PharmaExpert
RESEARCH LABORATORY

ЛАБОРАТОРИЯ СТРУКТУРНО-ФУНКЦИОНАЛЬНОГО КОНСТРУИРОВАНИЯ ЛЕКАРСТВ
LABORATORY OF STRUCTURE-FUNCTION BASED DRUG DESIGN

КОМПЬЮТЕРНОЕ ПРОГНОЗИРОВАНИЕ СПЕКТРОВ БИОЛОГИЧЕСКОЙ АКТИВНОСТИ ОРГАНИЧЕСКИХ СОЕДИНЕНИЙ

Д.А. Филимонов

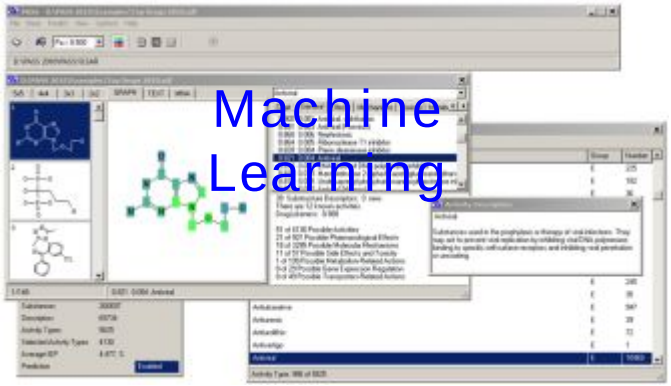
Институт биомедицинской химии им. В.Н. Ореховича РАМН, Москва

ИБМХ

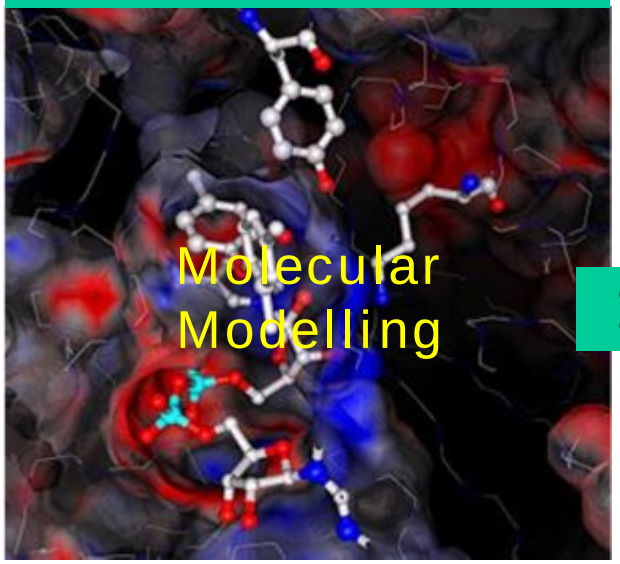
Методы биоинформатики

Фундаментальная теория

Универсальный закон природы



Ab initio **принципы**



Обучение на примерах

Единичная оценка

Пример лекарственной субстанции

http://www.drugs.com/plavix.html

Brand Names : Plavix
Generic Name: Clopidogrel

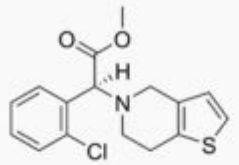
Plavix (clopidogrel) keeps the platelets in your blood from coagulating (clotting) to prevent unwanted blood clots that can occur with certain heart or blood vessel conditions.

http://en.wikipedia.org/wiki/Clopidogrel

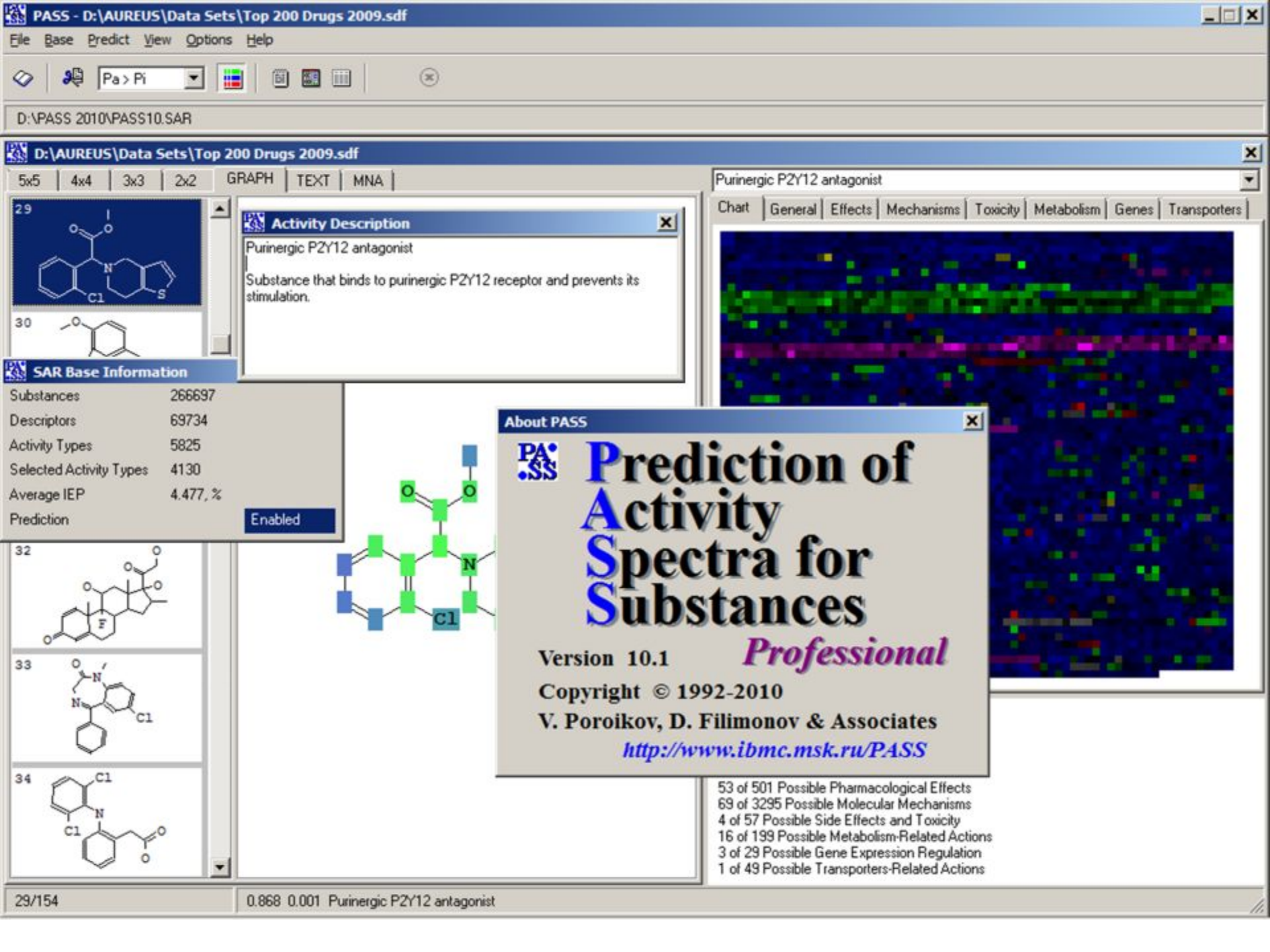
Clopidogrel is an oral, thienopyridine class antiplatelet agent used to inhibit blood clots in coronary artery disease, peripheral vascular disease, and cerebrovascular disease. It is marketed by Bristol-Myers Squibb and Sanofi-Aventis under the trade name Plavix. The drug works by irreversibly inhibiting a receptor called P2Y12, an adenosine diphosphate ADP chemoreceptor. Adverse effects include hemorrhage, severe neutropenia, and thrombotic thrombocytopenic purpura (TTP).

Клопидогрел (Clopidogrelum) — **лекарственный препарат**, **снижающий склонность тромбоцитов к агрегации**.

