Computerised Drug Design

MOLECULAR DOCKING

- Molecular docking is a computational method to identify the architecture of compounds generated by two or more distinct molecules.
- Docking is widely used to anticipate the interaction between ligand and target protein in terms of affinity and activity.

MOLECULAR DOCKING

- Docking plays a critical role in rational drug design. Considering the biological and pharmacological importance of docking studies, much effort has been made to improve the algorithms for docking prediction.

MOLECULAR DOCKING

- Docking is a mathematical technique that anticipates the preferable orientation of one molecule (may be drug, which has ligand) relative to another (may be target protein, which has binding site) when they are linked together to create a stable complex.

MOLECULAR DOCKING

- Using scoring functions (binding energy), it is possible to estimate the strength of the connection or binding affinity across two compounds based on their preferential orientation.

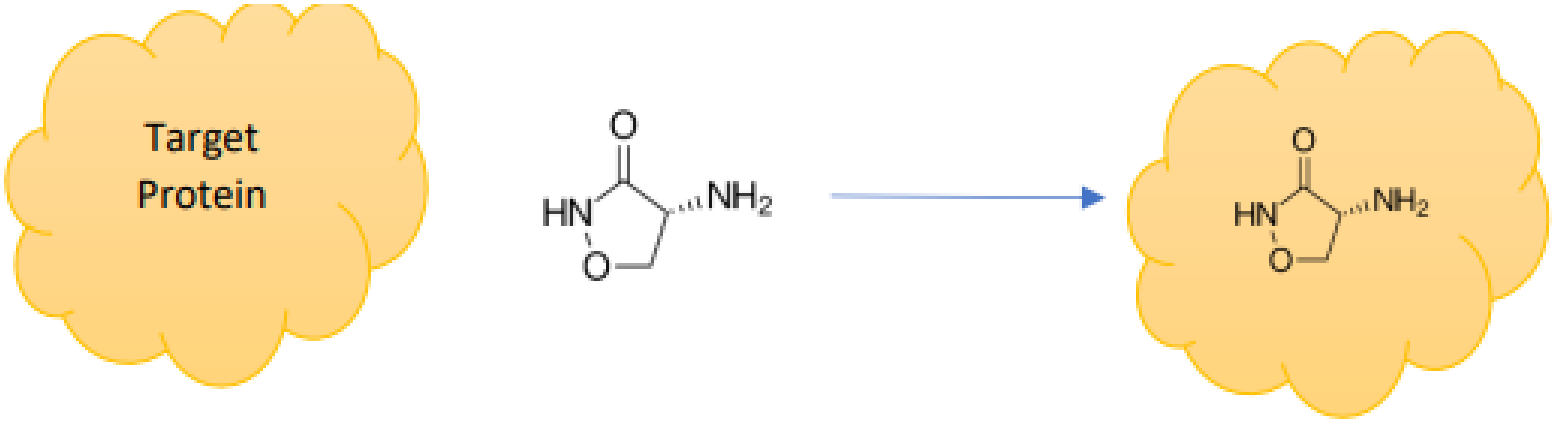
MOLECULAR DOCKING

- Signal transduction is dependent on the interactions of physiologically significant substances such as proteins, nucleic acids, carbohydrates, and lipids.

MOLECULAR DOCKING

- The goal of docking studies is to optimize the shape of both the ligand and protein, as well as the relative orientation of the protein and ligand, to reduce the total system's free energy.

MOLECULAR DOCKING



Types of Docking

- **Rigid docking**

Assuming the compounds are inflexible, we are seeking a rearrangement of one of the compounds in three-dimensional space that results in the best match to the other compounds in parameters of a scoring system. The ligand's conformation can be formed with or without receptor binding activity.

Types of Docking

- **Flexible docking**

In conjunction with transformation, we evaluate molecular flexibility to identify confirmations for the receptor and ligand molecules as they exist in the complex.

