ISBN: 978-81-970675-0-1

4. Medicinal Chemistry

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4.1 Definition:

The scientific field of medicinal or pharmaceutical chemistry, situated at the junction of chemistry and pharmacy, contributes to the creation and advancement of pharmaceutical medications.

4.1.1 Introduction:

Organic chemistry, biochemistry, computational chemistry, pharmacology, molecular biology, statistics, and physical chemistry are all combined in the extremely interdisciplinary field of medicinal chemistry. It includes the finding, development, and interpretation of the biologically active substances' mechanisms of action at the molecular level.

One way to think of medicinal chemistry is as the synthesis of molecular pharmacology and synthetic chemistry with an emphasis on the study of surface area ratiometry (SAR) of therapeutic compounds.

Using improved methods and a broader understanding of various associated sciences, medicinal chemistry remains a key component of drug research and development. The majority of compounds used as medications are organic compounds, which are typically classified into two broad classes:

"biologics" (infliximab, erythropoietin, insulin glargine), which are essentially medicinal preparations of proteins (natural and recombinant antibodies, hormones etc.), and small organic molecules (atorvastatin, fluticasone, clopidogrel etc.).

As metallodrugs, inorganic and organometallic chemicals (such as platinum, lithium, and gallium-based agents like cisplatin, lithium carbonate, and gallium nitrate, respectively) can also be classified as medicines. The research and treatment of diseases and illnesses linked to inorganic metals in biological systems is the focus of the field of medicinal inorganic chemistry, which looks at the function of metals in medicine (metallotherapeutics).

Numerous metallotherapeutics have been licensed for the treatment of various conditions, including diabetes (e.g., V and Cr), bipolar disorder (e.g., Li), cancer (e.g., include Pt, Ru, Gd, Ti, Ge, V, and Ga), and antimicrobials (e.g., Ag, Cu, and Ru). Other fields of research include radiopharmaceuticals (e.g., ^{186}Re for treatments, ^{99m}Tc for diagnostics), genomics, proteomics, and diagnostic agents (e.g., MRI: Gd, Mn; X-ray: Ba, I).

4.2 History:

Plants have long been utilized as medicine for a variety of disorders. They are mentioned in the chronicles of the ancient civilizations of China, Egypt, India, and Babylon.The medicinal qualities of plants were explained by the Written by the Romans and the ancient Greeks, they are documented in the works of Galenus and Hippocrates. During that period, some metals and metal salts were also utilized.

Various "Materia Medica" and pharmacopeia collected traditional uses of plants during the Middle Ages. The herbals written by Nicolas Culpeper (1649), John Parkinson (1640), and John Gerard (1596) offer some insight. into this popular application of herbs. Many practical tropical plants were added as a result of exploration in the seventeenth and eighteenth century.

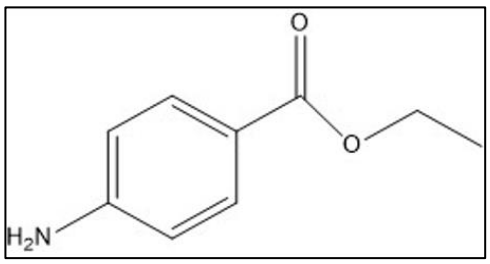
In surgery, general anaesthetics such as diethyl ether (1842), nitrous oxide (1845), and chloroform (1847) were first used in 1842.Additionally, antiseptics like phenol (1860) and iodine (1839) created a significant role in the surgical procedure's success. It was also stated that chloral (trichloroethanal) (1869) has hypnotic properties.

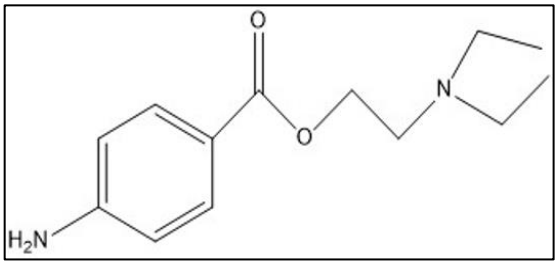
While herbalists were aware of the usage of willow bark as a pain reliever, it wasn't until the 1870s that salicylic acid, a component of the bark, was shown to have analgesic properties.

Paracetamol, or p-hydroxyacetanilide, and moreover, phenacetin (1886) was acknowledged as a pain reliever. In an effort to lessen the harmful effects of salicylic acid on the stomach, aspirin was first introduced in 1899 by acetylation. But its manner of operation wasn't determined until 1971. Cocaine's local anaesthetic effect was first documented in 1884, despite the fact that its structure was unknown at the time. Benzocaine (1892) and procaine (1905) were discovered as a result of several alterations made to cocaine.

The earliest hypotheses regarding the connections between chemical structure and biological activity started to take shape in the middle of the 1800s.

Due to the observation made by Crum-Brown and Fraser (1869) that there is a "relationship between the physiological action of a substance and its chemical composition," it is possible for cells to react to signals from certain molecules.

