BIOLOGICAL ACTIVITY PROFILING AS A TOOL FOR VIRTUAL SCREENING

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Introduction

Since the majority of pharmaceuticals have a pleiotropic action exhibiting both pharmacotherapeutic and adverse/toxic effects, profiling of their biological activity in silico allows selecting the most relevant screens for particular compounds and filtering out substances that might exhibit hazard effects.

Based on the freely available information about biologically active compounds (PubChem, ChEMBL, DrugBank, etc.) new computational tools for estimation of biological activity have been developed (see below). The applied methods vary widely from the relatively simple pairwise chemical similarity assessment to more sophisticated ligand-based or target-based approaches.

Our group published the first study describing an approach to provide chemists with the information about the most relevant targets/assays for their compounds [1-3], and additional computational tools with similar functionality have been developed in other labs more recently as well.

No systematic comparison of the accuracy and predictivity of these web-services has been performed yet. Therefore, the aim of our study was to analyze the relative predictive power of the available services for predicting the biological activity profiles based on information about new pharmaceuticals approved by US FDA in 2011 [4].

Materials and methods

Criteria for selection of web-services, to be evaluated:

- Multiple biological activities (biological activity spectra) are predicted in one run.
- "Ready for prediction" (completely pre-trained computational systems).
- Freely accessible (not necessary to purchase a license).
- The approaches are described in papers published in the peer-reviewed journals.

The selected web-services:
ChemSpider (LASSO), PASS, SuperPred (CDK similarity) - ligand-based approaches.
CPI-DRAR, SEA (five different knowledge bases) - target-based approaches.

Criteria for selection of validation set:

- Newly published data.
- Compounds from the validation set reveal various biological activities.
- Compounds from the validation set belong to the diverse chemical classes.
- Biological activity of the compounds has been investigated in detail.

2011 FDA drug approvals

The US FDA approved 30 new therapies last year, including 11 first-in-class agents.

From 30 drug substances approved by FDA in 2012, 6 are biopreparations and 24 are synthetic drug-like substances (New Chemical Entities).

Two compounds have been excluded from further consideration due to the peculiarities of chemical structure and biological action: Gadobutrol - BBB imaging gadolinium-based contrast agent; Isolupane is iodine isotope I-123.

The list of drug substances with their biological activities, which was used as a validation set, is given below.

<table>
<thead>
<tr>
<th>Genomic Name (trade name)</th>
<th>Indication</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head ice</td>
<td>Causes neuronal excitation</td>
<td>F1YFNCE, F1YFNCE</td>
</tr>
<tr>
<td>Viscodrine (Vimizim)</td>
<td>Major depressive disorder</td>
<td>SelDarnarv, SelDarnarv</td>
</tr>
<tr>
<td>Andriene (Esidronate)</td>
<td>Hypertension</td>
<td>Angiopt 1 type</td>
</tr>
<tr>
<td>Rarabase (Relestase)</td>
<td>COPD exacerbations</td>
<td>Phosphodiesterase D inhibitor</td>
</tr>
<tr>
<td>Cadotzol (Sedodek)</td>
<td>Blood-brain barrier imaging agent</td>
<td>Gadobutrol-based contrast agent</td>
</tr>
<tr>
<td>Galaprotein (Galeplisib)</td>
<td>Moderate to severe, restless legs syndrome</td>
<td>Voltage-gated calcium channel inhibitor</td>
</tr>
<tr>
<td>Mucamistat (Mucamist)</td>
<td>Membrane-transporting melatonin receptor</td>
<td>deseratrons</td>
</tr>
<tr>
<td>Viropradastate (Virostat)</td>
<td>Neutrophilic and macrophage activation</td>
<td>PGEA-AGAl + NET Inhibitor</td>
</tr>
<tr>
<td>Alapaprapas (Alapapras)</td>
<td>Neutrophilic granulocyte releasing granulocyte</td>
<td>YU9035</td>
</tr>
<tr>
<td>Lactoprotein (Lactoplas)</td>
<td>Type 2 diabetes</td>
<td>Draparidpine 4 inhibitor</td>
</tr>
<tr>
<td>Mucoprotease (Mucoplas)</td>
<td>Mucosal immunity</td>
<td>Virostatase (Virostat)</td>
</tr>
<tr>
<td>Isolupane (Isolup)</td>
<td>IV and II inhibitor</td>
<td>Virostatase (Virostat)</td>
</tr>
</tbody>
</table>

Diverse chemical classes of 22 drug substances from the validation set:

- Antibiotic macrolide: Purines
- Benzofurans: Azacyclohexanes
- Benzimidazoles: Substituted benzoxinolines
- Pyridines: Cyclopentapyroles
- Tetraacyclohexoacetic acid: Macrolide antibiotics
- Quinazoline: Fluorobenzylamines
- Androstanes: Pyrrolopyrimidines

Validation Criteria.

Since no one compound has been tested against all possible kinds of biological activity, the only parameter that can be used to characterize the relative predictivity of web-services is: Sensitivity = TP/NA, where TP - true positives; NA - number of "actives".

Results

Validation results are presented in diagrams below (1 – ChemSpider; 2 – CPI-DRAR; 3 – PASS Online; 4 – SEA; 5 – SuperPred).

Y axis – the number of activities that can be predicted by each web-service; blue - the number of predicted activities; red - the number of unpredicted activities.

Acknowledgement. The work was partially supported by RFBR grant No. 12-07-00597.

References:
3. http://www.pharmaceutixPASSOnline