

Computer-aided drug discovery by prediction of biological activity spectra for substances



Lagunin Alexey

Institute of Biomedical Chemistry of Russian Academy of Medicinal Science

Outcome for R & D of Pharmaceuticals:

New targets

~500 targets are currently in use;
5,000-10,000+ are expected in a few years.

New ligands

More efficacy;
more safety
(less adverse & toxic effects).

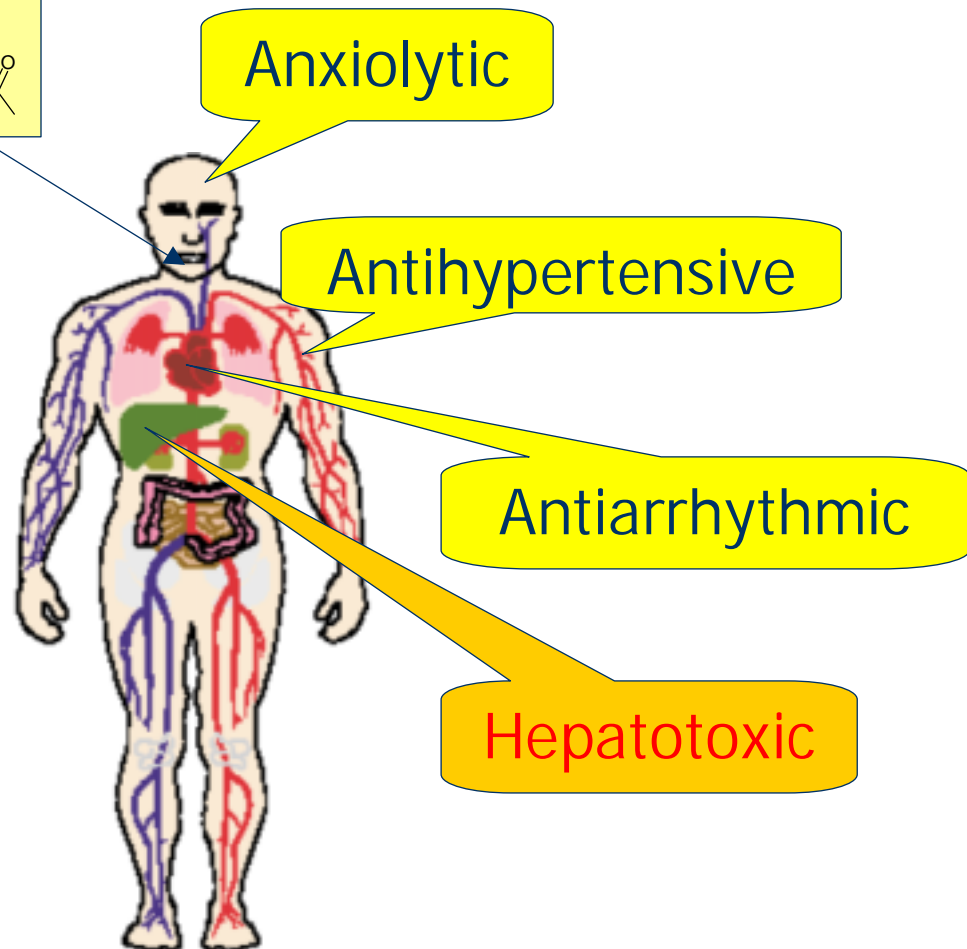
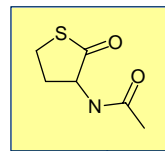
“New” Patients

Genotyping,
Individual responses to the drugs.

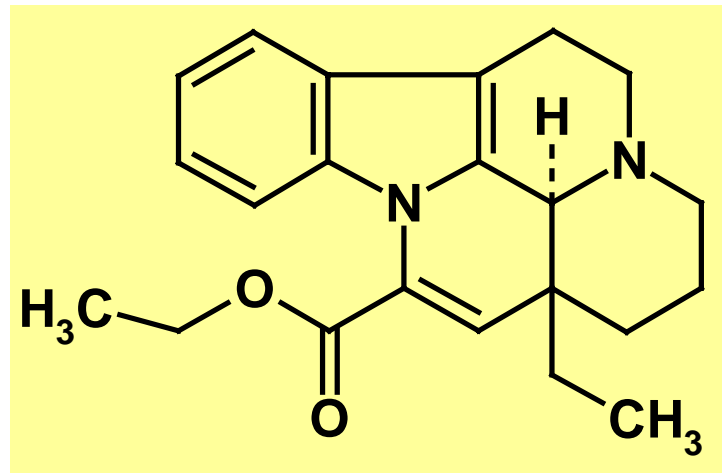
**Better understanding of individual responses to drugs
– Personalized Medicine.**

Pharmacotherapeutic Action is the Results of Drug Interaction with a Human Organism

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



Example: Some Biological Activities Found for Vinpocetine after 25+ Years of Study



Psychotropic
Acute neurological disorders treatment
Cognition disorders treatment
Antihypertensive
Antiarrhythmic
Antiischemic
Antihypoxic
Vasodilator
Thrombolytic
Lipid peroxidase inhibitor
Alpha 2 adrenoreceptor antagonist
Sedative
Abortion inducer

...

Some pharmaceuticals withdrawn from clinical trials or from the market due to the toxicity.

6-Azauracil, Sorivudine
(Antiviral, Antitumor)

Neurotoxicity.

Troglitazone
(Antidiabetic)

Hepatotoxicity.

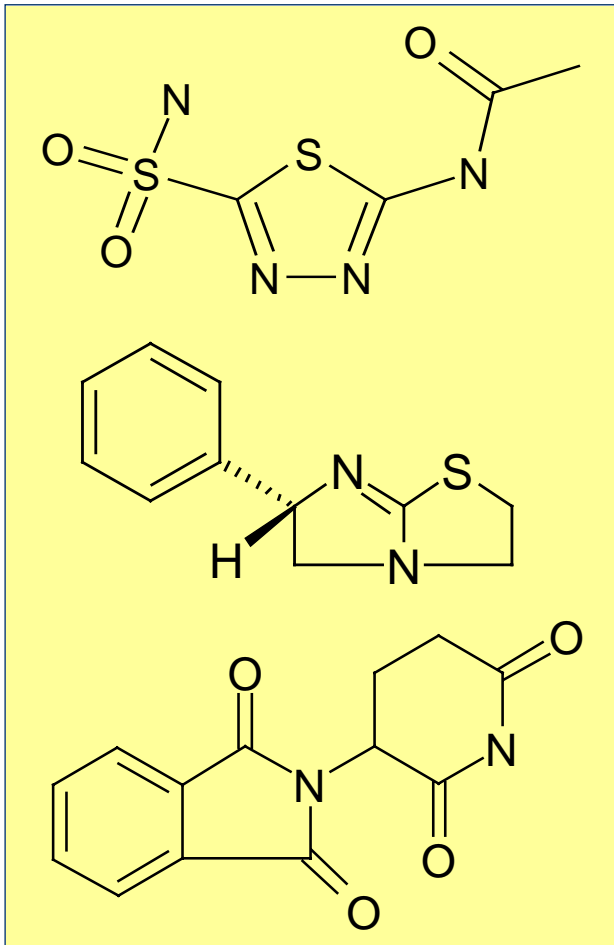
**Phenylpropanolamine
Hydrochloride**
(Decongestant)

**Risk of hemorrhagic
stroke.**

Baycol
(Anticholesterol)

Rhabdomyolysis.

