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Modern trends in drug discovery process

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ABSTRACT

The number of factors that determine the biological asset the number of compounds is so great and diverse that scientists cannot use them all. It is necessary to estimate the toxicity of newly synthesized substance, its effect on various body systems and possible incompatibility for use. First, the drug-like compound must show high level of biological activity, selectivity, and duration of the therapeutic effect. It should be chemically pure and have high storage stability, and the cost of its production should not be too high. When biologically active compounds enter the body and start interaction with many cells in metabolic processes, it needs this requires careful study. Most of the metabolic processes of drugs in the body are processes of their inactivation. However, in some cases, in the process of metabolic transformations, compounds with higher biological activity are formed.

Keywords *QSAR, drug design, research, chemistry.*

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INTRODUCTION

The struggle against diseases has been waged by mankind for a long time. People discovered the first medicines by chance and received them from the nature: plants (leaves, bark, fruits, roots, stems), animals and minerals. Synthetic substances with biological action firstly appeared in the 19th century in parallel with the rise of organic chemistry.

Second half of the 20th century was marked by a significant increase in the average life expectancy of people. This is largely due to the development of new drugs and developing novel therapeutic strategies. In recent years, there has been significant progress in all areas accompanying the drug development process, which is primarily due to the involvement in research of new technologies.

Despite many publications, which contain the keywords "drug design" or "drug discovery", our work, largely based on the materials of summarizing articles on the issues under consideration over the past 10 years, seems to be very relevant. The purpose of the publication is to systematize various approaches to drug development with an emphasis on the introduction of modern technologies from related fields and the use of in silico screening. In addition we want to give some view on the most promising directions for the development of drug design in the future. Medicines are biologically active substances of an endo- or exogenous nature, legally permitted for the prevention and treatment of human diseases. The mechanism of action of a drug in a living organism consists of three stages:

- diffusion into the target location;
- target recognition and chemical interaction with it on by certain affinity;
- activation of the target as a result of structural changes during drug-receptor interactions.

The target is usually understand as set of receptors, enzymes, cell organelles, cells, tissues, organs etc.

The development of a drug substance begins beforehand the synthesis and includes target identification, search for a lead compound, and optimization of its structure. It takes about 7-10 years to create a new drug and costs from 100 to 500 million dollars. According to statistics, it is usually necessary to test about 10,000 substances to identify an appropriate drug candidate.

The main directions of the search and development of new biologically active substances are:

- copying of known physiologically active substances;
- chemical modification of the structure of known synthetic and natural medicinal substances (modification of the structure of antibiotics by radical insertion made it possible to obtain numerous drugs with improved pharmacological properties);
- introduction of the pharmacophore group into the molecule of a new substance (for example, a family of anticancer drugs was obtained by introducing N,N-dichlorodiethylamine or aziridine fragments into various substances);

- molecular modeling (obtaining a number of medicinal substances that act on the central nervous system like a natural neurotransmitter - GABA);
- making of combined drugs;
- the methods of combinatorial chemistry (synthesis of large amount of new compounds per day and make preliminary biological screening);
- the search for antimetabolites of drug metabolism (acyclovir, a highly effective drug, is built on the basis of metabolites study);
- prodrug strategy.

Biologically active substances are, as a rule, complex organic compounds, the activity of which depends on the structure of the molecule and the arrangement of its radicals or pharmacophores. Molecular design, or targeted design of compounds with desired properties, is one of the main problems of modern chemistry. The main trouble caused by the finding relationship between structure and action, which is extremely ambiguous and, cannot be formulated strictly. However, the search for only highly active molecules is insufficient to achieve the main goal, because we should also take into account other important features like the low toxicity of the synthesized compounds, their pharmacokinetic parameters, ways of their biotransformation, and possible side effects.

Also, it is necessary that the drug candidate should have a certain set of physicochemical properties that ensure the distribution of the substance in the body. The biological response of an organism to a drug primarily depends on its solubility in biological fluids, which has a significant effect on the bioavailability i.e., absorption, filtration, diffusion, etc. Hydrophilic substances are of great importance, since they are delivered to specific targets via the blood stream. The solubility of a compound is also related to its release from the dosage form and the rate at which it is excreted from the body.