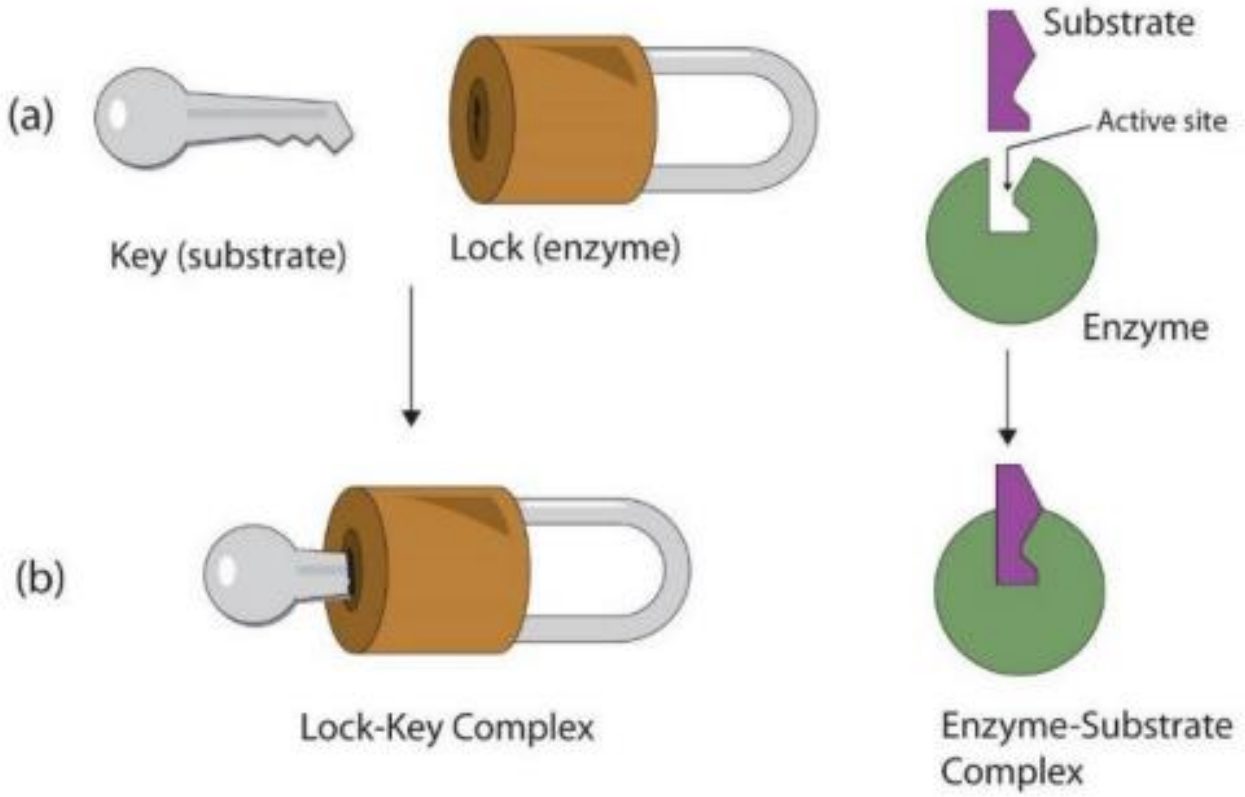
Theories

- **Lock & Key Theory**:

Emil Fischer created a concept termed the "lock-andkey model" in 1890, as seen in Figure, to describe how biological processes operate.

Theories

- **Lock & Key Theory**:



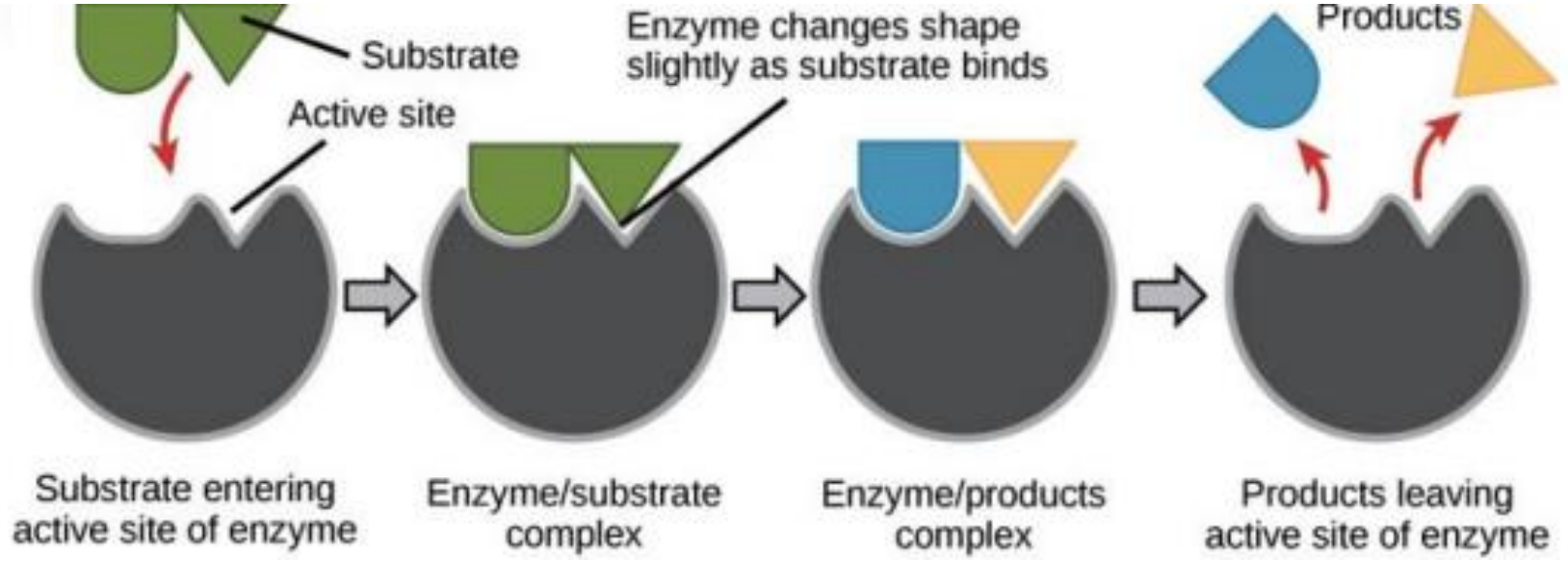
Theories

- **The induced-fit theory:**

Daniel Koshland proposed the "induced fit theory" in 1958. The fundamental concept is that throughout the character recognition, both the ligand and target, as seen in figure, adapt to one another by modest conformational changes until an ideal match is reached.

Theories

- **The induced-fit theory**



Molecular Docking Approaches

- Monte carlo approach

It creates a randomized conformation, translations, and rotation of a ligand in an active site. It assigns an initial configuration value. Then it develops and scores a new configuration. It determines if the new configuration is kept using the Metropolis criterion. (Metropolis criterion- If a new approach outperforms the prior one, it is approved instantly.

Molecular Docking Approaches

- **Matching approach**

This strategy emphasizes idleness, the optimal location of the ligand atom in the site determined, resulting in a ligand–receptor arrangement that might also need improvement.

Molecular Docking Approaches

- **Ligand fit approach**

Ligand fit is a word that refers to a quick and precise methodology for docking small molecules ligands into protein active sites while taking shape complementarity into account.

Molecular Docking Approaches

- **Point complimentarily approach**

These techniques are focused on comparing the shapes and/or chemical properties of different molecules. Blind Docking: This technique was developed to identify potential peptide ligand binding sites and mechanisms of action by scanning the full interface of target molecules.

Prediction of Activity Spectra for Substance

The development of a new compound is associated with a high risk of obtaining a negative result due to the possible detection of side pharmacological effects, toxicity, etc. Predicting the main and side effects at an early stage of research can significantly reduce the costs and risk of conducting research.