Examples of New Indications for Old Drugs



Acetazolamide

Diuretic

Antiepileptic

Levamisole

Anthelmintic

Immunostimulator

Thalidomide

Hypnotic

Teratogen

Angiogenesis inhibitor

A Huge Number of Compounds is Registered in the Existing Databases

CAS > 32,000,000

Beilstein > 7,500,000

ACD > 2,500,000

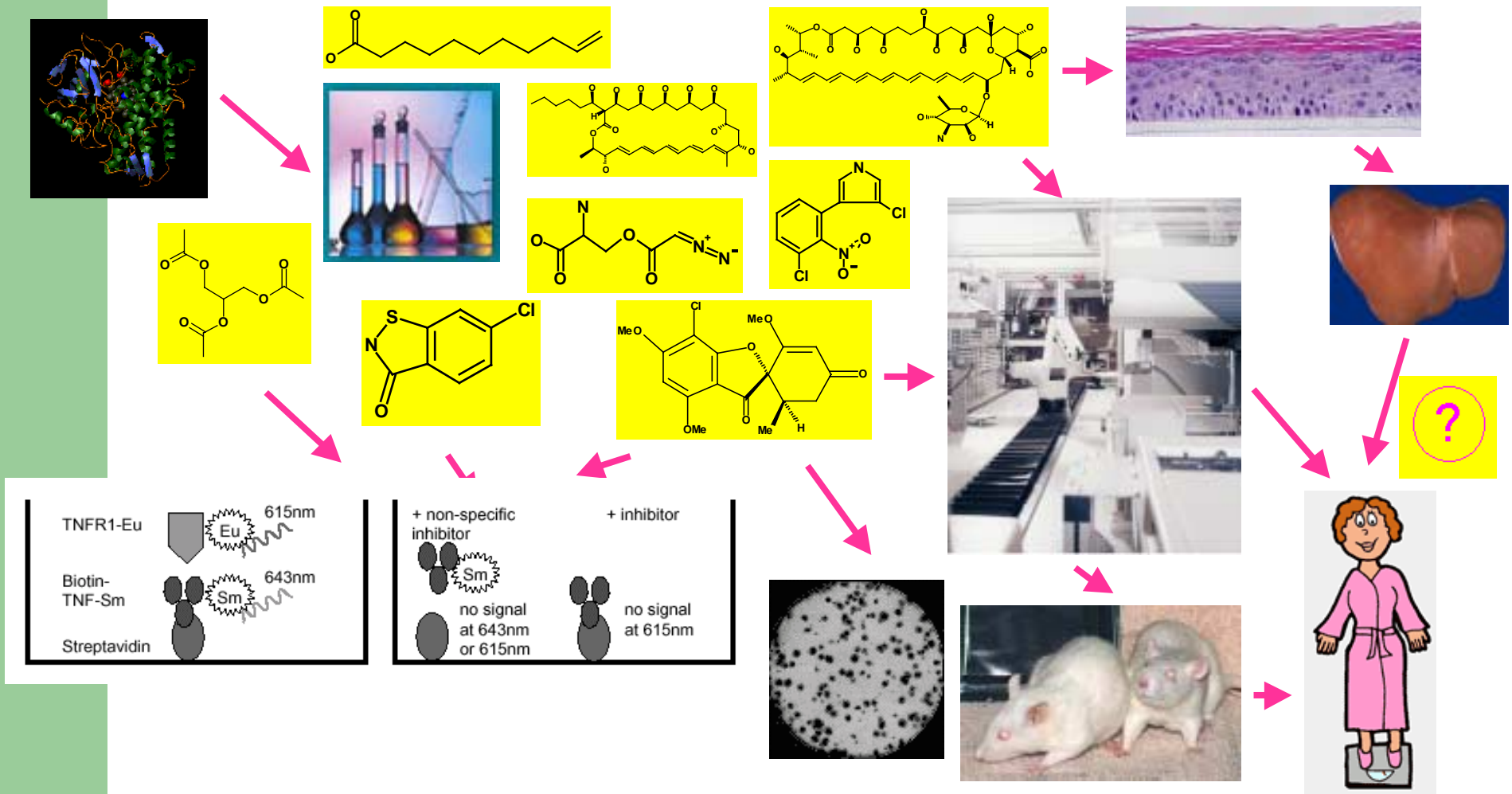
ChemDiv ~ 400,000

InterBioScreen ~ 250,000

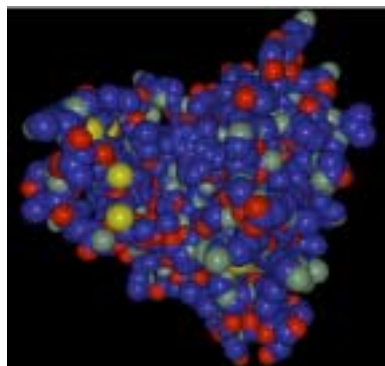
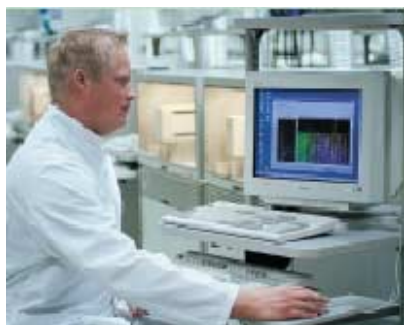
ChemBridge ~ 250,000

...

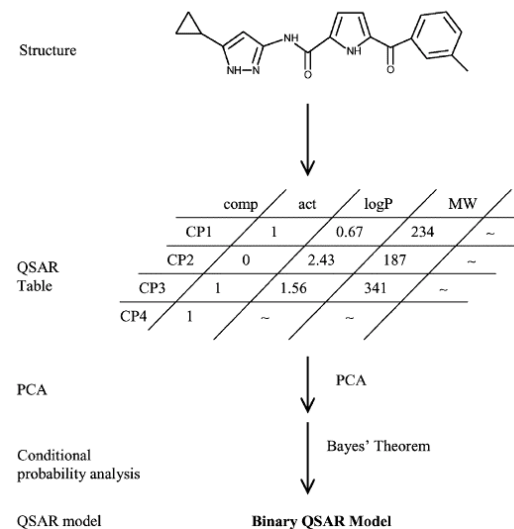
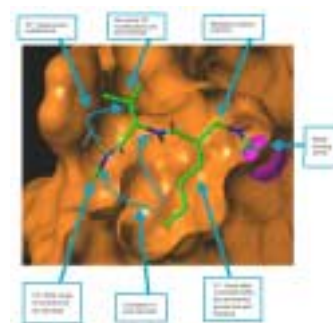
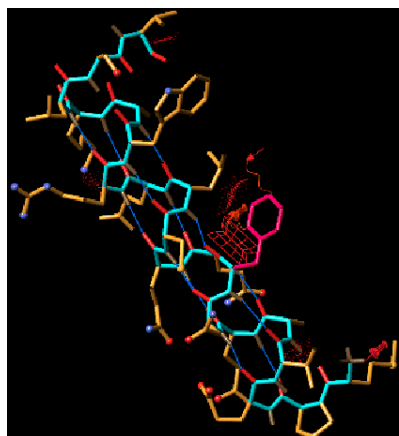
It Is Impossible to Test Experimentally Each Compound Vs. All Known Screens