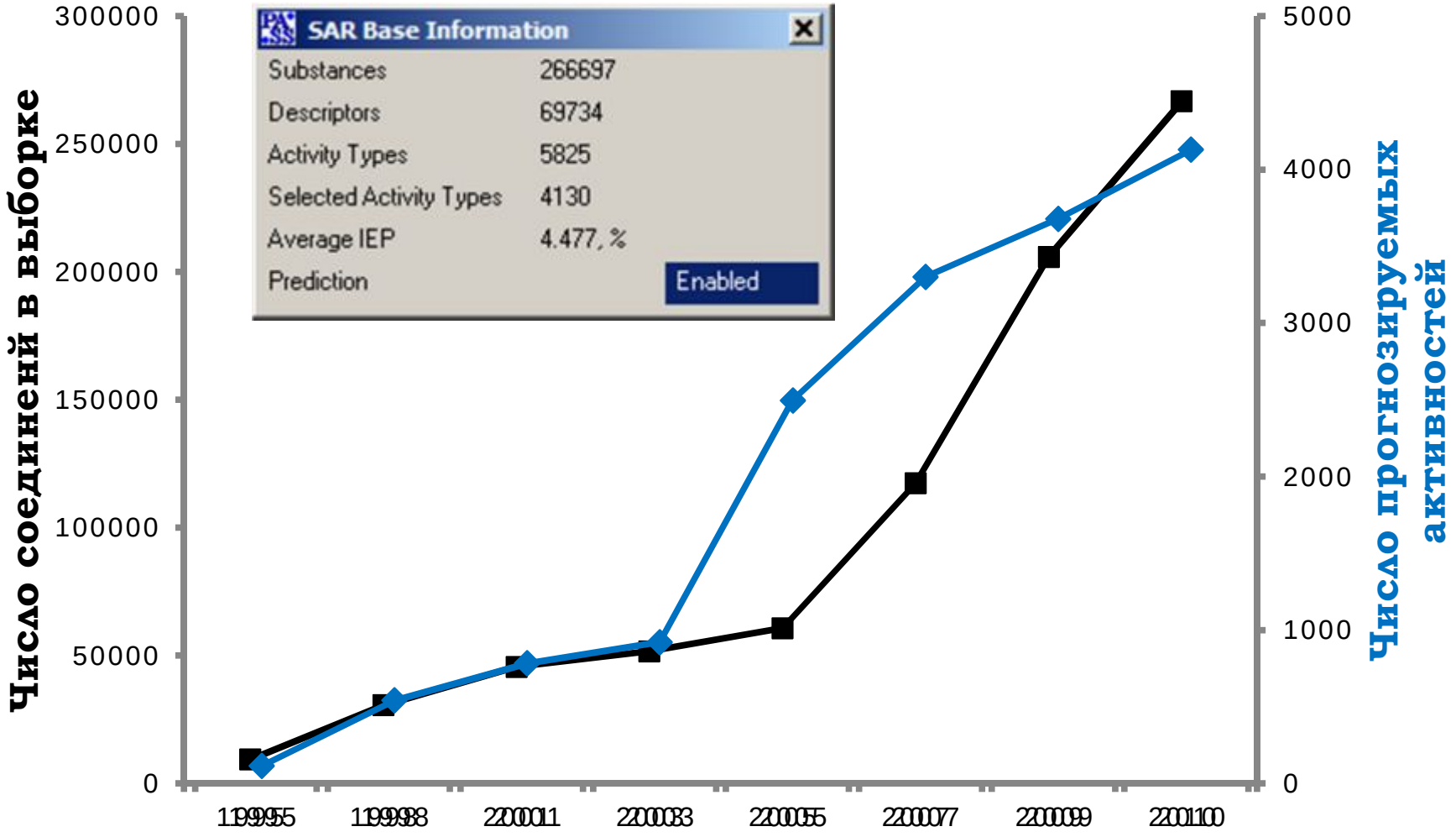
Clopidogrel



Systematic (IUPAC) name	
(+)-(*S*)-methyl 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4*H*)-yl)acetate	
Identifiers	
CAS number	113665-84-2
ATC code	B01AC04
PubChem	CID 60606
DrugBank	APRD00444
ChemSpider	54632 ✓
UNII	A74586SNO7 ✓
KEGG	D07729 ✓
ChEMBL	CHEMBL1771 ✓
Chemical data	
Formula	$C_{16}H_{16}ClNO_2S$
Mol. mass	321.82 g/mol
SMILES	eMolecules & PubChem
InChI	[show]
Pharmacokinetic data	
Bioavailability	>50%
Protein binding	94–98%
Metabolism	Hepatic
Half-life	7–8 hours (inactive metabolite)
Excretion	50% renal 46% biliary


PASS - D:\AUREUS\Data Sets\Top 200 Drugs 2009.sdf
File Base Predict View Options Help
Pa > Pi
D:\PASS 2010\PASS10.SAR
D:\AUREUS\Data Sets\Top 200 Drugs 2009.sdf
5x5 4x4 3x3 2x2 GRAPH TEXT MNA
Activity Description
Purinergic P2Y12 antagonist
Substance that binds to purinergic P2Y12 receptor and prevents its stimulation.
SAR Base Information
Substances 266697
Descriptors 69734
Activity Types 5825
Selected Activity Types 4130
Average IEP 4.477, %
Prediction Enabled
Purinergic P2Y12 antagonist
Chart General Effects Mechanisms Toxicity Metabolism Genes Transporters
About PASS
Prediction of Activity Spectra for Substances
Professional
Version 10.1
Copyright © 1992-2010
V. Poroikov, D. Filimonov & Associates
http://www.ibmc.msk.ru/PASS
53 of 501 Possible Pharmacological Effects
69 of 3295 Possible Molecular Mechanisms
4 of 57 Possible Side Effects and Toxicity
16 of 199 Possible Metabolism-Related Actions
3 of 29 Possible Gene Expression Regulation
1 of 49 Possible Transporters-Related Actions
29/154
0.868 0.001 Purinergic P2Y12 antagonist

Обучающая выборка PASS



Спектр биологической активности:

Весь комплекс

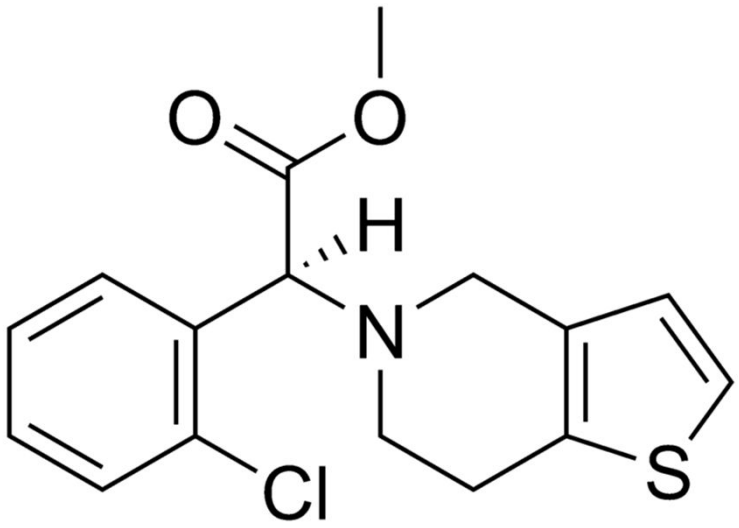
- ✓ **фармакологических эффектов**
- ✓ **биохимических механизмов действия**
- ✓ **эффектов специфической токсичности и побочного действия**
- ✓ **эффектов взаимодействия с системой метаболизма**
- ✓ **эффектов влияния на генную экспрессию**
- ✓ **эффектов влияния на белки-транспортеры**

которые вещество способно вызывать при некоторых условиях взаимодействия с биологическими объектами, без учета особенностей конкретных экспериментов.

Активности представлены качественно.

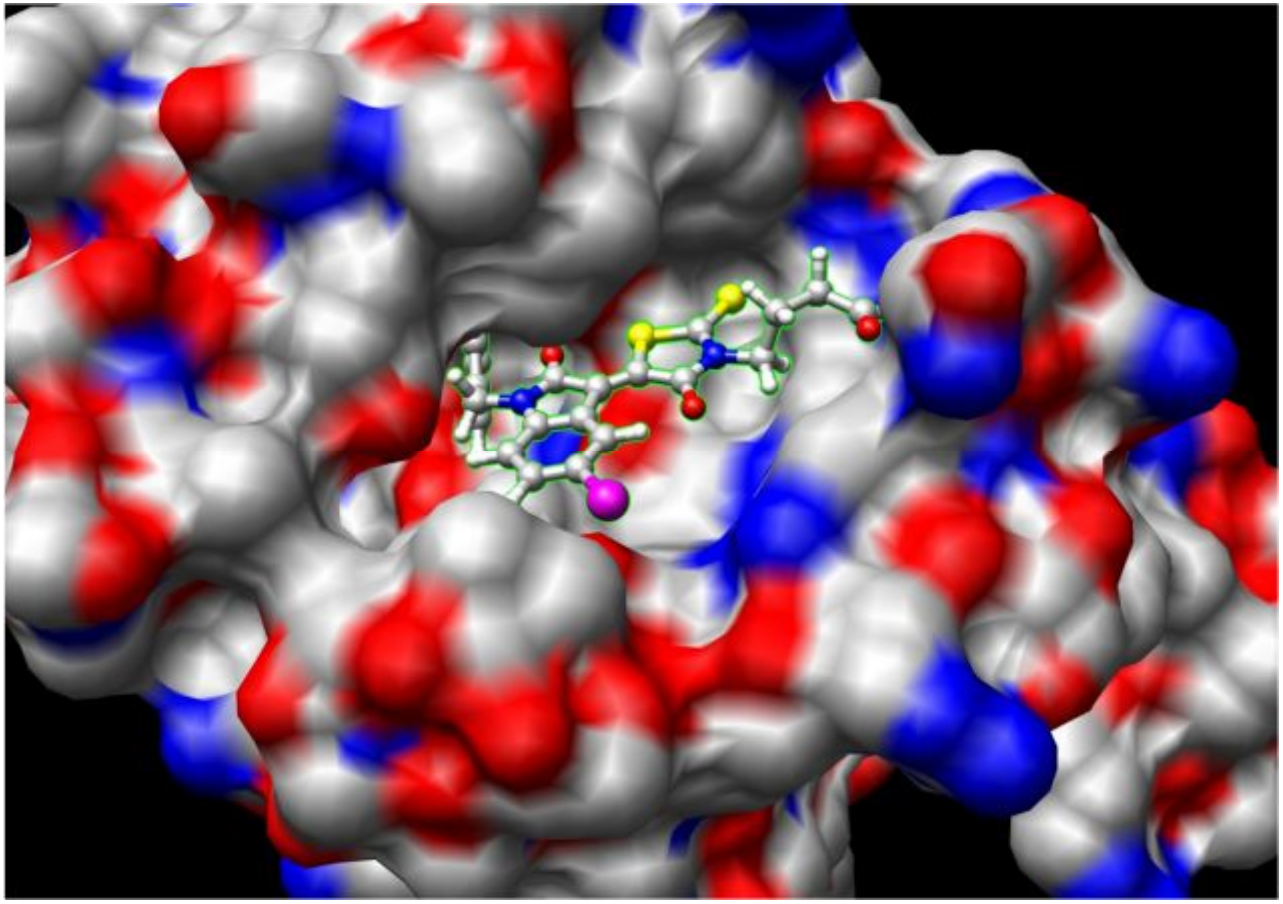
Принцип «презумпции невиновности»:
вещество не обладает теми видами биологической активности, которые не указаны в его спектре.

Представление структуры молекулы



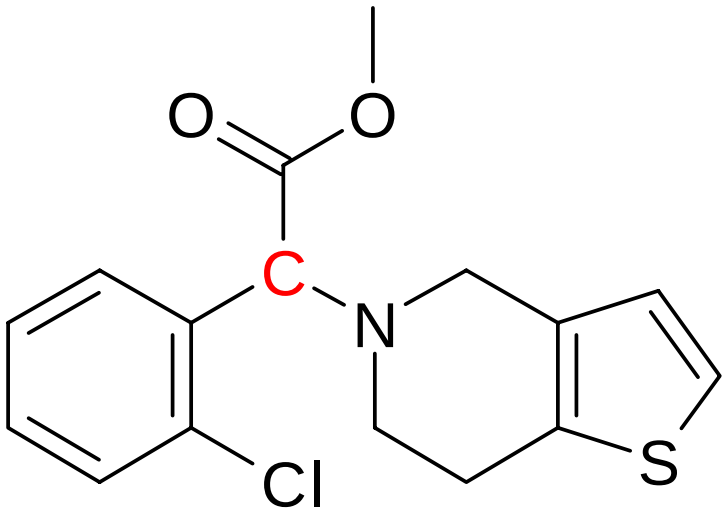
Поэтому структурная формула однозначно определяет свойства молекулы.

Представление структуры молекулы



Дескрипторы многоуровневых атомных окрестностей (MNA) **основаны на идее описания отдельных атомов молекулы с учетом их окружения**.

