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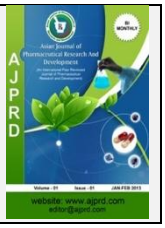

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Review Article

Drug Discovery and its Applications

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A B S T R A C T

The document provides a comprehensive overview of organic and inorganic chemistry, drug design and discovery, and medicinal chemistry. It defines organic and inorganic compounds, highlighting their structural differences and properties. Additionally, it outlines current good laboratory practices (GLP) and regulatory aspects associated with chemical research and development. In the realm of drug design and discovery, the document emphasizes the complex process involved, spanning identification, synthesis, validation, and optimization of potential drug candidates. Various techniques such as computer-aided drug design (CADD), molecular docking, quantitative structure-activity relationship (QSAR), and prediction of absorption, distribution, metabolism, and excretion (ADME) parameters are discussed. The section on medicinal chemistry delves into the interdisciplinary nature of the field, combining aspects of organic chemistry, pharmacology, and biology. It explores the historical development of medicinal agents and the role of regulatory agencies in ensuring drug safety and efficacy. Overall, the document highlights the skills acquired, including the ability to differentiate between organic and inorganic compounds, knowledge of regulatory practices, proficiency in using chemical modelling tools for prediction, and understanding of drug design processes. It provides a holistic understanding of the theoretical foundations, practical applications, and regulatory considerations within these interconnected fields.

Key Word: -Drug Design and Discovery, Computer-Aided Drug Design (CADD), Molecular Docking.

A R T I C L E I N F O: Received 09 Feb 2024 ; Review Complete 13 April ; Accepted. 29 May 2024 ; Available online 15 June. 2024

Cite this article as:
Jadhav SS, Rohane SH, Redasani VK, Drug Discovery and its Applications, Asian Journal of Pharmaceutical Research and Development. 2024; 12(3):176-186 DOI: http://dx.doi.org/10.22270/ajprd.v12i3.1416

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INTRODUCTION

Understanding of Organic and Inorganic Chemistry
Organic and Inorganic compounds

Organic compound, one of a large class of chemical compounds in which one or more carbon atoms are covalently paired with other elements atoms, most commonly hydrogen, oxygen, or nitrogen. Examples of organic compound includes methane (CH_4), ethane (C_2H_6) etc.

Inorganic compound, any substance during which two or additional chemical components (usually aside from carbon) square measure combined, nearly continuously in definite proportions. Examples embrace metal carbonate, carbonate, etc.[1]

Current Good laboratory Practices

The definition of the term "Good Laboratory Practice" itself, that identifies GLP as "a quality system connected with the organisational method and therefore the conditions beneath that non-clinical health and environmental safety studies square measure planned, performed, monitored, recorded, archived and rumoured." will be thought-about as associate example of a quick and correct definition.

GLP is an official regulation that was created by the FDA in 1978. The OECD (Organisation for Economic Co-operation and Development) Principles of Good Laboratory Practice were first created by an Expert Group on GLP set up in 1978 under the Special Programme on the Control of Chemicals.

Introduction of Some Regulatory Aspects

Concerns associated with the effectuality and safety of medicine has caused most governments to develop regulative agencies to supervise development and selling of drug merchandise and medical devices. Use of associate drug carries with it a point of risk of an adverse event. However, there are unfortunate circumstances within which medicine have caused extended hurt. The hurt has return from drug merchandise containing ototoxic impurities, from medicine with unrecognized severe adverse reactions, from adulterate

drug merchandise, and from pretend or counterfeit medicine. as a result of these problems, effective drug regulation is needed to make sure the protection and effectuality of medicine for the overall public.

Drug Design and Discovery

A drug discovery programme initiates as a result of there's a illness or clinical condition while not appropriate medical product out there and it's this unmet clinical would like that is that the underlying driving motivation for the project. Developing a replacement drug from original plan to the launch of a finished product may be a complicated method which might take 12–15 years and value in way over $1 billion.

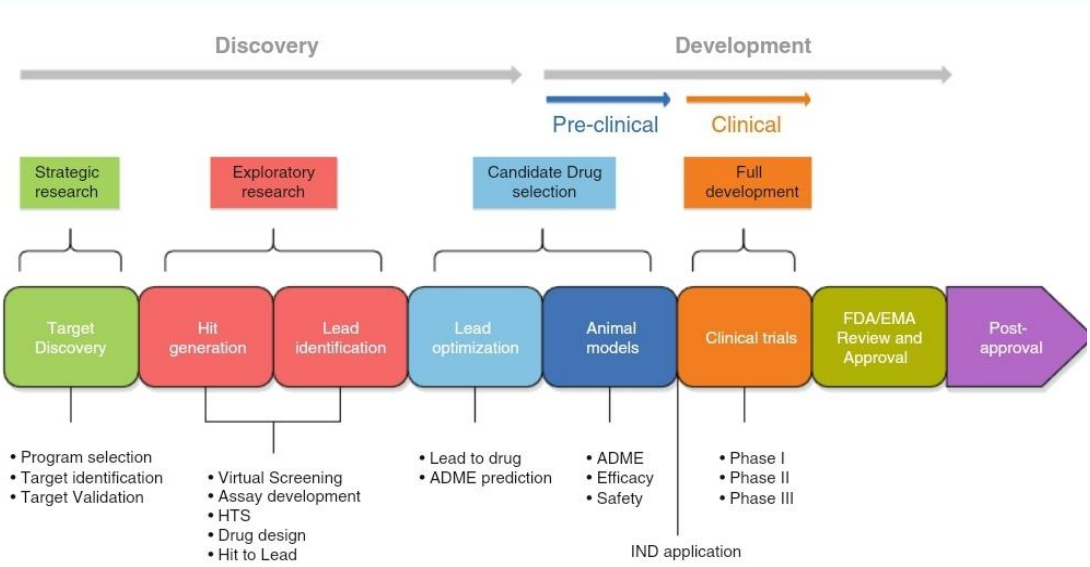


Figure 1: Schematic representation of drug discovery and development process

Computer-aided drug style (CADD) techniques area unit used for the speedy assessment of chemical libraries so as to guide and speed up the early-stage development of recent active compounds. CADD entails an enormous variety of procedure methodologies like virtual screening, virtual library style, lead improvement, Delaware novo style, and then forth.

