A2, %	A3, %	A4, %	A5, %	A6, %
Captopril	44,6	-	-	-	-	81,7	-
Enalapril	65,5	37,8	50,9	-	-	50,6	
Lisinopril	61,8	33,6	-	-	44,2	56,0	-
Prindopril	60,9	33,4	-	37,2	35,3	39,5	
Quinapril	65,1	38,3	-	37,0	-	42,9	
Ramipril	63,3	38,6	36,9	40,9	-	37,3	
Monopril	30,9	-	-	-	70,7	63,2	31,3
Pirazetam	81,7	43,3	42,5	-	38,6	34,2	-
Amlodipin	-	-	-	-	-	-	-
Hydrochlorothiazide	-	-	-	-	-	-	63,2

Pa values exceeding 30% are presented for several biological activities: A1 - Acetylcholine M2 receptor agonist; A2 - Acetylcholine release stimulant; A3 - 5 Hydroxytryptamine release stimulant; A4 - GABA receptor antagonist; A5 - X-Pro dipeptidase inhibitor; A6 - Glutamate receptor agonist.

Patrolling behavior of mice in the cross-maize, as an express estimate for sedative, psychostimulative, tranquilizer, and nootropic actions)



Salimov R. et al., *Pharmacol. Biochem. Behav.*, 1995, **52**: 637–640.

Influence of Perindopril on patrolling behavior of mice in a cross-maize

	Control			1 mg/kg			4 mg/kg			8 mg/kg	
	N	M	SEM	N	M	SEM	N	M	SEM	N	M	SEM
F_PtrN	14	5,2	0,2	14	5,6	0,5	14	5,1	0,4	13	5,2	0,5
S_PtrN	10	5,8	0,5	11	4,5*	0,2	14	5,2	0,3	12	5,8	0,4
PatrlN	14	1,9	0,2	14	2,1	0,2	14	2,1	0,1	14	1,9	0,2
F_ChTm	14	23,7	8,7	14	11,9	2,0	14	9,9	2,1	14	10,7	3,0
F_GlTm	14	24,6	2,1	14	22,4	2,9	14	33,2	5,9	14	21,3	3,2
T_ChTm	14	76,0	14,9	14	47,6*	3,1	14	54,2*	5,3	14	42,4*	2,5
T_GlTm	14	160,1	8,6	14	152,4	8,3	14	167,6	16,1	14	158,8	16,8
R_TrnN	14	5,9	0,7	14	3,3*	0,8	14	4,1	0,7	14	3,9	0,7
L_TrnN	14	2,7	0,5	14	4,4*	0,9	14	2,9	0,6	14	3,3	0,3
rl_Ind	14	0,7	0,1	14	0,5	0,1	14	0,6	0,1	14	0,5	0,1
S_VisN	14	4,8	0,8	14	4,5	1,0	14	4,7	0,6	14	5,4	0,8

*** - statistical significance in comparison with control ($p<0,05$)**

Influence of Pirazetam on patrolling behavior of mice in a cross-maize

	Control			100 mg/kg			300 mg/kg		
	N	M	SEM	N	M	SEM	N	M	SEM
F_PtrN	15	5,9	0,4	15	5,5	0,5	15	4,5*	0,2
S_PtrN	13	4,8	0,4	13	5,1	0,3	14	5,4	0,4
PatrlN	15	1,9	0,1	15	1,9	0,1	15	2,1	0,1
F_ChTm	15	17,7	3,0	15	20,8	7,8	15	11,6	2,7
F_GlTm	15	19,9	1,9	15	26,4	2,9	15	25,0	2,9
T_ChTm	15	45,2	2,7	15	48,0	2,9	15	46,1	3,6
T_GlTm	15	148,4	9,4	15	164,2	10,4	15	135,1	6,1
R_TrnN	15	5,2	0,5	15	4,5	0,5	15	3,4*	0,5
L_TrnN	15	2,9	0,4	15	3,1	0,4	15	4,5*	0,5
F_PasN	15	3,7	0,4	15	4,3	0,4	15	4,1	0,2
rl_Ind	15	0,6	0,0	15	0,6	0,1	15	0,4*	0,1
S_VisN	15	6,9	0,8	15	5,4	0,6	15	4,3*	0,8

*** - statistical significance in comparison with control ($p<0,05$)**

NOOTROPIC ACTION OF SOME ANTIHYPERTENSIVE DRUGS: COMPUTATIONAL PREDICTION AND EXPERIMENTAL TESTING

Kryzhanovsky S.A., Salimov R.M.
Institute of Pharmacology of Rus. Acad. Med. Sci.,
Bldg.8, Baltiyskaya Str., Moscow, 125315

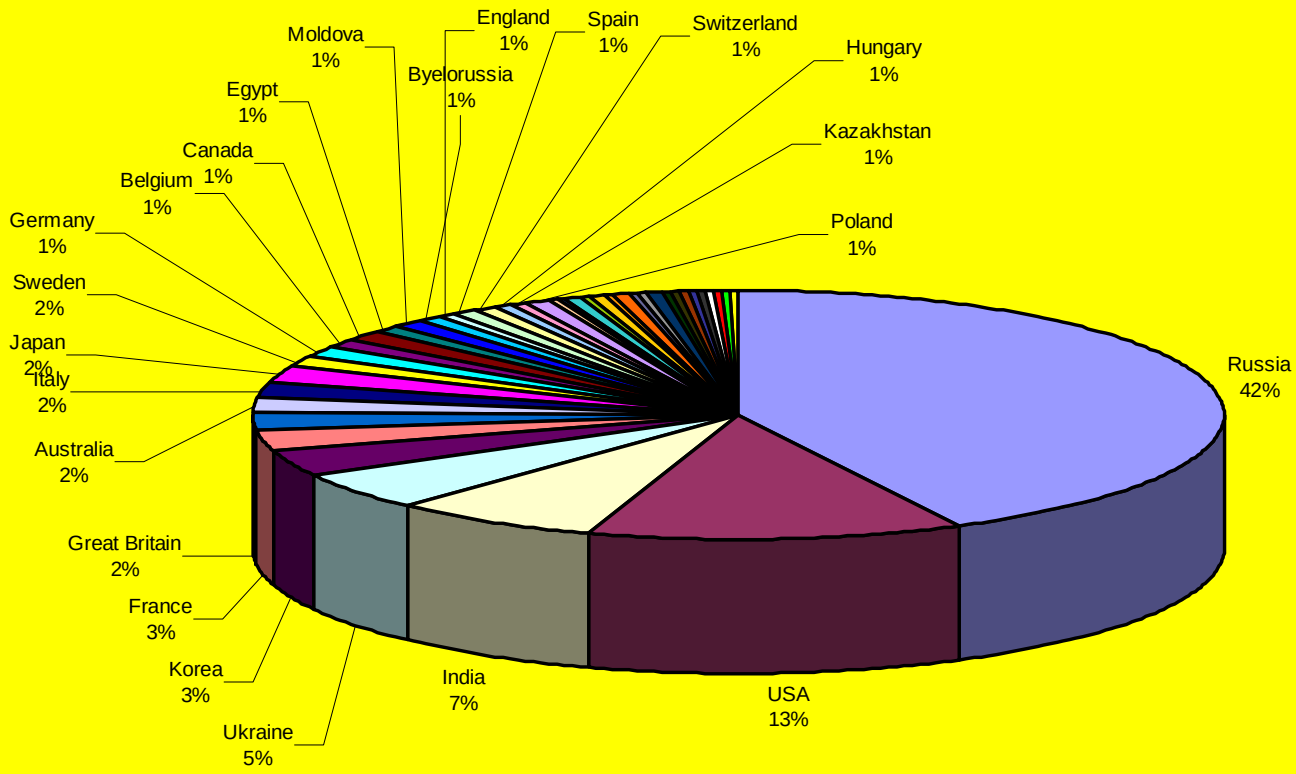
Lagunin A.A., Filimonov D.A., Gloriozova T.A., Poroikov V.V.
Institute of Biomedical Chemistry of Rus. Acad. Med. Sci.,
Bldg. 10, Pogodinskaya Str., Moscow, 119121

On the basis of computational prediction of biological activity spectra using computer program PASS several antihypertensive drugs belonging to the group of ACE inhibitors have been selected for testing of nootropic activity. Experiments were conducted on mice by the test of spontaneous orientation (patrolling behavior) in the cross-maze. It was found that perindopril in dose of 1 mg/kg, and quinapril and monopril in doses of 10 mg/kg improved the patrolling behavior in the maze. This effect is similar to the effects of standard nootropic drugs piracetam and meclofenoxate (in doses of 300 and 120 mg / kg, respectively). The observed nootropic effect of some ACE inhibitors are likely to be unrelated to their antihypertensive effect, since the nootropic action took place only at relatively low doses of perindopril, quinapril and monopril and was not observed with further increase in dose. Identification of nootropic action of the commonly used in clinical practice antihypertensive drugs lead to new clinical applications with regard to the relevant individual peculiarities of patients.

Pharmaceutical Chemistry Journal, 2011.

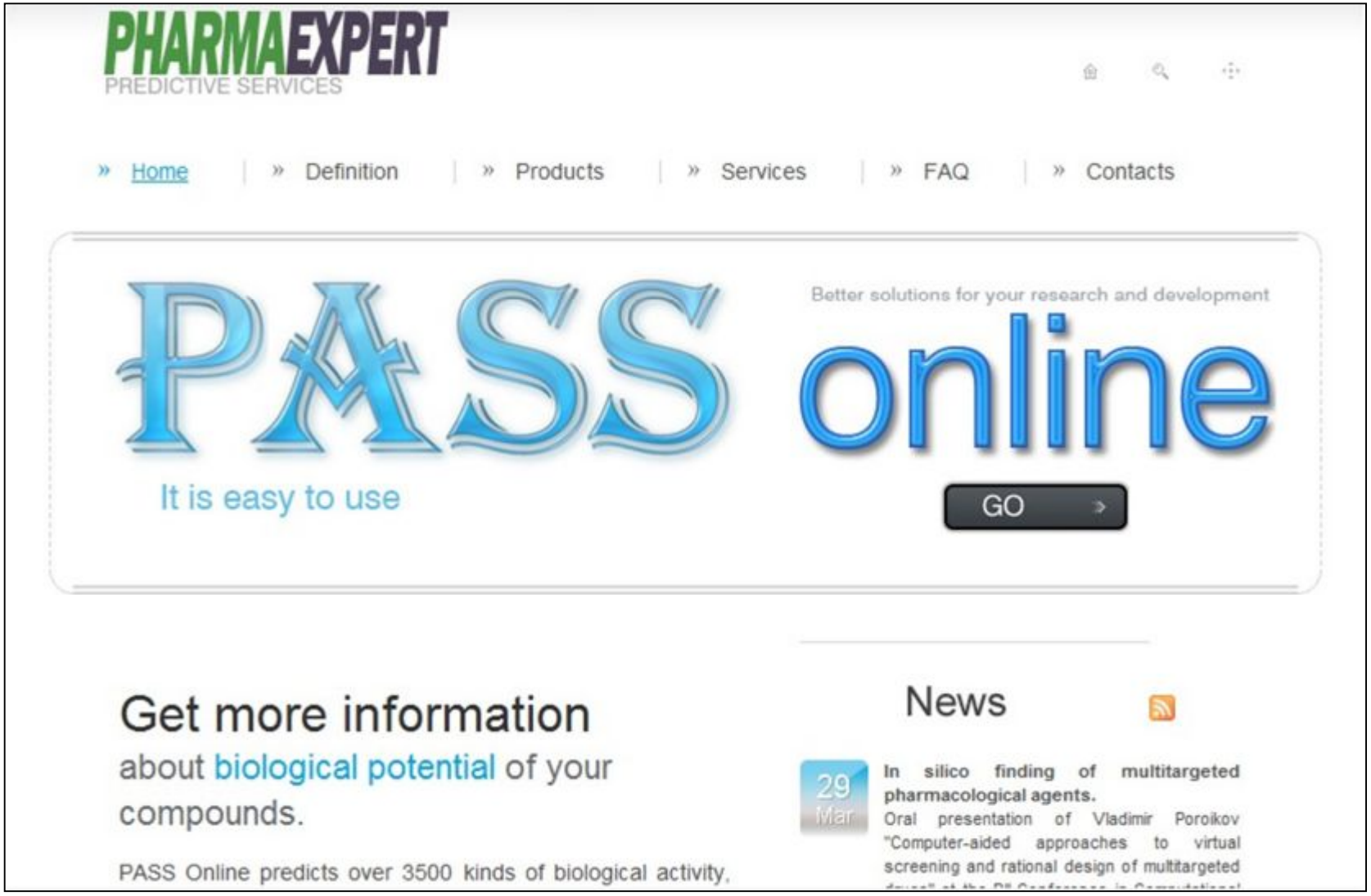
PASS Predictions are available via Internet

(http://pharmaexpert.ru/passonline)



Statistics of 01.01.2011: >7,500 users, >200,000 predictions

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...