Despite the optimistic assessments of the current situation with drug development in the literature, in the full sense of the word, rational design of effective drugs for etiotropic or pathogenetic therapy becomes possible only nowadays thanks to breakthroughs in metabolomics, genomics, and computer technologies. Until recently, almost every drug was created by trials only. The search strategy for biologically active compounds is largely determined by whether the three-dimensional structures of the bioligand molecule and the target receptor are known. In this case, knowledge of the structure of the receptor is more valuable, which allows straight modeling.

Direct modeling is one of the best approaches to drug design. For within its framework the structure of the ligand-receptor complex is reconstructed with the calculation of conformations and affinity. Docking procedures assess the complementarity of identified structures to a given active site. For searches, it is convenient to use the extensive databases of known compounds available. Many software packages have been developed for the practical implementation of this approach. The main methodological difficulties of docking are associated with considering the conformations of the ligand, receptor flexibility, and the construction of the evaluation function.

De novo methods, when the structure of target molecules is refashioned by gradual building based on small fragments placed in the active site of the receptor, by minimizing the steric factor and maximizing the binding energy. The computer procedures used predicted structures that should have a high affinity for the receptor. The disadvantages of this methodology are the relatively low reliability of assessing the affinity of ligands for binding and too general rules for constructing molecules.

Indirect approaches are based primarily on the construction of relationships "structure-activity" (Quantitative Structure - Activity Relationship (QSAR)) and pharmacophore modeling. In pharmacophore analysis, it is assumed that the main contribution to the ligand-receptor interaction is made by some functional groups, therefore, they can be considered responsible for the relationship between structure and activity. Most often, potential donors and acceptors in the implementation of hydrogen and coordination bonds are considered as such structural elements. As a rule, the analysis includes two stages: identification of pharmacophore groups and spatial alignment of active conformations of a few molecules or their force fields for a better understanding of key structural features. To date, a significant number of programs have been developed for the practical implementation of this approach. It is obvious that the use of pharmacophore modeling will expand with the emergence of new information on ligand-receptor complexes, improvement of the force fields of molecular mechanics and methods for accounting for solvation, and integration with other approaches. Recently, there has been a tendency to move from the use of simple statistical correlations to the use of interpretable descriptors and techniques like CoMFA (Comparative Molecular Field Analysis, or 3D QSAR), using the combination of three-dimensional force fields obtained using a suitable "chemical probe" exhibiting a certain type of biological activity.

To create a drug, firstly, we need information about the pathological process in the body, as well as the development of an therapeutic strategy. Previously, various metabolic transformations in cells were traditionally considered, and groups of compounds for screening were selected based on the structure of metabolites or regulators.