Molecular arrival has become associate degree progressively vital tool for drug discovery. The molecular arrival approach may be accustomed model the interaction between alittle molecule and a macromolecule at the atomic level, which permit U.S. to characterize the behaviour of tiny molecules within the binding website of target proteins similarly on elucidate elementary organic chemistry processes. The arrival method involves 2 basic steps: prediction of the substance conformation similarly as its position and orientation among these sites (usually cited as pose) and assessment of the binding affinity. These 2 steps area unit associated with sampling strategies and rating schemes, severally.[2]

Chemistry of medicinal agents

Medicinal chemistry is an interdisciplinary field of study combining aspects of organic chemistry, physical chemistry, pharmacology, microbiology, biochemistry, as well as computational chemistry.

Medicinal chemistry is a study that encloses the design, development, and synthesis of pharmaceutical drugs. The discipline combines expertise from chemistry, especially synthetic organic chemistry, pharmacology, and other biological sciences. It is also part of medicinal chemistry the evaluation of the properties of existing drugs. The use of plants, minerals, and animal parts as medicines has been recorded since the most ancient civilizations. With the evolution of the knowledge the means for drug discovery also evolved. New molecules with potential pharmaceutical interest, "hits', are natural products, or compounds generated by computational chemistry, or compounds from a screening of chemical libraries, from combinatorial chemistry, and from pharmaceutical biotechnology. The "hit" compound is improved for its pharmacologic, pharmacodynamics and pharmacokinetic properties by chemical or functional group modifications, transforming it into a lead compound. A lead compound should have a known structure and a known mechanism of action. The lead compound is further optimized to be a drug candidate that is safe to use in human clinical trials.

Medicinal chemistry involves the

- Synthesis of various drug molecules. Discovery of new methods of synthesis for a drug.
- Structure Activity Relationship (SAR) is the relationship between the chemical structure of a molecule and its biological activity. Medicinal chemists use the techniques of chemical synthesis to insert new chemical groups into the biomedical compound and test the modifications for their biological effects.
- Receptor interactionswith the drug.
- ADME study of absorption, distribution, metabolism, and excretion of a drug.

KNOWLEDGE GAINED.

UNDERSTANDING OF ORGANIC AND INORGANIC CHEMISTRY

Organic and Inorganic compounds

Organic compounds are defined as the compounds that contain carbon as one of their constituents whether it be in the solid, gaseous, or liquid state. The organic compounds have various theories where they are described, like structural formulas, space-filled models, and Lewis structures.

Organic compounds are generally identified using the instrument mass spectra.

Inorganic compounds.

An inorganic compound is a chemical compound lacking both carbon-carbon (C-C) and carbon-hydrogen (C-H) covalent bonds. A *chemical compound* is made up of two or more elements that are chemically bonded together.

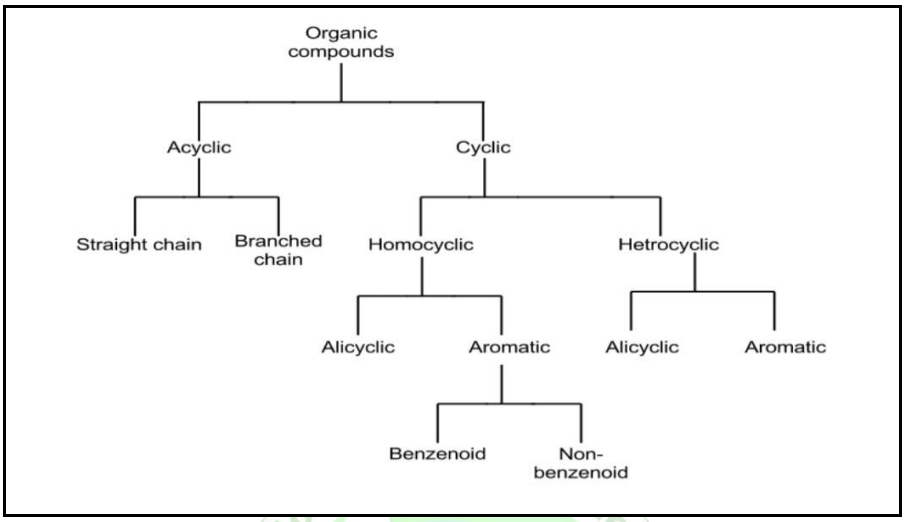


Figure 2: Classification of organic Compounds

Table 1: Difference between organic and inorganic chemistry

Organic Chemistry	Inorganic Chemistry
Organic compound are solid liquids and gases	Inorganic compounds are generally solids
Low melting points & low boiling points	High melting points & high boiling points
Usually decompose on heating	Usually do not decompose on heating
Volatile in nature	Non-Volatile in nature
Inflammable, easily catch fire	Non inflammable, easily catch fire
Do not conduct electricity	Conduct electricity
Slow to react with other chemicals	Often undergo fast chemical reaction
Mostly Colourless compounds	Mostly colourful compounds

Current Good laboratory Practices

GLP embodies a set of principles that provides that provides a framework within which laboratory studies are planned, performed, monitored, and archived and reported. GLP applies to non-clinical studies conducted for the assessment of the safety or efficacy of products in development (including pharmaceuticals) for people, animals, and the environment. GLP, a data and operational quality system, is not the same as standards for laboratory safety – appropriate gloves, glasses and clothing to handle lab materials safely.

Good Laboratory Practice is defined in the OECD 6 principles as "a quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.

Principles of Good laboratory Practices-:

1. Test Facility Organisation and Personnel.
2. Quality Assurance Programme (QAP).
3. Facilities. .
4. Apparatus, Material and Reagents.
5. Test systems.
6. Test and Reference Substances.
7. Standard Operating Procedures (SOP).
8. Performance of the Study.
9. Reporting of Study Results.
10. Storage and Retention of Records and materials.