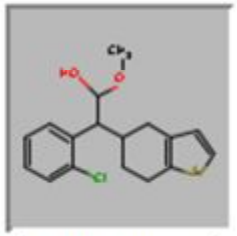
Get Prediction

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 Online Predictions

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

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

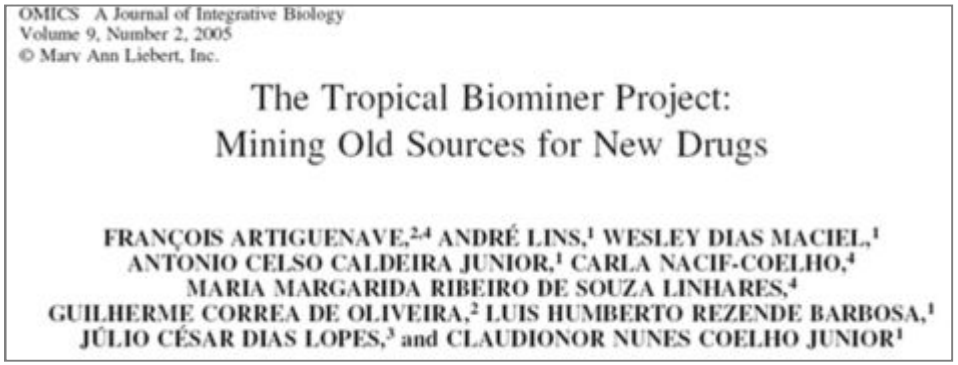
journal homepage: http://www.elsevier.com/locate/ejmech

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



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]

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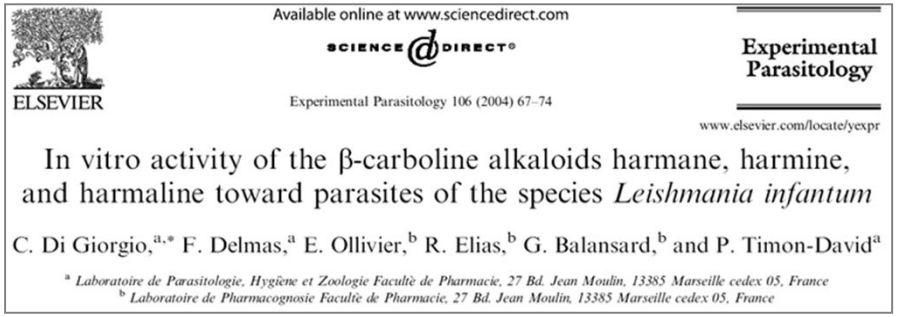
Bioorganic & Medicinal Chemistry Letters

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



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Experimental Parasitology

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

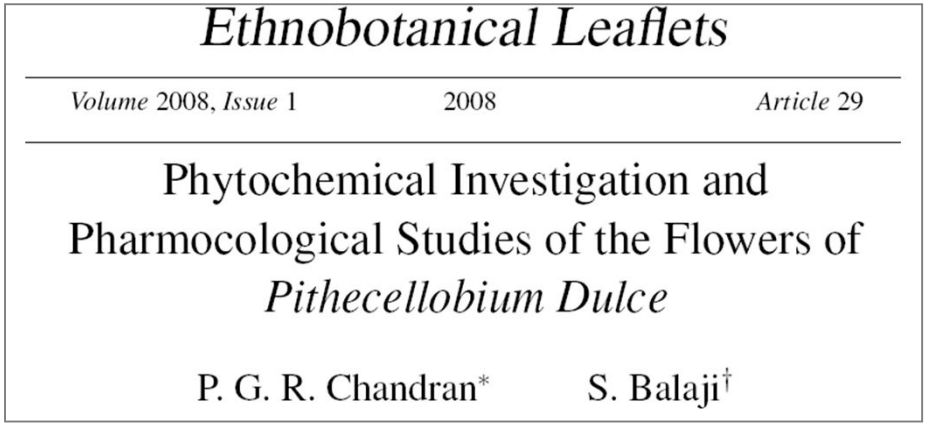
journal homepage: http://www.elsevier.com/locate/ejmech

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 Biophotochimie et Mutagénèse Environnementale (EA 3784, FR 3098 – ECCOREV), Université Aix-Marseille, Faculté de Pharmacie, 27 Bd Jean Moulin, 13385 Marseille, Cedex 05, France
[b] Laboratoire HTE, case 552, (UMR 6263) – Université Paul Cézanne, Faculté St Jérôme, 13397 Marseille, Cedex 20, France
[c] CRMO (IFR 88-ISM) – 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 Pharmocological Studies of the Flowers of *Pithecellobium Dulce*

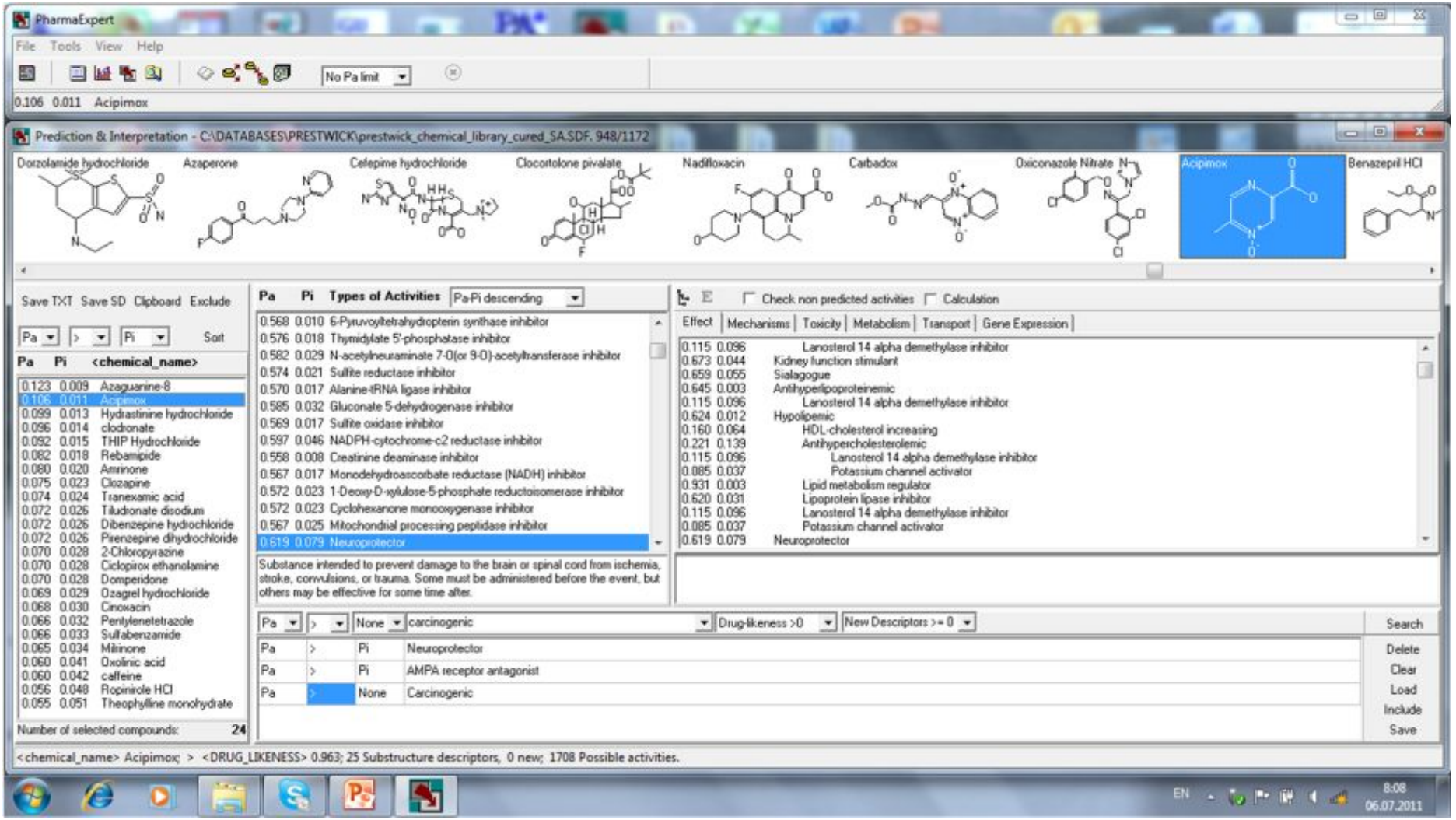
P. G. R. Chandran* S. Balaji†

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

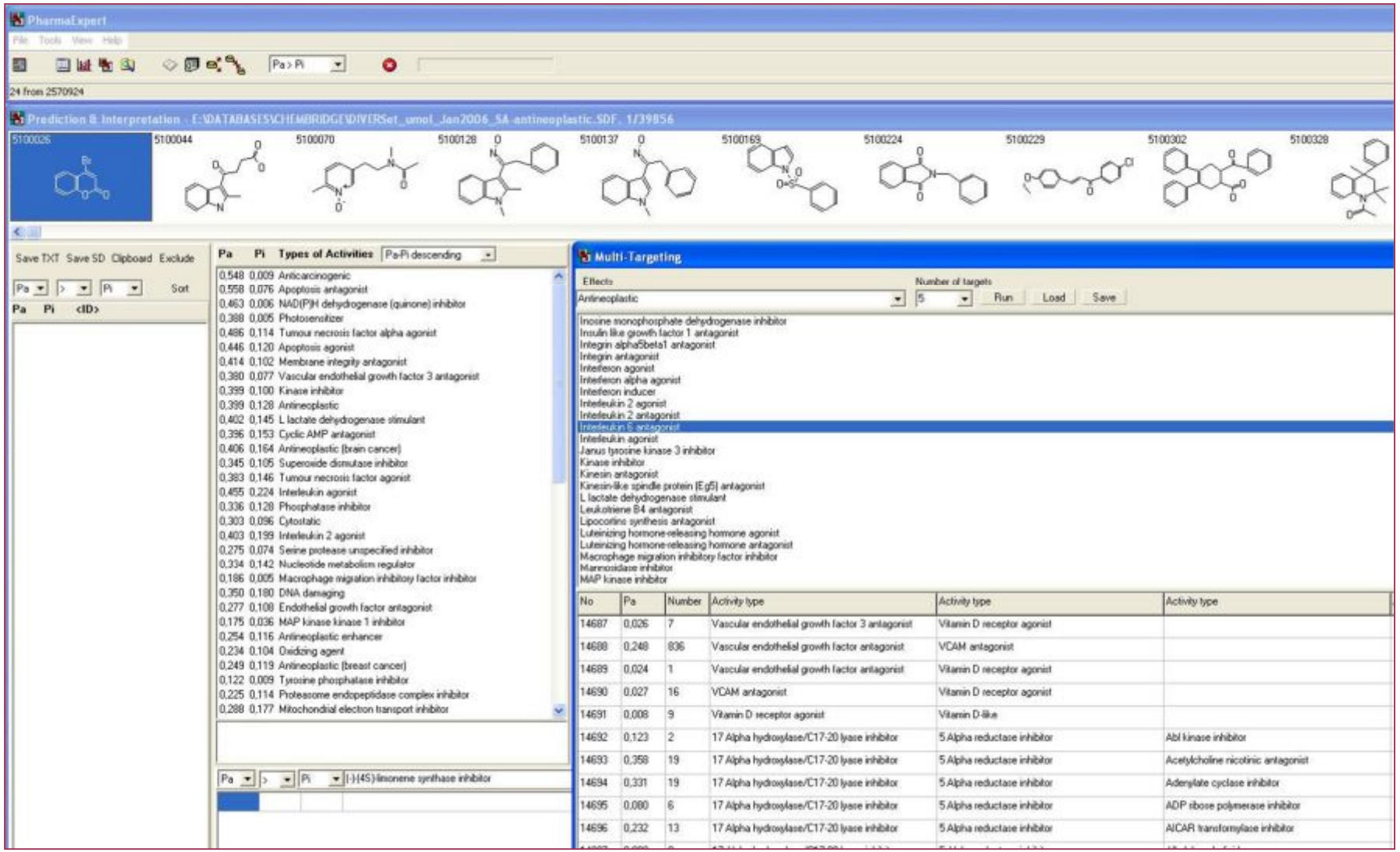
Outline

- Chemical compounds & biological activity
- Computational approaches to prediction of biological activity.
- PASS: Prediction of Activity Spectra for Substances
- **PharmaExpert: Tool for analysis of PASS predictions**
- GUSAR: General Unrestrained Structure-Activity Relationships
- Summary