Evaluation of compounds in silico is “the method of choice”



$$\begin{aligned} \text{BRR} &= 0.35(\pm 0.18) \log P + 1.93(\pm 0.48) I(\text{Bi}) \\ &+ 1.15(\pm 0.60) I(\text{F}) - 1.06(\pm 0.53) I(\text{BiBr}) \\ &+ 2.75(\pm 0.64) I(\text{RNNO}) - 0.48(\pm 0.30) \\ n &= 41, \quad r = 0.933, \quad r^2 = 0.871, \quad s = 0.398, \\ F &= 47.4, \quad P < 0.001 \end{aligned}$$



Is It Possible to Predict General Biological Potential of the Molecule Under Study?

Yes, by the analysis of its chemical structure comparing to the structures of known pharmaceutical agents.

Similarity Estimations:

Chemical similarity.

With molecules from the same chemical classes.

If Tanimoto coefficient exceeds 70%, the same biological activity is suggested.

Pharmacological similarity.

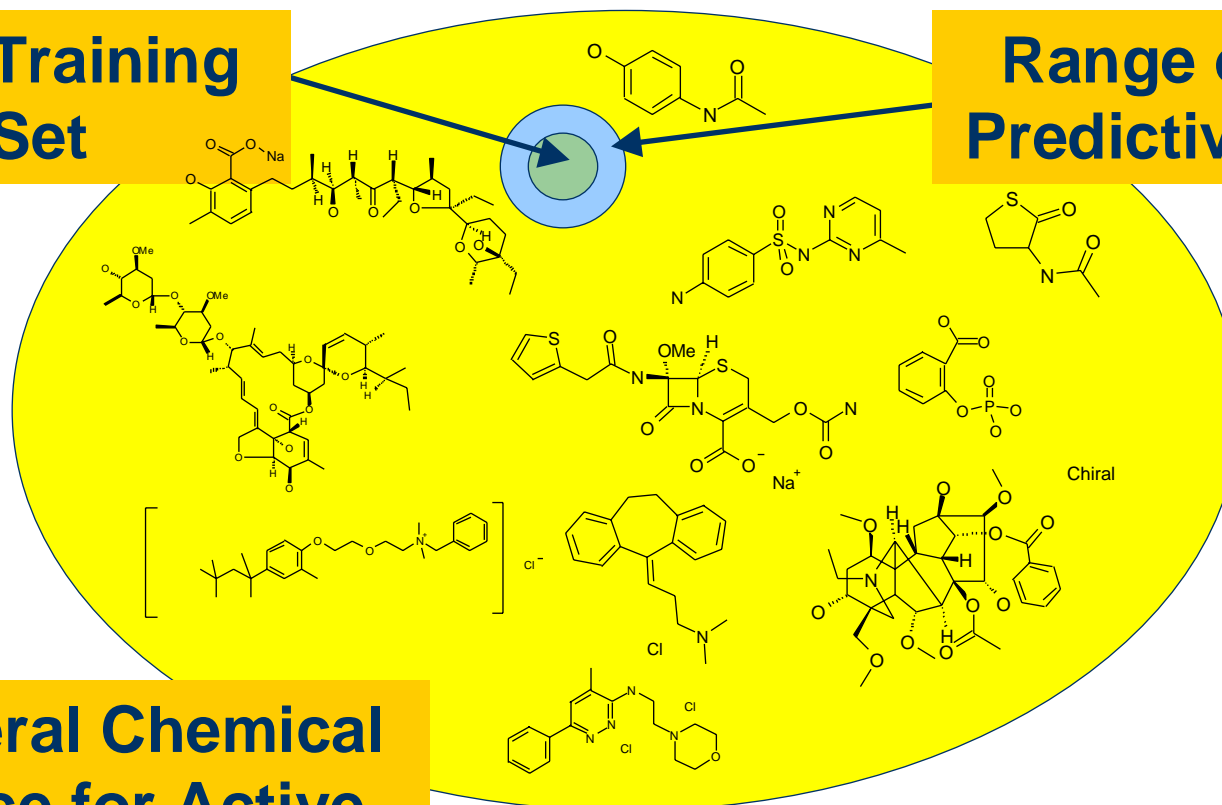
With classes of molecules that have the same biological activity.

If probability of belonging to the same class of activity exceeds a certain threshold, then ...

Predictivity for Poor Covering of Chemical Space (by ChemSim)