Introduction of Some Regulatory Aspects

Regulatory authority and organizations are responsible in effective drug regulation required to ensure the safety, efficacy and quality of drugs, as well as the accuracy and appropriateness of the drug information available to the public. Regulatory bodies provide strategic, tactical and operational direction and support for working within regulations to expedite the development and delivery of safe and effective healthcare products to individuals around the world. Every country has its own regulatory agencies which are holding the all the regulatory matters of that country relating to the drug substances.[4]

Major Regulatory Agencies World Wide

Table 2: Different countries and their regulatory authorities

Country	Name of Regulatory Authority
USA	Food and Drug Administration (FDA)
UK	Medicines and Healthcare Products Regulatory Agency (MHRA)
Australia	Therapeutic Goods Administration (TGA)
India	Central Drug Standard Control Organization (CDSCO)
Canada	Health Canada
Europe	European Medicines Agency (EMEA)
Denmark	Danish Medicines Agency
Costa Rica	Ministry of Health
New Zealand	Medsafe - Medicines and Medical Devices Safety Authority
Sweden	Medical Products Agency (MPA)
Netherlands	Medicines Evaluation Board
Ireland	Irish Medicines Board

DRUG DESIGN AND DISCOVERY

Introduction to Drug discovery process

Drug discovery is a multifaceted process, which involves identification of a drug chemical therapeutically useful in treating and management of a disease condition. This process involves the identification of candidates, synthesis, characterization, validation, optimization, screening and assays for therapeutic efficacy. When a molecule avails its satisfactory results in these investigations, it will commence the process of drug development subsequent to clinical trials.

It takes about 12 - 15 years from discovery to the approved medicine and requires an investment of about US $1 billion.

Drug Discovery process proceeds through following five steps

1. Step 1: Discovery and Development
2. Step 2: Preclinical Research
3. Step 3: Clinical Development
4. Step 4: FDA Review
5. Step 5: FDA Post-market Safety Monitoring

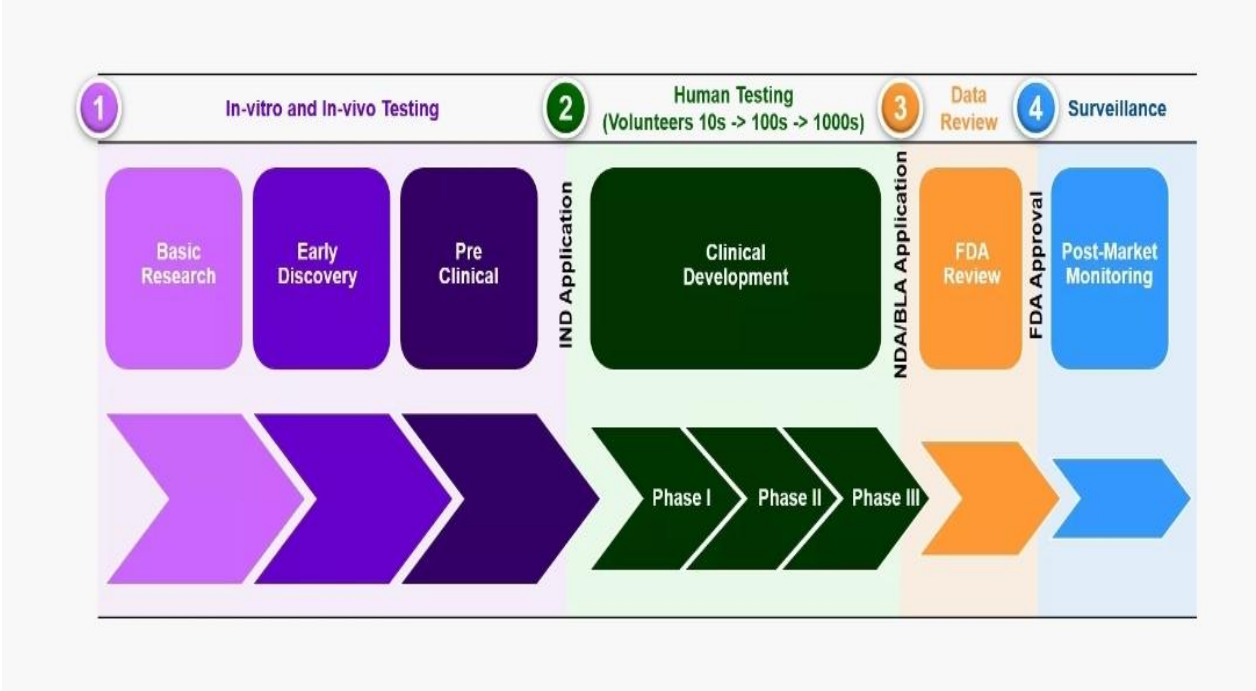


Figure 3: Overview of Drug Discovery Process

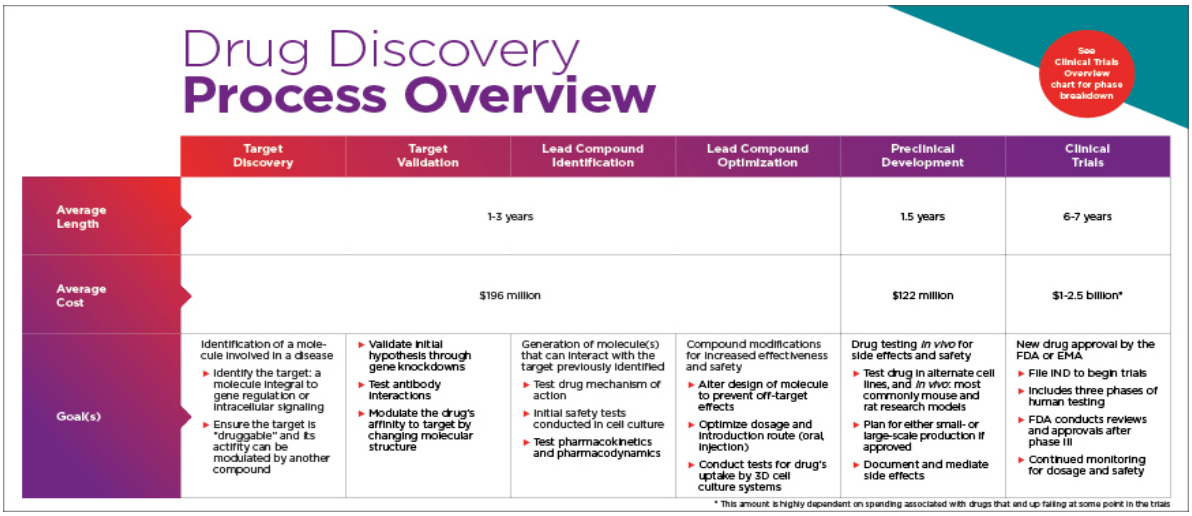


Figure 4: Detailed Drug Discovery Process

Epidemiology of Diarrhoea

Diarrhoea is a leading cause of illness and death among children in developing countries, where an estimated 1.3 thousand million episodes and 4 million deaths occur each year in under-fives. Worldwide, these children experience an average of 3.3 episodes each year, but in some areas the average exceeds nine episodes each year. Where episodes are frequent, young children may spend more than 15% of their days with diarrhoea (Figure 1.1). About 80% of deaths due to diarrhoea occur in the first two years of life. The main cause of death from acute diarrhoea is dehydration, which results from the loss of fluid and electrolytes in diarrhoeal stools. Other important causes of death are dysentery and undernutrition.[5]

