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Computer-Aided Drugs and Design

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Abstract – Discovery and development of new drugs is generally known as a very complex process which takes a lot of time and resources. Advances in the fields of biochemistry, molecular biology and cell biology, facilitated by developments in genomics and proteomics, are producing a large number of novel biological targets that may be exploited for therapeutic intervention. Although the phrases computer-aided drug design may seem to imply drugs discovery lies in the hands of the computational scientist who are able to manipulate molecules on the computer screens, the drugs design process is actually a complex and interactive one, involving scientists from many disciplines working together to provide many types of information.

Keywords: Computer-aided drug design**,** majors types of approaches in CADD, structure based drugs design, ligand based drugs design, general aspects computational chemistry, drugs design with help of software, application of CADD

Introduction- "**Computer aided drugs design uses computational chemistry to discover, enhance, or study drugs and related biologically active molecule**". Advances in the fields of biochemistry, molecular biology and cell biology, facilitated by developments in genomics and proteomics, are producing a large number of novel biological targets that may be exploited for therapeutic intervention. To facilitate the discovery of novel therapeutic agents, rational drug design methods in combination with structural biology offer great potential. The Computer-Aided Drug Design (CADD) Center was created to foster

collaborative research between biologists, biophysicists, structural biologists and computational scientist[1]. Drugs design is most commonly used to activate or inhibit function of a biomolecule such as a protein, which turns result in therapeutic benefits to patient. This modeling often to mention as computer aided drugs design. Finally, drug design that depends on the knowledge of the three dimensional structure bimolecular targets is known as structure based drugs design[2].

The latest technological advances (QSAR/QSPR, structure-based design, combinatorial library design, cheminformatics & bioinformatics); the growing number of chemical and biological databases; and an explosion in currently available software tools are providing a much improved basis for the design of ligands and inhibitors with desired specificity[3]. Drugs design is the inventive process of finding new medication based on the knowledge of a biological target selected drugs designed in small organic molecules and they are complementary shape into target and oppositely charged to the bimolecular target[4].

History: Pharmaceutical industry has started during 1880-1930 period where chemical companies established research laboratories to formed new drugs, isolated active chemicals from natural products, and researched them for biological activity[5]. The concept of nineteenth century; Paul Ehrlich during his M.D. thesis research, discovered that methylene blue selectively attached to nerve fibers. Following with this monitoring Ehrich's developed the ideas (systematically study the effects and various chemical effects in laboratory) developed therapeutics and chemotherapy (the process to study of synthesizing and testing many chemicals and biological effect)[6]. The early days the evaluation of drugs design and study of structural activity of drugs to develop by software and QSAR is quantitative study of interaction between small organic molecules and biological macromolecules study to analyze them[6]. Calculate property of molecules (e.g., absorption, distribution, metabolism of small organic molecules in living organisms) and their experimentally determined all biological activity[7]. Still play in important role.