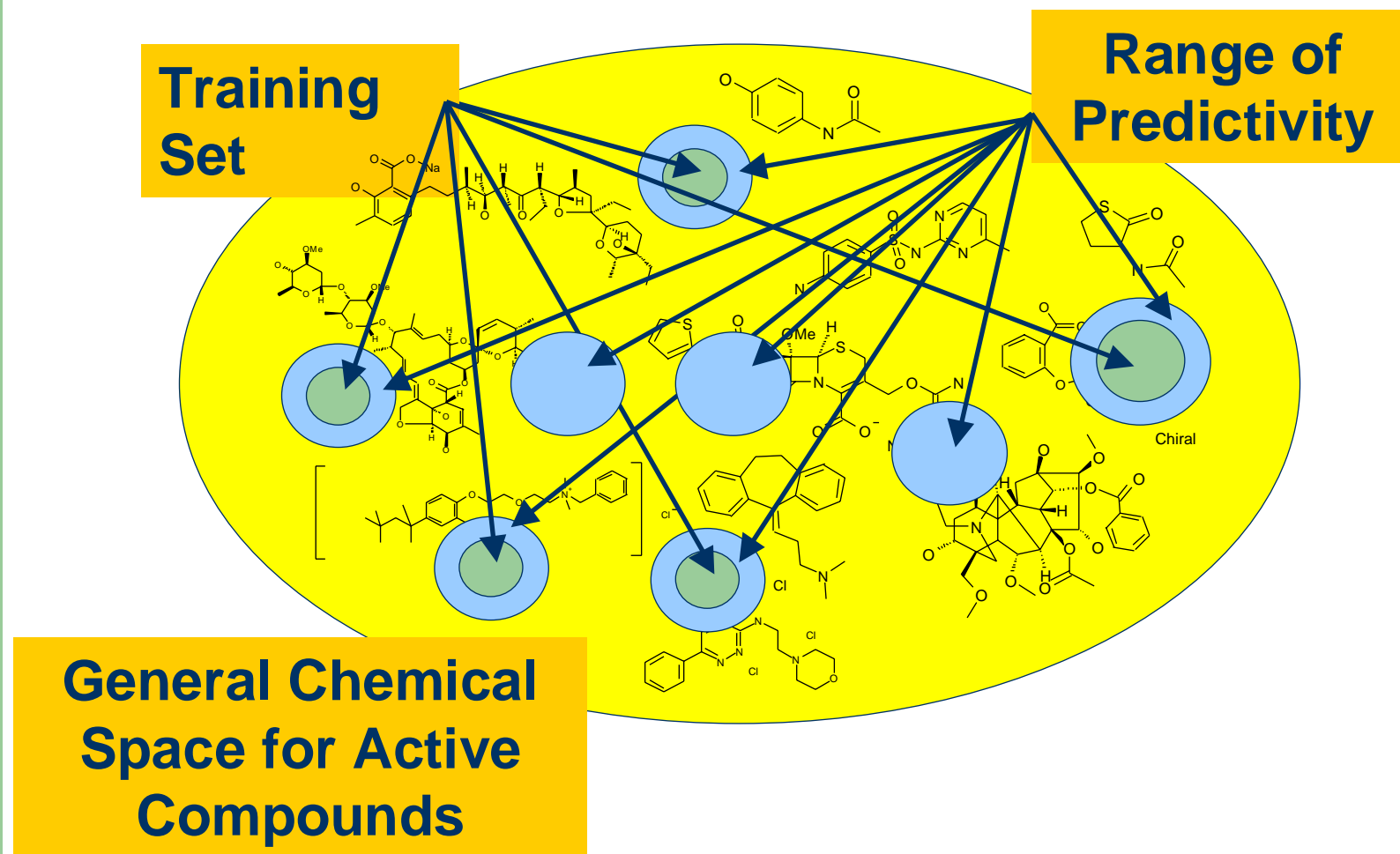
Training Set

Range of Predictivity



General Chemical Space for Active Compounds

Predictivity for Better Covering of Chemical Space (by PharmSim)



Impact of the Chemical Structure

Basic information about biological activity of chemical compound is contained in its structural formula.

At the early stage of medicinal chemistry R & D only structural formula is available.

It is difficult to synthesize proposed structures and to test them in experimental assays.

It is easy to evaluate them in silico.

Impact of Both Chemistry & Biology

Basic information about **potential** biological activity of chemical compound is contained in its structural formula.

If potential biological activity will be found by experiment, depends on:

Assay (in vitro, in vivo, in animals, in human);

State of biological system (expression of receptors, etc.);

Dosage & route of administration;

PK; ...

Biological Activity Spectrum

- All potential activities caused by the compound in biological entities are presented by **Biological Activity Spectrum of the Substance**.
- ***Biological Activity Spectrum:***
 - (1) is defined as an "intrinsic" property of the compound;
 - (2) represents each activity qualitatively.
 - Qualitative description of activities provides the basis to include the data collected from many different sources into the training set.

Examples of Biological Activity Types

Acetylcholinesterase inhibitor
Alcoholdehydrogenase inhibitor
Alpha 2 adrenoreceptor antagonist
5HT2 receptors agonist

...

Antihypertensive
Anticonvulsant
Antiviral (HCV)

...

Mutagenic
Carcinogenic

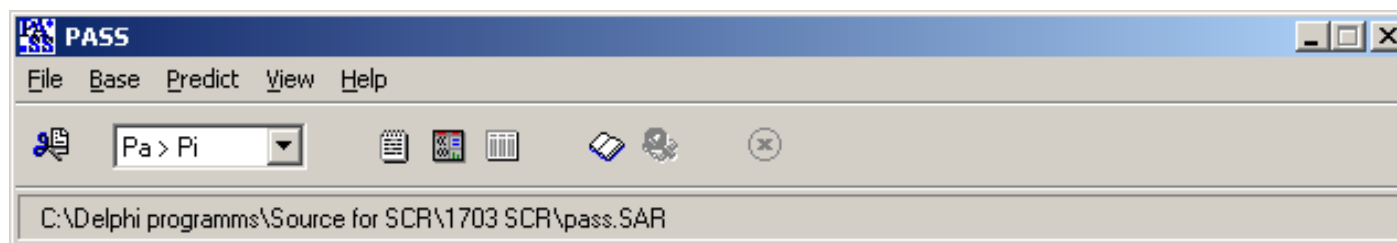
...

Mechanisms

Effects

Toxicity

PASS: Prediction of Activity Spectra for Substances



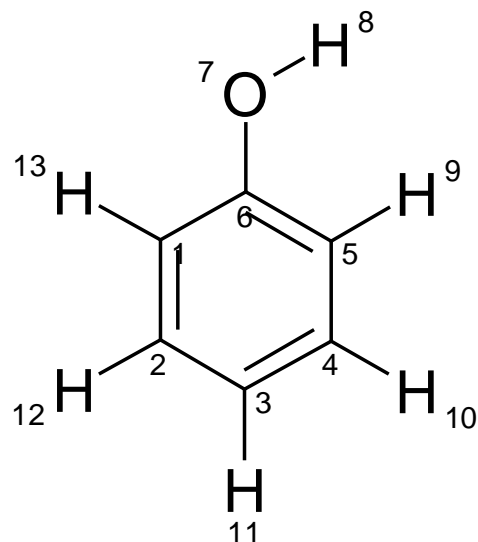
The 'SAR Base Information' dialog box displays the following statistics:

Substances	45660
Activity Types	1482
Descriptors	41644
Selected Activity Types	900
Minimal Number	3
Average MEP	15.009, %
Prediction	<input checked="" type="checkbox"/> Enabled

On the basis of compound's structural formula PASS predicts 900 types of biological activity, including pharmacological effects, mechanisms of action, carcinogenicity, teratogenicity, etc.

PASS Input for Nicotinic Acid

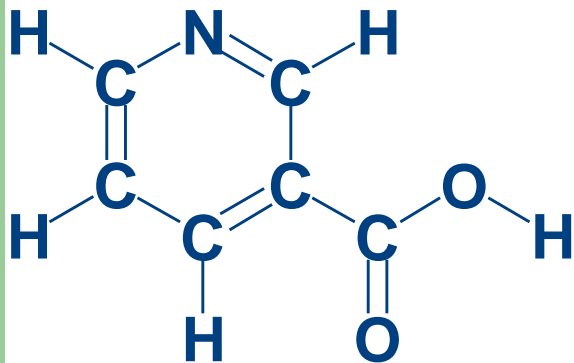
Multilevel Neighborhoods of Atoms descriptors



MOL file

Atom	MNA/1	MNA/2
1	C(CC-H)	C(C(CC-H)C(CC-O)-H(C))
2	C(CC-H)	C(C(CC-H)C(CC-H)-H(C))
3	C(CC-H)	C(C(CC-H)C(CC-H)-H(C))
4	C(CC-H)	C(C(CC-H)C(CC-H)-H(C))
5	C(CC-H)	C(C(CC-H)C(CC-O)-H(C))
6	C(CC-O)	C(C(CC-H)C(CC-H)-O(C-H))
7	-O(C-H)	-O(C(CC-O)-H(-O))
8	-H(-O)	-H(-O(C-H))
9	-H(C)	-H(C(CC-H))
10	-H(C)	-H(C(CC-H))
11	-H(C)	-H(C(CC-H))
12	-H(C)	-H(C(CC-H))
13	-H(C)	-H(C(CC-H))