Prediction of Activity Spectra for Substance

For a preliminary assessment of the spectrum of biological activity of the predicted compounds based on structural formulas, the PAS (Prediction of Activity Spectra for Substance) computer system was used, which provides an opportunity to evaluate the pharmacological effects, mechanisms of action and specific toxicity of the substance.

Prediction of Activity Spectra for Substance

The PASS system differs from similar developments: an expanded list of predicted types of biological activity; the input of chemical information in the form of a structural formula familiar to a chemist; automatic coding of the chemical structure with fragmentary codes of the superposition of substructures of the FCSP, new, significantly more stable algorithms for establishing the structure-activity relationship.

Prediction of Activity Spectra for Substance

The forecast is carried out by "comparing" the structure of the proposed chemical compound with the database available in the package of the program itself.

Prediction of Activity Spectra for Substance

The combined application of the logical-structural approach to the formation of structures by the computer forecast of the PASS program provides higher accuracy and reliability of preliminary data.

Prediction of Activity Spectra for Substance

The PASS program is of great importance at the initial stage of the molecular design of ALS, since it allows us to assess the feasibility of synthesizing target compounds in terms of their possible pharmacological activity.

Prediction of Activity Spectra for Substance

An analysis of the probability of cardiotropic activity has shown that all the studied compounds presumably have a sufficiently high cardiotropic activity, with the exception of substance S4. This assumption is in good agreement with the structure of this compound, which, unlike other synthesized compounds, contains an N-amide fragment.

Prediction of Activity Spectra for Substance

The computer prognosis of S3 substance shows a high probability of manifestation of both cardiotropic and antianginal and antihypoxic activities. This fact suggests the presence of positive cardiotonic properties.

Prediction of Activity Spectra for Substance

Vasodilating central and peripheral effects, as well as ionotropic activity, are predicted with high probability for all hypothetical compounds except S4. This fact can be explained by the presence of an isoquinoline heterocycle, as well as two methoxy groups at positions 6 and 7, which is a unifying feature with the ancestor of myotropic antispasmodics papaverine.

Prediction of Activity Spectra for Substance

The most expected manifestations of the types of activity for synthesized compounds obtained by analysis in the PASS program.

PHARMACOPHORE MODELLING

The pharmacophore concept was introduced by Paul Ehrlich in the early 1900s. Then, the term pharmacophore was coined by Schueler in his 1960 book Chemobiodynamics and Drug Design, and was defined as “a molecular framework that carries (phoros) the essential features responsible for a drug’s (pharmacon) biological activity.”

PHARMACOPHORE MODELLING

In 1997, IUPAC (International Union of Pure and Applied Chemistry) defined pharmacophore as the sum of steric and electronic properties that are required for the interaction of a molecule with a target and thus provide the biological activity.

PHARMACOPHORE MODELLING

A pharmacophore does not represent a real molecule or a set of chemical groups, but is an abstract concept; “A pharmacophore is the pattern of features of a molecule that is responsible for a biological effect,” which captures the essential notion that a pharmacophore is built from features rather than defined chemical groups.

PHARMACOPHORE MODELLING

Each atom or group of a compound that shows features associated with molecular recognition can be converted into a pharmacophore pattern. Molecular pharmacophore patterns can be hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), positive features, negative features, aromatic rings, hydrophobic features and their combinations.

PHARMACOPHORE MODELLING

A pharmacophore model includes several patterns arranged in a particular 3D (three dimensional) pattern. Each pattern is depicted by a typical sphere containing radius that determines the deviation tolerance from the exact position. There are also various other displaying ways. These patterns can be displayed as a single pattern or their combination.

Approaches of Pharmacophore Modeling

There are two principal approaches of pharmacophore modeling that are used in the drug discovery process: Ligand-based pharmacophore modeling and structure-based pharmacophore modeling.

Approaches of Pharmacophore Modeling

In the ligand-based pharmacophore modeling approach, novel ligands are designed by using a set of active ligands available. This approach is employed if the target structure is not available. In a similar manner, the structure-based pharmacophore approach is employed when the structure of the target protein is available.