1960s review the target-drug interaction

1980s Automation high-throughput target/drug selection

1980s Databases (information technology): combinatorial libraries

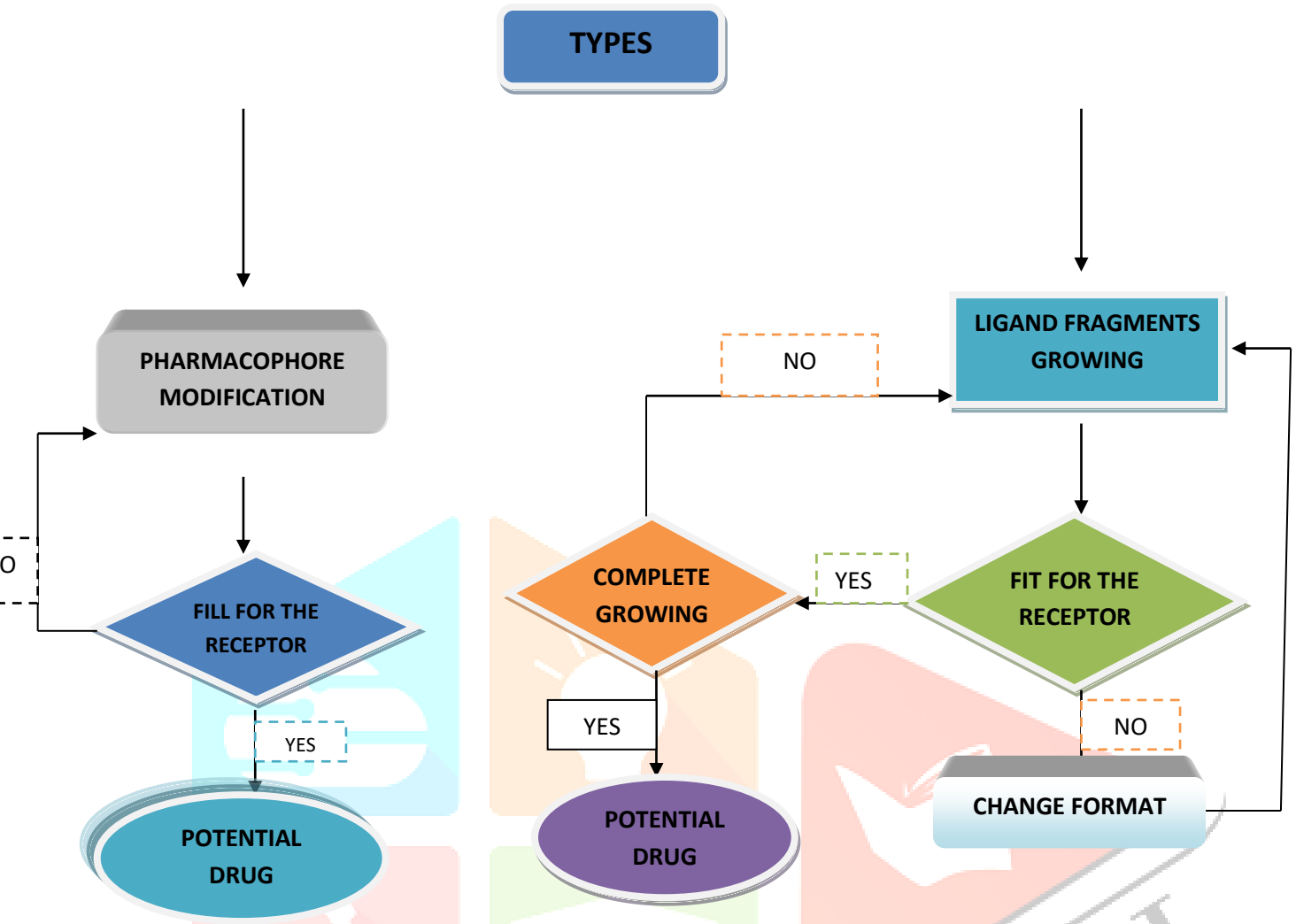
1990s Fast computer: docking

1990s Fast computer: assembly genomic-based target selection

2000s vast information handling: pharmacogenomics

Major types of approaches in CADD

Most commonly, drugs are organic small molecule produced through chemical synthesis, but biopolymer-based drugs (also known as biologics) produced through biological processes are becoming increasingly more common. In addition, mRNA-based gene silencing technologies may have therapeutics applications[8].



Flow charts of two strategies of structure-based drug design

There are mainly two types of approaches of drugs design through CADD is the following:

1. Structure based drug design
2. Ligand based drug design

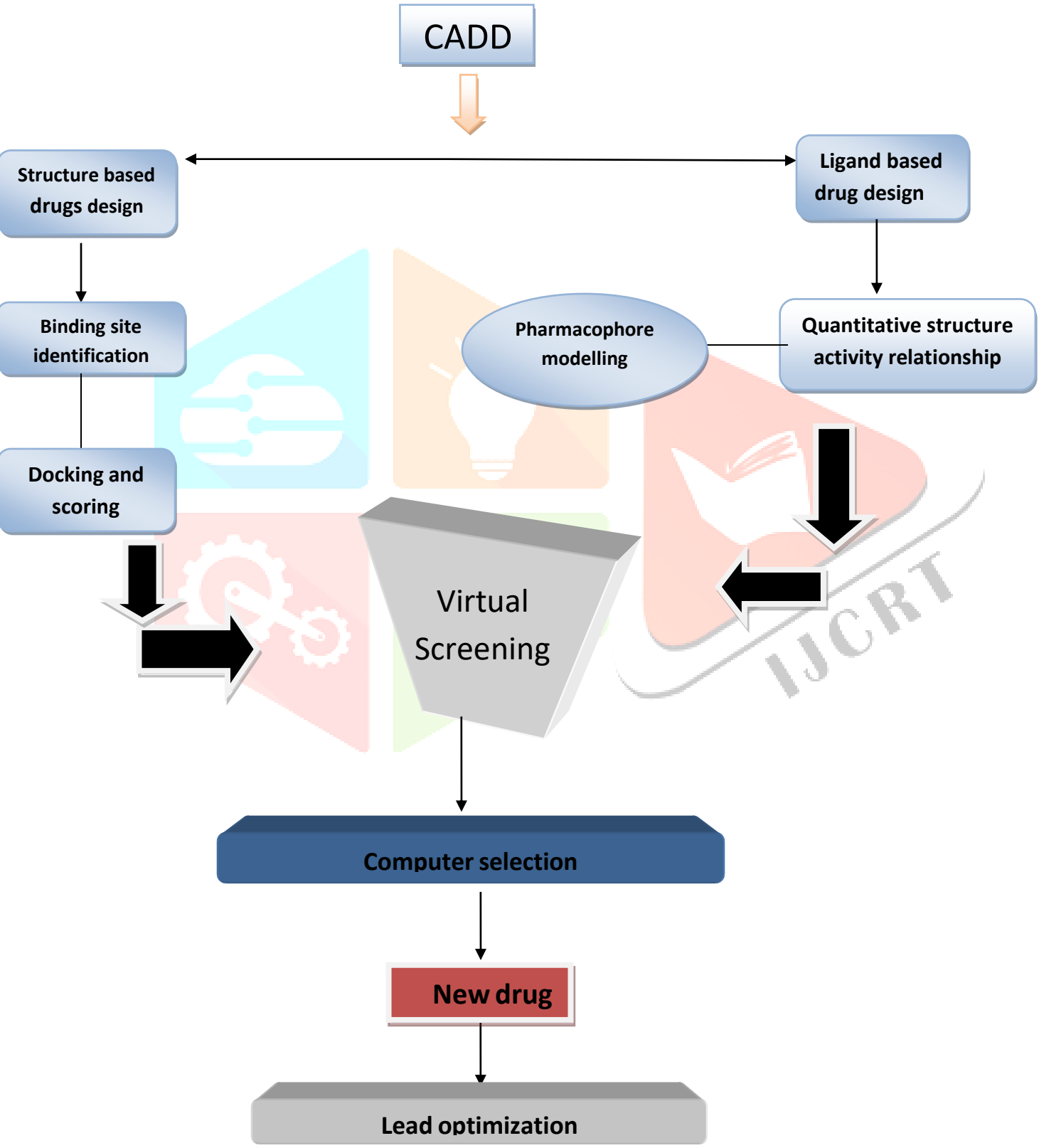


Figure 2: General representation of working for CADD.

1. Structure based drugs design

"Structure based drugs design is the design and optimization of a chemical structure with the goal of identifying a compound suitable for clinical testing - a drug candidate". Structure based design is target protein and performed with available in structure models, they are provided by x-ray diffraction, nuclear magnetic resonance or molecular stimulate (homologous protein modelling, etc)[9]. The interaction or bio affinity for all tested compounds calculate after the process of docking: to design a new drug molecule, which show better interaction with target protien[10]. It played a tremendous role in the discovery and development of several registered drugs and clinical candidates for example zanamivir, nelfinavir and aleglitazar. In contrast structure-based designing is relatively new agrochemical industry and at present, no products in the market that are directly investigated with the use of this approach. However, there are several databases and software program where structured-based design has a strong impact. The major databases resources used in drug discovery program. Different approaches used in the discovery of lead molecule through computational are discussed in the following section[11].