Дескрипторы многоуровневых атомных окрестностей – MNA

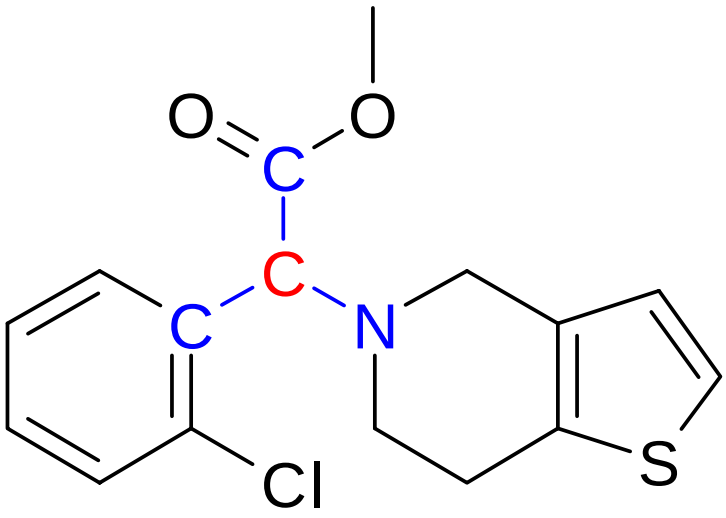


MNA/0: **-C**

Филимонов Д.А., **Поройков В.В**. (2006) **РХЖ**, L, (2), 66-75.

Filimonov D.A., Poroikov V.V. (2008) In: *Chemoinformatics Approaches to Virtual Screening*. Eds. Alexandre Varnek and Alexander Tropsha. Cambridge (UK): RSC Publishing, 182-216.

Дескрипторы многоуровневых атомных окрестностей – MNA

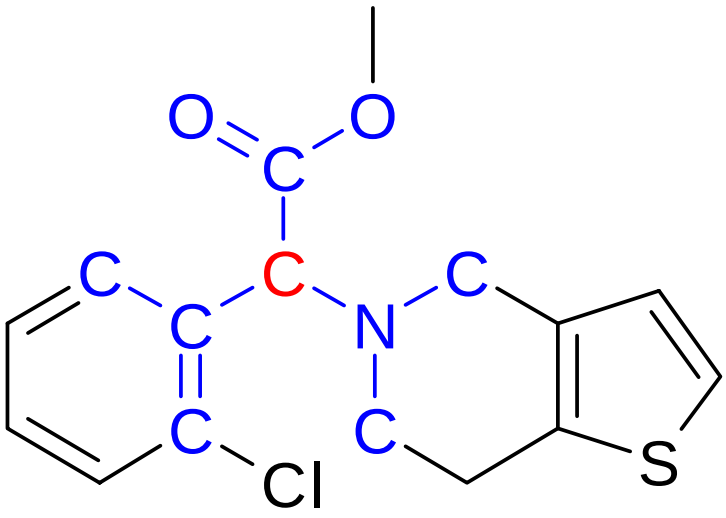


MNA/1: **-C**(CN-H-C)

Филимонов Д.А., **Поройков В.В**. (2006) **РХЖ**, L, (2), 66-75.

Filimonov D.A., Poroikov V.V. (2008) In: *Chemoinformatics Approaches to Virtual Screening*. Eds. Alexandre Varnek and Alexander Tropsha. Cambridge (UK): RSC Publishing, 182-216.

Дескрипторы многоуровневых атомных окрестностей – MNA

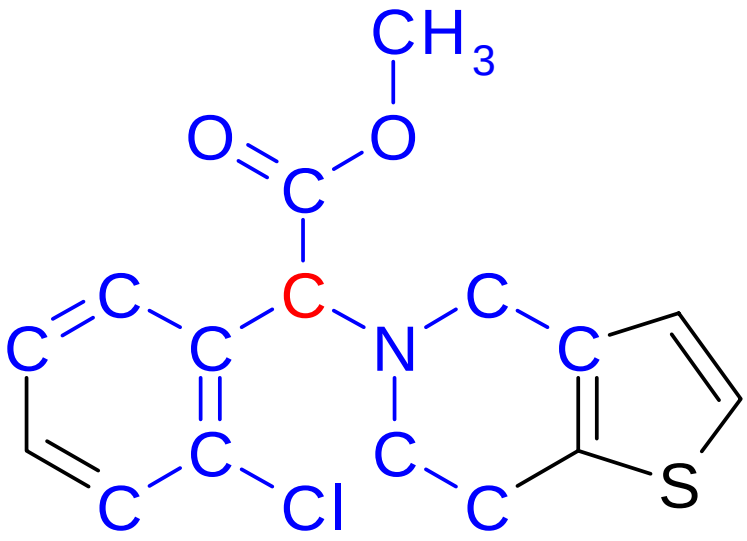


MNA / 2: **-C**(C(CC-**C**)N(CC-**C**)-H(-**C**)-C(-**C**-O-O))

Филимонов Д.А., **Поройков В.В**. (2006) **РХЖ**, L, (2), 66-75.

Filimonov D.A., Poroikov V.V. (2008) In: *Chemoinformatics Approaches to Virtual Screening*. Eds. Alexandre Varnek and Alexander Tropsha. Cambridge (UK): RSC Publishing, 182-216.

Дескрипторы многоуровневых атомных окрестностей – MNA

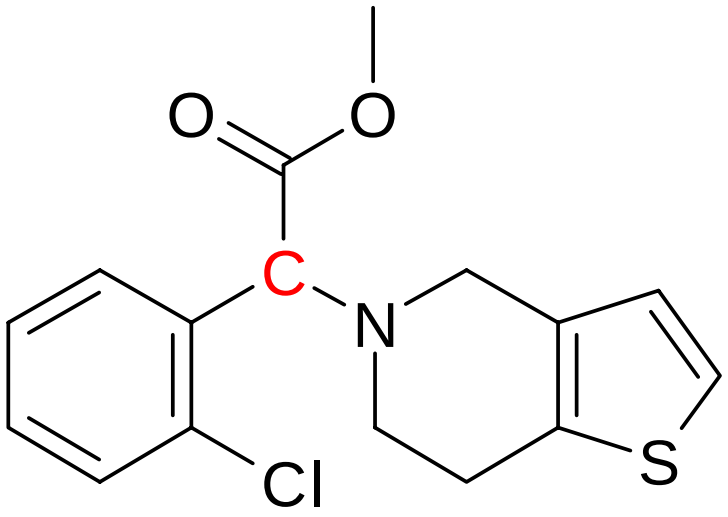


MNA / 3: **-C**(C(C(**CC**-H)C(CC-Cl)**-C**(CN-H-C))
N(C(CN-H-H)C(CN-H-H)**-C**(CN-H-C))
-H(**-C**(CN-H-C))
-C(**-C**(CN-H-C)-O(-C)-O(-C-C)))

Филимонов Д.А., **Поройков В.В**. (2006) **РХЖ**, L, (2), 66-75.

Filimonov D.A., Poroikov V.V. (2008) In: *Chemoinformatics Approaches to Virtual Screening*. Eds. Alexandre Varnek and Alexander Tropsha. Cambridge (UK): RSC Publishing, 182-216.

Дескрипторы многоуровневых атомных окрестностей – MNA

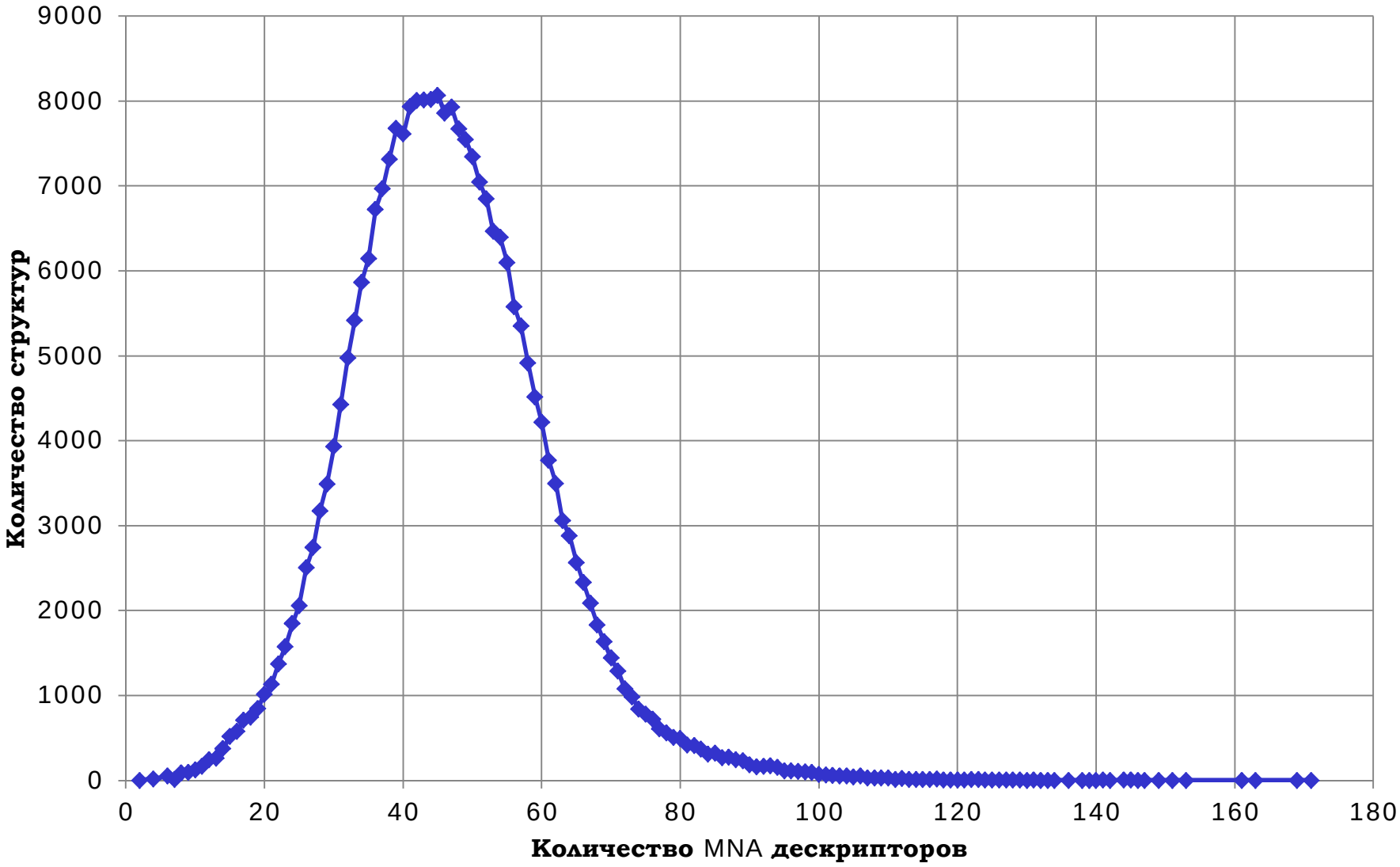


HC	C(C(CCC)C(CC-H-H)S(CC))
CHHHO	C(C(CCC)C(CS-H)-H(C))
CHHCC	C(C(CCC)N(CC-C)-H(C)-H(C))
CHHCN	C(C(CCS)C(CC-H)C(CN-H-H))
CHCC	C(C(CCS)C(CN-H-H)-H(C)-H(C))
CHCCN	C(C(CC-H-H)N(CC-C)-H(C)-H(C))
CHCS	C(C(CC-H)C(CC-H)-H(C))
CCCC	C(C(CC-H)C(CC-C)-H(C))
CCCS	C(C(CC-H)C(CC-C)-Cl(C))
CCCCl	C(C(CC-H)C(CC-Cl)-H(C))
CCOO	C(C(CC-H)C(CC-Cl)-C(CN-H-C))
NCCC	C(C(CC-H)S(CC)-H(C))
OC	N(C(CN-H-H)C(CN-H-H)-C(CN-H-C))
OCC	S(C(CCS)C(CS-H))
SCC	-H(C(CC-H))
ClC	-H(C(CC-H-H))
	-H(C(CN-H-H))
	-H(C(CS-H))
	-H(-C(CN-H-C))
	-H(-C(-H-H-H-O))
	-C(C(CC-C)N(CC-C)-H(-C)-C(-C-O-O))
	-C(-H(-C)-H(-C)-H(-C)-O(-C-C))
	-C(-C(CN-H-C)-O(-C)-O(-C-C))
	-O(-C(-H-H-H-O)-C(-C-O-O))
	-O(-C(-C-O-O))
	-Cl(C(CC-Cl))

