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

Vladimir Poroikov

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

http://www.ibmc.msk.ru
Outline

• Biological activity: many faces of the entity
• Identification of the most promising targets
  - Net2Drug
• Identification of the most promising lead compounds
  - PASS
  - PharmaExpert
  - GUSAR
• Examples of applications
• Summary
Due to biological activity, chemical compound may be used as a medicine for treatment of certain disease. Due to biological activity, chemical compound may cause adverse or toxic effects in human.
Depending on the Dose and Route of Administration, the Substance May Be either Drug or Poison

**Botox**

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

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

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

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

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

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

For example, “... popular statins, prescribed to decrease pathologically elevated cholesterol levels, interfere with cholesterol biosynthesis at the C\textsubscript{5} level (hydroxymethyl glutarate), and therefore interfere with the biosynthesis of farnesyl residues, cholic acids, sexual hormones and corticosteroids; it is really surprising that these drugs do not produce more severe side effects. Olanzapine, a successful neuroleptic and one of the top-selling drugs, acts as a highly unspecific, nanomolar antagonist of at least ten different neurotransmitter receptors.

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

Source: Thomson Reuters Integrity
Examples of Adverse and Toxic Effects Due to the Multitargeted Drug Action

Structure  →  Biological Activity  →  Drug/Chemical

Antiviral, Antitumor, Neurotoxicity  →  Sorivudine

Antidiabetic, Hepatotoxicity  →  Troglitazone

Antiarthritic, Antiinflammatory, COX-2 inhibitor, Heart attack  →  Vioxx
If some positive outcomes could be found in the multitargeted drugs action?
Needs for Multi-Targeted (Anticancer) Agents

- In order to optimize the efficacy of single target therapy, we should be able to identify in each patient the oncogene to which the tumor is addicted, if any, but this is at present unrealistic.

- In many tumors, cross-talks between different signalling networks have been identified and inhibition of a single pathway might not be sufficient to hamper tumor progression.

- Almost invariably patients treated with single target agents acquire pharmacological resistance and undergo relapse, often due to the activation of alternative signalling pathways.

Simple Case of Negative Feedback

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

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

Groupe d'Étude en Physiopathologie Endocrinienne, Centre National de la Recherche Scientifique, UPR1524, Institut Cochin de Génétique Moléculaire, Université René Descartes-Paris V, 75014 Paris, France
Multitargeted Drugs: The End of The “One-Target-One Disease Philosophy?”

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

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

Jordi Mestres, Elisabet Gregori-Puigjané, Sergi Valverde and Richard V. Sule

The availability of interactome data increased substantially in a total of 4767 unique interactions, where every drug is connected to the network through one or more drug–target interactions. This approach implicitly models the drug–target network with an increased number of nodes and edges, which can capture the complexity of drug–target interactions in a more realistic manner.

Novel paradigms for drug discovery: computational multitarget screening

Kacha Jenwitheesuk, Jeremy A. Horst, Kasey L. Rivas, Wesley C. Van Voorhis and Ram Samudrala

Synergistic drug combinations tend to improve therapeutically relevant selectivity


Drug combinations often exhibit increased synergy of action, while the adverse effects of individual drugs are generally more pronounced when used alone.

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

CRISTIÁN ROBERT MUÑTEANU, ALEXANDRE L. MAGALHÃES, EUGENIO URIARTE and HUMBERTO GONZÁLEZ-DÍAZ

The Multi-Target QPDR (Quantitative Comparative Protein Drug Response) classification model is a powerful tool for understanding the complex interactions between drugs and cancer-related proteins. By using star graph topological indices, this model provides insights into the selectivity and efficacy of drug combinations.

Analysis of multiple compound–protein interactions reveals novel bioactive molecules

Hiroaki Yabuuchi, Satoshi Nishiki, Hiromu Takematsu, Tomomi Iida, Takatsugu Hirokawa, Takafumi Hara, Tepppei Ogawa, Yohsuke Minowa, Gozoh Tsujimoto and Yasushi Okuno

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

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

Abstract: For centuries, the science of pharmacology has been evolving to understand the interactions between monosubstances, mixtures of bioactive compounds, and natural plant extracts, focusing on synergistic therapeutic effects.

Bivalent β-Carbolines as Potential Multitarget Anti-Alzheimer Agents

Kai-Uwe Schmidtke, Friedemann Gaube, Dirk Schepmann, Bernhard Wünsch, Jörg Heilmann, and Thomas Winckler

Alzheimer's disease (AD) is a prevalent neurodegenerative disorder with multifactorial causes. Multitargeted treatments are necessary to address the complex pathophysiological mechanisms underlying AD. Inhibitors of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) improve cholinergic signaling in the central nervous system and thus AChE inhibitors are a key component in the treatment of AD.
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How Many Drug Targets are There?  