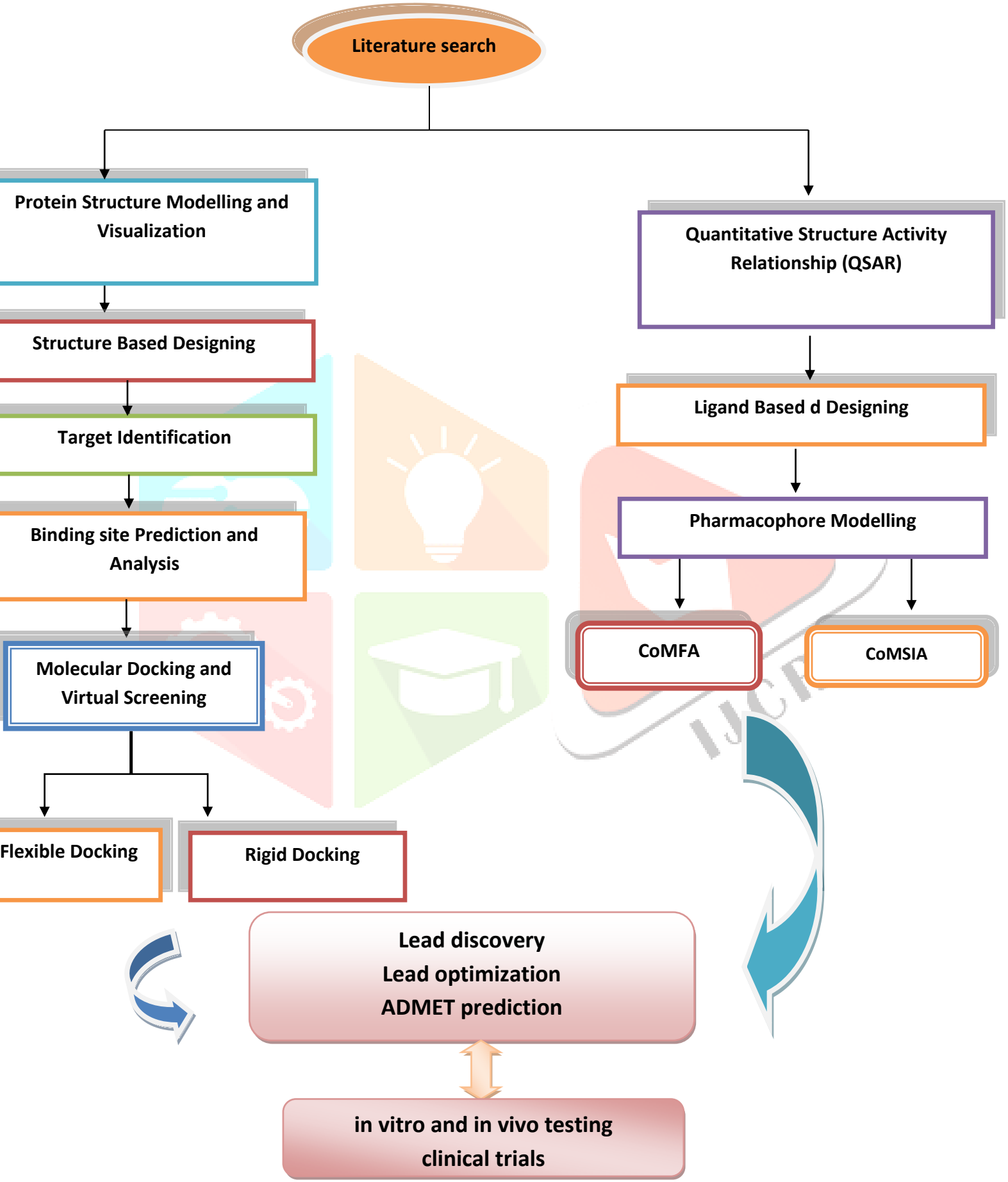


Fig. - Application of molecular modelling approaches in drug discovery and design

2. Ligand-based designing

- **"Ligand based drug design is an approach used in the absence of the receptor 3D information and it relies on knowledge of molecules that bind to the knowledge target of interest".** Then, this model can be further used to design new molecular entities that interact with the target. On the other hand, ligand based drugs design can also quantitative structure-activity relationship (QSAR) in which a correlation between calculated properties of molecules and their experimentally determined biological activity is derived, to predict the activity of new analogs[12]. It uses statistical methods to correlate the activity of ligand to structural information. The ligand based drugs designing is an alternative protocol, plays a tremendous role when the structure of target protein is unknown or cannot be predicted by available modelling method[13]. The different approaches used in ligand-
  Based drugs designing are discussed in following section.
- **Pharmacophore modelling**
- **Quantitative Structure-Activity Relationship**
- **CoMFA**
- **CoMSIA**

