Personal Experience of Russian Researcher’s Collaboration with U.S. Investigators

Vladimir Poroikov, Prof. Dr.

Institute of Biomedical Chemistry
Moscow, Russia
My first visit to the United States
(University of Alabama at Birmingham, October, 1989)
PASS: Prediction of Activity Spectra for Substances

Structure of new compound

Estimating the probability that it has a particular biological activity

Predicted biological activity spectrum

<table>
<thead>
<tr>
<th>Pa</th>
<th>Pi</th>
<th>for Activity:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.853</td>
<td>0.020</td>
<td>Anxiolytic</td>
</tr>
<tr>
<td>0.694</td>
<td>0.035</td>
<td>Sedative</td>
</tr>
</tbody>
</table>

Totally, predicts about 700 biological activities.
To provide the possibility of bioactivity prediction worldwide, PASS Inet system has been developed (http://ibmc.msk.ru/PASS).

Currently: http://way2drug.com/passonline
Computer-assisted mechanism-of-action analysis of large databases including 250,000 chemical compounds registered by NCI

Supported by the CRDF Grant # RC1-2064 (2000-2001).
PASS Predictions Searchable in NCI DB Browser (http://cactus.nci.nih.gov)

More than 64 million PASS predictions included.
More than 700 activities available.
Predictions separately searchable by probabilities of activity and inactivity.
Both types combinable by logical AND.
Predictions searchable by probability ranges (in subintervals of 0.0 – 1.0).
PASS searches combinable with any other search criteria.
Combined Search: PASS Antiangiogenesis Prediction & Name (Fragment) Exclusion

Database status: 250251 open structures ready for searching. Mail Wolf-D. Thelenfeldt for bug reports, comments and questions (and CC to Marc C. Nicklaus if you like).

<table>
<thead>
<tr>
<th>Query Type</th>
<th>Negate</th>
<th>Query Data Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASS Prediction Range...</td>
<td>0.9-1.0</td>
<td>[E_PASS_DATA_PA(31S)]</td>
</tr>
<tr>
<td>PASS Prediction Range...</td>
<td>0.0-0.2</td>
<td>[E_PASS_DATA_Pl(319)]</td>
</tr>
<tr>
<td>Name Search...</td>
<td>acid</td>
<td>[Name fragment, ignore nu]</td>
</tr>
<tr>
<td>Name Search...</td>
<td>amide</td>
<td>[Name fragment, ignore nu]</td>
</tr>
<tr>
<td>Exact Structure...</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tautomer-tolerant FS/SS search:

Connect query fields by: AND \(\bigcirc\) OR \(\bigcirc\) XOR \(\bigcirc\)

Max. number of hits and search time: 100 hits, 90 seconds

Output Format: HTML Table with Samples preferably 3D

Output Sort: NSC Number

Page loads: 0.003 Queries: 0.00348
Database status: 250251 open structures ready for searching.
Mail Wolf-D. Ihlenfeldt for bug reports, comments and questions (and CC to Marc C. Nicklaus if you like).

**Search Results: Hitlist**

Operations with this Dataset of 83 Structures:

- **Data Retrieval:**
  - Format: SDFile
  - 3D
  - Fields: NSC Number, Molecular Number, Name (ACD)

- **Visualization:**
  - GIF Image Gallery

- **Miscellaneous:**
  - Restart Query (at first record)