<table>
<thead>
<tr>
<th>Class of drug target</th>
<th>Species</th>
<th>Number of molecular targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targets of approved drugs</td>
<td>Pathogen and human</td>
<td>324</td>
</tr>
<tr>
<td>Human genome targets of approved drugs</td>
<td>Human</td>
<td>266</td>
</tr>
<tr>
<td>Targets of approved small-molecule drugs</td>
<td>Pathogen and human</td>
<td>248</td>
</tr>
<tr>
<td>Targets of approved small-molecule drugs</td>
<td>Human</td>
<td>207</td>
</tr>
<tr>
<td>Targets of approved oral small-molecule drugs</td>
<td>Pathogen and human</td>
<td>227</td>
</tr>
<tr>
<td>Targets of approved oral small-molecule drugs</td>
<td>Human</td>
<td>186</td>
</tr>
<tr>
<td>Targets of approved therapeutic antibodies</td>
<td>Human</td>
<td>15</td>
</tr>
<tr>
<td>Targets of approved biologicals</td>
<td>Pathogen and human</td>
<td>76</td>
</tr>
</tbody>
</table>

Figure 2 | Frequency distribution for small-molecule drug potencies.
Dichotomous Modeling of Regulatory Networks in NetFlowEx program

Active node
Inactive node

Inactive edge of activation
Active edge of inhibition
Active edge of activation

Edge property
State of node $i$ $S_i = 1$

$S_k = 1$
$S_k = 0$

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

Primary states

Effect

**Input Data for Breast Cancer Modeling**

**Regulatory network**
TRANSPATH® database

Fragment: 2336 edges and 1405 nodes

**Microarray data for breast cancer**
Cyclonet database
[http://cyclonet.biouml.org](http://cyclonet.biouml.org)

- HER2/neu-positive breast carcinomas.
- Ductal carcinoma.
- Invasive ductal carcinoma and/or a nodal metastasis.
- Generalized breast cancer.
Simulation of normal cell processes

- Housekeeping genes
- Cell cycle complexes
- Cell cycle regulatory proteins
- Proteins regulating cell cycle and apoptosis
- Apoptotic proteins

Inactive
Active

Time steps

Proteins/genes
Simulation of pathological processes

Generalized breast cancer

Proteins/genes

- Cell cycle complexes
- Cell cycle regulatory proteins
- Proteins regulating cell cycle and apoptosis
- Apoptotic proteins

Time steps

Inactive
Active
## Identified drug targets

<table>
<thead>
<tr>
<th>Effect</th>
<th>Mechanism</th>
<th>HER2/neu positive breast carcinomas,</th>
<th>Ductal carcinoma</th>
<th>Invasive ductal carcinoma and/or a nodal metastasis</th>
<th>Generalized breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell cycle arrest</td>
<td>Cyclin D1:CDK4, Cyclin D1:CDK6 (G1 phase)</td>
<td>CYCD1, CYCLIN D1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell cycle arrest</td>
<td>Cyclin E:CDK2 (G1/S phase), Cyclin A:CDK2 (S phase)</td>
<td>CYCE, CYCLIN E, CDK2, PLK1, AKT-1</td>
<td>SYK</td>
<td>SRC</td>
<td>N/A</td>
</tr>
<tr>
<td>Cell cycle arrest</td>
<td>Cyclin B:CDK1 (G2/M phase)</td>
<td>SYK</td>
<td>SYK</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Induction of apoptosis</td>
<td>Cytochrome C</td>
<td>BCL-2</td>
<td>N/A</td>
<td>RAF-1, GRB-2, PKC, RACK1</td>
<td>Alpha5 Beta1 Fibronectin receptor, Fibronectin</td>
</tr>
<tr>
<td>Induction of apoptosis</td>
<td>Caspase-3</td>
<td>M KK4, PI3K, M KK6, P38ALPHA, CRKL, HPK1</td>
<td>N/A</td>
<td>VEGF-A, VEGFR-2, HIF-1ALPHA</td>
<td>N/A</td>
</tr>
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</table>
### Some Double and Triple Targets’ Combinations Identified For Breast Cancer