General aspects of computational chemistry

The basis of all further considerations is finding out case in there is relationship between chemical structure in the compound and its biological activity and what form this relationship takes

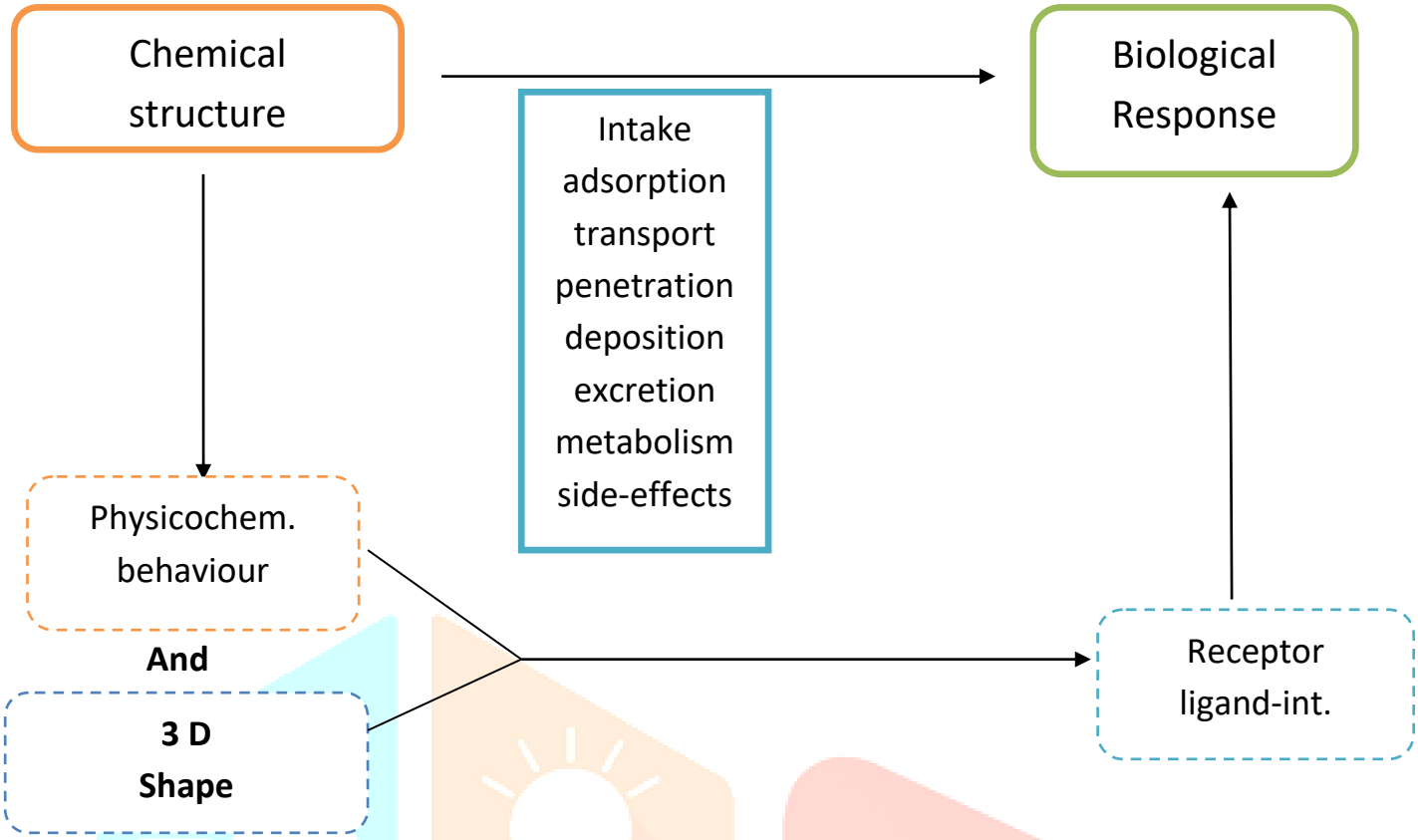


Fig. Structure-activity relationships

That the biological activity can only be observed when the active compound and the biological receptor interact with each other and form a stable complex for a while, and then it's possible to make suggestions as to the structure-activity relationships. The distribution of positive and negative charges, of polar and non polar zones and of hydrophilic and hydrophobic regions on the surface of the molecule, the capacity to form hydrogen bridges with the receptor, and overall lipid- or water like behaviour[14].