### Sample Structures

<table>
<thead>
<tr>
<th>NSC Number</th>
<th>Formula</th>
<th>CAS</th>
<th>#Names</th>
<th>Sample Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>7965</td>
<td>C₇H₅ClN₅</td>
<td>3397-62-4</td>
<td>8</td>
<td>6-chloro-1,3,5-triazine-2,4-diamine</td>
</tr>
<tr>
<td>96665</td>
<td>C₁₆H₂₀O₄</td>
<td>(None)</td>
<td>7</td>
<td>5-methoxy-4-(2-methyl-3-(3-methyl-2-butenyl)-2-oxiranyl)-1-oxaspiro[2,5]octan-6-ol</td>
</tr>
<tr>
<td>10374</td>
<td>C₅H₈ClNO₃</td>
<td>691-80-5</td>
<td>1</td>
<td>N-(chloroacetyl)alanine</td>
</tr>
<tr>
<td>13914</td>
<td>C₅H₈ClN₅</td>
<td>32998-04-2</td>
<td>1</td>
<td>6-chloro-N²,N²-dimethyl-1,3,5-triazine-2,4-diamine</td>
</tr>
<tr>
<td>32859</td>
<td>C₅H₈ClNO₃</td>
<td>6092-17-3</td>
<td>1</td>
<td>ethyl chloroacetylcarbamate</td>
</tr>
<tr>
<td>32864</td>
<td>C₆H₁₁ClN₂O₂</td>
<td>7248-86-4</td>
<td>1</td>
<td>N-(chloroacetyl)-N'-isopropylurea</td>
</tr>
<tr>
<td>33713</td>
<td>C₁₀H₁₂O₃</td>
<td>(None)</td>
<td>1</td>
<td>2,2,5,5-tetramethyltetrahydro-3-furanyl acetate</td>
</tr>
<tr>
<td>51808</td>
<td>C₁₂H₈F₂N</td>
<td>401-17-2</td>
<td>2</td>
<td>2,5-difluoro-N-(4-fluorophenyl)aniline</td>
</tr>
</tbody>
</table>
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.

Predictions of Broad Activity Spectra for Large Chemical Databases: 64 Million PASS Results made Searchable on the Enhanced NCI Database Browser

Marc C. Nicklaus, Computer-Aided Drug Design (CADD) MiniCore Facility, Lab. of Medicinal Chemistry, CCR, NCI, NIH, Frederick, and Vladimir V. Poroikov, Dmitrii A. Filimonov and Alexey A. Lagunin, Laboratory of Structure-Function Based Drug Design, Institute of Biomedical Chemistry, Russian Academy of Medical Sciences, Moscow
Computer-Aided Discovery of New HIV-1 Integrase Inhibitors (ISTC/BTEP project # 3197/111)
2005-2008

Institute of Biomedical Chemistry of RAMS, Moscow (Vladimir Poroikov team - computer-aided drug discovery).

Institute of Organic Chemistry of RAS, Moscow (Svyatoslav Shevelev team - chemical synthesis of potential ant-HIV agents).

Institute of Physical-Chemical Biology of MSU, Moscow (Marina Gottikh team - testing of potential anti-HIV agents in vitro).

National Cancer Institute, NIH, Frederick, MD (Marc Nicklaus - molecular modelling, Vinay Pathak - testing in cell culture).
217 compounds were selected as hits, synthesized (or purchased from vendors of commercially available samples)

187 compounds were tested in vitro on inhibition for strand transfer and 51 compounds were tested on inhibition for 3’ processing.

18 compounds were identified as HIV-1 integrase inhibiting agents with IC$_{50}$ values in the micromolar and sub-micromolar range.

For 3 most active compounds results were further confirmed by in vitro testing at NCI.

The discovered compounds belong to the chemical series where this activity was unknown (NCEs).

WHAT'S YOUR RESEARCH ABOUT?

GETTING GRANTS!
Roadmap Data: New Possibilities for Computer-Aided Drug Discovery

Vladimir Poroikov, Dmitry Filimonov, Marc Nicklaus

Institute of Biomedical Chemistry of Rus. Acad. Med. Sci., Moscow, Russia; Laboratory of Medicinal Chemistry, NCI/NIH, Frederick, MD, USA

235th ACS Meeting, April 6-10, 2008, New Orleans, LA, CINF-58
The first round: 45 compounds purchased; 16 active at IC₅₀<50 µM; 4 active at IC₅₀~1 µM.
The second round: 15 compounds designed and obtained from IOC, all – inactive at IC₅₀<10 µM.
The third round: 148 compounds obtained from ChemNav, the syntheses of (up to) 20 compounds are underway, 10 known reference drug compounds ordered. All compounds will be tested in one cell-based and three enzymatic assays (IN, RT, PR) at ImQuest (contract of NCI with ImQuest is under preparation).