The modern development of genomics and proteomics makes it possible to accurately identify the targets responsible for the pathogenesis of a particular disease. Genome sequencing leads to the discovery of new targets, many of which are involved in the development of pathologies. According to last data, about a quarter of the developments of pharmaceutical companies are already based on genomics investigations.
There are numerous procedures for identifying targets. Most often, molecular genetic approaches are used to determine the function of a gene, as well as directed changes in its expression in DNA, messenger RNA, or protein product. In addition to total sequencing of the nucleotide sequence, modern technologies are used such as positional cloning, the creation of libraries of EST-labeled repeats. Also, great hopes are pinned on the development of methods of functional cloning, bioinformatics and chemogenomics, an area designed to bind a variety of chemicals and a variety of biological targets.
For precise interaction with a biological target, it is necessary to develop a lead compound – a substance that exhibits the necessary biological activity in relation to a specific target. In each specific case, such compounds have their own criteria.
There are a lot of sources of such basic compounds, but recently most of them have been found by total screening of combinatorial libraries. Similar collections are intensively created by every pharmaceutical company, and many are commercially available. The efficiency of the search for a leader compound is determined by the composition of the library, the availability of information on the spatial structure of the target receptor, and the method of recording the biological response during screening. It has been shown that libraries based on de novo design are significantly more efficient than random collections. Success in combinatorial chemistry make it possible to create small collections that combine “drug similarity” with structural diversity. At the same time, the problem of virtual libraries, which are a source of compounds with the desired pharmacological characteristics, is closely related to the problem of molecular similarity and structural diversity.
Each synthesized compound must pass a series of biological tests for a specific type of activity. This stage can take a long time. Nowadays, total screening allows you to test about a huge number of compounds with great efficiency, but all the same, these indicators are far from the required ones. Therefore, at this stage, a significant improvement of this method is possible, primarily due to the technologies for assessing the "drug similarity" and screening out "hopeless" structures. Among the main innovations are: NMR-based screening, pharmacophore analysis, virtual screening, total docking, chemo- and bioinformatics methods.
Another approach to the search for leading compounds is pharmacophore analysis. A pharmacophore is understood as a special arrangement of functional groups in the three-dimensional structure of a molecule, which is necessary for its interaction with a target. The display of the pharmacophore makes it possible to formulate the criteria to be met by the leader compounds and is the basis for virtual screening. The improvement of computer technology makes it possible to search for successful compounds more effectively in vast databases. Finally, this is due to the combination of pharmacophore analysis and QSAR methods, the development of a multi-point system of "fingerprints", finding molecular similarity, the application of evolutionary methodology.
Recent advances in the search for lead compounds are related to virtual screening. Under this concept, in silico screening technics are often combined - from modeling based on homology to total docking and pharmacophore analysis. The development of computer technology and information databases makes this process one of the cheapest ways to find leading compounds. Virtual screening systems are especially effective in cases where, in addition to information about the structure of ligands and receptors and knowledge of the general laws of drug action, there is access to an extensive database of compounds characterized by the required chemical diversity. So, one of the most acute problems facing the developers of virtual screening platforms is the problem of drug similarity, which is closely related to the limited number of compounds that, according to some characteristics, can exhibit appropriate biological activity. If the structure of the receptor is considered rigidly fixed, then the existing algorithms make it possible to carry out searches at a high speed and very efficiently, which, however, is not applicable to flexible structures. This approach is actively developing due to the increase in the number of remote databases available via the Internet and the significant expansion of the Protein Data Bank.
The huge flow of information received by specialists in the field of genomics, total screening and combinatorial synthesis has led to the need to develop research at the intersection of chemistry, biology, mathematics, computer technologies in the framework of new areas, which include chemo- and bioinformatics. The applied methods cover a wide range of problems - from the synthesis and improvement of databases to the analysis of molecular similarity and the construction of QSAR models. Computer processing of information is carried out at the level of molecular structure descriptors, hence, the problem of finding new, especially 3D-descriptors, determining the bounds of their applicability, and also their use for the analysis of molecular resemblance is especially important.