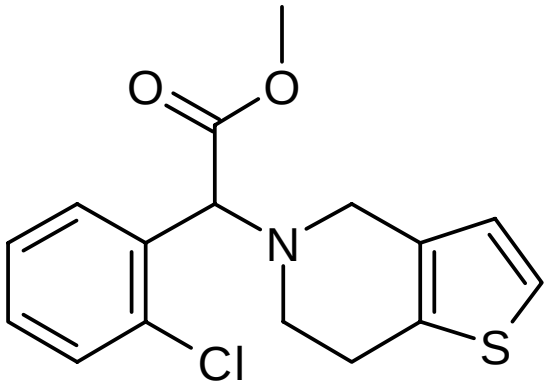
Филимонов Д.А., **Поройков В.В.** (2006) **РХЖ**, L, (2), 66-75.

Filimonov D.A., Poroikov V.V. (2008) In: *Chemoinformatics Approaches to Virtual Screening*. Eds. Alexandre Varnek and Alexander Tropsha. Cambridge (UK): RSC Publishing, 182-216.

Дескрипторы многоуровневых атомных окрестностей – MNA



Пример органического соединения в PASS



Спектр активности

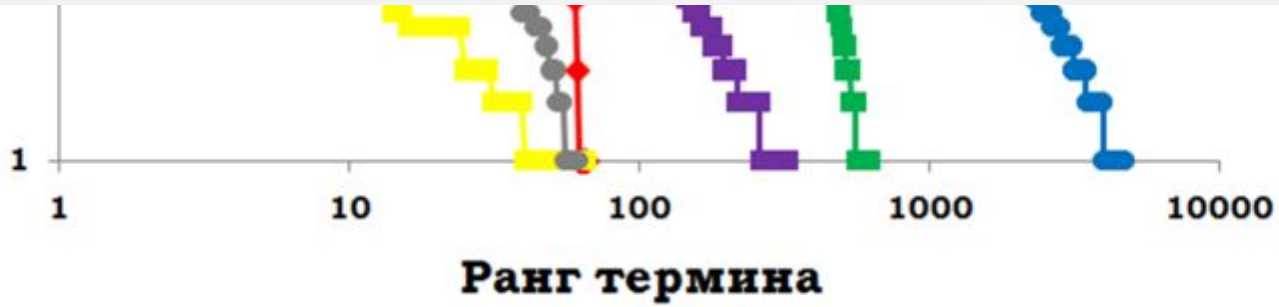
Acute neurologic disorders treatment
Antianginal
Antiarthritic
Anticoagulant
Antipsoriatic
Antithrombotic
Atherosclerosis treatment
CYP2C19 inhibitor
CYP2C9 inhibitor
CYP3A4 substrate
Hyperthermic
Neuroprotector
Platelet aggregation inhibitor
Purinergic P2T antagonist
Purinergic P2Y12 antagonist

Структурные дескрипторы

HC	C(C(CCC)C(CC-H-H)S(CC))
CHHHO	C(C(CCC)C(CS-H)-H(C))
CHHCC	C(C(CCC)N(CC-C)-H(C)-H(C))
CHHCN	C(C(CCS)C(CC-H)C(CN-H-H))
CHCC	C(C(CCS)C(CN-H-H)-H(C)-H(C))
CHCCN	C(C(CC-H-H)N(CC-C)-H(C)-H(C))
CHCS	C(C(CC-H)C(CC-H)-H(C))
CCCC	C(C(CC-H)C(CC-C)-H(C))
CCCS	C(C(CC-H)C(CC-C)-Cl(C))
CCCCl	C(C(CC-H)C(CC-Cl)-H(C))
CCOO	C(C(CC-H)C(CC-Cl)-C(CN-H-C))
NCCC	C(C(CC-H)S(CC)-H(C))
OC	N(C(CN-H-H)C(CN-H-H)-C(CN-H-C))
OCC	S(C(CCS)C(CS-H))
SCC	-H(C(CC-H))
ClC	-H(C(CC-H-H))
	-H(C(CN-H-H))
	-H(C(CS-H))
	-H(-C(CN-H-C))
	-H(-C(-H-H-H-O))
	-C(C(CC-C)N(CC-C)-H(-C)-C(-C-O-O))
	-C(-H(-C)-H(-C)-H(-C)-O(-C-C))
	-C(-C(CN-H-C)-O(-C)-O(-C-C))
	-O(-C(-H-H-H-O)-C(-C-O-O))
	-O(-C(-C-O-O))
	-Cl(C(CC-Cl))

Термины биологической активности в PASS

501	**фармакологический эффект**
3295	**биохимических механизмов действия**
57	**эффектов специфической токсичности и побочного действия**
199	**терминов метаболизма**
29	**эффектов влияния на генную экспрессию**
49	**эффектов влияния на белки-транспортеры**



Алгоритм прогноза спектра биологической активности органических соединений PASS

По структуре молекулы
в виде множества из m **дескрипторов** $\{D_1, \ldots, D_m\}$
для каждой активности A_k
подсчитываются значения B_k:

$$B_k = (S_k - S_{0k}) / (1 - S_k * S_{0k})$$

$$S_k = \mathrm{Sin}[\sum_i \mathrm{ArcSin}(2P(A_k | D_i) - 1) / m]$$

$$S_{0k} = 2P(A_k) - 1$$

$P(A_k)$ **- априорная вероятность найти вещество с активностью** A_k

$P(A_k | D_i)$ **- условная вероятность активности** A_k **у молекулы, имеющей дескриптор** D_i

Алгоритм прогноза спектра биологической активности органических соединений PASS

Частотные оценки вероятностей $P(A_k)$ и $P(A_k \mid D_i)$:

$$P(A_k) = N_k / N, \qquad P(A_k \mid D_i) = N_{ik} / N_i$$

N - **общее количество веществ в выборке**;

N_i - **количество веществ, содержащих дескриптор** D_i **в описании структуры**;

N_k - **количество веществ, содержащих активность** A_k **в спектре активности**;

N_{ik} - **количество веществ, содержащих и дескриптор** D_i **в описании структуры, и активность** A_k **в спектре активности**.

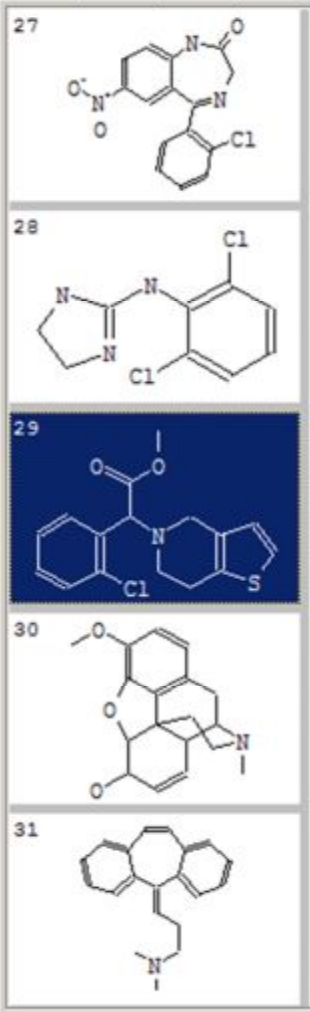
$$P(A) = \frac{\sum_i \sum_k g_k(D_i) w_k(A)}{\sum_i \sum_k g_k(D_i)} \qquad P(A \mid D_i) = \frac{\sum_k g_k(D_i) w_k(A)}{\sum_k g_k(D_i)}$$

Филимонов Д.А., **Поройков В.В.** (2006) **РХЖ**, L, (2), 66-75.

Результат прогноза PASS

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

5x5 | 4x4 | 3x3 | 2x2 | GRAPH | DATA | MNA



Спектр активности

Acute neurologic disorders treatment
Antianginal
Antiarthritic
Anticoagulant
Antipsoriatic
Antithrombotic
Atherosclerosis treatment
CYP2C19 inhibitor
CYP2C9 inhibitor
CYP3A4 substrate
Hyperthermic
Neuroprotector
Platelet aggregation inhibitor
Purinergic P2T antagonist
Purinergic P2Y12 antagonist

No Selected Activity

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

23 of 4130 Possible Activities at Pa > 0.500

0.974	0.004	Neuroprotector
0.966	0.005	Hyperthermic
0.868	0.001	Purinergic P2Y12 antagonist
0.868	0.005	Acute neurologic disorders treatment
0.846	0.005	Antithrombotic
0.825	0.009	Muramoyltetrapeptide carboxypeptidase inhibitor
0.810	0.004	CYP2C9 inhibitor
0.800	0.010	CYP2C9 substrate
0.687	0.022	CYP2C substrate
0.659	0.004	CYP2C19 inhibitor
0.622	0.005	Platelet aggregation inhibitor
0.600	0.020	CYP2C19 substrate
0.598	0.019	Antianginal
0.563	0.012	Atherosclerosis treatment
0.585	0.045	CYP3A4 substrate
0.625	0.088	Antiinflammatory, pancreatic
0.561	0.041	CYP2 substrate
0.517	0.036	Cytochrome P450 inhibitor
0.501	0.019	Angiogenesis stimulant
0.512	0.031	Analgesic
0.595	0.141	Phobic disorders treatment
0.507	0.060	CYP3A substrate
0.524	0.190	NADH dehydrogenase (ubiquinone) inhibitor