<table>
<thead>
<tr>
<th>No</th>
<th>Number of compounds</th>
<th>Activity type</th>
<th>Activity type</th>
<th>Activity type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>Bcl2 antagonist</td>
<td>Cyclin-dependent kinase 2 inhibitor</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>Bcl2 antagonist</td>
<td>Myc inhibitor</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>Bcl2 antagonist</td>
<td>Phosphatidylinositol 3-kinase beta inhibitor</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>Cyclin-dependent kinase 2 inhibitor</td>
<td>Myc inhibitor</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>Hypoxia inducible factor 1 alpha inhibitor</td>
<td>Myc inhibitor</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>Hypoxia inducible factor 1 alpha inhibitor</td>
<td>Phosphatidylinositol 3-kinase beta inhibitor</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>Myc inhibitor</td>
<td>Phosphatidylinositol 3-kinase inhibitor</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>Bcl2 antagonist</td>
<td>Myc inhibitor</td>
<td>Phosphatidylinositol 3-kinase beta inhibitor</td>
</tr>
</tbody>
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  - PharmaExpert
  - GUSAR

• Examples of applications

• Summary
PASS: Prediction of Activity Spectra for Substances
The key persons in PASS development

PASS (Prediction of Activity Spectra for Substances)

Российская Федерация
СВИДЕТЕЛЬСТВО
об официальной регистрации программы для ЭВМ
№ 2006613275

PASS (Prediction of Activity Spectra for Substances)

Правообладатель(и): Филимонов Дмитрий Алексеевич (RU), Поройков Владимир Васильевич (RU), Горюнова Татьяна Андреевна (RU), Лагунин Алексей Александрович (RU)

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

Зарегистрировано в Реестре программ для ЭВМ 15 сентября 2006 г.

Руководитель Федеральной службы по интеллектуальной собственности, патентам и товарным знакам

Б.П. Самикин
PASS Approach is Described in Detail:


http://pharmaexpert.ru/passonline
How PASS Predicts Biological Activity Spectrum?

Structure of new compound

Estimating the probability that it has a particular biological activity

Predicted biological activity spectrum

Anxiolytic
Sedative
5HT1A Inhibitor
Carcinogen

<table>
<thead>
<tr>
<th></th>
<th>Pa</th>
<th>Pi</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiolytic</td>
<td>0.853</td>
<td>0.020</td>
<td>Anxiolytic</td>
</tr>
<tr>
<td>Sedative</td>
<td>0.694</td>
<td>0.035</td>
<td>Sedative</td>
</tr>
</tbody>
</table>
Structural Formula of Acetylsalicylate
MNA Descriptors of Acetylsalicylate
Biological Activity Predicted for Acetylsalicylate
Online Biological Activity Prediction with PASS

http://pharmaexpert.ru/passonline
Input of the Structural Formula (Clopidogrel)
Results of Prediction for Clopidogrel

<table>
<thead>
<tr>
<th>Pa</th>
<th>Pi</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.947</td>
<td>0.005</td>
<td>Neuroprotector</td>
</tr>
<tr>
<td>0.801</td>
<td>0.007</td>
<td>Antithrombotic</td>
</tr>
<tr>
<td>0.740</td>
<td>0.037</td>
<td>Amyotrophic lateral sclerosis treatment</td>
</tr>
<tr>
<td>0.697</td>
<td>0.005</td>
<td>Platelet aggregation inhibitor</td>
</tr>
<tr>
<td>0.687</td>
<td>0.012</td>
<td>Acute neurologic disorders treatment</td>
</tr>
<tr>
<td>0.679</td>
<td>0.013</td>
<td>Atherosclerosis treatment</td>
</tr>
<tr>
<td>0.625</td>
<td>0.009</td>
<td>Sleep disorders treatment</td>
</tr>
<tr>
<td>0.597</td>
<td>0.010</td>
<td>Angiogenesis inhibitor</td>
</tr>
<tr>
<td>0.596</td>
<td>0.025</td>
<td>Analgesic</td>
</tr>
<tr>
<td>0.667</td>
<td>0.099</td>
<td>Cardioprotectant</td>
</tr>
<tr>
<td>0.634</td>
<td>0.082</td>
<td>Hepatotoxic</td>
</tr>
<tr>
<td>0.605</td>
<td>0.075</td>
<td>Dopamine D4 agonist</td>
</tr>
<tr>
<td>0.549</td>
<td>0.022</td>
<td>Antianginal</td>
</tr>
<tr>
<td>0.536</td>
<td>0.032</td>
<td>Antipsoriatic</td>
</tr>
<tr>
<td>0.520</td>
<td>0.051</td>
<td>Antiarthritic</td>
</tr>
<tr>
<td>0.435</td>
<td>0.004</td>
<td>Platelet antagonist</td>
</tr>
<tr>
<td>0.423</td>
<td>0.009</td>
<td>Glutamate (mGluR1) antagonist</td>
</tr>
<tr>
<td>0.412</td>
<td>0.011</td>
<td>Glutamate (mGluR group I) antagonist</td>
</tr>
<tr>
<td>0.426</td>
<td>0.035</td>
<td>Monoamine uptake inhibitor</td>
</tr>
<tr>
<td>0.410</td>
<td>0.030</td>
<td>Anticoagulant</td>
</tr>
</tbody>
</table>
Over Forty Publications with Independent Confirmation of PASS INet Predictions

