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8. Medicinal Chemistry

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Abstract:

Medicinal chemistry involves designing and developing of pharmaceutical drugs. Medicinal chemistry deals with the identification, synthesis, and development of medicinally active compounds. Quantitative structure –activity relationship (QSAR) and quantitative structure property relationship (QSPR) studies are important in silico methods in rational drug design. The goal of this medicinal chemistry is to produce pharmacologically active drugs. QSAR and QSPR Methods are having the goal to optimize the existing leads in order to improve their medicinal property and physicochemical properties. These methods also gives the information about biological activities of untested and yet unavailable compounds. QSAR study is good prediction tool for investigating drug activity and binding capacity on specific receptors.

Keywords: *QSAR, SAR, Drug discovery strategies, conventional synthesis, combinatorial synthesis. And computer aided drug design.*

8.1 Introduction:

Medicinal or pharmaceutical chemistry is the branch of chemistry involved basically with designing and developing pharmaceutical drugs. It involves the identification, synthesis and development of new chemical entities suitable for therapeutic purpose. It also includes the study of existing drugs, their biological properties and their quantitative structure-activity relationships. It concerns the discovery, the development, the identification and interpretation of the mode of action of biologically active compounds at the molecular level. It also includes study, identification, and synthesis of the metabolic product of both synthetic and naturally occurring drugs and related compounds.

Medicinal chemistry is interdisciplinary science which covers the biochemistry, pharmacology, molecular biology, immunology, toxicology, pharmacology on one side. on other side it covers chemistry based disciplines such as physical chemistry, crystallography, spectroscopy, and computer based information technologies.

It is the branch of chemistry concerned with the design, development and synthesis of pharmaceutical drugs. Medicinal chemistry is also involves the designing and developing of pharmaceutical drugs. It also includes the study of existing drugs, their biological properties, and their Quantitative structural activity relationship (QSAR).

Medicinal chemistry involves the isolation, characterization, synthesis, mechanism of action of compounds that can be used as medicines in the treatment of diseases. It is the linkage between structure and biological activity of compounds.

Medicinal chemistry covers three critical steps.

A. Discovery step
B. Optimization step
C. Development step

A. Discovery step:

It deals with the therapeutic target that is enzyme, transport group, receptor etc. and the identification and production of new active substances interacting with the selected target. Such compounds are usually called lead compounds. The sources of Lead compounds are

- From natural products.
- Chemical libraries.
- Computational medicinal chemistry.
- Green chemistry

Importance of lead molecules:

- Lead compounds are having potential to treat particular disease.
- It is chemical compound or natural product which is having biological activity against disease.
- Lead identification and optimization plays an important role in drug discovery process.

B. Optimization step:

It deals with improvement of the lead structure. The optimization process takes primarily into account the increase in potency, selectivity and toxicity. Its characteristics provide analysis of structural activity relationships to produce understanding of the molecular mode of action such as pharmacokinetic parameters that is absorption, distribution, oral bioavailability of lead compounds.

C. Development step:

This step involves the identification of candidates, synthesis, characterization, validation, screening, and assays for therapeutic efficacy. Once compound has shown its significances in these investigations, it will initiate the process of drug development earlier to clinical trials. It involves the improvement of pharmacokinetic properties and fine tuning of

pharmaceutic properties of the active substances in order to render them suitable for clinical use. This chemical formulation process consist in the preparation of better absorbed compounds, of sustained release formulations, of water soluble derivatives or in the elimination properties related to patience compliance (causticity, irritation, painful injections, undesirable organoleptic properties).

Structural activity relationship: The analysis of biological effects of chemical upon its molecular structure. Molecular structure and biological activity are correlated by observing the results of systemic structural modifications**.** Structural activity relationship is qualitative not quantitative relationship.

8.2 QSAR:

It is method that gives the information about activity, reactivity, specificity, properties and characterization of an unknown set of molecules which is based upon the analysis of structures of molecules to their respective activity and property. It is the mathematical relationship between the biological activity and physicochemical parameters. QSAR try to identify and quantify the physicochemical properties of a drug and to check whether any of these properties has an effect on biological activity or not. Quantitative structure activity relationship (QSAR) is one of the widely used techniques in ligand based drug designing method.

A quantitative structure activity relationship related to quantitative chemical structure to a biological activity. QSAR plays an important role in drug discovery process because their application can save time and human resources. For the prediction of QSAR model several parameters are important. On One side some different statistical methods are used to check the linear and non linear behavior of data set. On another side selection techniques are used to reduce the model complexity. QSAR model can be useful in the discovery of new compounds with improved potency. The molecules which show interesting activity will be synthesized.

Table 8.1: Structural activity relationship v/s quantitative structure activity relationship.