PASS Output for Nicotinic Acid



21 Substructure descriptors; 0 new.
Exclude structure with activities:

Antihypercholesterolemic

Atherosclerosis treatment

Cholesterol antagonist

Cyclic AMP phosphodiesterase stimulant

Hypolipemic

Nucleotide metabolism regulator

Spasmolytic

198 Possible activities at Pa > Pi.

Pa Pi for Activity:

0.892 0.007 Lipid metabolism regulator

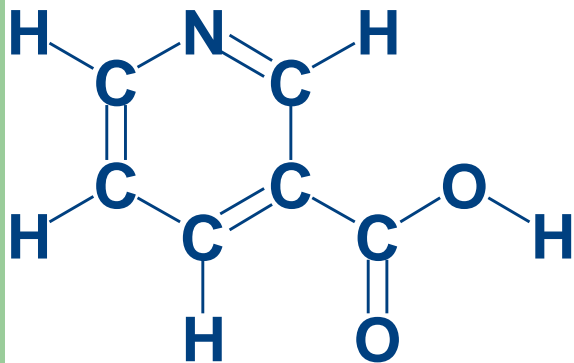
0.819 0.006 Fibrinolytic

0.794 0.016 Cholesterol synthesis inhibitor

0.758 0.007 **Antihypercholesterolemic**

0.751 0.007 **Cholesterol antagonist**

PASS Output for Nicotinic Acid



21 Substructure descriptors; 0 new.

Exclude structure with activities:

Antihypercholesterolemic

Atherosclerosis treatment

Cholesterol antagonist

Cyclic AMP phosphodiesterase stimulant

Hypolipemic

Nucleotide metabolism regulator

Spasmolytic

198 Possible activities at Pa > Pi.

Pa **Pi** for Activity:

0.892 0.007 Lipid metabolism regulator

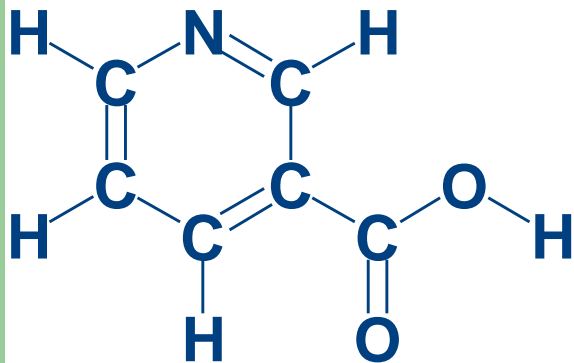
0.819 0.006 Fibrinolytic

0.794 0.016 Cholesterol synthesis inhibitor

0.758 0.007 Antihypercholesterolemic

0.751 0.007 Cholesterol antagonist

PASS Output for Nicotinic Acid



21 Substructure descriptors; 0 new.

Exclude structure with activities:

Antihypercholesterolemic

Atherosclerosis treatment

Cholesterol antagonist

Cyclic AMP phosphodiesterase stimulant

Hypolipemic

Nucleotide metabolism regulator

Spasmolytic

198 Possible activities at Pa > Pi.

Pa Pi for Activity:

0.892 0.007 Lipid metabolism regulator

0.819 0.006 Fibrinolytic

0.794 0.016 Cholesterol synthesis inhibitor

0.758 0.007 Antihypercholesterolemic

0.751 0.007 Cholesterol antagonist

PASS Robustness (Experiment)

- 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 was calculated for each type of activity.

Poroikov V.V., Filimonov D.A., Borodina Yu.V., Lagunin A.A., Kos A. J. Chem. Inf. Comput. Sci., 2000, 40 (6,) 1349-1350.

PASS Robustness (Results)

If we remove up to 60% of information from the training set, the accuracy of prediction is still satisfactory.

Despite the incompleteness of data in the training set, accuracy of SAR analysis and prediction results is reasonable.

PASS Evaluation Vs. NCI DTP Anti-HIV Screening Results

Open NCI Database (250,251 compounds):

Tested in anti-HIV assay: 42,689 compounds

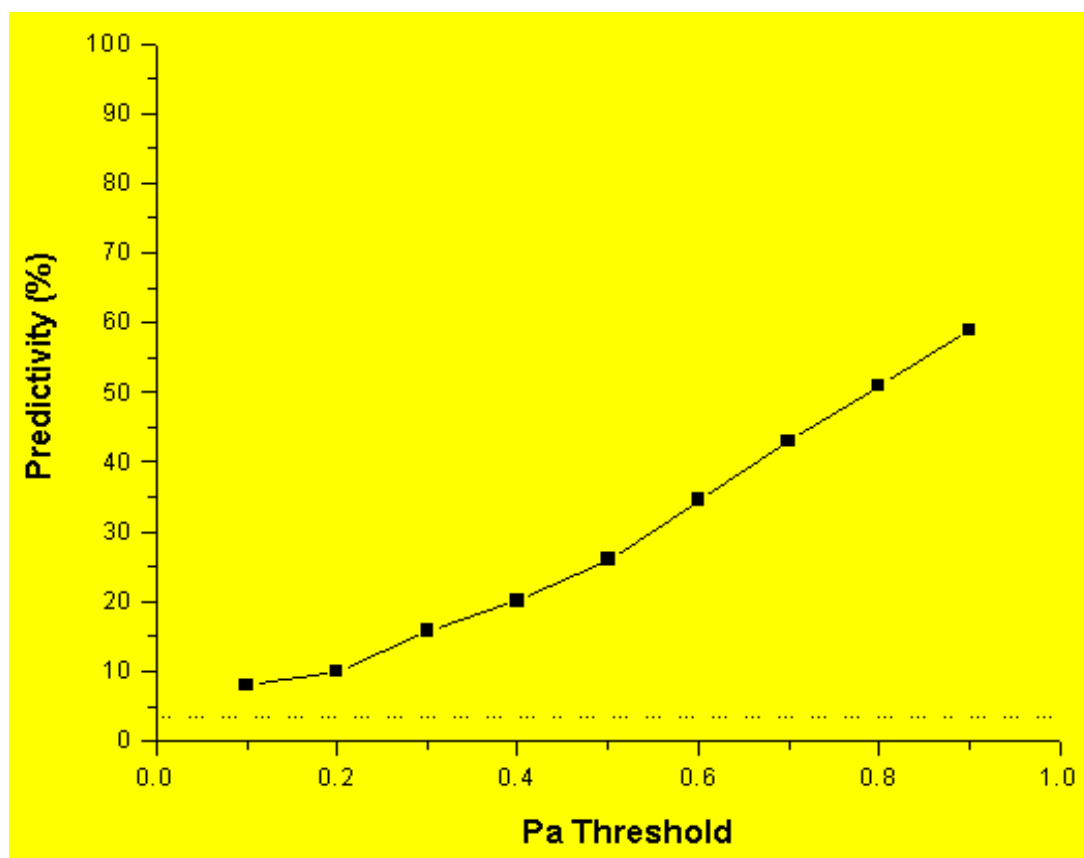
“Actives” (A & MA): 1,505 compounds

“Inactives”:
41,185 compounds

Percentage of actives: $1,540/42,689 = 3.52\%$.