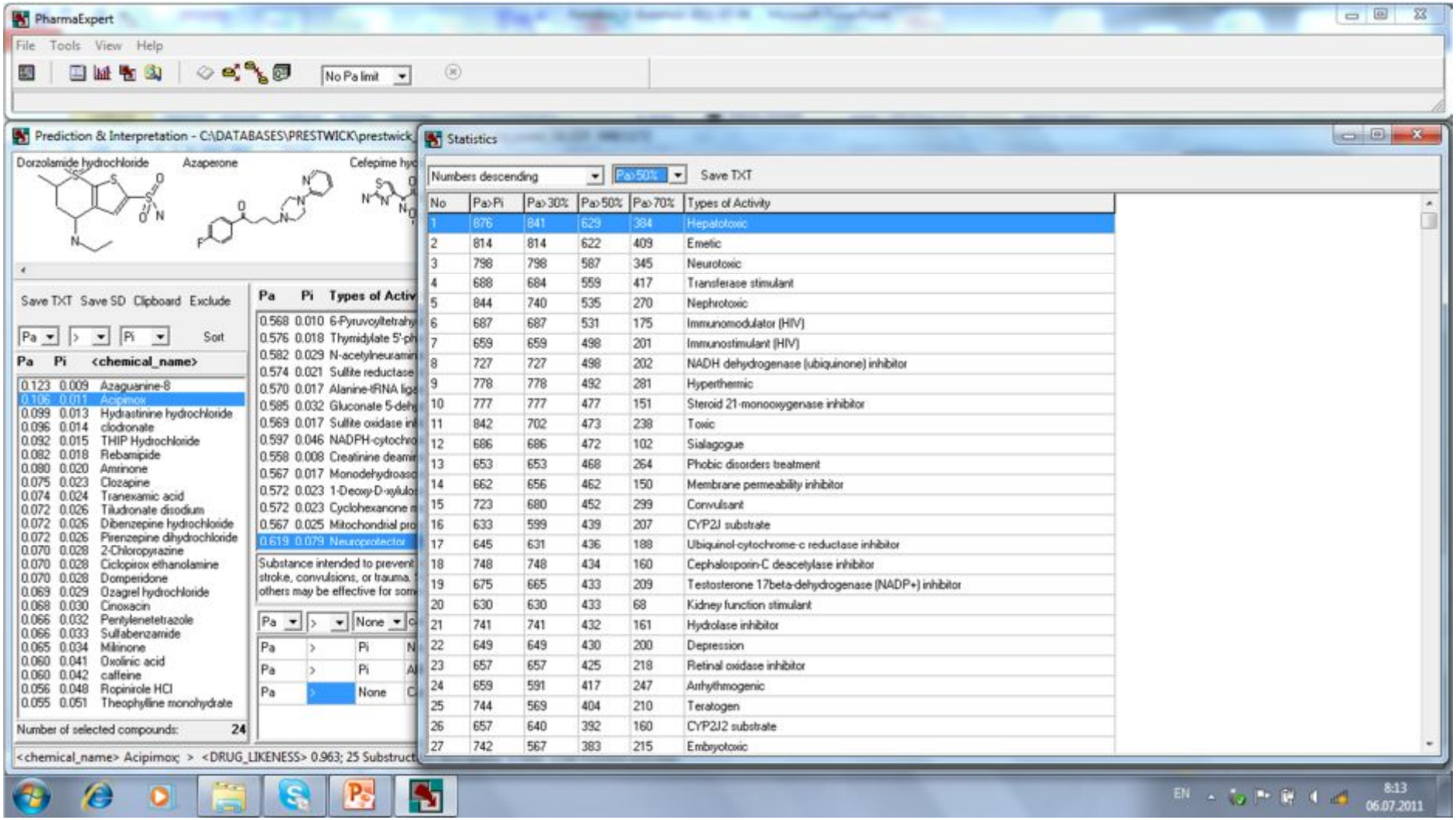
PharmaExpert: Search for Compounds with the Required Activity Profile



PharmaExpert: Selection of Multi-Targeted Anticancer Agents in ChemBridge DVS Database



PharmaExpert: Statistics of Activities in Particular Chemical Library



PharmaExpert: Drug-Drug Interaction Analysis

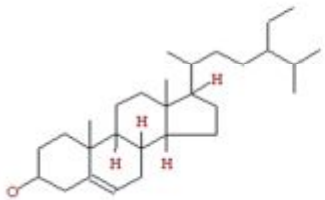
PharmaExpert

File Tools View Help

Pa > Pi

Drug-Drug Interactions

Beta-sistosterol



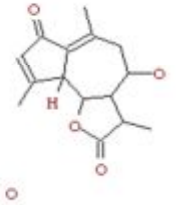
Additive or Synergistic Effects and Actions

Effects

- Antineoplastic
- Antineoplastic (multiple myeloma)
- Antiinflammatory, ophthalmic
- Antileukemic
- Antineoplastic (breast cancer)
- Antifungal

Myc inhibitor 0.680 0.002	Antineoplastic 0.758 0.014
Transcription factor inhibitor 0.683 0.053	Antineoplastic 0.758 0.014
Phospholipase C inhibitor 0.714 0.006	Antineoplastic 0.758 0.014
Antineoplastic 0.521 0.065	Antineoplastic
Antineoplastic 0.521 0.065	Farnesoid X receptor agonist

Austricine



Pharmacokinetic Drug-Drug Interactions

Metabolism

- CYP7A1 inhibitor
- CYP2B6 substrate
- CYP1A inhibitor
- CYP3A4 inhibitor
- CYP2C9 inducer
- CYP2C9 inhibitor
- CYP3A2 substrate

CYP2B6 substrate 0.323 0.106	CYP2B6 inhibitor 0.307 0.368

Transporters and Blood Proteins

- P-glycoprotein substrate

P-glycoprotein substrate 0.417 0.077	P-glycoprotein substrate 0.387 0.101

Additive or Synergistic Toxic and Side Effects

- Hematotoxic
- Toxic
- Hypercholesterolemic
- Hepatotoxic
- Embryotoxic
- Teratogen

Hematotoxic 0.626 0.109	Hematotoxic 0.397 0.261

Pharmacodynamic Drug-Drug Interactions

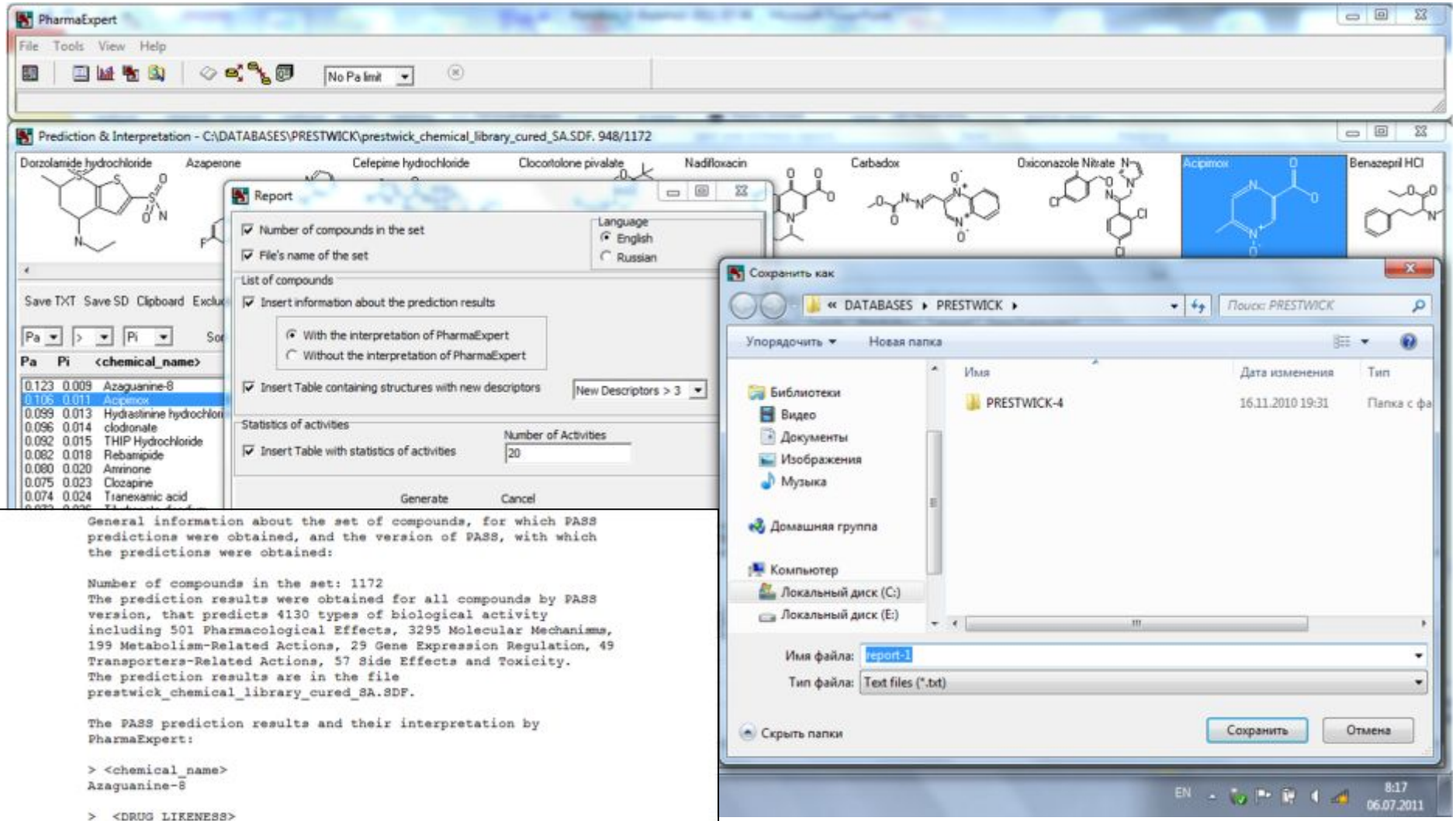
- Cytochrome P450 inhibitor
- GABA receptor antagonist
- H+-transporting two-sector ATPase inhibitor
- Growth factor agonist
- Interleukin agonist
- Transcription factor inhibitor

Transcription factor NF kappa B inhibitor 0.638 0.058 Transcription factor inhibitor 0.683 0.053	Transcription factor inhibitor 0.691 0.047 Transcription factor NF kappa B inhibitor 0.661 0.045

Слайд 79 из 79 | Оформление по умолчанию | английский (США)

