Alternative variables in preclinical drug discovery: promises and challenges

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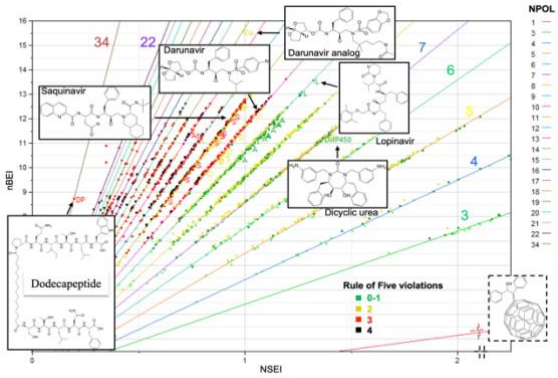
The pharmacological entities that reach the patients are the result of a directed multiparameter (multivariable) optimization process. The resulting chemical entities are specific for the targeted biological process and highly potent towards the precise macromolecular entity (i.e. enzyme, nucleic acid). At the molecular level this implies: i) high affinity and specificity for the molecular target (low K_i, IC_{50}); ii) favorable physico-chemical properties (small size, low MW and low polar surface area -PSA- or equivalent). Additionally, favorable pharmaco-kinetic properties need to be optimized to emphasize their therapeutic potential in the patient. Thus, the variable selection is critical to optimize the process.

Since the pioneering efforts of P. Ehrlich with salvarsan over a century ago, the most important variable was the 'activity' of the ligand (chemical entity) to the biological target, and the optimization was followed by comparing activities and chemical structures in the iconic 'SAR-tables' of medicinal chemistry articles.

Rapid and expanded chemical synthesis strategies put in the hands of the medicinal chemist extended libraries of compounds that could be screened by HTS and assayed by robotic methods. The accumulated biochemical and structural knowledge of the last quarter of the twentieth century, accelerated the optimization of affinity towards the target by the use of X-ray crystallography and NMR in the methodology known as Structure-Based Drug Design (SBDD). However, high affinity compounds are only one part of what makes a successful drug.



Page of AtlasCBS displaying compounds active against the HIV protease

Since 2005, new variables (Ligand Efficiency Indices, LEIs) have been introduced to monitor and optimize the drug discovery process combining the affinities (K_i, IC_{50}, K_D) with other critical physico-chemical parameters such as size (MW), polarity (PSA, Log P) and others[1]. These 'alternative variables' permit an effective graphical representation of Chemico-Biological Space in efficiency planes that allow an easy navigation in drug discovery space (i.e. AtlasCBS)[2]. The lecture will present the definitions, applications, utility, and future use of these new variables to optimize drug discovery and possibly to 'design' drugs by computerized algorithms[3-4]

(1) Abad-Zapatero, C. *Ligand efficiency indices for effective drug discovery*. Expert Opinion on Drug Discovery. 2007. 2 (4): 469-488.
(2) Abad-Zapatero, C. *Ligand Efficiency Indices for Drug Discovery. Towards an Atlas-Guided Paradigm*. Elsevier/Academic Press. 2013.
(3) Abad-Zapatero, C., Champness, EJ, Segall MD. *Alternative variables in drug discovery: promises and challenges*. *Future Med. Chem.* 2014; 6(5): 577-593.
(4) Abad-Zapatero, C. Ligand efficiency indices for effective drug discovery: a unifying vector formulation. *Expert Opinion on Drug Discovery*. 2021. https://tandfonline.com/loi/iedc20