Publications and presentations: 4 journal articles, 1 book chapter, 6 abstracts published; 5 oral presentations (3 at the American Chemical Society Meetings), 2 posters.
QSAR Modeling Using Large-Scale Databases: Case Study for HIV-1 Reverse Transcriptase Inhibitors

Olga A. Tarasova,* † Aleksandra F. Urusova, † Dmitry A. Filimonov, † Marc C. Nicklaus, ‡ Alexey V. Zakharov, ‡ and Vladimir V. Poroikov†

† Institute of Biochemical Chemistry, 10-8, Pogodinskaya St., 119121, Moscow, Russia
‡ CADD Group, Chemical Biology Laboratory, Center for Cancer Research, National Cancer Institute, National Institutes of Health, DHH, NCI-Frederick, 376 Boyles St., Frederick, Maryland 21702, United States

Supporting Information

ABSTRACT: Large-scale databases are important sources of training sets for various QSAR modeling approaches. Generally, these databases contain information extracted from different sources. This variety of sources can produce inconsistency in the data, defined as sometimes widely diverging activity results for the same compound against the same target. Because such inconsistency can reduce the accuracy of predictive models built from these data, we are addressing the question of how best to use data from publicly and commercially accessible databases to create accurate and predictive QSAR models. We investigate the suitability of commercially and publicly available databases to QSAR modeling of antiviral activity (HIV-1 reverse transcriptase (RT) inhibition). We present several methods for the creation of modeling (i.e., training and test) sets from two, either commercially or freely available, databases: Thomson Reuters Integrity and ChEMBL. We found that the typical predictivities of QSAR models obtained using these different modeling set compilation methods differ significantly from each other. The best results were obtained using training sets compiled for compounds tested using only one method and material (i.e., a specific type of biological assay). Compound sets aggregated by target only typically yielded poorly predictive models. We discuss the possibility of “mix-and-matching” assay data across aggregating databases such as ChEMBL and Integrity and their current severe limitations for this purpose. One of them is the general lack of complete and semantic/computer-parsable descriptions of assay methodology carried by these databases that would allow one to determine mix-and-matchability of result sets at the assay level.
**COMPUTER-AIDED DESIGN AND BIOLOGICAL TESTING OF NOVEL COMPOUNDS TOWARDS PREVENTION AND CURE OF HIV/AIDS**

*RFBR/NIH Project # 13-04-91455*

**Co-PIs:** Marc C. Nicklaus, Ph.D. (NCI/NIH)
Vladimir Poroikov, Dr. Sci. (IBMC)

The first round: 45 compounds purchased; 16 active at IC$_{50}$$<50$ µM; 4 active at IC$_{50}$$\sim1$ µM.
The second round: 15 compounds designed and obtained from IOC, all – inactive at IC$_{50}$$<10$ µM.
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**Publications and presentations:** 4 journal articles, 1 book chapter, 6 abstracts published;
5 oral presentations (3 at the American Chemical Society Meetings), 2 posters.
Exchange by people (mobility)

Yulia Borodina
Our graduate student and PhD student.
Currently works at FDA.

Vladimir Potapov
Our graduate student.
Currently works at MIT.

Alexey Zakharov
Our graduate student and PhD student.
After post-doc position in NCI, currently works at NCATS.
Which pre-requisites are crucial for successful scientific collaboration?

*I would add “a long-term”...*

Complementary:
- Background
- Experience
- Facilities

Mutual:
- Efforts, efforts, efforts...

*Acting in this way, you will obtain non-additive value results, which no one team could achieve working separately.*
Good luck!