As a rule, in medicinal chemistry, after finding the base compound, its synthetic modification is carried out to increase the activity and selectivity of action and minimize side effects. A certain system of functionalization of the lead compounds has been formed, but its capabilities are significantly expanded with the involvement of computer modeling to construct the "structure-activity" relationship. Screening out unpromising compounds reduces the amount of synthetic work and speeds up overall optimization.
Rational use of computer modeling allows to get away from the assembling of the empirical dependencies and create collections of new compounds. As already noted, the availability of information about the three-dimensional structure of the receptor or ligand-receptor complex makes it possible to carry out structure-based design. Knowledge of the target structure accelerates optimization by establishing biologically active drug conformation and its spatial orientation during interaction. The methodological basis for rational optimization of basic compounds in the absence of data on the structure of the receptor is QSAR, within which correlations between biological activity and structural descriptors for several similar compounds are revealed using statistical methods. The goals of modeling the relationship "structure-activity" are identification and analysis of the factors that determine this biological response, for a better understanding of the system under study and predicting the properties of new compounds. The essential points here are the assumption of the possibility of a numerical description of the structure by descriptors and the same mechanism of action of substances.
Currently, there is a change from the traditional extra-thermodynamic methodology to a three-dimensional description of structures, which is especially important when there are differences in the structure of the unchanged part of the molecules. Of course, computer modeling of biological activity does not yet guarantee the creation of drugs, however, it significantly accelerates this process at the stage of optimization of the lead compound.
The manifestation of the desired biological activity by a certain substance at the level of target molecules or cells does not guarantee its further use as a medicine. Now, an insignificant share of compounds that have shown the corresponding activity reaches the drug market. The elimination of other substances often occurs only at the expensive final stage of clinical trials. Screening of compounds with low bioavailability, unable to overcome biological barriers or having "false" activity due to the presence of reactive groups, should be carried out as early as possible.
Since clinical trials are preceded by tests in cell cultures and animals, it is important to be able to transfer the results of these studies to humans. Early prediction of pharmacokinetic and metabolic properties is of paramount importance. There is a need to develop in silico methods for assessing ADMET properties, such as bioavailability, penetration through the blood-brain barrier, and the degree of plasma protein binding. It is the prediction of "drug similarity" and the toxicity of compounds that will increase the efficiency of clinical trials and the entire process of drug development. Computer modeling of ADMET properties is difficult by the many physiological mechanisms that determine them and the small amount of reliable experimental data. At the same time, methods have been developed for predicting the direction and rate of metabolism and clearance - characteristics that largely determine the effectiveness of drugs. Improving the quality of the results of modeling the pharmacokinetic properties of new compounds is inextricably linked with the clarification of physiological and biochemical mechanisms and the transition from empirical correlations "structure-property" to the construction of models for predicting specific parameters. The potential of this area is demonstrated, for example, by the development of drugs for the treatment of Alzheimer's disease.

CONCLUSION

The constant improvement of the drug development process is due to its marked interdisciplinarity and the ability to attract the modern achievements in related fields: genomics, proteomics, biochemistry, molecular biology, medicine, pharmacology, computer modeling etc.
The rapid development of medicinal chemistry creates the conditions for the evolution from trials to accurately rational drug design when empirical synthesis with subsequent verification of activity gives way to the targeted synthesis of substances with the desired physicochemical properties and biological effects.
It is difficult to predict in advance exactly which approaches will enter research use, but there is no doubt that decoding the genome and improving information technologies will significantly change the process of drug development. With the establishment of new targets and the refinement of metabolic pathways, the possibilities for rational drug design are expanding. This trend should be expected to intensify as understanding of the genome improves. It is obvious that the role of computer modeling at different stages of drug development will steadily increase.