A random selection would therefore preserve this ratio.

PASS Application Increases the Number of “Actives” in the Selected Sub-Set from 2.2 to 16.8 Times



Poroikov V., et al. PASS Biological Activity Spectrum Predictions in the Enhanced Open NCI Database Browser. J. Chem. Inform. Comput. Sci., 2003, 43 (1) 228-236

Some Examples of Predicted Biological Activity Confirmed by the Experiment

Cognition Enhancers, Anxiolytics, Anticonvulsants.

Geronikaki A. et al. (2003). Abstr. Intern. Symp. On Drug Discovery and Process Research, Kolhapur Jan. 23-25, p.26-28.

Antihypertensive, ACE inhibitor, NEP inhibitor.

Lagunin A. et al. (2003). J. Med. Chem., 46(15), 3326-3332.

Antitumor

Pogrebnyak A.V. et al. (1998). Plant Resources (Rus), 34 (1), 61-64.

Islyaikin M.K. et al. (1997). Chemical & Pharmaceutical J. (Rus), 31 (8), 19-22.

Antibacterial

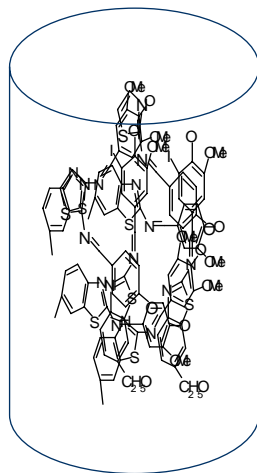
Maiboroda D.A. et al. (1998). Chemical & Pharmaceutical J. (Rus), 32 (6), 24-28.

...

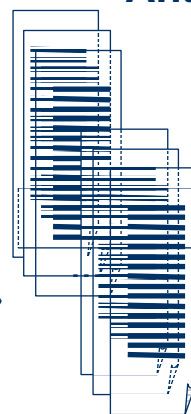
Cognition Enhancers, Anxiolytics and Anticonvulsants

Aristotelian University
Leuven University
University do Minho
Moscow State University
Moldova Institute of Chemistry
Institute of Organic Chemistry

5494 structures



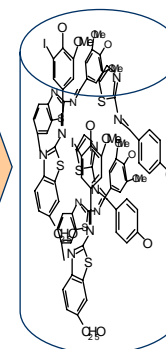
PASS



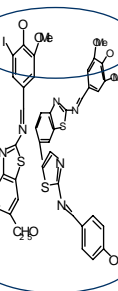
Prediction results

Anxiolytic
Cognition enhancer
Anticonvulsant

94



DEREK & 25 Experts



Experiment



Results

Anxiolytics

- from **10** tested compounds all have anxiolytic activity; **8** compounds have an equivalent or more activity in comparison with known anxiolytic

Cognition enhancers

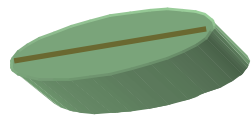
- from **10** tested compounds all have cognition enhancer activity; **6** compounds have an equivalent or more activity in comparison with known cognition enhancer

Anticonvulsants

- from **5** tested compounds all have anticonvulsant activity but no one has an equivalent activity in comparison with known anticonvulsant