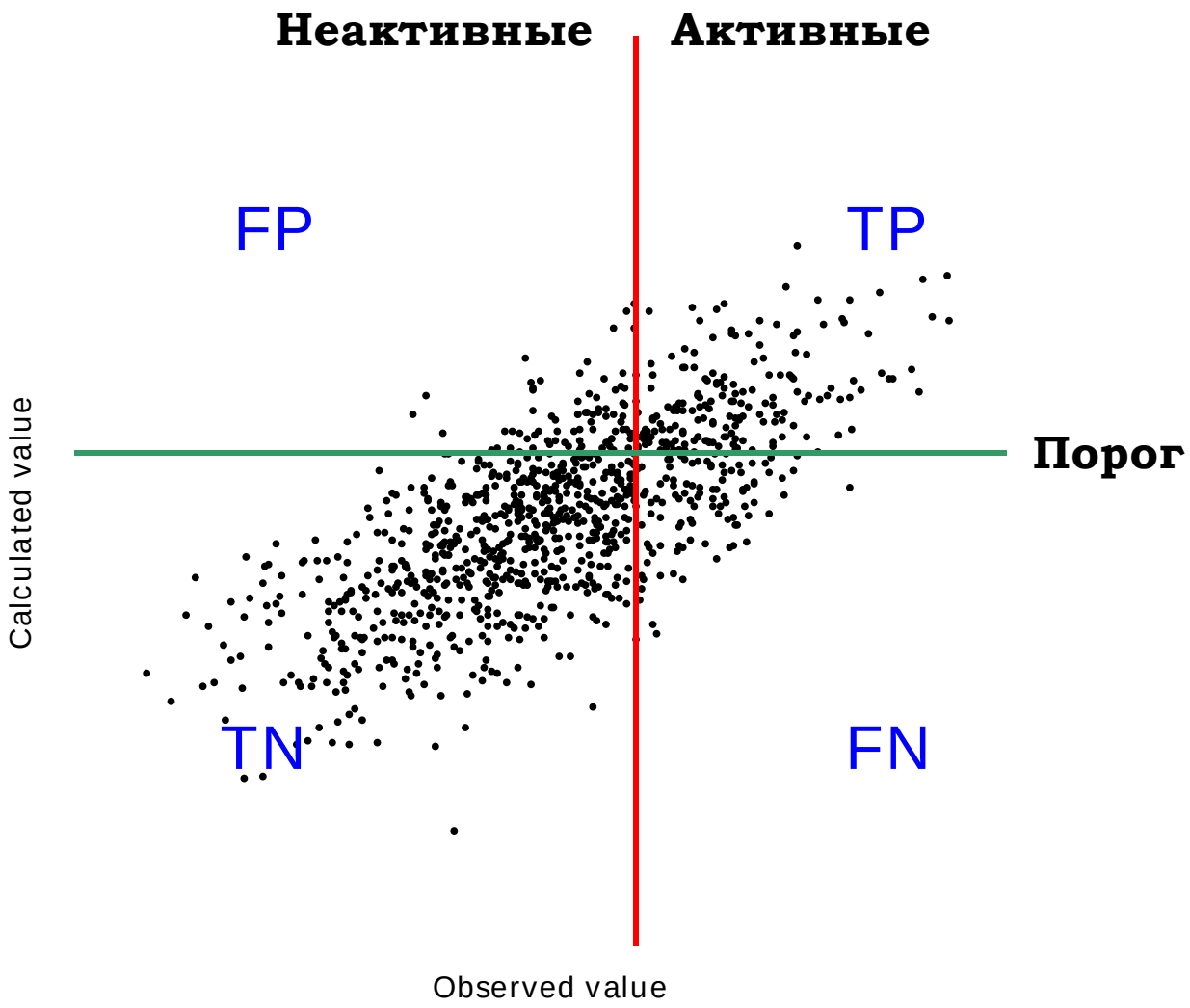
42 Substructure Descriptors; 0 new.

Drug-Likeness: 0.846

23 of 4130 Possible Activities
10 of 501 Possible Pharmacological Effects
4 of 3295 Possible Molecular Mechanisms
1 of 57 Possible Side Effects and Toxicity
8 of 199 Possible Metabolism-Related Actions
0 of 29 Possible Gene Expression Regulation
0 of 49 Possible Transporters-Related Actions

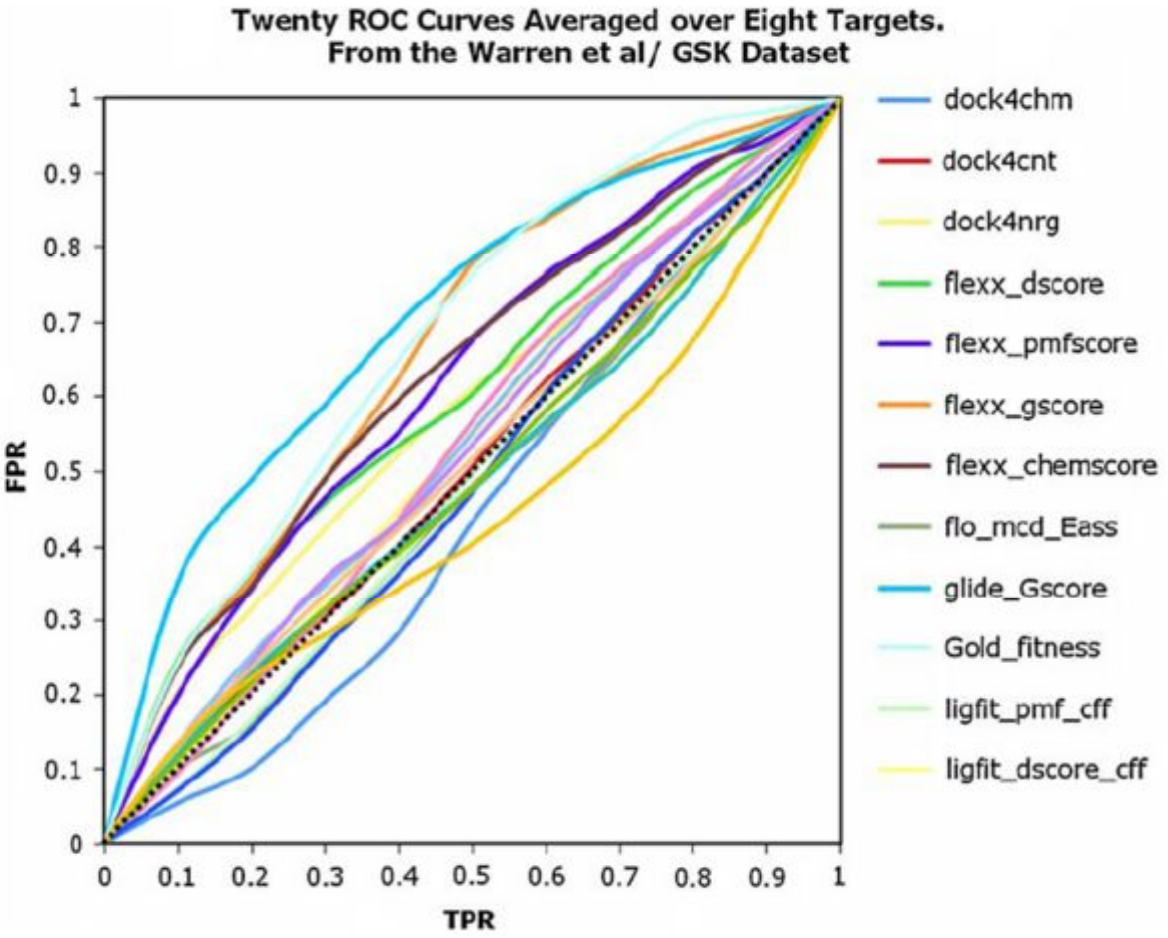
29/154

Задача классификации



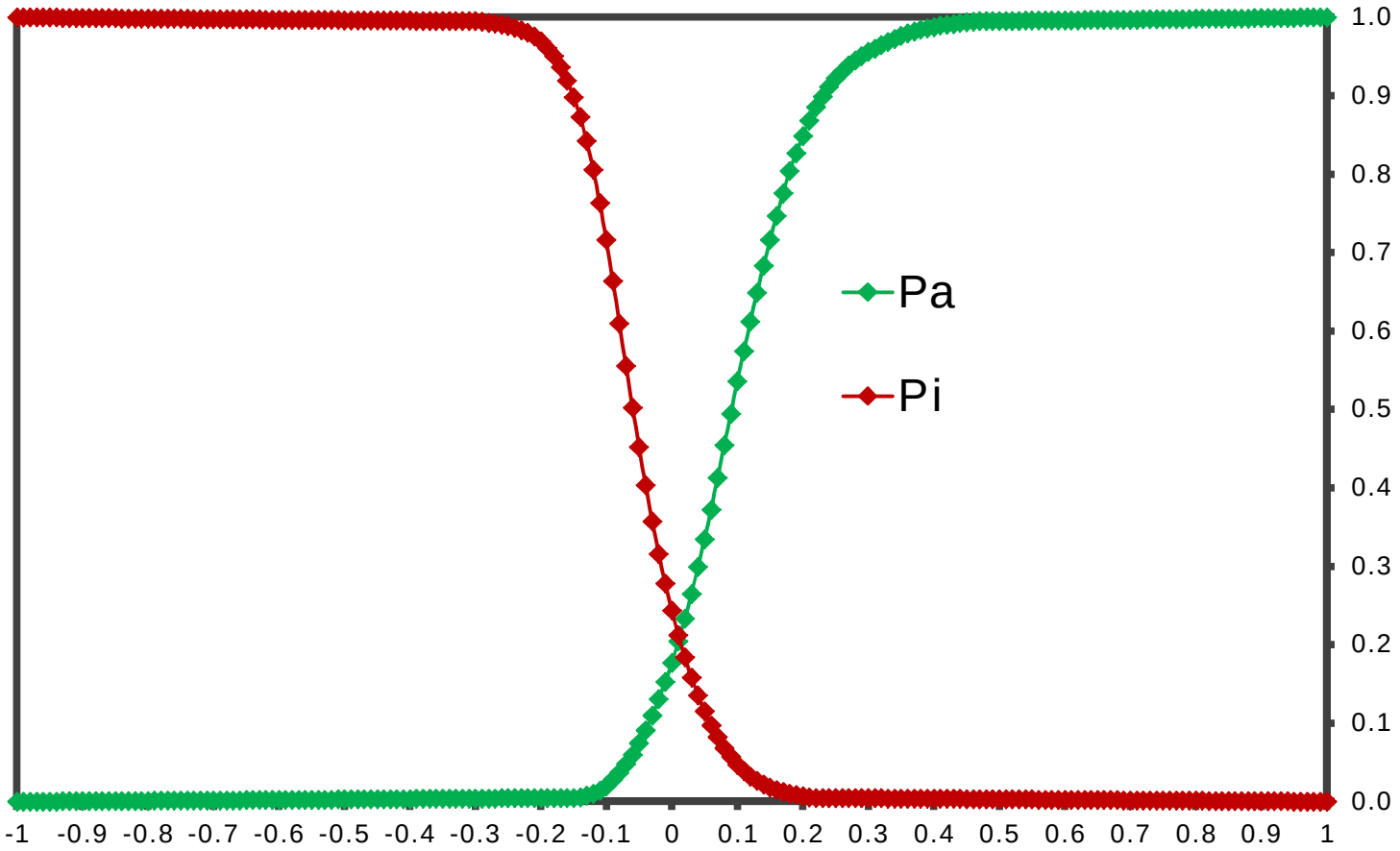
Критерий точности классификации

Fig. 6 Averaged ROC curves for twenty methods in the Warren study for which scores for all eight targets where available. Programs and scoring functions listed to the right of the graph