This can be show using a hypothetical active compound.

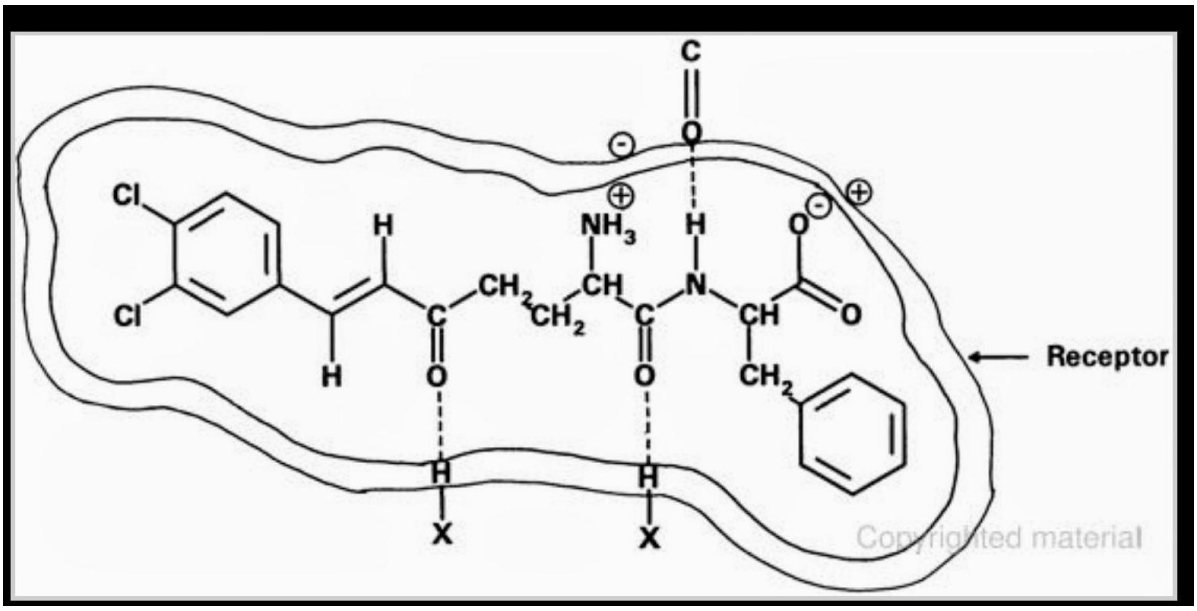


Fig.2. Interaction between substrate and receptor

Three possibilities should be mentioned in this context.

1) Quantitative structure –activity relationships
2) Molecular modelling of small molecules
3) Macromolecular modelling of large molecules such as proteins and nucleic acids

These data can be gained by experimental studies, such as protein nuclear magnetic resonance (NMR) or protein X-ray. Studies of homologous proteins can give useful information, too. This technique is used according to the knowledge available[15].

Drug Design with the help of software

The storage and retrieval of information for example, structure determined experimentally by X-ray crystallography for biologic targets (enzymes) and drug molecules, to develop information about toxicity and structural activity relationship (SAR). Based on the fine structure of the target molecules, a whole new ligand is constructed. This is just de novo discovery of a ligand. Ligbuild is a powerful tool to build a ligand[16].

