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Screening, Designing and its Physicochemical Properties Involved in Drug Discovery

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Opinion Article

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DESCRIPTION

Finding a new drug against a specific target for a disease typically involves High-Throughput Screening (HTS), in which large libraries of chemicals are tested for their ability to modify the target. For example, if the target is a novel GPCR, compounds will be tested to see if they can inhibit or stimulate that receptor: if the target is a protein kinase, the chemicals will be tested to see if they can inhibit that kinase. Another function of HTS is to demonstrate how selective the compounds are for the chosen target, as the goal is to find a molecule that will interfere with only the chosen target and not with other, related targets. To that end, additional screening runs will be performed to determine whether the "hits" against the chosen target will interfere with other related targets a process known as cross-screening. Cross-screening is useful because the more unrelated targets a compound hits, the more likely it will cause off-target toxicity once it reaches the clinic.

These early screening runs are unlikely to yield a perfect drug candidate One of the first steps is to screen for compounds that are unlikely to be developed into drugs; for example, compounds that are hits in almost every assay, known as "pan-assay interference compounds" by medicinal chemists, are removed at this stage if they have not already been removed from the chemical library. Several compounds are frequently discovered to have some degree of activity, and if these compounds share common chemical features, one or more pharmacophores can be developed. At this point, medicinal chemists will attempt to improve certain properties of the lead compound using Structural-Activity Relationships (SAR):

- Increase activity against the selected target
- While decreasing activity against unrelated targets
- Improve the molecule's drug likeness or ADME properties

This process will necessitate several iterative screening runs, during which the properties of the new molecular entities are hoped to improve, allowing the preferred compounds to proceed to *in vitro* and *in vivo* testing for activity in the disease model of choice.

Ionization (pK_a) and solubility are two physicochemical properties associated with drug absorption; permeability can be determined by PAMPA and $Caco_3$. PAMPA is appealing as an early screen due to its low drug consumption and low cost when compared to tests with high correlation such as $Caco_3$, Gastro Intestinal Tract (GIT), and Blood-Brain Barrier (BBB).

As proposed by Lipinski's Rule of Five, a variety of parameters can be used to evaluate the quality of a compound or a series of compounds. Calculated properties such as c Log P to estimate lipophilicity, molecular weight, polar surface area, and measured properties such as potency, *in vitro* measurement of enzymatic clearance, and so on are examples of such parameters. Some drug likeness descriptors, such as Ligand Efficiency (LE) and Lipophilic Efficiency (LiPE), combine such parameters.

While HTS is a popular method for discovering new drugs, it is not the only one. It is frequently possible to begin with a molecule that already has some of the desired properties. Such a molecule could be extracted from a natural product or even an existing drug that could be improved (so-called "me too" drugs). Other methods are frequently used, such as virtual high throughput screening, which involves screening using computer-generated models and attempting to "dock" virtual libraries to a target.

Another method for drug discovery is *de novo* drug design, which involves predicting the types of chemicals that might (for example) fit into an active site of the target enzyme. Virtual screening and computer-aided drug design, for example, are frequently used to identify new chemical moieties that may interact with a target protein. To improve the potency and properties of new drug leads, molecular modeling and molecular dynamics simulations can be used as a guide. There is also a paradigm shift in the drug discovery community towards screening of smaller libraries (up to a few thousand compounds) rather than HTS, which is expensive and may only cover a limited chemical space. Fragment-Based Lead Discovery (FBDD) and protein-directed dynamic combinatorial chemistry are two examples. The ligands in these approaches are typically much smaller, and they bind to the target protein with lower affinity than HTS hits. Additional modifications to lead compounds are frequently required *via* organic synthesis. Protein X-ray crystallography of the protein-fragment complex is frequently used to guide such modifications. The benefits of these approaches are that they allow for more efficient screening, and the compound library, while small, typically covers a large chemical space when compared to other approaches.