Structural activity relationship	Quantitative structure activity relationship
Relationship between chemical or 3D of molecule and its biological activity.	Gives that idea that there is simple mathematical relationship between biological activity of drug and physicochemical properties.
It can help to insert new chemical groups into the biomedical compound and test the results.	QSAR attempt to finds consistent relationship between biological activity and molecular properties. So that these rules can be helped to evaluate the activity of new compounds.
It is done by X-rays and NMR techniques.	It is done by procedure known as linear regression analysis by the least square method**.**

Structural activity relationship	Quantitative structure activity relationship
Structure activity relationship is technique to find qualitative relationship between chemical structure and biological activity.	QSAR models are theoretical models that relate a quantitative measure of chemical structure to a biological property.

Importance of QSAR and drug design:

- To modify the chemical structure of the lead compound to retain the desirable biological activity while minimizing unwanted pharmacological, physical and chemical properties.
- QSAR studies can be applied to design, identify and synthesize new drugs or molecules to optimize absorption, distribution, metabolism, excretion and toxicity profile of identified molecules from various sources to cure the diseases.
- A major goal of Quantitative Structure Activity Relationship (QSAR) studies is to find a mathematical relationship between the activity under investigation, and one or more descriptive physicochemical parameters and descriptors related to the structure of the molecule.

QSAR parameters:

The parameters used in QSAR are measure of the potential contribution of its group to particular biological activity of the parent drugs.

- Lipophillic parameters: partition coefficient,
- Electronic parameters: Hammet constant, dipole moment.
- Steric parameters: Molar refractivity, verloop steric parameter.
- Polarizability parameters: molar volume, parachor.
- Miscellaneous parameters: Topological parameter.

Combinatorial chemistry:

The Combinatorial Chemistry is a scientific method in which a large number of chemical entities are synthesized by condensing a small number of chemical compounds together in all combinations defined by a small set of chemical reactions.

Combinatorial technologies produce new compounds in practically with unlimited number. Combinatorial chemistry is which collects the techniques for the synthesis of multiple compounds at same time. It is one of the important new technology developed by researchers in the pharmaceutical industry to reduce the time and cost associated with producing effective and competitive new drugs. It is technique by which large no. of different but structurally similar molecules are produced rapidly and submitted to pharmacological assay. This reaction uses same reaction conditions with same reaction vessels to produce large number of analogues.

8.3 Drug Discovery:

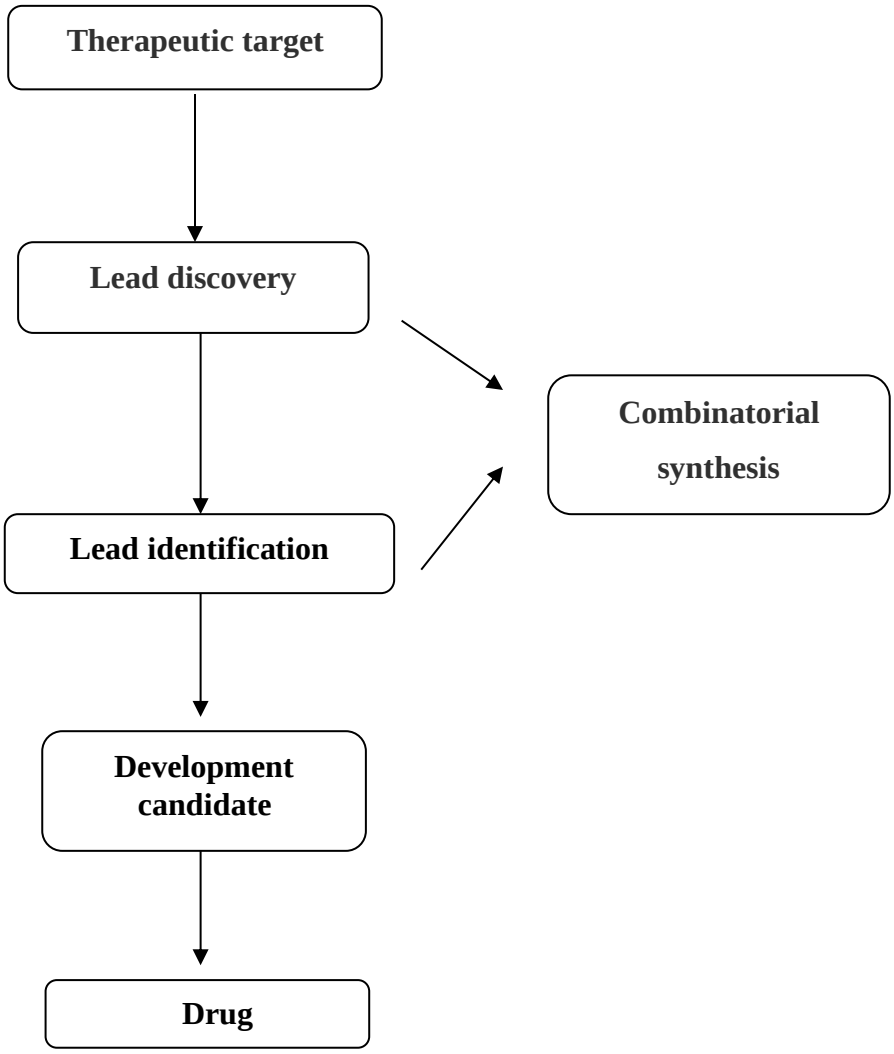

Figure 8.1: Drug Discovery

Strategies:

Conventional synthesis	Combinatorial synthesis
Only one compound can be synthesized at a time.	A range of compounds are synthesized at a time
Requires more time	Requires less time
More expensive	Less expensive
Slower lead generation	Faster lead generation

Role of combinatorial chemistry in drug discovery:

- By producing larger, more diverse compound libraries, companies increase the probability that they will find novel compounds of significant therapeutic and commercial value.
- It provides immobilization strategies which allows high throughput and multiple parallel approaches to drug discovery.

Advantages of combinatorial chemistry:

- Mixed combinatorial synthesis produces chemical pool.
- More opportunities to produce lead compounds.
- From combinatorial chemistry the identification, isolation, purification and synthesis is very easy.
- Combinatorial approach can give million of compounds in same time as it will take to generate one compound by traditional method synthesis.

Techniques used in combinatorial chemistry:

A. Solid phase synthesis.

- Solid support method.
- Parallel synthesis.
  - a. Manual
  - b. Automated
- Mixed combinational synthesis.
- Mixed & split combinatorial synthesis.

B. Solution phase technique.

A. Solid phase synthesis:

In this synthesis, reactant is bound to insoluble resin bead, reagents are added to the solution in excess. The resulting products are isolated by using simple filtration which traps the bead while the excess reagent is washed.

Requirements:

a. Solid support.
b. Protective groups.
c. An anchor or linker.

Parallel synthesis:

It is process which is used to produce a single reaction product is produced in each reaction vessel. Parallel synthesis, individual peptides are synthesized in separate reaction vessels.

Mixed combinatorial synthesis.

- To use a standard synthetic method to produce a large range of different analogues where each reaction vessel or tube contains a mixture of products.
- The identities of the structures in each vessel are not known with certainty.
- By using mixed combinatorial synthesis lead molecule can be identified.
- It involved in the synthesizing large numbers of compounds quickly each mixture is tested for activity as the mixture.
- Inactive mixtures are stored in combinatorial libraries.
- Active mixtures are studied and are used to identify active component.

Mixed and split combinatorial synthesis:

The split –mix combinatorial synthesis is the rapid synthesis of larger libraries of compounds. On each polymer bead type of compound can be prepared. The split and combine approach is one of the classic strategies in combinatorial chemistry.

B. Solution phase technique:

It is the process in which allows reaction to accommodate solid support. It leads to the formation of mixture of product. This helps to find the development of new mixture.

Disadvantages:

- Difficult to remove unwanted material from reaction mixtures.
- Purification step is necessary at each step for each product.
- Other practical problems.

Table 8.2: Difference between solid phase and solution phase technique:

Sr. No	Parameter	Solid phase technique	Solution phase technique
1	Reagent	Excess	Optimum unless purification done.
2	Purification	Easy	Can be difficult.
3	Automation	Easy	Difficult.
4	Reaction	Suitable for new substance.	Suitable any organic reaction.
5	Scale-up	Expensive	Easy and inexpensive.
6	Dependence of reaction development	Mainly on -support -linkers	Time

Computer Aided Drug Design:

Drug design with the help of computer is very useful. It represents the computational methods and resources that are used to facilitate the drug design an discovery of new therapeutic solutions. It may be used at any of the following stages of drug discovery:

- Hit identification using virtual screening (structure- or ligand based design)
- Hit-to-lead optimization of affinity and selectivity (structure-based design, QSAR, etc).
- Lead optimization, optimization of other pharmaceutical properties while maintaining affinity.

8.4 Conclusion:

In the medicinal chemistry, drugs are discovered by screening test of compounds, synthesized in laboratory or obtained from natural sources. Then Studies are conducted to get information on the mechanism of drugs action. QSAR is basically used to study the biological activities of drugs. It is also used to build models which can predict the physical and chemical properties and activities of organic compounds. A computational method give the information about drug structure with physical and biochemical properties of the drug and produces the efficacy of the drug. The computational methods used to model drug chemistry. It allows the observation in three –dimensions of a drug interaction with the protein or drug. Drug interaction with enzymes or receptors which leads to the structural features that are required in discovery and designing of new medicinally active drugs.

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