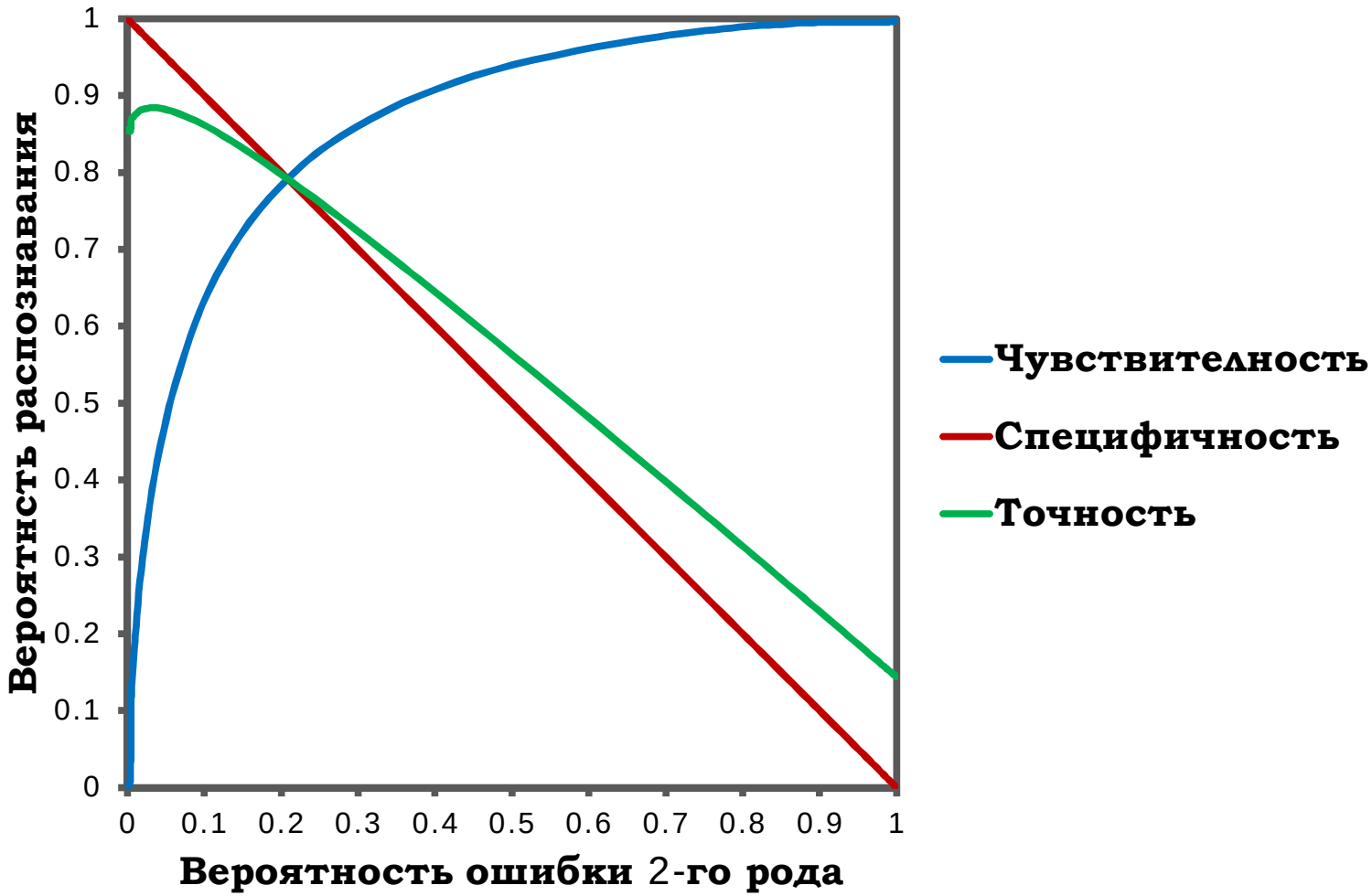
Anthony Nicholls. What do we know and when do we know it? J. Comput. Aided. Mol. Des. 2008

Задача классификации в PASS



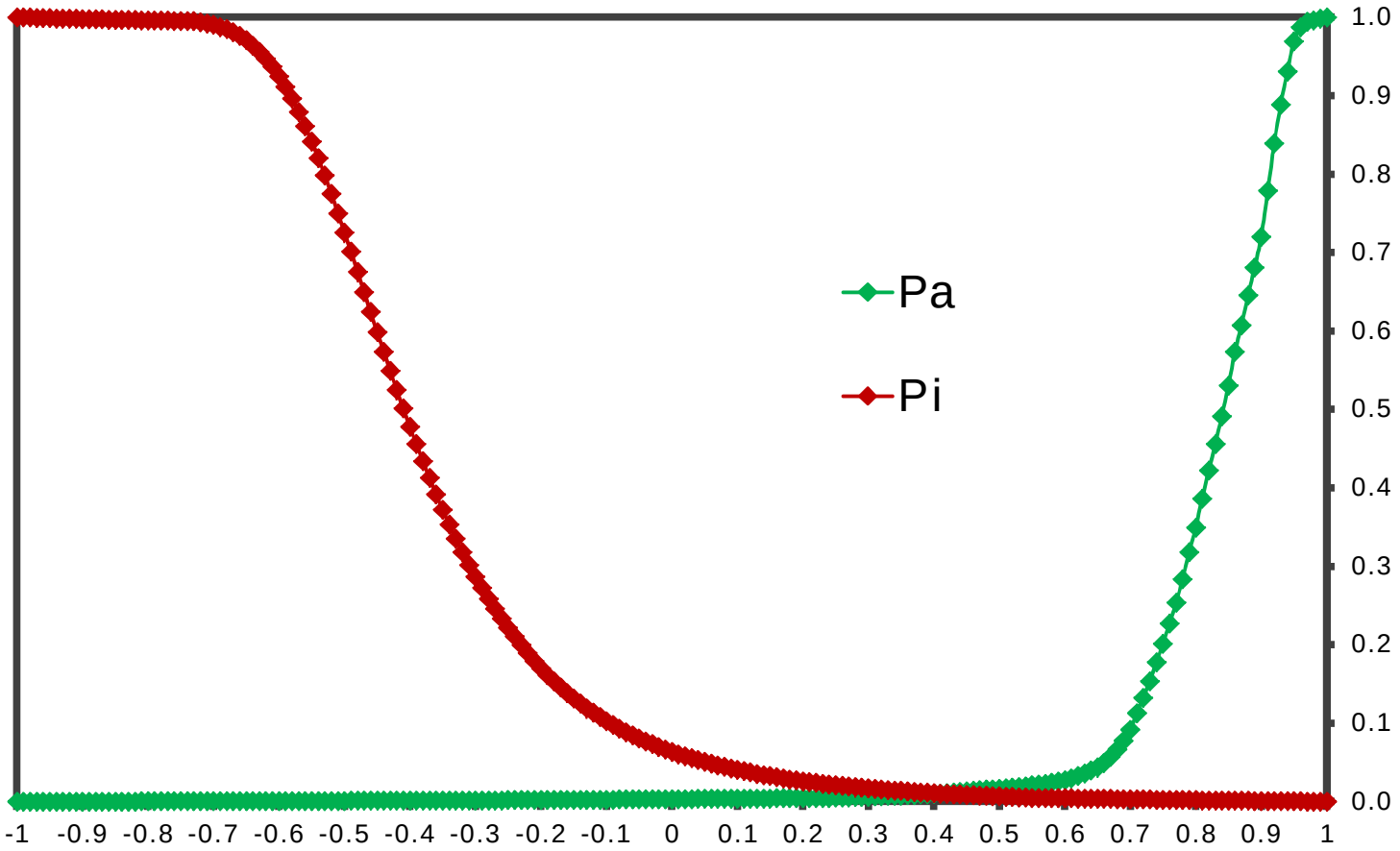
Pa(B) **и** Pi(B) **– функции** B**-статистики, вычисляемые по обучающей выборке с исключением по одному. Фармакологический эффект «Противоопухолевое».**