Пуск | PharmaExpert | Microsoft PowerP... | Encarta | 10:39

PharmaExpert: Generation of the Report




```
General information about the set of compounds, for which PASS
predictions were obtained, and the version of PASS, with which
the predictions were obtained:

Number of compounds in the set: 1172
The prediction results were obtained for all compounds by PASS
version, that predicts 4130 types of biological activity
including 501 Pharmacological Effects, 3295 Molecular Mechanisms,
199 Metabolism-Related Actions, 29 Gene Expression Regulation, 49
Transporters-Related Actions, 57 Side Effects and Toxicity.
The prediction results are in the file
prestwick_chemical_library_cured_SA.SDF.

The PASS prediction results and their interpretation by
PharmaExpert:

> <chemical_name>
Azaguanine-8

>  <DRUG_LIKENESS>
0.866

>  <ACTIVITY_PREDICTION>
  26  Substructure descriptors;  0  new.
  735  Possible activities.
0.990   0.000   Pterin deaminase inhibitor
0.956   0.001   Xanthine dehydrogenase inhibitor
0.887   0.000   Sepiapterin deaminase inhibitor
0.848   0.001   Queuine tRNA-ribosyltransferase inhibitor
0.784   0.013   Ribonuclease T1 inhibitor
```

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

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

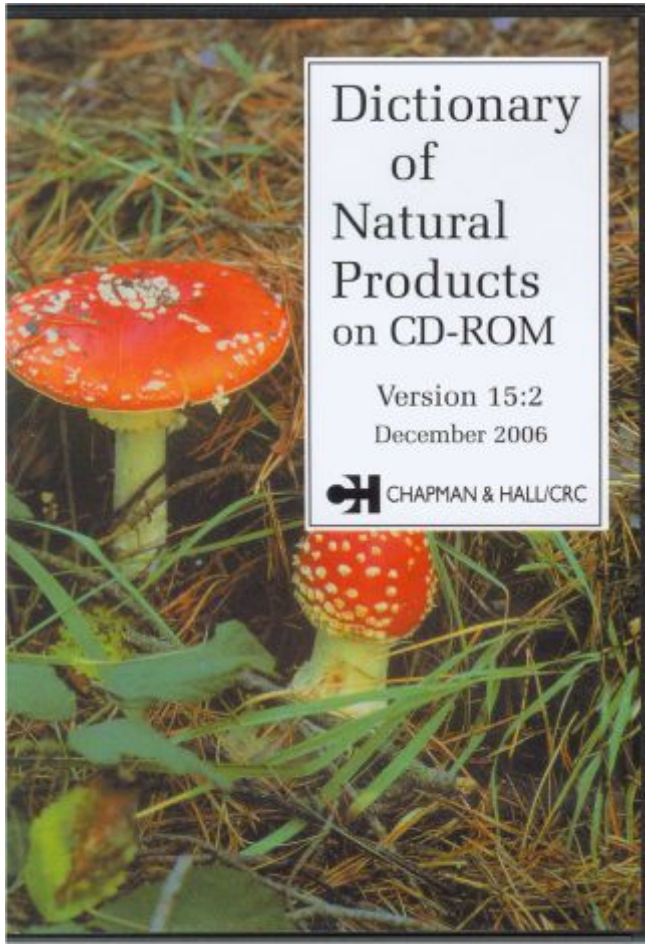
Alexey Lagunin, Dmitry Filimonov and Vladimir Poroikov*

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

Abstract: Natural products found a wide use in folk medicine. Presently, when routine development of new drugs faced a considerable challenge, they become an inspiration and valuable source in drugs discovery. Rather complex and diverse chemical structures of natural compounds provide a basis for modulation of different biological targets. Natural compounds exhibit a multitargeted action that may lead to additive/synergistic or antagonistic effects. Rational design of more safe and potent pharmaceuticals requires an estimation of probable multiple actions of natural products. Our software PASS can perform such estimation. It predicts with reasonable accuracy over 3500 pharmacotherapeutic effects, mechanisms of action, interaction with the metabolic system, and specific toxicity for drug-like molecules on the basis of their structural formulae. We analyzed PASS predictions utilizing PharmaExpert, which performs selection of compounds with multiple mechanisms of action, analysis of activity-activity relationships and drug-drug interactions. The paper describes an application of PASS and PharmaExpert to the evaluation of biological activity of natural compounds including marine sponge alkaloids, triterpenoids of lupane group, and their derivatives. Proposed computer-aided methods can generate combinatorial libraries of macrolides. They help to select the most promising pharmaceutical leads with the required properties. Case study, based on the analysis of biological activity spectra predicted for St John's Wort constituents, clearly demonstrates capabilities of computational methods in the evaluation of multitargeted actions, additive/synergistic and/or antagonistic effects of natural products.

Keywords: Natural products, computational evaluation, biological activity spectra prediction, PASS, multitargeted action, drug-drug

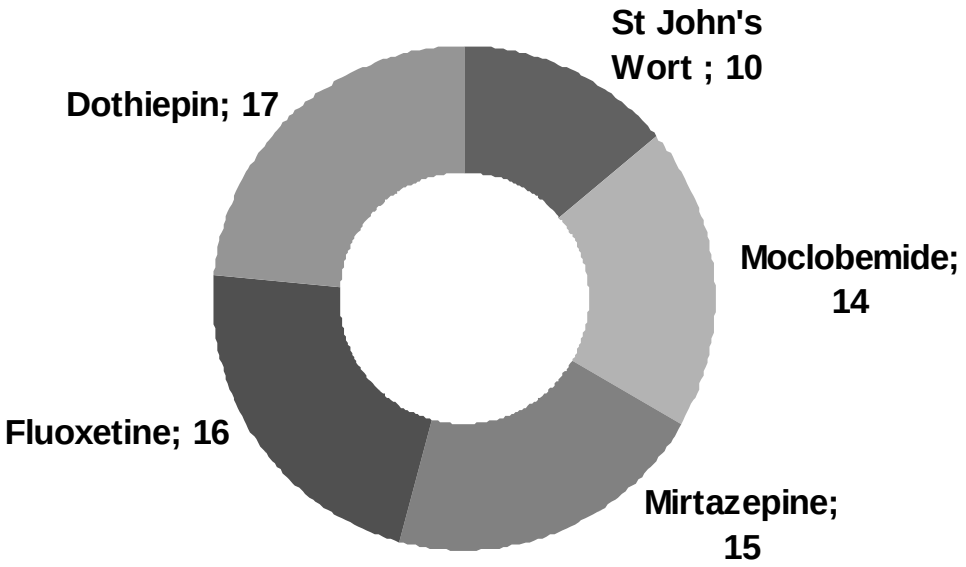
Dictionary of Natural Products (DNP) Database



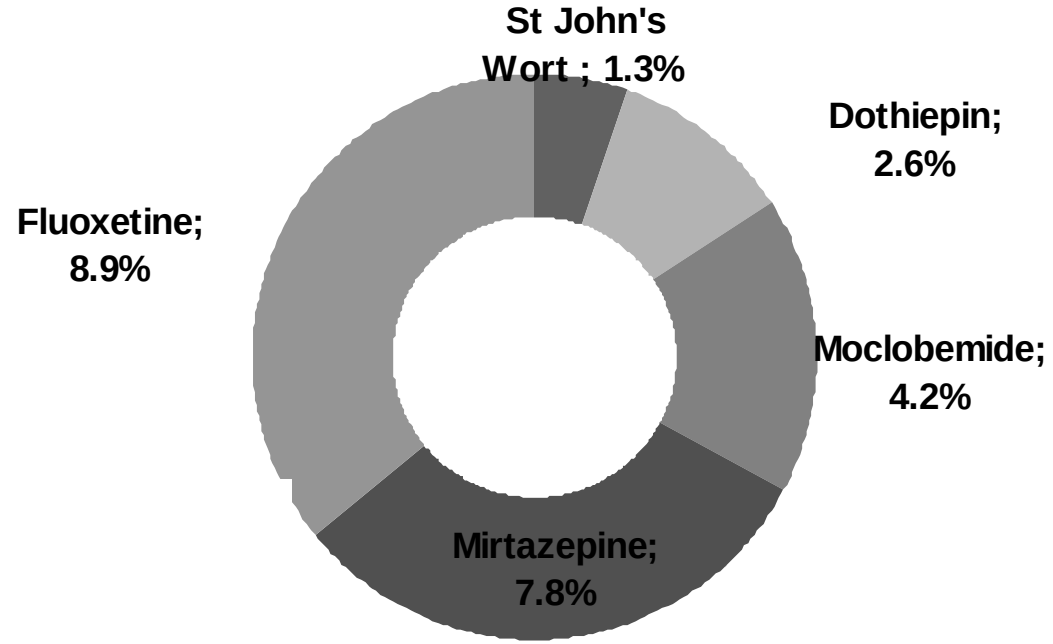
DNP contains the information about 200 000 compounds with different kinds of biological activity found in plants, animals, microorganisms, etc.

St. John’s Wort

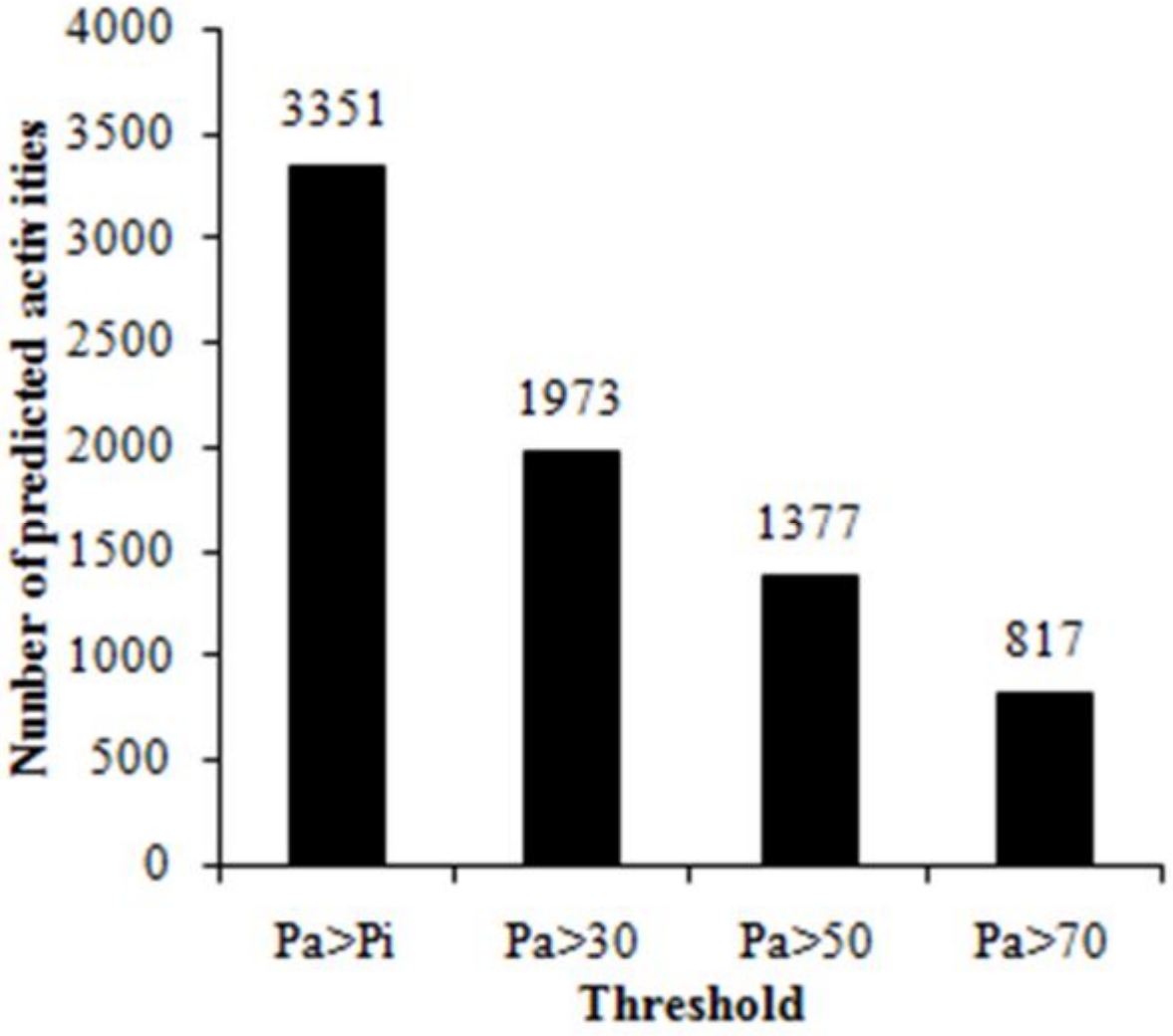
Adverse Effects (number)



