Ministry of Health of the Russian Federation
Volgograd State Medical University

Department of Pharmaceutical and Toxicological Chemistry

GENERAL PHARMACEUTICAL CHEMISTRY

COMPUTER MODELING OF DRUGS.

Lesson 4
IV term

Volgograd 2022

Discipline

GENERAL PHARMACEUTICAL CHEMISTRY

LESSON №4 Computer modeling of drugs.	Computer-aided drug design. Search and approval of the target. The role of computing in drug design. MM methods based on ligand structure. MM methods based on protein structure. Limitations of computer methods. Drug design perspective

QUESTIONS FOR THE LESSON

1. What is drug design?
2. What is a target? Target classification.
3. Search and approval of the target
4. The role of computing in drug design. What are the main computer techniques used?
5. What MM methods based on ligand structure are used?
6. What MM methods based on protein structure are used?
7. Limitations of computer methods.
8. Drug design perspective

At the molecular level, any disease is a malfunction of proteins and/or genes encoding them in one or more body tissues. The human genome contains about 20,000 coding proteins. Today, about 500 pharmacological targets are known - proteins (and, in recent years, genes) that are targeted by drugs.

At the same time, many diseases are caused by the dysfunction of not one, but at least 5-10 interconnected proteins and their encoding genes.

The directed development of new drugs with predetermined properties is called ***drug design***. The modern method of creating medicines is based precisely on the search for an exact target and the design of an active molecule (active drug substance) that must reach the target and act.

TARGET SEARCH

The basic concepts of drag design are *target* and *drug*.

A target is a biological molecule that is associated with a wide spectrum of distribution leading to disease. The targets are proteins - receptors and enzymes.

A drug is a chemical compound (usually low molecular weight) that specifically interacts with its target and thereby affects the processes inside the cell.

Biochemical classification of currently constitutional targets:

- ✓ receptors
- ✓ enzymes
- ✓ hormones and factors
- ✓ ion channels
- ✓ nuclear receptors
- ✓ DNA
- ✓ unknown targets

Search and approval of the target

- Based on information about the disease, researchers are looking for a potential target for the development of new drugs.
- As a result of the search, the target can be both already known and completely new receptors.
- More than half of all known drugs act on the same family of receptors (G protein-coupled receptors).
- Another genetic family - transport proteins.
- The third type of drug affects ion channels and enzymes.
- Targets, as well as possibly related genes, are isolated to study the function of the gene (target).
- The properties of the target gene are analyzed in models of the disease, which can be both cellular and animal models.
- ***The target is justified if the impact on the target has a beneficial effect on the disease model.***

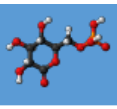
THE ROLE OF COMPUTING IN DRUG DESIGN

Currently, the role of computing technology continues to increase in drug design. It should be noted right away that the current level of development of computer techniques does not allow the development of a new drug using only computers. The main advantages provided by computational methods, in this case, are the reduction of time to market for a new drug and the reduction of development costs.

The main computer techniques used in drug design are

- Molecular Modeling (MM);
- Virtual screening;

- Design of new drugs de novo;
- Evaluation of the properties of "likeness to the drug";
- Modeling ligand-target binding

Target structure \ Ligand structure	known 	unknown ?
known 	*Structure-based design* *Rational Drug Design* *Molecular Docking* *Drug-Receptor Interaction*	de-novo *design* *Active Site Search* *Receptor based DD*
unknown ?	*QSAR(Qualitative Structure-Activity Relationship)* *Indirect DD* *Ligand-based DD* *Pharmacophore design*	*combinatorial chemistry* *high throughput screening*

MM METHODS BASED ON THE LIGAND STRUCTURE

If nothing is known about the three-dimensional structure of the target (which happens quite often), methods are used based on information about the structure of already known ligands and data on their activity.

The approach is based on the fact that the structure defines the properties. Based on the analysis of correlations between the structure of known compounds and their properties, it is possible to predict the structure of a new compound that has the desired properties (or, conversely, to predict properties for a known structure). Moreover, this approach is used both when modifying known structures to improve their properties, and when searching for new compounds using the screening of compound libraries.

Methods for determining the similarity of molecules (or fingerprint methods) consist in discretely taking into account certain properties of the molecule and comparing the resulting "fingerprint" with the fingerprint of a molecule with known properties (used as a sample). The properties of a molecule are called descriptors (for example, the number of hydrogen bond donors, the number of benzene rings, the presence of a certain substituent in a certain position, etc.) The degree of similarity is expressed by the Tanimoto coefficient, which varies in the range 0÷1. High similarity implies the similarity of the properties of the compared molecules and vice versa.