Antihypertensive, dual ACE/NEP inhibitors

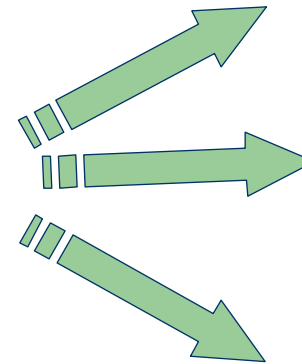
One Medicine → One Target



medicine

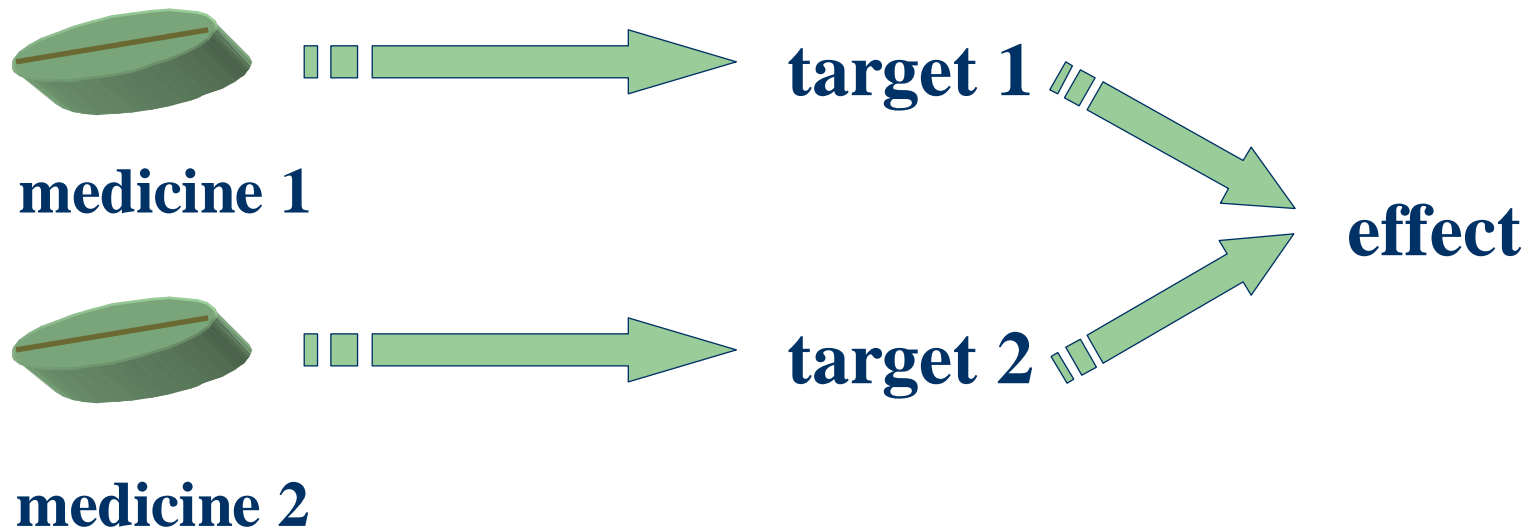


target

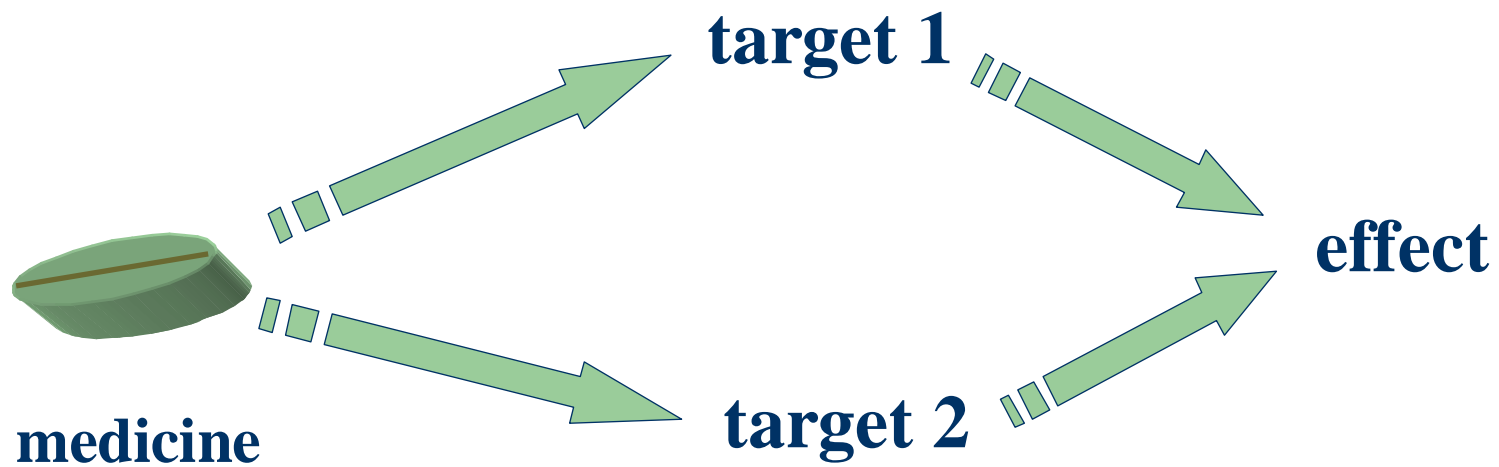


e
f
f
e
c
t
s

One Medicine → One Target



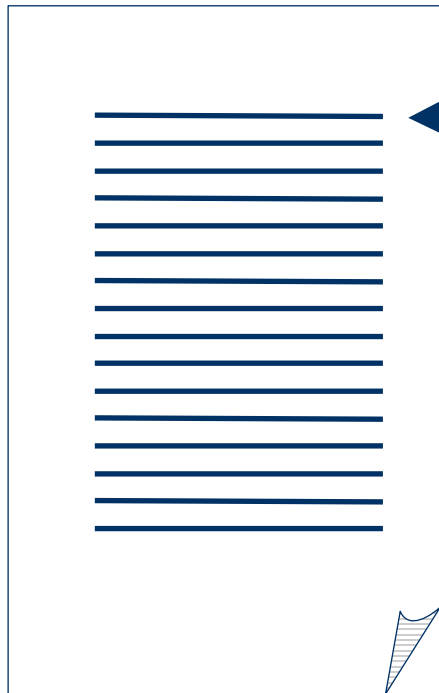
One Medicine → Two (or More) Targets



Examples

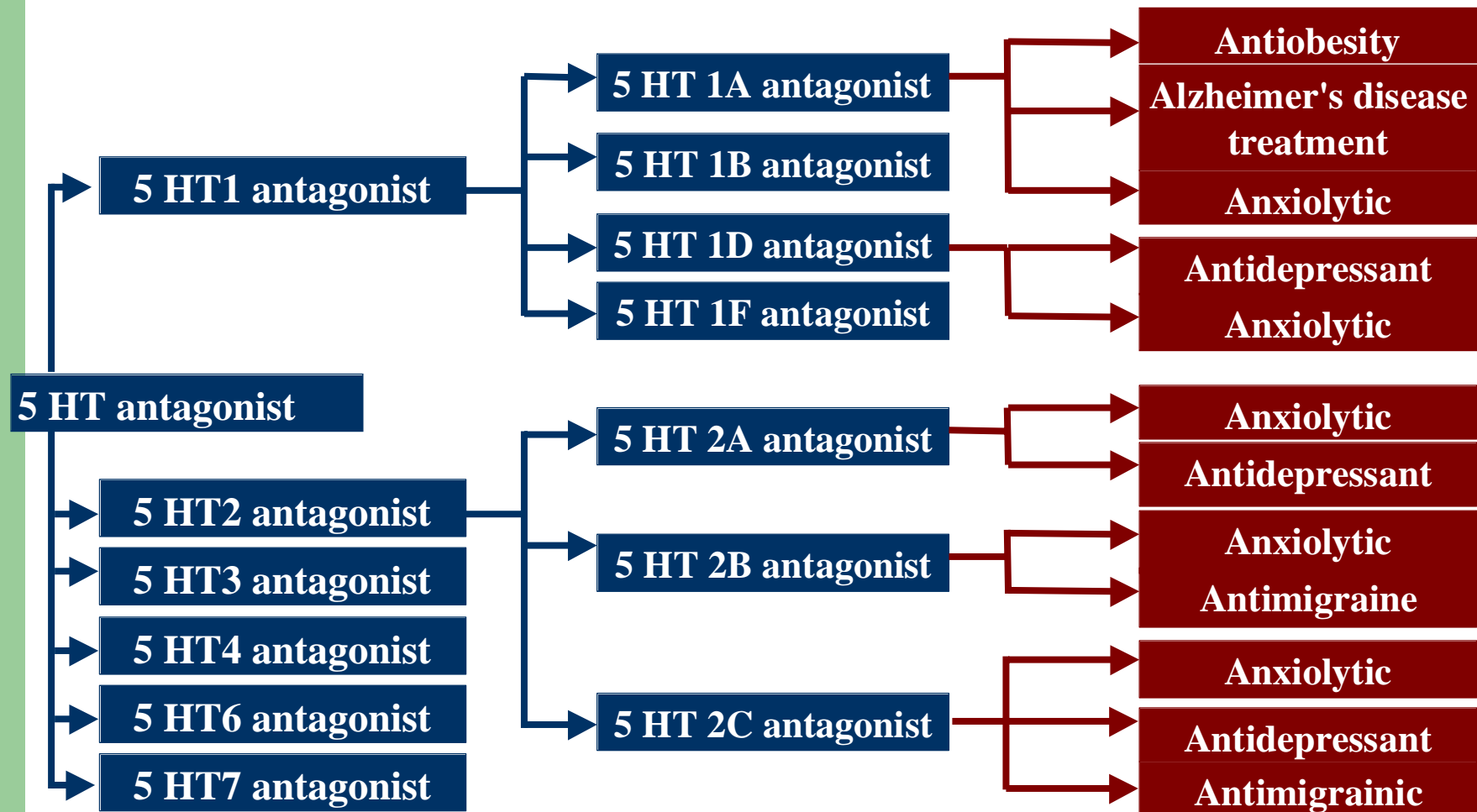
Anti-inflammatory agents	Lipoxygenase inhibitor Cyclooxygenase inhibitor
Antiallergic agents	Histamine H1 antagonist Thromboxane A2 antagonist
Antihypertensive agents	ACE inhibitor NEP inhibitor