Критерий точности прогноза PASS



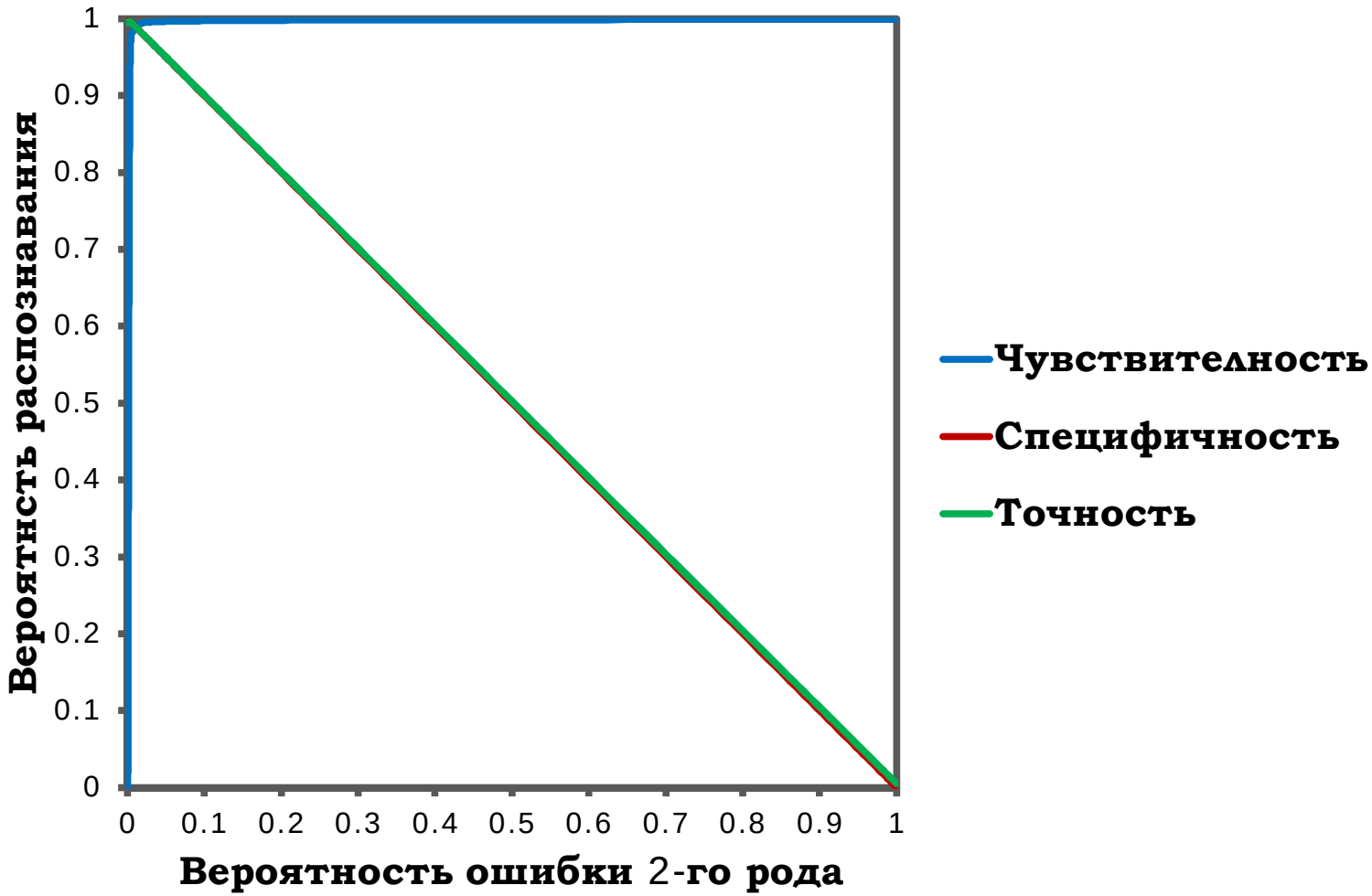
Фармакологический эффект «Противоопухолевое».
Инвариантная точность прогноза 0.87.

Задача классификации в PASS



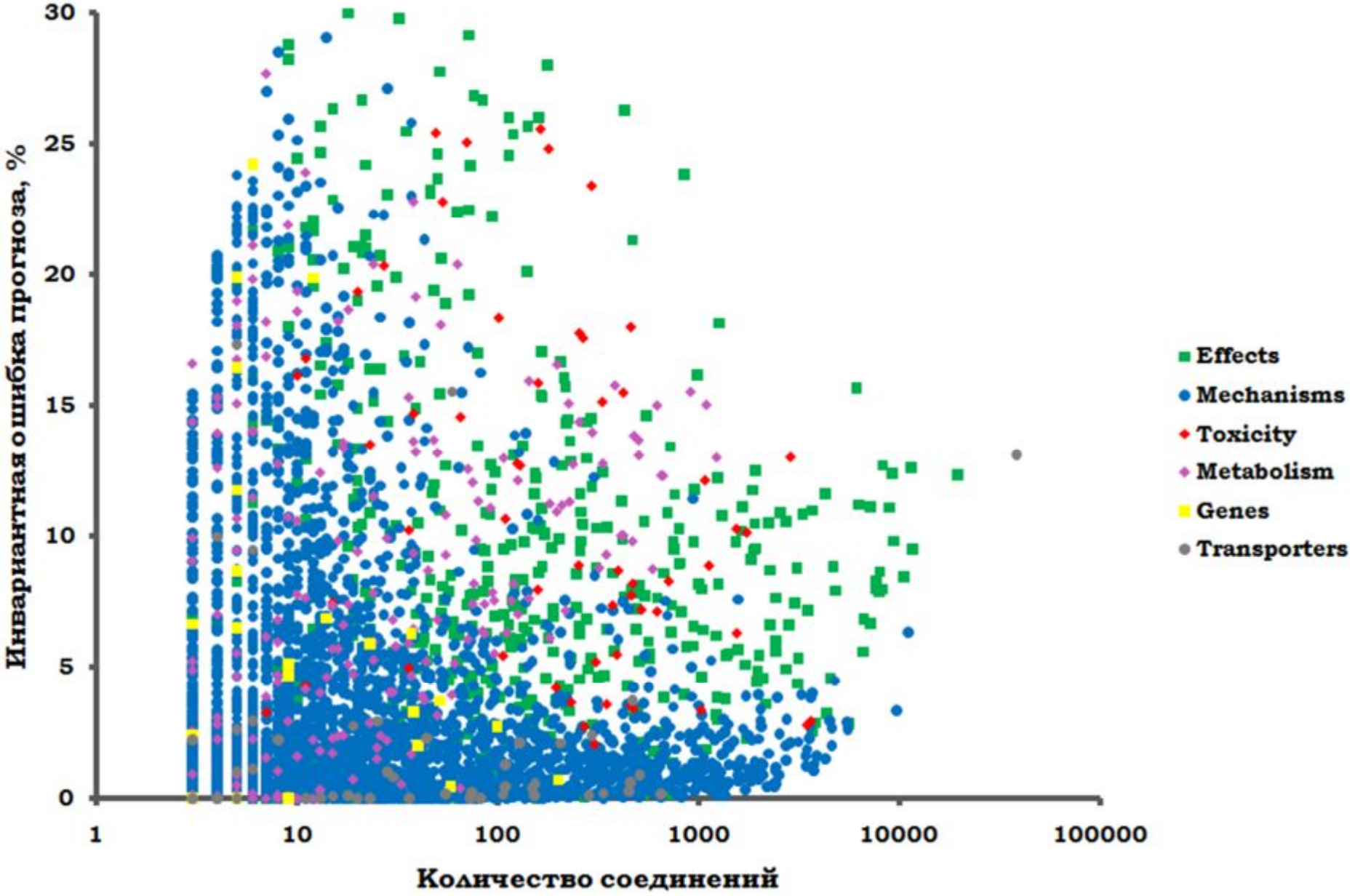
Pa(B) **и** Pi(B) **– функции** B**-статистики, вычисляемые по обучающей выборке с исключением по одному. Биохимический механизм действия** «Carbonic anhydrase inhibitor».

Критерий точности прогноза PASS



Биохимический механизм действия
«Carbonic anhydrase inhibitor».
Инвариантная точность прогноза 0.9986.

Валидация точности прогноза PASS



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.

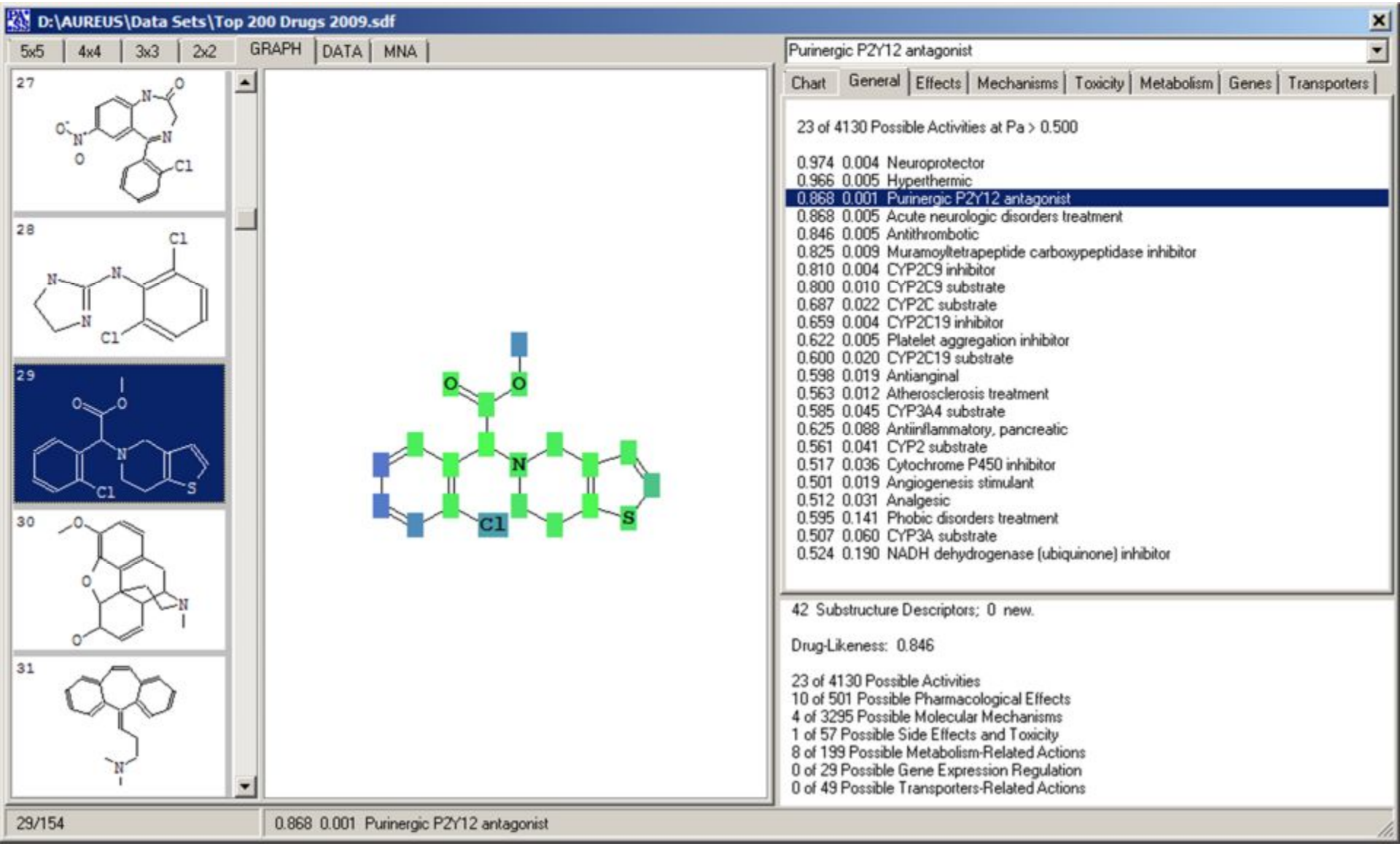
INTRODUCTION

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] In reality many biologically active compounds possess several types of activity. The computer system PASS *(Prediction of Activity Spectra for Substances)*[11−14] predicts simultaneously several hundred various biological activities. These are pharmacological effects, mechanisms of action, mutagenicity, carcinogenicity, teratogenicity, and embryotoxicity. PASS prediction is based on the analysis of structure−activity relationships of the training set including a great number of noncongeneric compounds with different biological activities. PASS once trained is able to predict