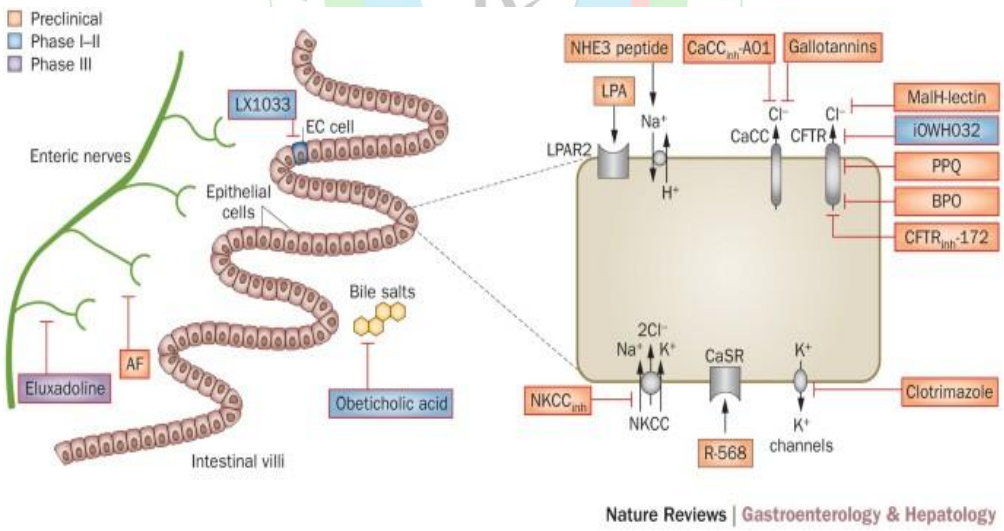
Three Types of Diarrhoea

Acute watery diarrhoea

Dysentery

Persistent diarrhoea

Target sites for Diarrhoea



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Quantitative structure-activity relationship (QSAR)

Quantitative structure-activity relationship (QSAR) is a computational or mathematical modeling method to reveal relationships between biological activities and the structural properties of chemical compounds. The underlying principle is that variations in structural properties cause different biological activities. Structural properties refer to physico-chemical properties, and biological activities correspond to pharmacokinetic properties such as absorption, distribution, metabolism, excretion, and toxicity. QSAR modeling helps prioritize a large number of chemicals in terms of their desired biological activities as an in silico methodology and, as a result, significantly reduces the number of candidate chemicals to be tested with in vivo experiments.

Quantitative structure–activity relationship (QSAR) analysis is a ligand-based drug design method developed more than 50 years ago by Hansch and Fujita (1964). Since the cost of obtaining new hit compounds in HTS platforms is rather high, QSAR modelling has been playing a pivotal role in prioritizing compounds for synthesis and/or biological evaluation. The QSAR models can be used for both hits identification and hit-to-lead optimization. In the latter, a favourable balance between potency, selectivity, and pharmacokinetic and toxicological parameters, which is

required to develop a new, safe, and effective drug, could be achieved through several optimization cycles. As no compound need to be synthesized or tested before computational evaluation, QSAR represents a labor-, time-, and cost-effective method to obtain compounds with desired biological properties. Consequently, QSAR is widely practiced in industries, universities, and research centres around the world.

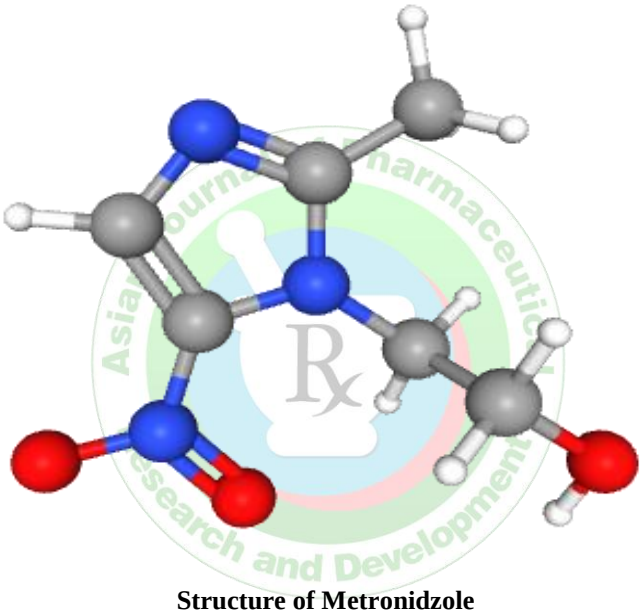
Pharmacophore: -

One of the most promising *in silico* concepts of computer-aided drug design (CADD) is that of the pharmacophore. The term *pharmacophore* was first coined by Paul Ehrlich in the early 1900s, but it was Monty Kier, who introduced the physical chemical concept of pharmacophore in a series of papers published between 1967 and 1971. The pharmacophore technique in modern drug discovery is extremely useful as an interface between the medicinal chemistry and computational chemistry, both in VS and library design for efficient hit discovery, as well as in the optimization of lead compounds to final drug candidates.

Types of pharmacophores

A pharmacophore model can be generated in two ways

1. **Ligand Based Pharmacophore Modelling**: -The LBP is usually carried out by extracting common chemical features from the 3D structures of a known set of ligands representative of fundamental interactions between the ligands and a specific macromolecular target.
2. **Structure- Based Pharmacophore Modelling: -** Structure-based pharmacophore (SBP) modeling is directly dependent on the 3Dstructures of macromolecular targets or macromolecule-ligand complexes. As the number of experimentally determined 3D structure of targets has grown to a very large number, SBP methods have attracted significant interest in the last decade.



Structure of Metronidzole

Molecular Docking

Docking is a method which predicts the preferred orientation of one molecule to a second when a ligand and a target are bound to each other to form a stable complex

Molecular Docking Molecular docking is the study of how two or more molecularstructures (e.g., drug and enzyme or protein) fit together. In a simple definition, docking is a molecular modeling technique that is used to predict how a protein (enzyme) interacts with small molecules (ligands).The method aims to identify correct poses of ligands in the binding pocket of a protein and to predict the affinity between the ligand and the protein.

