Journal of Cheminformatics

POSTER PRESENTATION Open Access

Rational, computer-aided design of multi-target ligands

J Achenbach*, E Proschak

From 6th German Conference on Chemoinformatics, GCC 2010
Goslar, Germany. 7-9 November 2010

Over the past two decades the "one drug – one target – one disease" concept became the prevalent paradigm in drug discovery. The main idea of this approach is the identification of a single protein target whose inhibition leads to a successful treatment of the examined disease. The predominant assumption is that highly selective ligands would avoid unwanted side effects caused by binding to secondary non-therapeutic targets.

In recent years the results of post-genomic and network biology showed that proteins rarely act in isolated systems but rather as a part of a highly connected network [1]. In addition this connectivity leads to more robust systems that cannot be interfered by the inhibition of a single target of that network and consequently might not lead to the desired therapeutic effect [2]. Furthermore studies prove that robust systems are rather affected by weak inhibitions of several parts than by a complete inhibition of a single selected element of that system [3].

Therefore there is an increasing interest in developing drugs that take effect on multiple targets simultaneously but is concurrently a great challenge for medicinal chemists. There has to be a sufficient activity on each target as well as an adequate pharmacokinetic profile [4]. Early design strategies tried to link the pharmacophors of known inhibitors, however these methods often lead to high molecular weight and low ligand efficacy.

We present a new rational approach based on a retrosynthetic combinatorial analysis procedure [5] on approved ligands of multiple targets. These RECAP fragments are used to design a large combinatorial library containing molecules featuring chemical properties of each ligand class. The molecules are further validated by machine learning models, like random forests and self-organizing maps, regarding their activity on the targets of interest.

* Correspondence: Achenbach@pharmchem.uni-frankfurt.de
Pharmaceutical Chemistry, Goethe University, 60438 Frankfurt am Main, Germany

Published: 19 April 2011

References

1. Jeong H, Mason SP, Barabási AL, Oltvai ZN: **Lethality and centrality in protein networks.** *Nature* 2001, **411**:41-42.
2. Kitano H: **Towards a theory of biological robustness.** *Molecular Systems Biology* 2007, **3**:137.
3. Agoston V, Csermely P, Pongor S: **Multiple weak hits confuse complex systems: a transcriptional regulatory network as an example.** *Phys Rev E* 2005, **71**:051909.
4. Morphy R, Rankovic Z: **Designing multiple ligands - medicinal chemistry strategies and challenges.** *Curr Pharm Design* 2009, **15**:587-600.
5. Lewell XQ, Judd DB, Watson SP, Hann MM: **RECAP - retrosynthetic combinatorial analysis procedure: a powerful new technique for identifying privileged molecular fragments with useful applications in combinatorial chemistry.** *J Chem Inf Comput Sci* 1998, **18**:511-522.

doi:10.1186/1758-2946-3-S1-P10
Cite this article as: Achenbach and Proschak: **Rational, computer-aided design of multi-target ligands.** *Journal of Cheminformatics* 2011 **3**(Suppl 1):P10.