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


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

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

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

C. Di Giorgio, a, b F. Delmas, a E. Olivier, b R. Elias, b G. Balansard, b and P. Timon-David a

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

PharmaExpert: Selection of Multitargeted Ligands
GUSAR: General Unrestricted Structure-Activity Relationships

Multitargeted QSAR

**GUSAR ONLINE**

**APPROACH TO YOUR QSAR MODELLING**

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

http://pharmaexpert.ru/gusar
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Finding of New Antihypertensive Agents with Dual Mechanisms of Action

About 30 mechanisms of antihypertensive action were available in PASS in 2001.

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

Compounds with predicted dual mechanisms of antihypertensive action were identified.

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

Some unknown combinations of the antihypertensive mechanisms were found.

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

ChemNavigator Library: The Biggest Source of Commercially Available Samples

iResearch™ Library

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

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

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

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

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

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

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

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

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

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

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

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

Galina Selivanova, Karolinska Institute, Sweden
Synergistic effect was observed between CPI and Rita in several breast cancer cell lines, but not in non-transformed mammary epithelial cell line.
Molecular mechanisms of Rita action and potential target proteins for a complementary compound

PI3-kinase
Targets’ Combinatorics: $\frac{N!}{((N-M)!M!)}$
Chemogenomics: Chemical Space (Estimated)

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

H. Kubinyi, 2004
Influence of Individual Atoms on a Particular Activity

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

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

This can be interpreted in the following way:

- If $P_a = 0$ and $P_i = 1$, then Red = 1, Green = 0.3, Blue = 0.3 – bright red color;
- If $P_a = 1$ and $P_i = 0$, then Red = 0.3, Green = 1, и Blue = 0.3 – bright green color;
- If $P_a = 0$ and $P_i = 0$, then Red = 0.3, Green = 0.3, Blue = 1 – bright blue color;
- If $P_a = 0.33$ and $P_i = 0.33$, then Red = 0.53, Green = 0.53, Blue = 0.53 – grey color.
Example: sulfathiazole has antibacterial activity, and also it is a weak antagonist of ET\textsubscript{A} receptors.
The fragment of sulfathiazole identified by PASS as having “positive” influence on $\text{ET}_A$ antagonistic activity:

1 sulfathiazole
$\text{ET}_A I_{50} = 69 \, \mu\text{M}$

2 sulfisoxazole
$\text{ET}_A I_{50} = 0.78 \, \mu\text{M}$

3 BMS-182874
$\text{ET}_A I_{50} = 0.15 \, \mu\text{M}$

4 BMS-193884
$\text{ET}_A K_i = 1.4 \, \text{nM}$

5 BMS-207940
$\text{ET}_A K_i = 0.010 \, \text{nM}$

From Sulfathiazole to Potent ET\textsubscript{A} Antagonist

\begin{itemize}
  \item \textbf{IC\textsubscript{50}:} 60 \textmu M
  \item 0.78 \textmu M
  \item 0.15 \textmu M
  \item 1.4 nM
  \item 0.01 nM
\end{itemize}
Afternoon session, 16:00-16:15

Olga Filz, IBMC

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

1. Multi-targeted agents may have advantages comparing to the ligands acting on a single target.

2. The most prospective targets and their combinations can be identified by different simulations of processes in regulatory pathways.

3. Compounds that likely have the targeted activities can be found by virtual screening in the databases of available samples.

4. In silico fragment-based design may be another prospective way of finding multitargeted ligands.
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Alla Stepanchikova, MSc
Alexander Dmitriev, PhD
Nastya Rudik, PhD
Dmitry Druzhilovsky, PhD Student
Olga Filz, PhD Student
Olga Koborova, PhD Student
Sergey Ivanov, Student

GeneXplain GMBH, Germany
Alexander Kel
Karolinska Institute, Sweden
Galina Selivanova, PhD
Aristotelian University of Thessaloniki, Greece
Athina Geronikaki, PhD
NCI-Frederick, USA
Marc Nicklaus, PhD
NTNU, Norway
Sergey Zotchev, PhD

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