Steps for Docking:

1. Select the molecule. Take receptor and ligand molecules for studies. Receptor moleculeas staticand ligandmoleculeasflexible.
2. Dockthemolecule.Dockthe ligandmoleculeintoabidingpocketinthereceptor.Generatethelargenumber ofpossibleorientations.
3. EvaluatethemodelEvaluatethemodel/Dockingresultbasedontheenergy.

Types of Docking:

Rigid Docking: In a rigid molecular docking, the molecules are referred toas rigid objects which cannot change their shape during the docking.

Flexible Docking: In a flexible docking, where molecules are referred to as flexible objects and they can change their shapes according to the ligand and target during docking process.

Docking of Metronidazole On Oxygen-insensitive NADPH nitroreductase using online platform mcule :

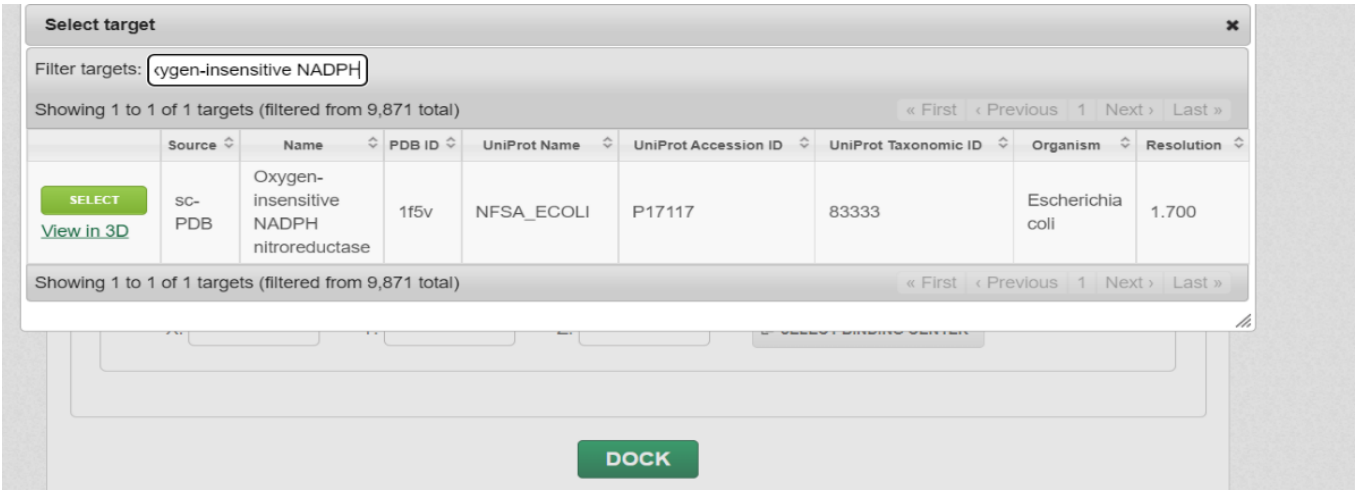


Figure 6: Target Selection

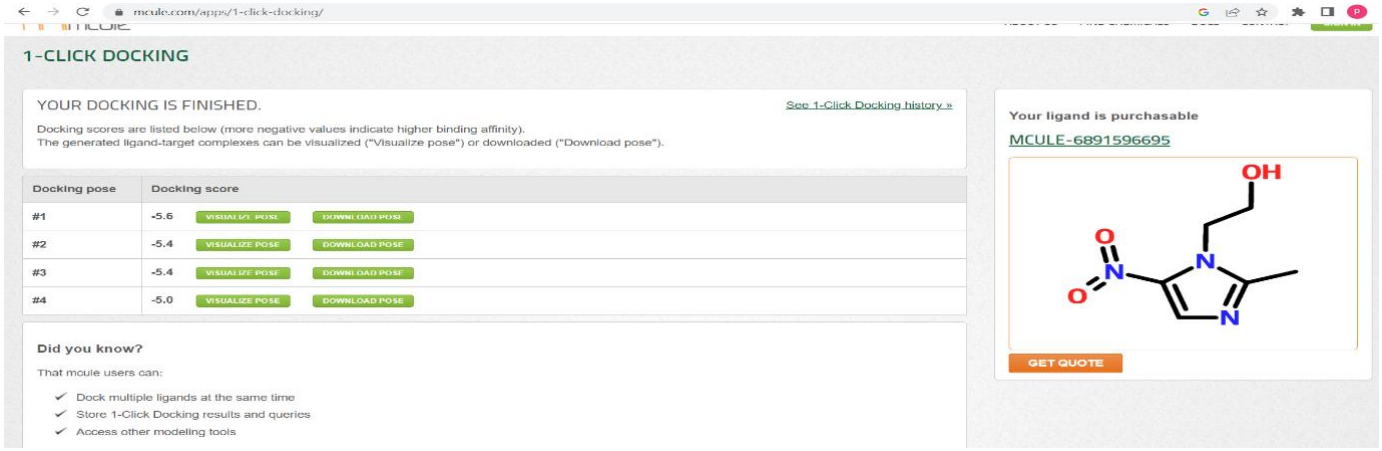


Figure 7: Docking Score

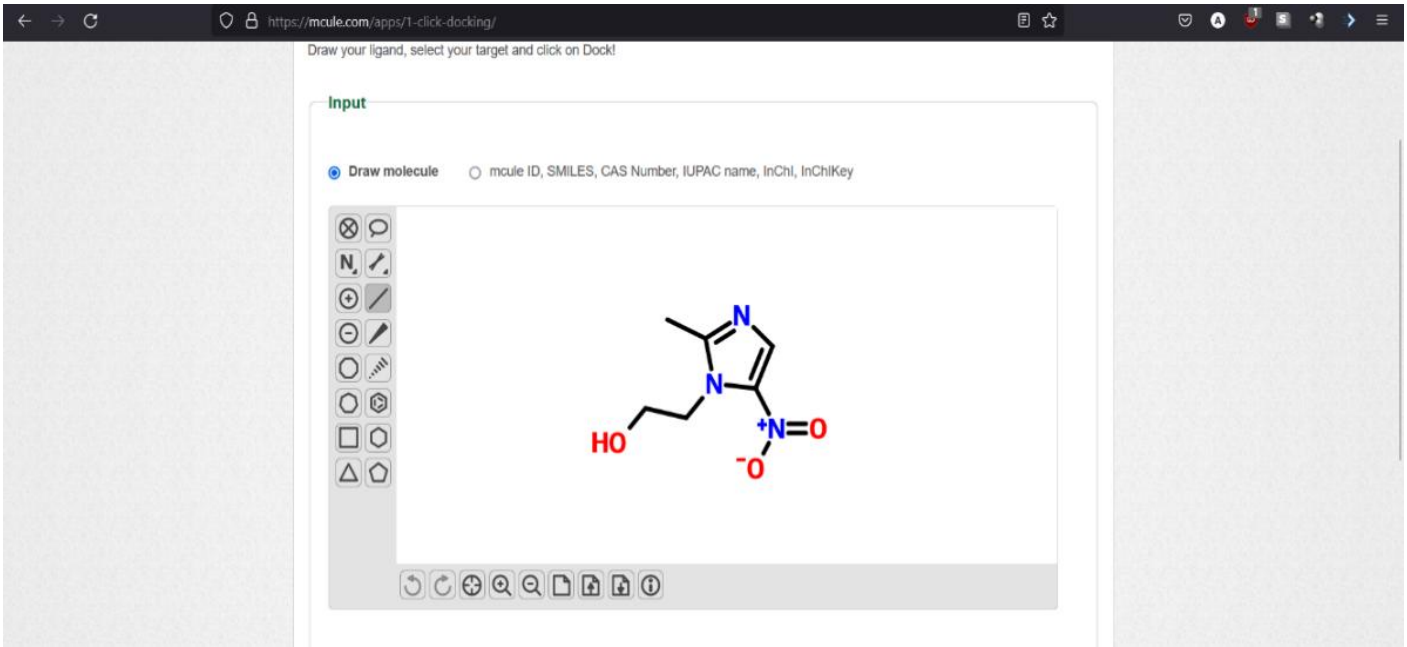


Figure 8: Docking of Metronidazole

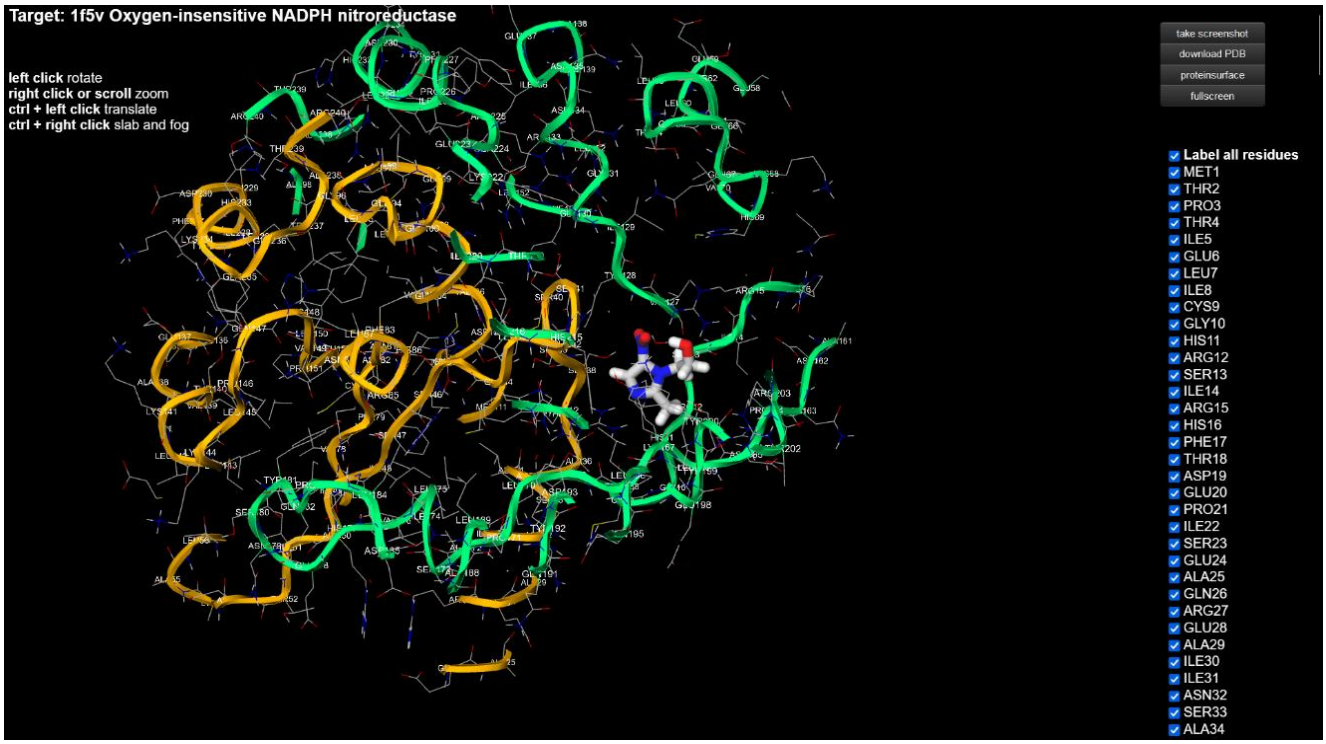


Figure 9: Result of Docking

PREDICTION OF ADME OF METRONIDAZOLE BY USING SWISSADME:

In drug discovery and development, researchers must examine the activity of a drug in the body to assess safety and toxicity. Drug metabolism and pharmacokinetics studies, such as ADME and toxicology studies, are a critical step in this process. The data collected tells researchers if a drug is viable and provides specific targets for future research and development. The Pharmacokinetic parameters, drug likeness and toxicity of a molecule can be studied using Free or paid online software's such as SwissAdme, Preadmet, etc.[8]

Absorption

Absorption describes how a chemical enters the body. Absorption relates to the movement of a chemical from the administration site to the bloodstream.

Distribution

Once a drug has been absorbed, it moves from the absorption site to tissues around the body. This distribution from one part of the body to another is typically accomplished via the bloodstream, but it can also occur from cell-to-cell.