Prediction result for a compound



← **Each type of biological activity may be used as a parameter for selection**

“Mechanism-Effect” Relationships



PharmaExpert – Software for “Mechanism-Effect” Relationships Analysis

“Mechanism-Effect” Relationships Database

Mechanisms of action:	1587
Effects:	418
Relationships:	2664

PharmaExpert
File Tools View Help

Prediction & Interpretation - D:\PharmaExpert Master\Example 1.SDF

Save TXT Save SD Clipboard Exclude
 # > < > >> # No: 3
 # 1 No: Interpretation of Effects Interpretation of Mechanisms
 Check non predicted activities Calculation

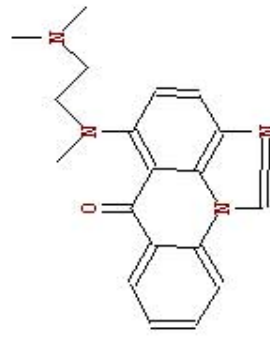
Pa	Pi	ID	Types of Activities	Pa-Pi descending	Types of Activities	Pa	Pi	Types of Activities
0.647	0.007		Histamine H1 receptor antagonist					Anxiolytic 0.437 0.047
0.668	0.077		Antihistaminic					GABA A receptor agonist 0.492 0.012
0.576	0.007		DNA intercalator					GABA receptor agonist 0.450 0.028
0.614	0.048		Antileishmanial					Benzodiazepine agonist 0.327 0.007
0.531	0.005		Benzodiazepine antagonist					5 Hydroxytryptamine 1D agonist 0.092 0.045
0.492	0.012		GABA A receptor agonist					Adenosine A1 receptor agonist 0.000 0.000
0.466	0.007		Benzodiazepine agonist partial					Antidepressant 0.271 0.104
0.510	0.059		Respiratory distress syndrome treatment					Benzodiazepine agonist 0.327 0.007
0.450	0.028		GABA receptor agonist					5 Hydroxytryptamine 1D agonist 0.092 0.045
0.598	0.180		Transferase inhibitor					Anthypoxic 0.467 0.266
0.471	0.075		Topoisomerase II inhibitor					Antipruritic 0.470 0.277
0.437	0.047		Anxiolytic					Histamine H1 receptor antagonist 0.647 0.007
0.480	0.123		Adenylate cyclase inhibitor					Histamine antagonist 0.357 0.036
0.363	0.029		Endothelin receptor antagonist					Renal disease treatment 0.302 0.122
0.409	0.078		Anticonvulsant					Endothelin receptor antagonist 0.363 0.029
0.357	0.036		Histamine antagonist					Antitoxic 0.307 0.133
0.327	0.007		Benzodiazepine agonist					Antidepressant, Imipramin-like 0.206 0.075
0.335	0.018		Antimalarial					Antiarhythmic 0.233 0.118
0.311	0.017		Anti-Helicobacter pylori					Adenosine A1 receptor agonist 0.000 0.000
0.351	0.062		Antineoplastic enhancer					Antiprotozoal 0.212 0.109

Number of selected compounds: 1

Search: 17 Alpha hydroxylase/C17-20 lyase inhibitor

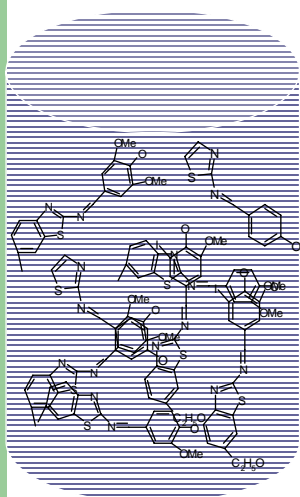
Delete
Clear
Load
Save

<ID> (3); 36 Substructure descriptors, 0 new; 57 Possible activities.



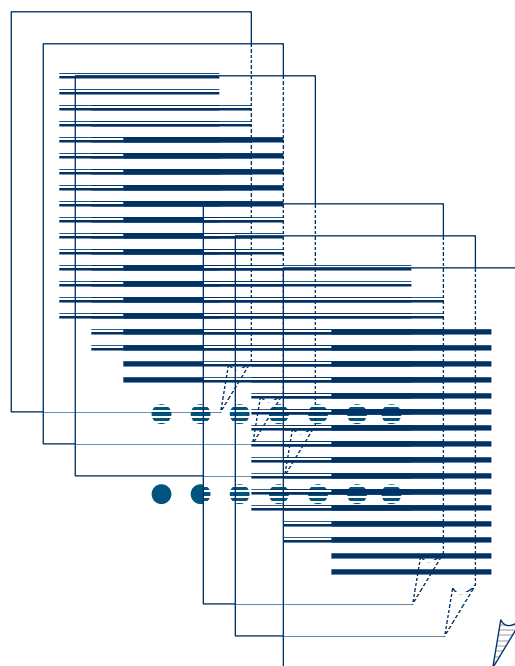
Search for ACE/NEP inhibitors

**~200.000
compounds**



**ChemBridge
AsInEx**

PASS

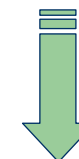
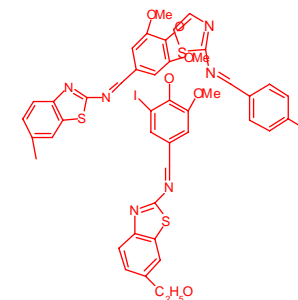


Results of prediction

**Pharma
Expert**



**4
ACE/NEP
inhibitors**



**Experimental
testing**

New PASS Applications Are Possible If The Appropriate Training Set Exists

- **Discriminating between drugs and non-drugs**
Anzali S. et. al. J. Med. Chem. 2001, 44, 2432-2437.
- **Biotransformation predictions**
Borodina Y. et. al. J.Chem.Inf.Comput.Sci., 2003, 43, 1636-1646
- **Semi-quantitative estimating of acute toxicity**
Lagunin A.A. et. al. J.P.P, 2003, Sept. Supl., S-57-58.
- **Quantitative prediction of biological effects using predicted activities as independent variables and self-consistent regression.**

<http://www.ibmh.msk.su/PASS>

*Prediction for Many Drug-
Like Compounds
Is Possible via Internet*



Acknowledgements

**Institute of Biomedical Chemistry
of Rus. Acad. Med. Sci., Moscow, Russia**

**Vladimir Poroikov, Prof, Head of Lab.
Dmitrii Filimonov , Ph.D.
Alla Stepanchikova
Denis Akimov, Ph.D. Stud.**

**Tatyana Glorizova
Yulia Borodina , Ph.D.
Nastya Sadym, Ph.D. Stud.
Maria Levchenko, Ph.D. Stud.**

**Lab. Med. Chem., NCI,
NIH, Frederik, M.D., U.S.
Marc Nicklaus, Ph.D.**

**Merck KGaA, Darmstadt, Germany
Soheila Anzali, Michael Krug,
Gerhard Barnikel**

**Civil Research and Development Foundation (CRDF), U.S.
INTAS, Europe
Royal Society, UK**