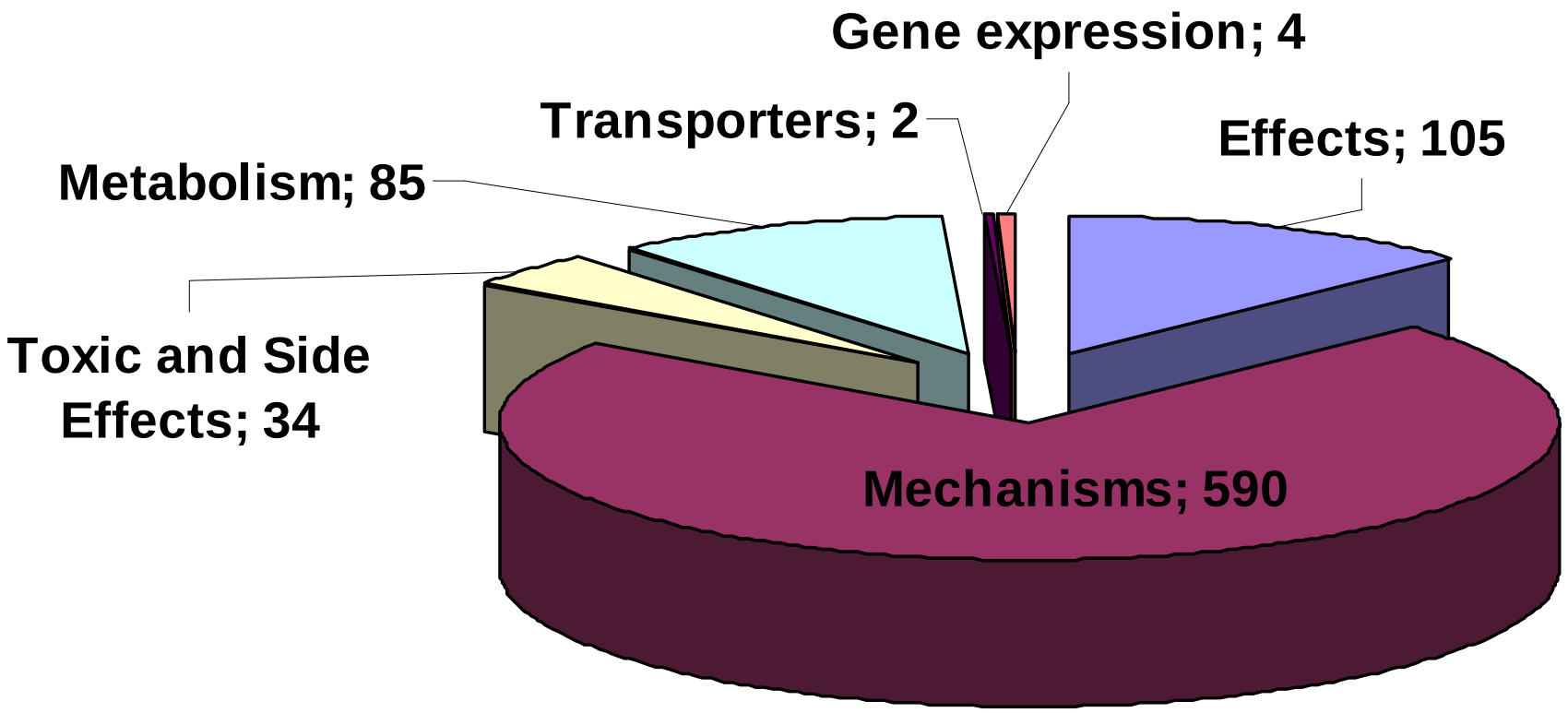
Adverse Effects (frequency)



Number of predicted biological activities at different thresholds



Predicted biological activity spectra for 93 components of St. John's Wort (Pa > 0.7)



Known biological activities predicted by PASS

Activity	IDs
Analgesic*	58, 61
Antibacterial	23, 80, 24, 48, 30
Antidepressant	7, 19, 1, 5, 3, 6, 13, 4
Antiinflammatory	55, 20, 21, 52, 54, 30, 32, 24, 22, 53, 49, 79, 80, 43, 27, 88, 76, 23, 35, 81, 50, 48, 68, 51, 78, 39, 91, 69, 77, 63, 31, 86, 28, 56, 38, 14, 92, 60, 93, 65, 42, 57, 82, 29
Antineoplastic	66, 43, 71, 61, 38, 72, 35, 24, 23, 33, 25, 80, 48, 16, 8, 42
Antioxidant	30, 20, 21, 32, 80, 22, 53, 52, 49, 79, 48, 27, 76, 78, 5, 91, 7, 81, 50, 29, 6, 51, 31, 92, 24, 82, 23, 54, 1, 83, 4, 55, 33, 93, 77, 87, 28, 56, 86, 14, 19, 41, 13, 85, 57, 2, 15, 36, 58, 84, 12
Antiseptic	25, 89, 84, 67, 86, 37, 74, 47
Antiulcerative	54, 85, 1, 41, 7, 5, 6, 36, 27, 55, 68, 35, 15, 86, 77, 89
Antiviral*	78, 87
Choleretic	50, 81, 51, 77, 86, 76, 27, 68, 88, 92, 2, 18, 93, 84, 56, 31
Photosensitizer	18
Spasmolytic	89, 85, 91, 29, 28, 58, 44

*Predicted at Pa>0.4

Known adverse effects predicted by PASS

Adverse Effect	ID
Dizziness	89, 37, 47, 74, 39, 75, 59, 84, 11, 70, 34, 30, 92
Dry mouth	89, 86, 75, 59, 47, 37, 74, 77
Headache	89, 52, 47, 74, 37, 30, 59, 75, 85, 84, 21, 79, 86, 34, 70, 11, 53, 49, 22, 91, 77, 32, 39, 65, 44, 62, 78, 48, 20, 56, 40, 38
Insomnia	52, 30, 14, 32, 79, 49, 22, 53, 31, 82, 59, 75, 92, 56, 11, 70, 34, 74, 37, 47, 93, 86, 89, 69, 77, 57, 84, 91, 48, 76, 83, 65, 78, 21, 62, 87, 28, 20, 38, 2, 80, 45, 16
Photophobia	18
Restlessness	59, 75, 86, 84, 47, 74, 37, 89, 77, 45, 34, 11, 70, 60, 56, 50, 81, 14, 73, 65, 44, 51, 67, 57, 64, 46, 82, 93, 92
Skin reactions	41, 36, 85, 67, 74, 47, 37, 34, 11, 70, 62
Tiredness	91, 78, 65, 39, 63, 75, 59, 44, 84, 40, 56, 77, 28, 72, 86, 38
Tremor	30, 32, 89, 22, 53, 49, 79, 52, 37, 47, 74, 48, 80, 76, 20, 75, 59, 14, 21, 92, 11, 34, 70, 31, 82, 93, 84, 57, 91, 58, 23, 83, 87, 78, 56, 28, 24, 86, 25, 62, 26, 77, 33, 17, 16, 67, 73, 27, 18
Vertigo	37, 47, 74, 75, 59, 85, 65, 11, 70, 34, 62, 61, 44, 68, 38, 69, 42, 41, 84, 63, 60, 86, 26, 35, 89, 45, 25, 77, 67, 39, 64, 73, 66, 91, 52, 46, 48, 40, 72, 8, 24, 71, 51, 23, 78, 56, 57, 76, 36, 80, 16, 18, 82, 90, 32, 81, 50, 21, 49, 22, 17, 53, 58, 93, 92, 43, 79, 31, 87, 2, 12, 28, 20

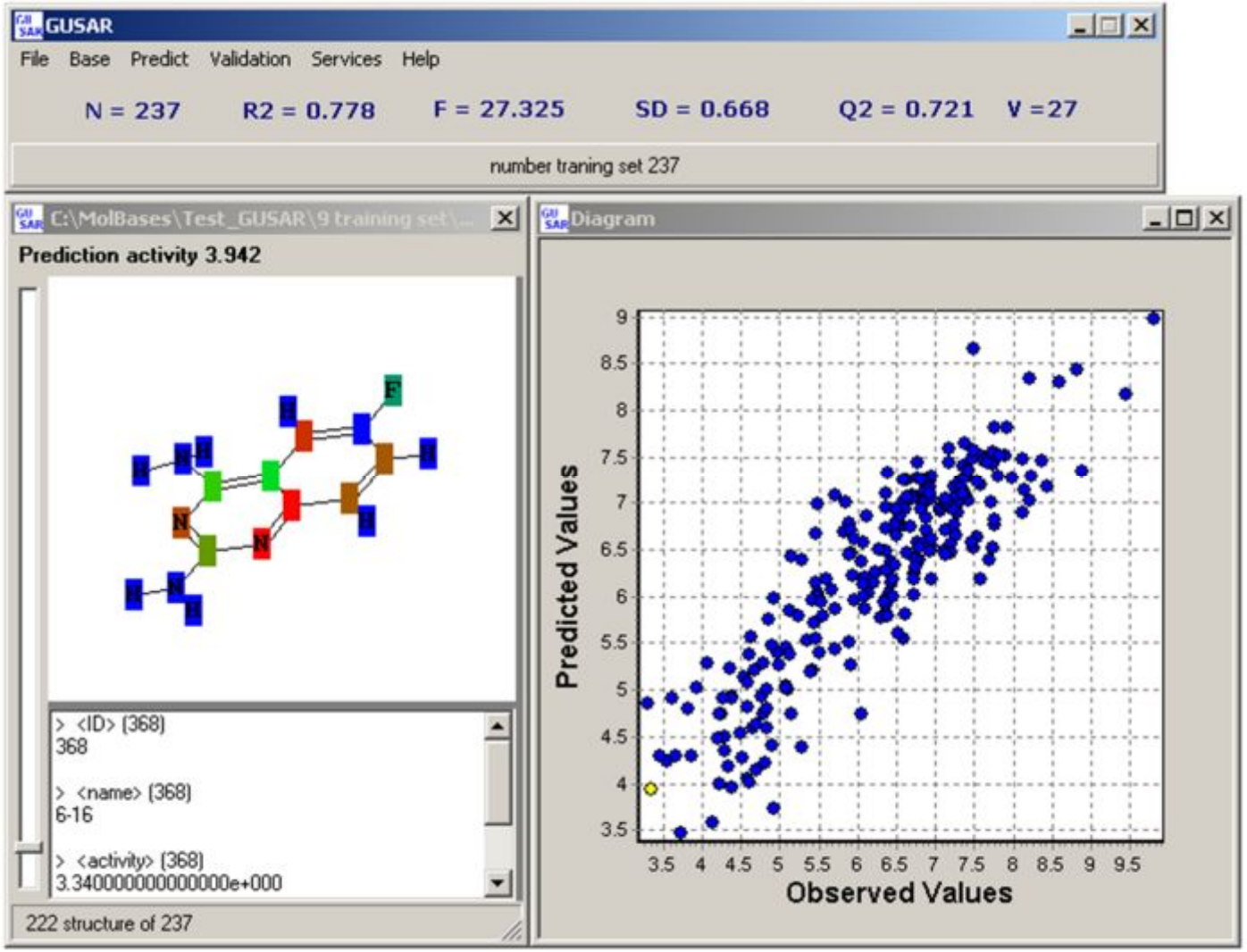
Additive/sinergistic effects predicted by PASS (for components of St. John's Wort extracted in two countries)

No	Serbia	Lithuania
1	Allergic conjunctivitis treatment	Allergic conjunctivitis treatment
2	Alopecia treatment	Alopecia treatment
3	Ankylosing spondylitis treatment	Ankylosing spondylitis treatment
4	Antidote, cyanide	-
5	Antidyskinetic	Antidyskinetic
6	-	Antiepileptic
7	Antihypoxic	-
8	Antiinflammatory	Antiinflammatory
9	Antimetastatic	Antimetastatic
10	Antimutagenic	-
11	Antineoplastic	Antineoplastic
12	-	Antineoplastic (gastric cancer)
13	-	Antiulcerative
14	….	……

Outline

- Chemical compounds & biological activity
- Computational approaches to prediction of biological activity.
- PASS: Prediction of Activity Spectra for Substances
- PharmaExpert: Tool for analysis of PASS predictions
- **GUSAR: General Unrestrained Structure-Activity Relationships**
- Summary

GUSAR: General Unrestricted Structure-Activity Relationships



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

QNA: Quantitative Neighborhoods of Atoms descriptors

$$P_i = B_i \sum_k (\mathrm{Exp}(-\tfrac{1}{2}C))_{ik} B_k$$

$$Q_i = B_i \sum_k (\mathrm{Exp}(-\tfrac{1}{2}C))_{ik} B_k A_k$$

$$A = \tfrac{1}{2}(IP + EA),$$

$$B = (IP - EA)^{-\frac{1}{2}},$$

IP is the first ionization potential,

EA is the electron affinity.