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	
8	0.700	0.036	antihypoxic	+
9	0.650	0.004	lipid peroxidase inhibitor	+
10	0.648	0.008	cognition disorders treatment	+
11	0.656	0.021	antiischemic	+
12	0.577	0.013	acute neurologic disorders treatment	+
13	0.540	0.039	spasmolytic	+
14	0.519	0.026	antianginal agent	
15	0.486	0.037	antihypertensive	+
16	0.449	0.035	antiarrhythmic	+
17	0.432	0.063	sympatholytic	
18	0.438	0.077	sedative	+
19	0.500	0.152	antiinflammatory, pancreatic	
20	0.328	0.020	antidepressant, imipramin-like	

Результат прогноза PASS



Пример применения прогноза PASS

Rational Design of Macrolides by Virtual Screening of Combinatorial Libraries Generated through in Silico Manipulation of Polyketide Synthases

Sergey B. Zotchev,[†] Alla V. Stepanchikova,[‡] Anastasia P. Sergeyko,[‡] Boris N. Sobolev,[‡] Dmitrii A. Filimonov,[‡] and Vladimir V. Poroikov*[,‡]

Department of Biotechnology, Norwegian University of Science and Technology, Trondheim, Norway and Institute of Biomedical Chemistry of Russian Academy of Medical Science, Moscow, Russia

Received October 14, 2005

Bacterial secondary metabolites display diverse biological activities, thus having potential as pharmacological agents. Although most of these compounds are discovered by random screening, it is possible to predict and re-design their structures based on the information on their biosynthetic pathways. Biosynthesis of macrolides, governed by modular polyketide synthases (PKS), obeys certain rules, which can be simulated in silico. PKS mode of action theoretically allows for a huge number of macrolides to be produced upon combinatorial manipulation. Since engineering of all possible PKS variants is practically unfeasible, we created Biogenerator software, which simulates manipulation of PKS and generates virtual libraries of macrolides. These libraries can be screened by computer-aided prediction of biological activities, as exemplified by analysis of erythromycin and macrolactin libraries. This approach allows rational selection of macrolides with desired biological activities and provides instructions regarding the composition of the PKS gene clusters necessary for microbial production of such molecules.

Introduction

Many biological species (bacteria, fungi, algae, sponges, plants, etc.) produce secondary metabolites with diverse biological activities, thus representing a rich source of potentially valuable pharmacological agents.[1,2] Currently, the majority of drugs derived from secondary metabolites were discovered by random screening of biological samples and subsequent rigorous testing. Examples of such compounds are amphotericin, erythromycin, cyclosporin A, paclitaxel, lovastatin, etc.[3]

Despite the utilization of high-throughput and ultra-high-throughput screening, major limitations of these approaches still

This approach was tested using macrolides as an example, which are assembled biosynthetically by the modular polyketide synthase (PKS) enzymes. The macrolides biosynthesized by bacteria and fungi display a wide range of activities, including antibacterial, antifungal, immunosuppressive, antitumor, etc.[7] The PKS architecture and their mode of action (see the next section) theoretically allow for an enormous number of macrolides to be produced upon combinatorial manipulation of these enzymes, which cannot be engineered and tested experimentally. Under combinatorial manipulations we mean all possible perturbations of the PKS system via module and domain

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

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

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

Received July 24, 2007

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

Introduction

For many years, clinicians have treated patients by combinations of drugs with different pharmacotherapeutic actions. It is being recognized that a balanced modulation of several targets can provide a superior therapeutic effect and a favorable side effect profile compared to the action of a selective ligand.[1] Compared to drug combinations, there are several advantages associated with ligands acting on multiple targets, such as the more predictable pharmacokinetic and pharmacodynamic properties that are a consequence of the administration of a single pharmaceutical substance, as well as improved patient compli-

dual-acting antihypertensive agents (dual angiotensin-converting enzyme/neutral endopeptidase inhibitors).[3] The current version of PASS predicts more than 3300 types of biological activity including pharmacotherapeutic effects, mechanisms of action, interaction with drug-metabolizing enzymes, side effects, and toxicity. To analyze the PASS prediction results, taking into account the mechanism-effect relationships, and to search for compounds with the desirable profiles of biological activity, PharmaExpert[4] software was developed. The current version of PharmaExpert, based on information extracted from the literature, contains about 5700 mechanism-effect relationships.

EFFECTS

0,850	0,004	Vascular (periferal) disease treatment
0,523	0,045	Amyotrophic lateral sclerosis treatment
0,320	0,196	Neurotrophic factor
0,850	0,004	Platelet aggregation inhibitor
0,626	0,038	Antiinflammatory
0,626	0,094	Antiinflammatory, pancreatic
0,626	0,094	Antiinflammatory, pancreatic
0,516	0,038	Antipsoriatic
0,516	0,038	Cytochrome P450 inhibitor
0,440	0,110	Complement factor D inhibitor
0,931	0,001	Antianginal
0,931	0,001	Anticoagulant
0,880	0,001	Antithrombotic
0,880	0,001	Purinergic P2Y12 antagonist
0,850	0,004	Platelet aggregation inhibitor
0,850	0,004	Antiischemic, cerebral
0,850	0,004	Platelet aggregation inhibitor
0,850	0,004	Nootropic
0,532	0,052	Alzheimer's disease treatment
0,532	0,052	Acetylcholine release stimulant
0,320	0,196	Neurotrophic factor
0,532	0,052	Acetylcholine release stimulant
0,320	0,196	Neurotrophic factor
0,850	0,004	Platelet aggregation inhibitor

Использование прогнозов PASS Inet

Navarrete-Vazquez G., Hidalgo-Figueroa S., Torres-Piedra M., et al. (2010). Synthesis, vasorelaxant activity and antihypertensive effect of benzo[d]imidazole derivatives. *Bioorganic & Medicinal Chemistry*, **18** (11): 3985–3991.

Mustafayeva K., Di Giorgio C., Elias R., et al. (2010). DNA-Damaging, mutagenic, and clastogenic activities of gentiopicroside isolated from *Cephalaria kotschyi* roots. *Journal of Natural Products*, **73** (2): 99–103.

Raja A.K., Vimalanathan A.B., Raj S.V., et al. (2010). Indispensable chemical genomic approaches in novel systemic targeted drug discovery. *Biology and Medicine*, **2** (3): 26-37.

Torres-Piedra M., Ortiz-Andrade R., Villalobos-Molina R., et al. (2010). A comparative study of flavonoid analogues on streptozotocinenicotinamide induced diabetic rats: Quercetin as a potential antidiabetic agent acting via 11b–Hydroxysteroid dehydrogenase type 1 inhibition. *European Journal of Medicinal Chemistry*, 45: 2606-2612.

Benchabane Y., Di Giorgio C., Boyer G., et al. (2009). Photo-inducible cytotoxic and clastogenic activities of 3,6-di-substituted acridines obtained by acylation of proflavine. *European Journal of Medicinal Chemistry*, **44**: 2459–2467.

Hernandez-Nunez E., Tlahuext H., Moo-Puc R., et al. (2009). Synthesis and *in vitro* trichomonicidal, giardicidal and amebicidal activity of *N*-acetamide(sulfonamide)-2-methyl-4-nitro-1*H*-imidazoles. *European Journal of Medicinal Chemistry*, **44** (7), 2975-2984.

Babaev E.V. (2009). Combinatorial chemistry at the university: ten years experience of research, educational and organizational projects. *Russsian Chemical Journal*, **53** (5), 140-152.

Ghadimi S., Ebrahimi-Valmoozi A.A. (2009). Lipophilicity, electronic, steric and topological effects of some phosphoramidates on acethylcholinesterase inhibitory property. *J. Iran. Chem. Soc.*, **6** (4): 838-848.

Gregirchak N.M., Kosyanchuk Ya.S. (2009). Studies of biological activity of newly synthesized compounds. *Proceedings of the National University of Food Technologies*, No.28, 27-30.

Database status: 250251 open structures ready for searching.

Bug reports, comments or questions?

Operations with this Dataset of 1 Structure:

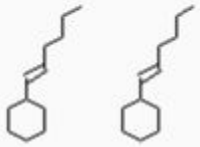
Data Retrieval: Format: SDFile | Output in 3D ☐ Strip H ☐ | Max #Records: 100 | Fields: NSC Number, Molecular Weight, Name (ACD) | Retrieve

Visualization: GIF Image Gallery | Display

Miscellaneous: Restart Query (at first record) | Execute

Structure

244860



	NSC Number	Formula	CAS	#Names	Sample Name
☑	244860	$C_{24}H_{44}$	(None)	0	No Name

SOLUTIONS
FOR YOUR RESEARCH

DRAW STRUCTURE

The applet cannot run because your java plug-in is not available.

Predict

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.

ACUTE RAT TOXICITY PREDICTION

In silico prediction of LD50 values for rats with four types of administration (oral, intravenous, intraperitoneal, subcutaneous, inhalation) by GUSAR software. The training sets were created on the basis of data from SYMYX MDL Toxicity Database. They include the information about ~10000 chemical structures with data on acute rat's toxicity represented on the LD50 values (log10 (mmol/kg)).

CHARACTERISTICS OF QSAR MODELS FOR RAT LD50 VALUES PREDICTIONS

Administration	Ntraina	Ntestb	Nmodels	R2c	Q2d	R2test	RMSEtest	Coverage, %h
Oral	6280	2692	40	0.61	0.57	0.59	0.57	97.5
Intraperitoneal	2480	1065	68	0.66	0.56	0.57	0.57	96.1
Intravenous	920	394	50	0.73	0.66	0.63	0.62	99.2
Subcutaneous	759	325	7	0.69	0.59	0.50	0.69	92.0

a - number of compounds in the training set;
b - number of compounds in the training set;
c - average R2 of the models calculated for the appropriate training set;
d - average Q2 of the models calculated for the appropriate training set;

Благодарности

ИБМХ РАМН, Москва, Россия

Александр Дмитриев
Алексей Захаров
Алексей Лагунин
Алла Степанчикова
Анастасия Рудик
Борис Соболев
Владимир Поройков
Дмитрий Дружиловский
Олег Гомазков
Ольга Коборова
Ольга Фильц
Сергей Иванов
Татьяна Брюшинина
Татьяна Глориозова

ВИНИТИ РАН, Россия

Валентина Блинова

Lab. Med. Chem., NCI, NIH, Frederik, M.D., U.S.

Marc Nicklaus **Marcus Sitzmann** **Igor Filippov**

Aristotelian University of Thessaloniki, Greece

Athina Geronikaki

Norwegian UniVersity of Science and Technology, Trondheim

Sergey Zotchev