Metabolism

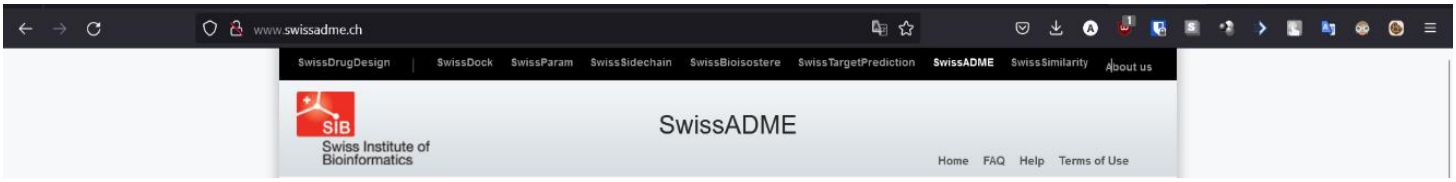
Drug metabolism is the biotransformation of a drug by organs or tissues (primarily the liver, kidney, skin or digestive tract) so that the drug can be excreted. To facilitate removal via faces or urine, the drug compound is altered to become more water-soluble.

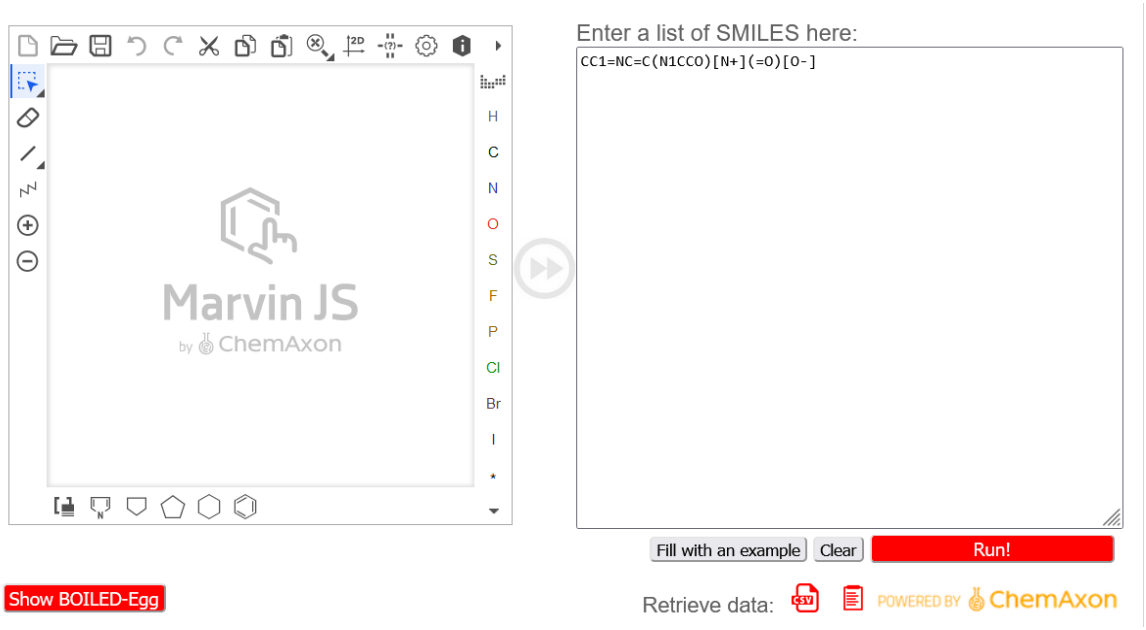
Excretion

Excretion is the process by which the metabolized drug compound is eliminated from the body. Researchers want to know how rapidly the drug is excreted and what pathway it takes to exit the body. Most drug excretion occurs as urine.

Steps for Prediction of ADME parameters using Swiss ADME tool are as below: -

1. Go to the Swiss ADME webpage by simply searching as Swiss ADME on Google.
2. Enter SMILES of the compound (Metronidazole) and press RUN.