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

Robert G. Parr et al. *J. Chem. Phys.*, 1978, 68(8), 3801-3807.

Gasteiger J, Marsili M. *Tetrahedron*, 1980, 36, 3219-3228.

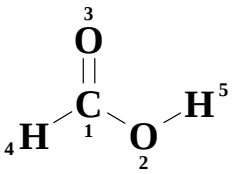
Rappe A K and W A Goddard III. *J. Ph. Ch.*, 1991, 95, 3358-3363.

D. Filimonov et al. in Proceedings of the QSAR 2004, Ankara, 2005, pp. 98-99.

D. Filimonov et al. Abstr. 3rd Internat. Symp. CMTPI 2005, Shanghai, 2005.

A. Lagunin et al. SAR and QSAR in Environmental Research 18 (2007), pp. 285-298.

QNA: Quantitative Neighborhoods of Atoms descriptors



a)

$$\mathbf{C} = \begin{vmatrix} 0 & 1 & 1 & 1 & 0 \\ 1 & 0 & 0 & 0 & 1 \\ 1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \end{vmatrix}$$

b)

$$\mathrm{Exp}\left(-\tfrac{1}{2}\mathbf{C}\right) = \begin{vmatrix} 1.40 & -0.59 & -0.57 & -0.57 & 0.14 \\ -0.59 & 1.27 & 0.14 & 0.14 & -0.54 \\ -0.57 & 0.14 & 1.13 & 0.13 & -0.02 \\ -0.57 & 0.14 & 0.13 & 1.13 & -0.02 \\ 0.14 & -0.54 & -0.02 & -0.02 & 1.13 \end{vmatrix}$$

c)

	EA	**IP**	*A*	*B*	**P**	**Q**
C	1.263	11.26	6.262	0.316	-0.00218	-0.1820
O	1.461	13.62	7.541	0.287	0.02944	0.3019
O	1.461	13.62	7.541	0.287	0.06199	0.5297
H	0.754	13.60	7.177	0.279	0.05812	0.4706
H	0.754	13.60	7.177	0.279	0.05304	0.3533

d)

(a) structural formula;
(b) connectivity matrix;
(c) exponent of the connectivity matrix;
(d) electron affinities (EA), ionization potentials (IP), parameters A and B, P and Q values for each of the atoms of *formic acid* molecule.

Self-Consistent Regression (SCR)

Self-consistent regression provides the means to develop a reliable QSAR/QSPR model using the training set with a large number of descriptors. SCR is based on the least-squares regularized method adopted for solving ill-imposed problems. During the SCR procedure the variables, which are worse for the description of independent variable, are removed from the model.

Filimonov D. et al. *Pharm. Chem. J.*, 2004, 1: 21-24.

Evaluation datasets for GUSAR

CDK2 (cyclin-dependent kinases 2) inhibitors	29, test 7
Dihydrofolate reductase (DHFR) inhibitors	237, test 124
Angiotensin-converting enzyme (ACE) inhibitors	76, test 38
Alpha-2 adrenoreceptor ligands	30
Estrogenic receptor-β ligands	21
Acute toxicity to Vibrio fischeri	56
Acute toxicity to Chlorella vulgaris	65
Acute toxicity to Tetrahymena pyriformis	200, test 50
CYP2A5 inhibitors	23, test 5
CYP2A6 inhibitors	23, test 5

were studied earlier using:

2D Cerius2/PLS, 3D Cerius2/PLS, ANN/2D, CoMFA, CoMSIAbasic, CoMSIAextra, EVA, GA/2D, GFA/ETA, GRID/GOLPE, HQSAR, MLR, PLS, SWR1/2D, SWR2/3D

N. Dessalew, P. Bharatam, European Journal of Medicinal Chemistry 42 (2007), pp. 1014-1027.
J. Jeffrey, A. Lee, F. Donald, J. Med. Chem. 47 (2004), pp. 5541-5554.
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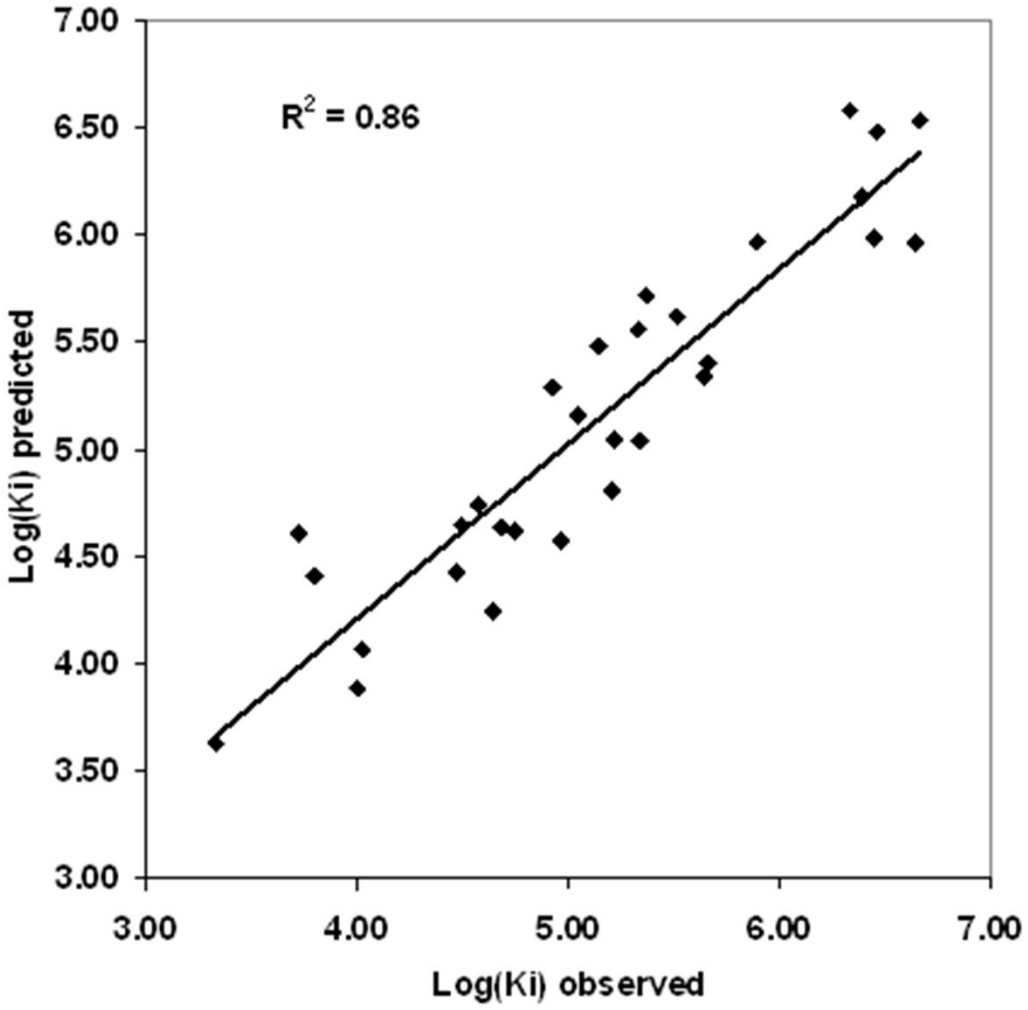
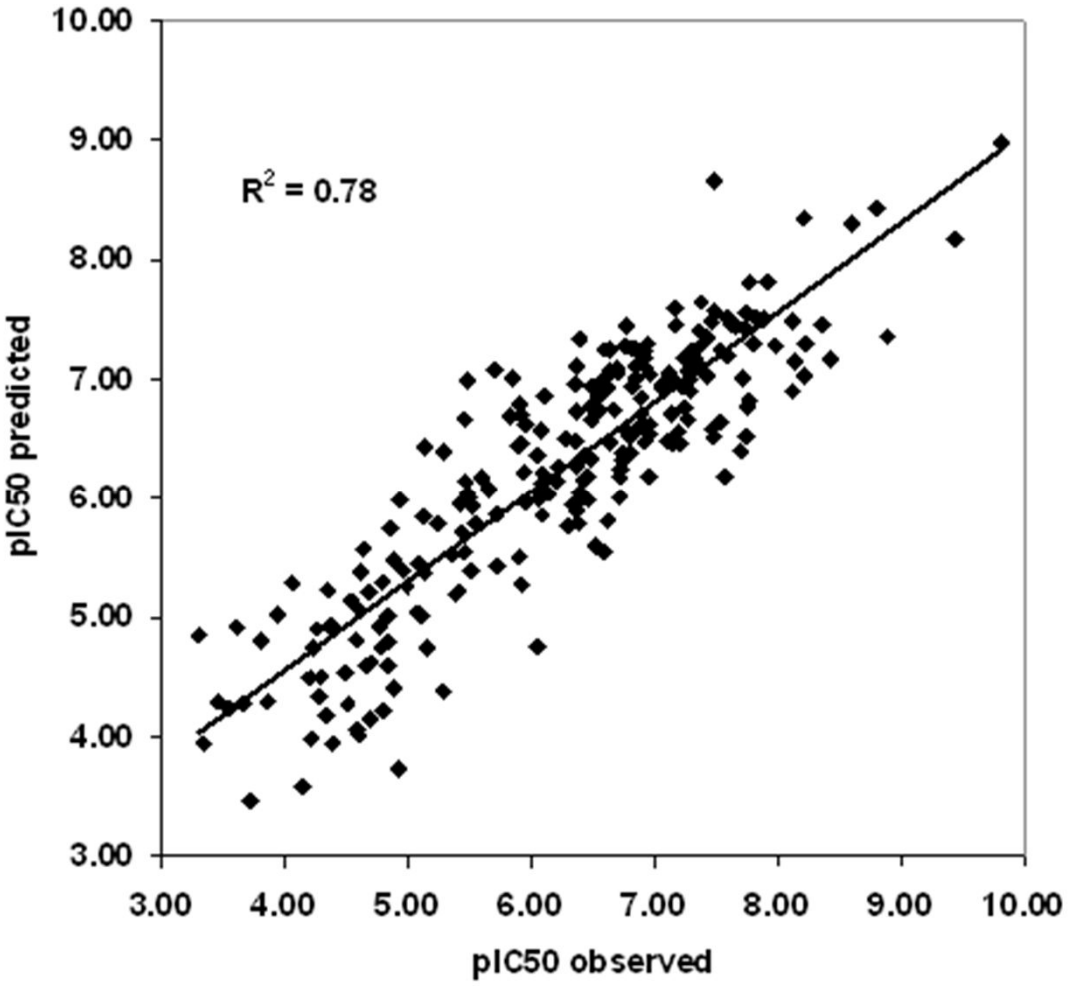
T. Netzeva et al., J. Chem. Inf. Comput. Sci. 44 (2004), pp. 258-265.
M. Cronin et al., Chemosphere 49 (2002), pp. 1201-1221.
A. Poso, J. Gynther, R. Juvonen, J. Comput.-Aided Mol. Design 15 (2001), pp. 195–202.