REFERENCES

1. An updated patent review: xanthine oxidase inhibitors for the treatment of hyperuricemia and gout (2011-2015) / R. Ojha, J. Singh, A. Ojha et al. Exp. Opin. Ther. Patents. 2017. Vol. 27. P. 311–345.
2. Synergetic Analgesia of Propentofylline and Electroacupuncture by Interrupting Spinal Glial Function in Rats / L. L. Liang, J. L. Yang, N. Lu et al. Neurochem. Res. 2010. Vol. 35. P. 1780–1786.
3. Structural and Conformational Studies on Carboxamides of 5,6-Diaminouracils-Precursors of Biologically Active Xanthine Derivatives / D. Marx G. Schnakenburg, S. Grimme, C. E. Müller Molecules. 2019. Vol. 24, issue 11. P. E2168.
4. New xanthine derivative B-YR-2 as antioxidant modulator of post-stroke damage of sensorimotor cortex neurons in rats / I. F. Belenichev, K. V. Aleksandrova, S. F. Nosach et al. Elixir Pharmacy. 2014. Vol. 76. P. 28286–28292.
5. Xanthine derivatives: a molecular modeling perspective / R. Suravajhala, R. Poddar, S. Nallapeta, S. Ullah. Agric. Bioinforma. New Delhi : Springer India, 2014. P. 283–291.
6. Franco R., Onatibia-Astibia A., Martínez-Pinilla E. Health benefits of methylxanthines in cacao and chocolate. Nutrients. 2013. Vol. 5. P. 4159–4173.
7. Ghose A. K., Viswanadhan V. N., Wendoloski J. J. A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A qualitative and quantitative characterization of known drug databases. J. Comb. Chem. 1999. Vol. 1, N 1. P. 55–68.
8. Keller T. H., Pichota A., Yin Z. A practical view of 'druggability'. Curr. Opin. Chem. Biol. 2006. Vol. 10, N 4. P. 357–361.
9. Oprea T. I. Property distribution of drug-related chemical databases. J. Comput. Aided Mol. Des. 2000. Vol. 14, N 3. P. 251–264.
10. Zhang M. Q., Wilkinson B. Drug discovery beyond the 'rule-of-five'. Curr. Opin. Biotechnol. 2007. Vol. 18, N 6. P.478–488.
11. Muegge I. Selection criteria for drug-like compounds. Med. Res. Rev. 2003. Vol. 23 (3). P. 302–321
12. Rognan D. The impact of in silico screening in the discovery of novel and safer drug candidates. Pharmacol. Therapeutics. 2017. Vol. 175. P. 47–66.
13. Sharma S., Kumar P., Chandra R. Overview of BIOVIA Materials Studio, LAMMPS, and GROMACS. Micro and Nano Technologies. 2019. P. 39–100.
14. Englert P., Kovacs P. Efficient heuristics for maximum common substructure search. J. Chem. Inf. Model. 2015. Vol. 55, issue5. P. 941–955.
15. Towards global QSAR model building for acute toxicity: Munro database case study / S. Chavan, I. A. Nicholls, B. C. G. Karlsson et al. Int. J. Mol. Sci. 2014. Vol. 15, issue 10. P. 18162–18174.
16. Calculation of molecular lipophilicity: State-of-the-art and comparison of log P methods on more than 96,000 compounds / R. Mannhold, G. I. Poda, C. Ostermann, I. V. Tetko. Pharm. Sci. 2009. Vol. 98, issue 3. P. 861–893.
17. Liu K., Feng J., Young S. S. PowerMV: a software environment for molecular viewing, descriptor generation, data analysis and hit evaluation. J. Chem. Inf. Model. 2005. Vol. 45, issue 2. P. 515–522.
18. A new approach to QSAR modelling of acute toxicity / A. A. Lagunin A. V. Zakharov, D. A, Filimonov et al. SAR QSAR Environ. Res. 2007. Vol. 18, N 3-4. P. 285–298.
19. QSAR model as a random event: A case of rat toxicity / A. P. Toropova, A. A. Toropov, E. Benfenati et al. Bioorg. Med. Chem. 2015. Vol. 23, issue 6. P. 1223–1230.
20. Biological activity, quantitative structure-activity relationship analysis, and molecular docking of xanthone derivatives as anticancer drugs / I. Miladiyah, J. Jumina, S. M. Haryana, M. Mustofa. Drug. Des. Devel. Ther. 2018. Vol. 12. P. 149–158.
21. Lessons learned from the fate of Astra Zeneca's drug pipeline: A five dimensional framework / D. Cook, D. Brown, R. Alexander et al. Nature Rev. Drug Discovery. 2014. Vol. 13. P. 419–431.
22. Fisone G., Borgkvist A., Usiello A. Caffeine as a psychomotor stimulant: mechanism of action. Cell. Mol. Life Sci. 2004. Vol. 61. P. 857–872.
23. Adenosine receptor antagonism causes inhibition of angiogenic activity ofhuman ovarian cancer cells / E. Barcz, E. Sommer, P. Janik et al. Oncol. Rep. 2000. Vol. 7. P. 1285–1291.
24. Design and synthesis of novel xanthine derivatives as potent and selective A2B adenosine receptor antagonists for the treatment of chronic inflammatory airway diseases / S. Basu, D. A. Barawkar, V. Ramdas et al. Eur. J. Med. Chem. 2017. Vol. 134. P. 218–229.
25. Синтез и поиск количественных соотношений "структура - свойство" в ряду 8-алкилзамещенных 7-R-3-метил-1Н-пурин-2,6(3Н,7Н)-диона / Д. А. Васильев, А. О. Прийменко, М. С. Казунин, Е. В. Александрова, А. С. Шкода, Б. А. Прийменко // Актуал. питання фармацевт. і мед. науки та практики. - 2011. - № 2. - С. 55-58.