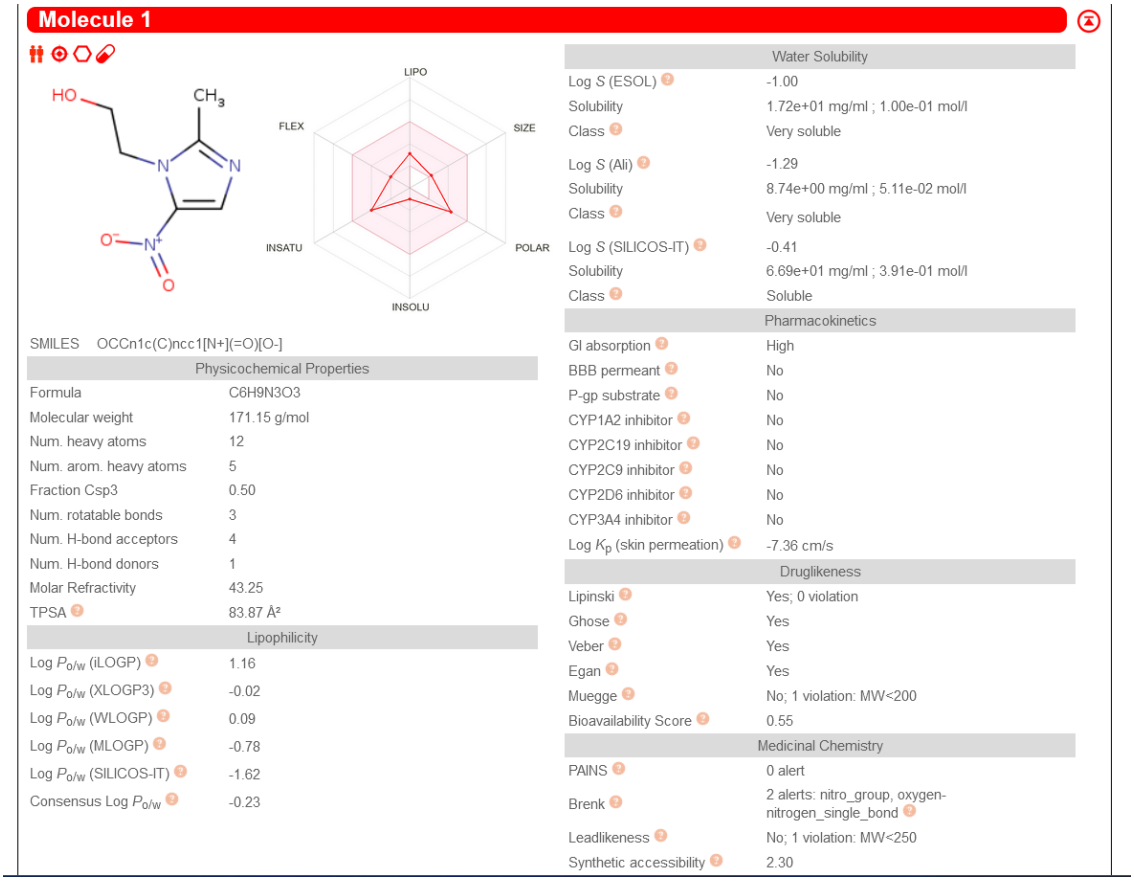


Figure 10: SwissADME of Metronidazole

- **Lipophilicity:** -The partition coefficient between *n*-octanol and water (log $P_{o/w}$) is the classical descriptor for Lipophilicity. It has a dedicated section in SwissADME due to the critical importance of this physicochemical property for pharmacokinetics drug discovery.
- **Water Solubility:** -Having a soluble molecule greatly facilitates many drug development activities, primarily the ease of handling and formulation.
- **Pharmacokinetics:** -Specialized models, whose predictions are compiled in the Pharmacokinetics section, evaluate individual ADME behaviours of the molecule under investigation.
- **Drug-likeness:** - As defined earlier, "drug-likeness" assesses qualitatively the chance for a molecule to become an oral drug with respect to bioavailability.
- **Medicinal Chemistry:** - The purpose of this section is to support medicinal chemists in their daily drug discovery

endeavours. Two complementary pattern recognition methods allow for identification of potentially problematic fragments.

INTRODUCTION TO MEDICINAL CHEMISTRY

Introduction to Medicinal Chemistry

Medicinal chemistry is concerned with the discovery, design, synthesis, and interactions of a pharmaceutical agent (drug) with the body. Medicinal chemistry was defined by IUPAC specified commission as "it concerns the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds at the molecular level.

Medicinal chemistry is mainly concerned with small organic molecules both natural and synthetic. Compounds in clinical use are primarily small organic compounds. Organometallic compounds, biopharmaceuticals, and inorganic compounds are also used in medicine as therapeutics.

In particular, medicinal chemistry in its most common practice—focusing on small organic molecules—encompasses synthetic organic chemistry and aspects of natural products and computational chemistry in close combination with chemical biology, enzymology and structural biology, together aiming at the discovery and development of new therapeutic agents.

Practically speaking, it involves chemical aspects of identification, and then systematic, thorough synthetic alteration of new chemical entities to make them suitable for therapeutic use.

It covers the synthetic and computational aspects of the study of drugs and agents currently in development in relation to their biological activity (biological activities and properties), i.e. understand their structure-activity relationship (SAR).[11]

An Overview of Medicinal Chemistry

Medicinal chemistry is an interdisciplinary field of study combining aspects of organic chemistry, physical chemistry, pharmacology, microbiology, biochemistry, as well as computational chemistry.

Medicinal chemistry is concerned with the discovery, design, synthesis, and interactions of a pharmaceutical agent (drug) with the body.

Medicinal chemistry is mainly concerned with small organic molecules both natural and synthetic. Compounds in clinical use are primarily small organic compounds. Organometallic compounds, biopharmaceuticals, and inorganic compounds are also used in medicine as therapeutics.

History and development of medicinal agents:

- **3500 BC-** Sumerians reported use of opium
- **3000 BC-** Chinese reported use of ephedra (Ma Huang)
- **1793 –** Faureroy and Vauquehin established the Ecole Supurieure de Pharmaciei.e. first incorporate chemistry into pharmacy curriculum.
- **1803 –** Derosome isolated a salt from opium
- **1817-** Serturner demonstrated the alkaline nature of opium
- **1818 –** Meissner proposed the term alkaloids
- **1820 –** Isolation of morphine, quinine and atropine
- **1842 -** onward general anaesthetics were introduced, antiseptics like iodine and phenol were used in surgery
- **1853 –** Hennery proposed the relationship between the functional groups, modifiers and their reactivities.
- **1875 –** Carl buss isolated salicylic acid from spirea ulmaria.
- **1884 -** Phenazone was synthesize, local anaesthetic action of cocaine was reported
- **1890 –** Hoffmann named acetyl salicylic acid as aspirin.
- **1892 –** Benzocaine was obtained by structural modification of cocaine
- **1894 –** Ehrlichreported lock and key theory
- **1899- 1901 -** Meyer and Overton related distribution coefficient with biological activity
- **1910 –** Barger and Dale examined the response of various tissues to muscarine
- **1911 –** Barbiturates were introduced as sedative
- **1920- 1930 –** Identification of Vitamin deficiency diseases and elucidation of structure of vitamins.
- **1930 –** Structure of steroidal hormones.
- **1926- 1946 –** Synthetic antimalarial like chloroquine were introduced as a substitute of quinine
- **1935–**Domagk observed antimicrobial effect of sulphonamide dye stuff
- **1940 –** Florey and Heaton isolated benzyl penicillin.
- **1944 – 1949 –** Isolation of antibiotics e.g. streptomycin, chloramphenicol and tetracycline's
- **1950–1960 –** Semi synthetic corticosteroids like prednisolone and betamethasone were prepared.

Skills Acquired

- We acquired the skill required for the handling of chemical substance.
- We acquired skill about how to differentiate organic and inorganic compounds.
- We understood about regulatory aspects in pharmaceuticals. Pharmaceutical regulations can be defined as the combination of legal, administrative and technical measures that governments take to ensure the safety, efficacy and quality of medicines as well as the relevance and accuracy of product information.
- We have overviewed the different regulatory bodies of different countries such as USA [FDA], India [CDSCO], Canada [Health Canada] etc.
- We get to know about the current good laboratory practice and how to follow CGLP while practice.

- We acquired skill about how to draw chemical structure using different online tools [Chem Sketch].
- We learned about prediction of ADME parameters of drug molecule by using different online platforms such as Swiss ADME, PreAdmet etc.Swiss ADME website allows you to compute physicochemical descriptors as well as to predict
- ADME parameters, pharmacokinetic properties, drug like nature and medicinal chemistry friendliness of one or multiple small molecules to support drug discovery.
- We understood about the procedure for performing docking of molecule with the target protein with the help of mcule platform.
- We have also learned about the in perpetration of results of docking. Molecular techniques that are used to model a molecule modelling includes computational.
- We understood about green chemistry and its aspects.
- We learned about the medicinal chemistry is concerned with the discovery, design and interaction of pharmaceutical agent.

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