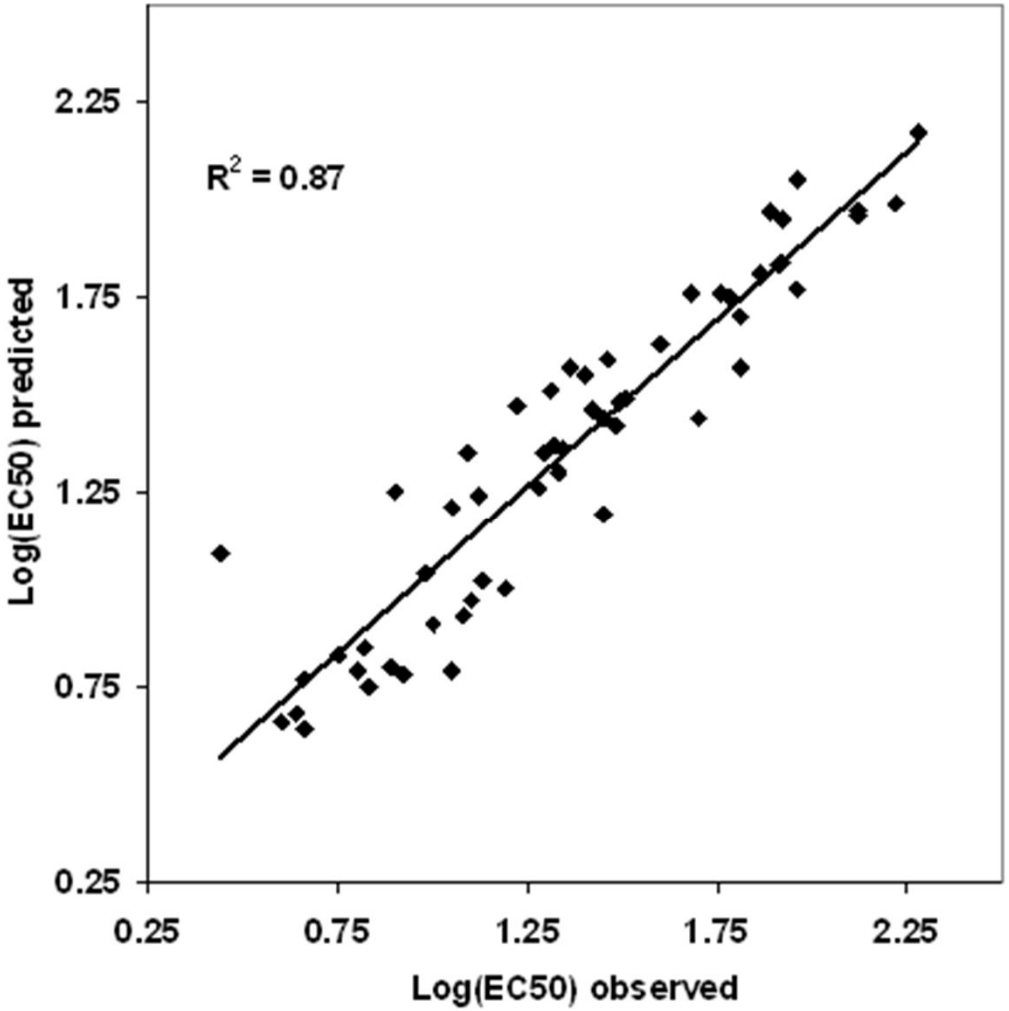
Alpha-2 Adrenoreceptors Ligands



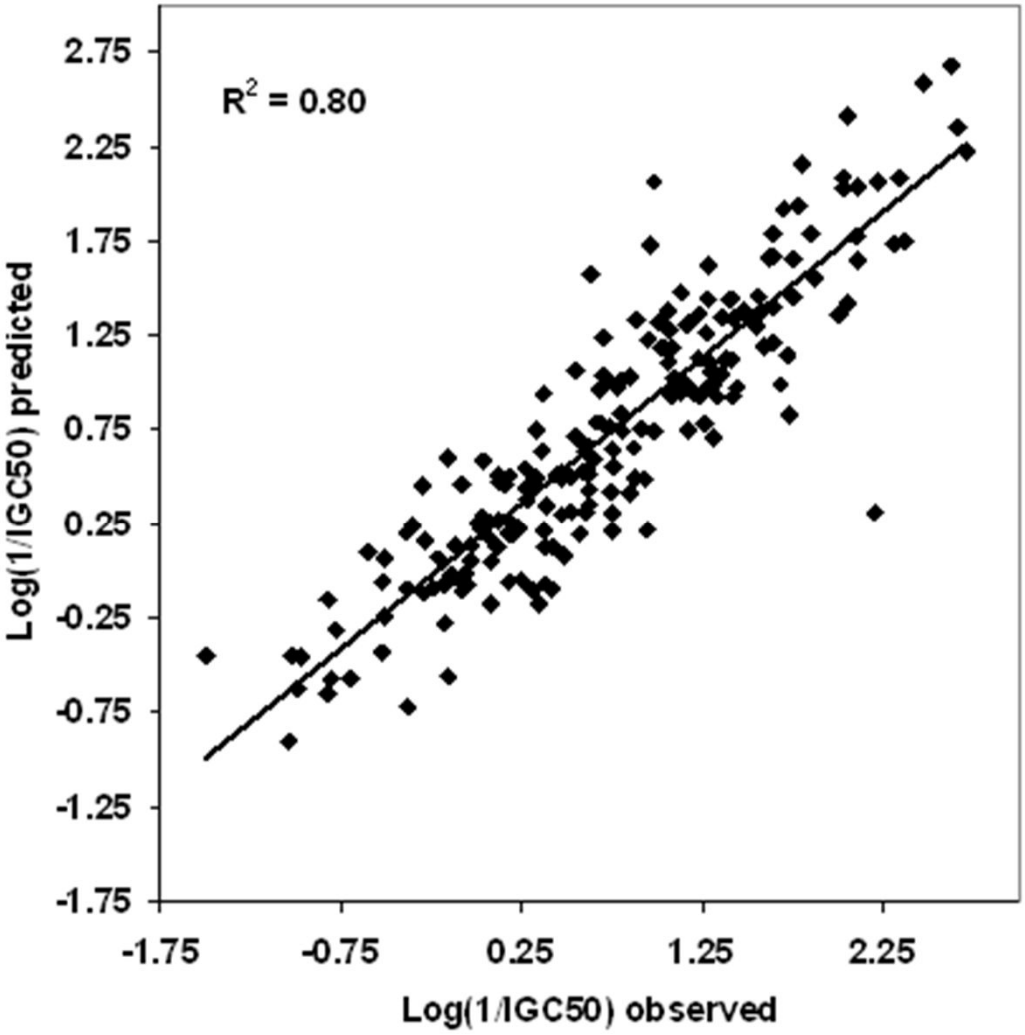
DHFR Inhibitors



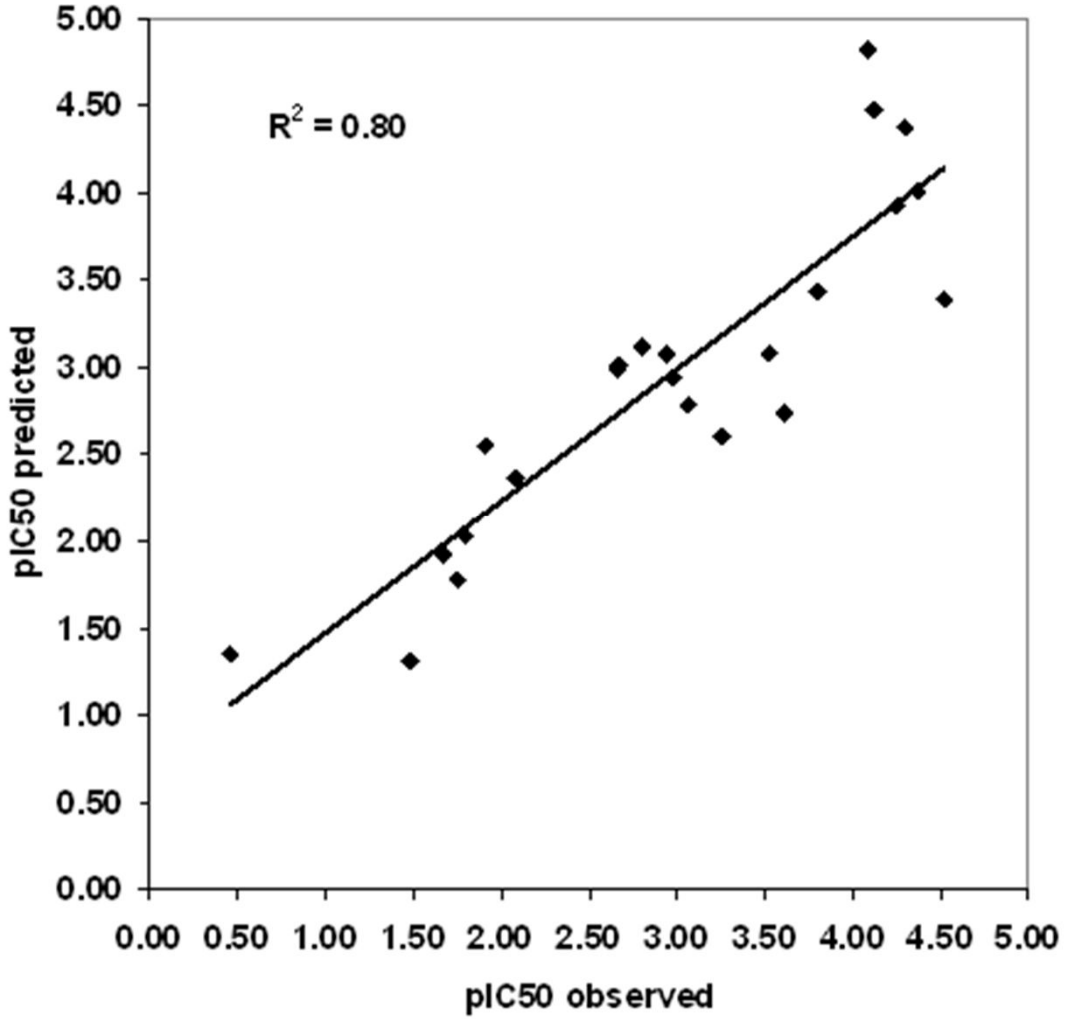
Vibrio Fischery Acute Toxicity



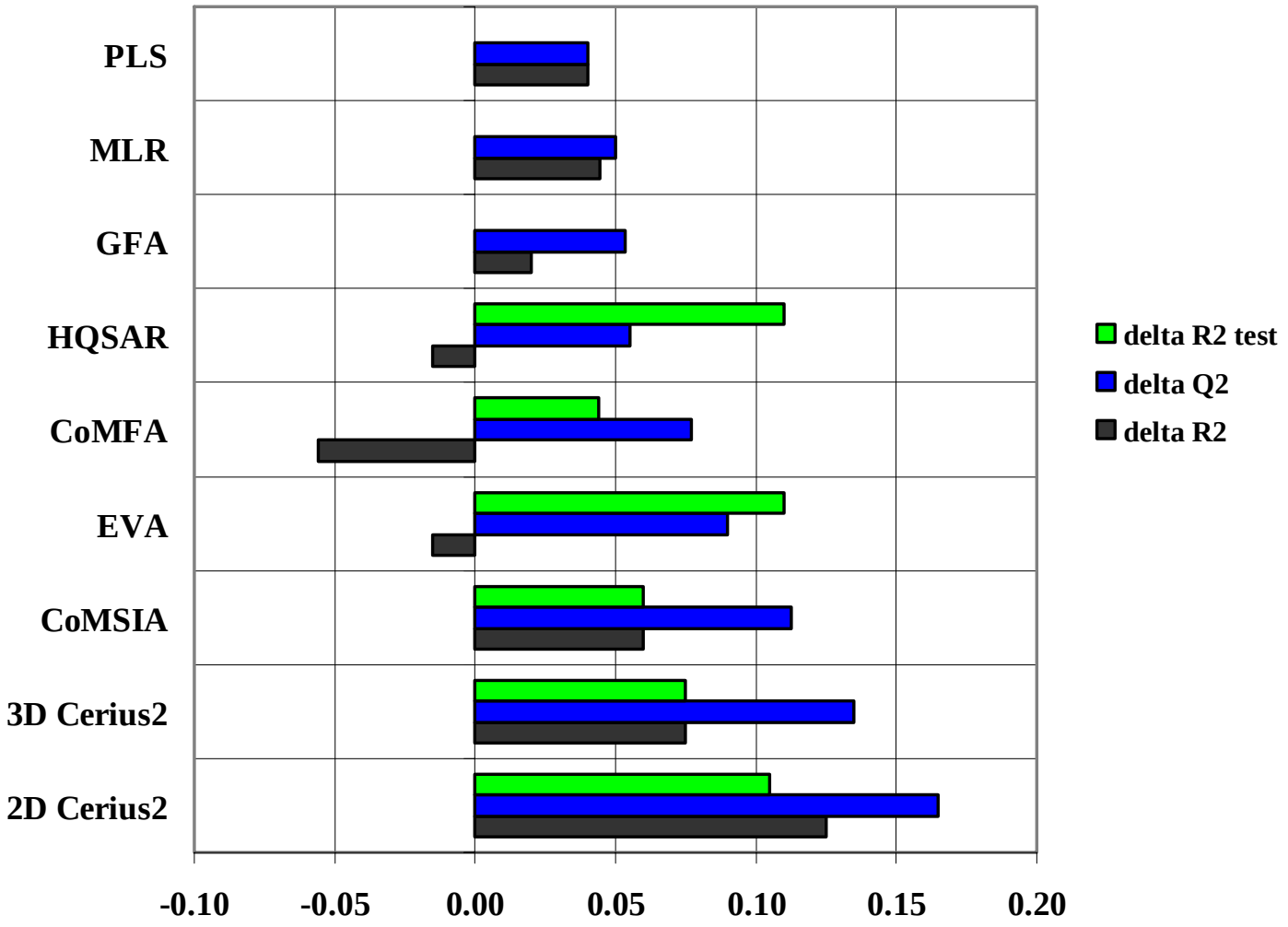
Tetrahymena Pyriformis Acute Toxicity



CYP2A6 Inhibitors



Comparison of prediction accuracy with some other methods



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

SAR and QSAR in Environmental Research
Vol. 20, Nos. 7–8, October–December 2009, 679–709

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QNA-based 'Star Track' QSAR approach†

D.A. Filimonov*, A.V. Zakharov, A.A. Lagunin and V.V. Poroikov

Institute of Biomedical Chemistry of Russian Academy of Medical Sciences, Moscow, Russia

(*Received 6 July 2009; in final form 1 October 2009*)

In the existing quantitative structure–activity relationship (QSAR) methods any molecule is represented as a single point in a many-dimensional space of molecular descriptors. We propose a new QSAR approach based on Quantitative Neighbourhoods of Atoms (QNA) descriptors, which characterize each atom of a molecule and depend on the whole molecule structure. In the 'Star Track' methodology any molecule is represented as a set of points in a two-dimensional space of QNA descriptors. With our new method the estimate of the target property of a chemical compound is calculated as the average value of the function of QNA descriptors in the points of the atoms of a molecule in QNA descriptor space. Substantially, we propose the use of only two descriptors rather than more than 3000 molecular descriptors that apply in the QSAR method. On the basis of this approach we have developed the computer program GUSAR and compared it with several widely used QSAR methods including CoMFA, CoMSIA, Golpe/GRID, HQSAR and others, using ten data sets representing various chemical series and diverse types of biological activity. We show that in the majority of cases the accuracy and predictivity of GUSAR models appears to be better than those for the reference QSAR methods. High predictive ability and robustness of GUSAR are also shown in the leave-20%-out cross-validation procedure.

Keywords: QNA; QSAR; biological activity; toxicity; GUSAR

Just accepted for publication (July 5th, 2011):

ELSEVIER

European Journal of Medicinal Chemistry
journal homepage: www.elsevier.com/locate/ejmech

Synthesis, Antifungal Activity and QSAR study of 2-Arylhydroxynitroindoles

Galina V. Kokurkina[a] ,Mikhail D. Dutov[a,] *, Svyatoslav A. Shevelev[a], Sergey V. Popkov[b], Alexey V. Zakharov[c] and Vladimir V. Poroikov[c]

[a]*Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation*
[b]*Mendeleev University of Chemical Technology of Russia, 125047 Moscow, Russian Federation*