Methods based on known coordinates of ligand atoms are called ***Quantitative Structure-Activity Relationship (QSAR) methods***. One of the most used methods of this group is the method of comparative analysis of molecular fields (CoMFA, Comparative Molecular Field Analysis). This method consists in approximating the three-dimensional structure of a ligand by a set of molecular fields that separately characterize its steric, electrostatic, donor-acceptor, and other

properties. The CoMFA model is built from a multiple regression analysis of ligands with known activity and describes a ligand that should bind well to the target of interest in terms of molecular fields. The resulting set of fields tells where the ligand should have a bulky substituent and where it should be small, where it should be polar and where it should not be, where it should be a hydrogen bond donor, and where it should be an acceptor, and so on.

The model can be used in the tasks of virtual screening of compound libraries, acting in this case as an analog of a pharmacophore. The most important disadvantage of this method is that it has a high predictive power only for closely related classes of compounds; when trying to predict the activity of a compound of a different chemical nature than the ligands used to build the model, the result may not be sufficiently reliable.

It is obvious that the reliability of modeling, as well as the efficiency of the entire process of designing a new drug, can be significantly increased if data are taken into account not only on the structure of the ligands but also on the structure of the target protein. Methods that take into account these data are collectively called "structural information-based drug design" (SBDD, Structure-Based Drug Design).

MM METHODS BASED ON PROTEIN STRUCTURE

Due to the growing potential of structural biology, it is increasingly possible to establish the experimental three-dimensional structure of a target or build its molecular model based on homology with a protein whose three-dimensional structure has already been determined.

The most commonly used methods for determining the three-dimensional structure of biomacromolecules with high resolution (3 Å) are nuclear magnetic resonance (NMR) spectroscopy and X-ray crystallography (X-ray diffraction analysis).

Typically, a study based on structural data also takes into account data on target mutagenesis to establish which amino acid residues are most important for protein function and ligand binding. This information is especially valuable when optimizing the constructed model.

The three-dimensional structure of the target, in addition to being able to explain the molecular mechanism of the ligand-protein interaction, is used in ***molecular docking***, or computer simulation of the ligand-protein interaction. Docking uses as starting information the three-dimensional structure of the protein (at this stage of technology development, as a rule, conformationally immobile), and the structure of the ligand, the conformational mobility, and interposition with the receptor which is modeled in the process of docking. The result of docking is the conformation of the ligand that best interacts with the protein binding site. In

reality, due to many approximations, the evaluation function does not always correlate with the corresponding experimental binding energy.

Docking allows you to save money and time by carrying out a procedure similar to high-throughput screening on computer systems. This procedure is called virtual screening, and its main advantage is that for real pharmacological tests, one does not need to purchase an entire library of a million compounds, but only "virtual prototypes". Usually, to avoid errors, screening and docking are used simultaneously, mutually complementing each other.

With the increase in computer power and the advent of more correct and physical algorithms, docking will better estimate the energy of protein binding to the ligand, will begin to take into account the mobility of protein chains and the influence of the solvent. However, it is not known whether virtual screening will ever completely replace the real biochemical experiment; if so, then this obviously requires a qualitatively new level of algorithms that are currently unable to absolutely correctly describe the interaction of a ligand with a protein.

LIMITATIONS OF COMPUTER METHODS

Despite all their promise, computer methods have several limitations that must be taken into account to correctly imagine the possibilities of these methods.

First of all, a mandatory experimental verification of the results obtained is necessary. That is, close cooperation of scientific groups conducting a computer experiment with other experimental groups is implied.

In addition, computer methods are not yet able to take into account the entire variety of the effect of a drug on the human body, so these methods are not able to significantly reduce clinical testing, which takes up the bulk of the time in the development of a new drug.

Thus, to date, the role of computer methods in drug design is reduced to speeding up and reducing the cost of research preceding clinical trials.

DRUG DESIGN PERSPECTIVE

Drug design is the future of the pharmaceutical industry. The targeted design of new drugs has already become an important part of modern society, making it possible to defeat many diseases that were not previously possible to cure. In the future, new science-intensive applications will be able to take drug design to an even higher level, when such serious diseases as cancer, AIDS, Alzheimer's disease, and other ailments of mankind will finally be defeated.