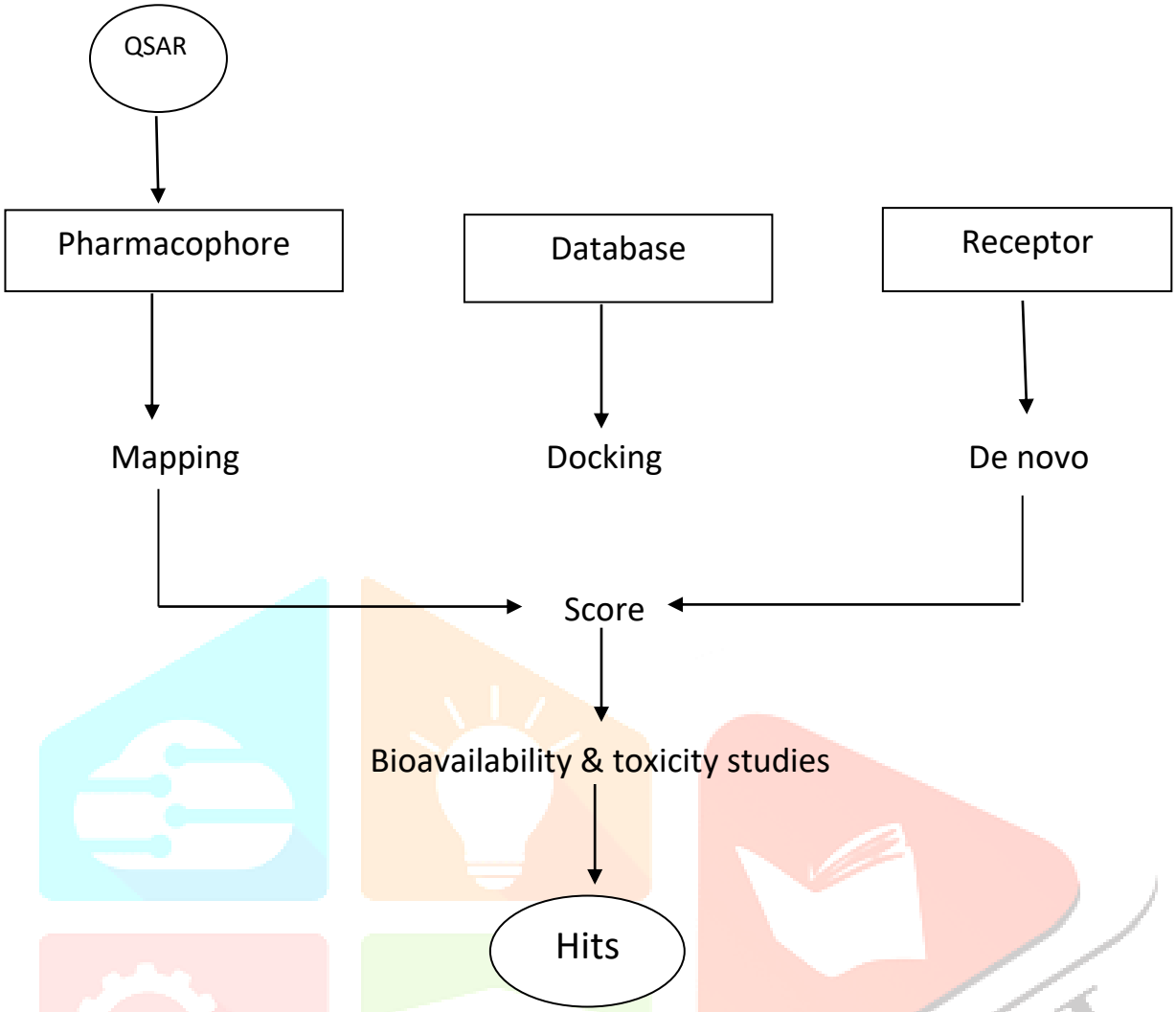


Fig. Flowchart for drug design

Application of Computer-aided Drugs Design

- As rule we do not develope the software required in the field of computational chemistry ourselves, but buy it from reputable software companies.
- Use of computing power to steamline drug discovery and development process.
- Leverage of chemical and biological information about ligands and/or targets to identify and optimize new drugs.
- Inhibitors of Dihydrofolate reductase.
- Design of conformationally restricted cyclopeptides for the inhibition of cholate uptake of heepatocytes.

Conclusion

Computer-aided drugs design, contributes to the section and synthesis of new materials and it guide the design of catalyst. New quantum mechanical techniques underlie the understanding of electronic properties of material and have advanced the level of precision at which molecules of at least moderate size can be modelled[17]. In the past years through computer-aided drugs design many impressive research achieved so it will play a very important role in the near future. The discovery of a new lead/drug using recent Computer-aided drugs design paradigms require a systematic understanding of the molecular and pathological condition induced by disease. However, computer-aided drugs design can assist researchers studying interaction between drugs and receptors.

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