[c] *Institute of Biomedical Chemistry of Russian Academy of Medical Sciences,119121 Moscow, Russian Federation*

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Cyclization of ketoximes
Fungicidal activity
QSAR

ABSTRACT

A series of 2-arylhydroxynitroindoles were prepared and tested for antifungal activity *in vitro*. The preliminary bioassays indicated that some compounds are comparable to the commercial fungicide (triadimefon). To further explore the structure – activity relationships, the data set of the seventeen structures and their quantitative values of antifungal activities were used for QSAR modeling. Based on the obtained QSAR models four new chemical compounds were designed, synthesized and tested in fungicidal assays. Reasonable correspondence between the experimental and predicted values of antifungal activity was observed.

QSAR Modelling of antifungal activities

Table 3. QSAR modeling of antifungal activities results.

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

R^2 – determination coefficient

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

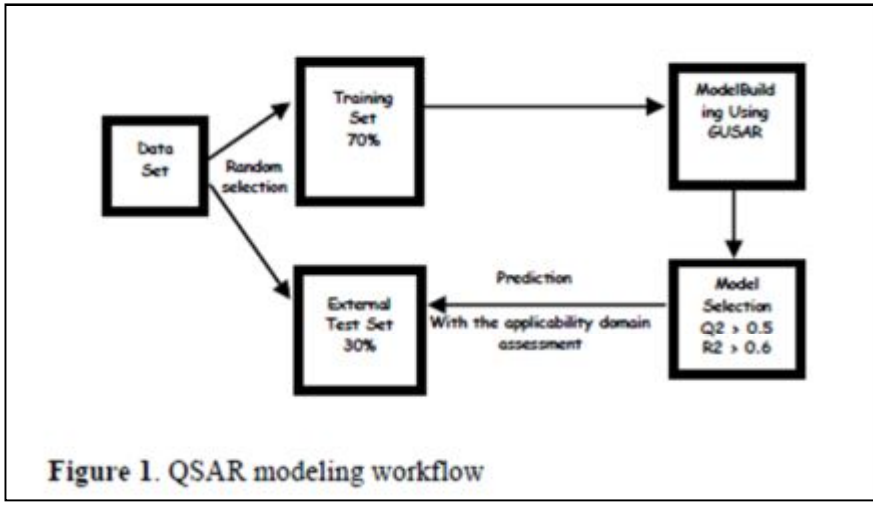

Figure 1. QSAR modeling workflow

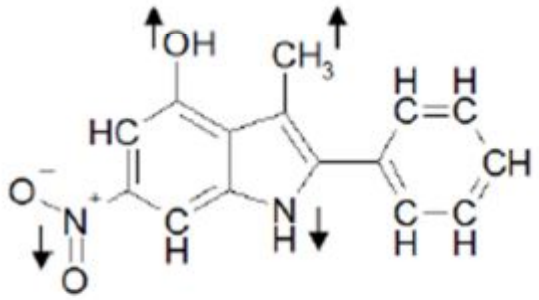

Figure 2. Atom contribution into the antifungal activity.

Comparison of computational predictions with the experiment

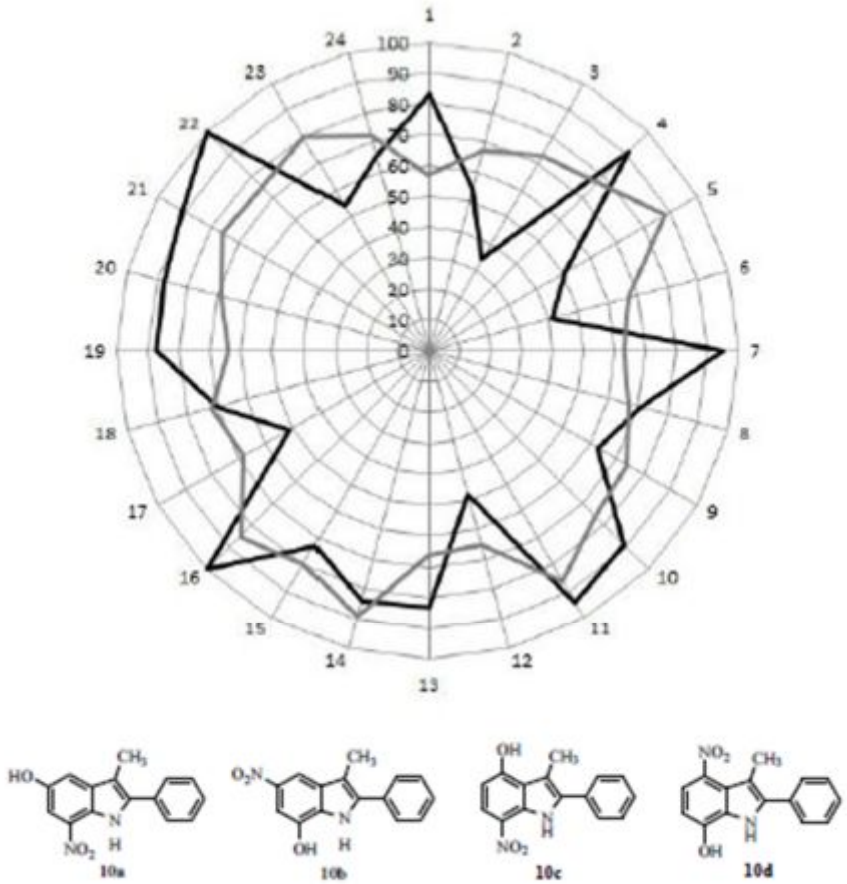

Figure 3. Comparison of the experimental (**black line**) and predicted (grey line) antifungal activities for compounds **10a** (1-6), **10b** (7-12), **10c** (13-18), **10d** (19-24). 1-6, 7-12, 13-18 and 19-24 are activities against *B.s.*, *F.m.*, *F.o.*, *R.s.*, *S.s.* and *V.i.*, respectively. Average RMSE values calculated for each activity vary from 12 to 25; for each compound – from 12 to 28. All values are given in percent of inhibition at 30 μg mL^{-1} concentration of the compound.

GUSAR-Based Web-Service

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

- Chemical compounds & biological activity
- Computational approaches to prediction of biological activity.
- PASS: Prediction of Activity Spectra for Substances
- PharmaExpert: Tool for analysis of PASS predictions
- GUSAR: General Unrestricted Structure-Activity Relationships
- **Summary**

Summary

- ✓ Computer-aided approaches is useful for finding of hits and their optimization to lead compounds.
- ✓ PASS predictions allow to identify the most relevant biological screens for testing of particular chemical compounds.
- ✓ PharmaExpert provides the means for selection of chemical compounds with desirable biological activity spectra (incl. multitargeted actions).
- ✓ GUSAR can be used as an universal tool for solving various QSAR/QSPR problems.
- ✓ Predictive web-services are freely available from http://pharmaexpert.ru