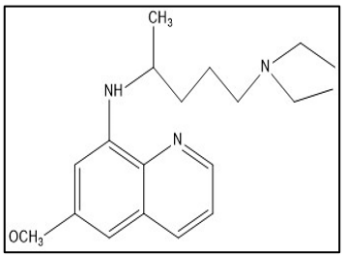


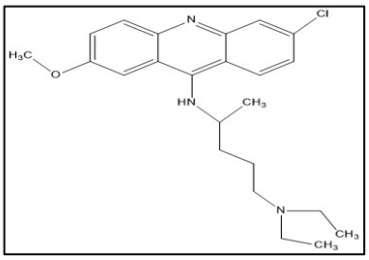


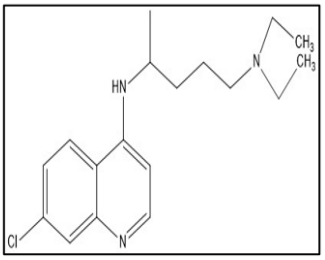
Benzocaine **Procaine**

Ehrlich proposed in the 1890s that physiologically active substances had unique receptors and that there were "lock and key" interactions between them. The 20th century witnessed the identification of diseases caused by vitamin deficiencies and the clarification of the composition of several vitamins.

As a result, quinine was replaced with synthetic antimalarials such pamaquine (1926), mepacrine (1932), and later chloroquine.







Pamaquine **Mepacrine** **Chloroquine**

Throughout the 1960s, there were several advancements in the structures of different vitamins, which altered pharmaceutical chemistry.

It was shown that pregnant women who took the sedative thalidomide were more likely to give birth to infants with birth defects (S isomer).

Due to the teratogenic effect, there was a significant tightening of the requirements pertaining to medication safety and registration. Second, Hansch established correlations in 1964 between the biological activity of various aromatic hydrocarbons and substituent effects (Hammett parameters).

These QSAR started to offer a framework for choices to be made when organizing a research program and for the methodical creation of medications.

4.3 How Come Medicinal Chemistry is Necessary?

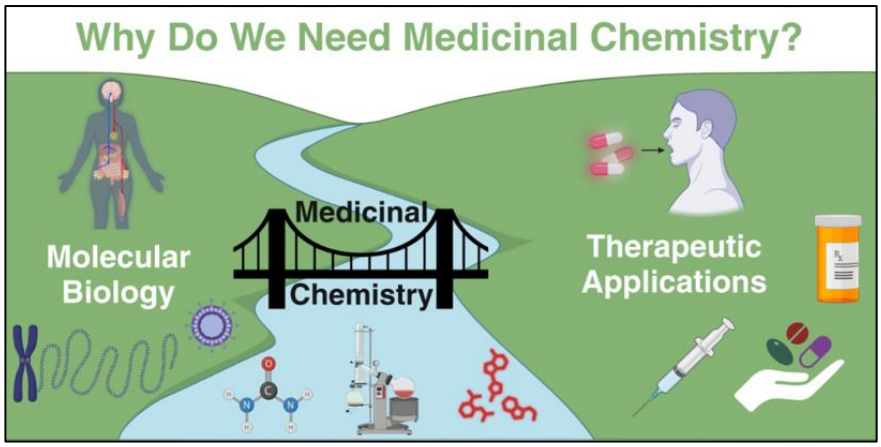


Figure 4.1: Need Medicinal Chemistry

- To know drug ADME and the physico-chemical characteristics of drug compounds.
- To know the pharmacological and therapeutic bases in chemistry.
- To know the basic pharmacophores for medications used in medical therapy.
- To know the relationships between structure and activity along with drug-target interactions.
- To know drug metabolism's chemical pathways.
- Use in deciding on medication therapy decisions.

4.4 Key Elements of Medicinal Chemistry:

A. Drug Discovery:

- Discovering and evaluating novel therapeutic targets, creating and manufacturing lead compounds, and refining their composition and characteristics.

B. Drug Development:

- Evaluating the safety and effectiveness of medication candidates through preclinical and clinical research, as well as creating formulations for administration

C. Drug Optimization:

- Medicinal molecules' structure and characteristics can be changed to enhance their safety profile, pharmacokinetic characteristics, potency, and selectivity.

D. Mechanism of Action Studies:

- Researching the molecular processes by which medications interact with biological targets and provide therapeutic results.

E. Drug Metabolism and Pharmacokinetics:

- Pharmacokinetic qualities—the study of how medications are transported, metabolized, excreted, and absorbed in the body—and improving these properties.

F. Analytical Chemistry:

- Creating and utilizing analytical methods for the purpose of characterizing and measuring medications and their metabolites.

G. Computer-Aided Drug Design:

- Designing, optimizing, and forecasting the interactions of pharmacological compounds with biological targets through the use of computational techniques and software.

H. Toxicology and Safety:

- Evaluating the safety profile of medication candidates by conducting thorough in vitro and in vivo testing for any possible harmful effects on different organs and systems.

4.5 Role of Structure Activity Relationship (SAR) in Medicinal Chemistry:

A key idea in medicinal chemistry is the structural-activity relationship (SAR), which investigates the connection between a drug's molecular structure and biological action.

SAR research offers important insights into the molecular causes of medication toxicity and efficacy.

A. Lead Optimization:

- Medicinal chemists can enhance the potency, selectivity, and pharmacokinetic feature s of lead compounds by optimizing their structure with the aid of SAR studies.
- Chemists can make specific changes to a drug molecule to improve its therapeutic pot ential and uncover important structural elements that contribute to its biological activit y by analyzing its surface area ratio (SAR).

B. Target Identification:

- Since SAR investigations show the molecular interactions between a medicine and its target, they can also help with target identification. Medicinal chemists can determine possible binding sites and infer structural requirements for binding to the target by analyzing the surface rheology (SAR) of a series of drugs.

C. Predicting Biological Activity:

- Based on their structural resemblance to existing active chemicals, SAR models can be used to predict the biological activity of novel drug candidates. By using this information, fewer rigorous experimental tests may be required to determine which chemicals should be evaluated further.

D. Mechanism of Action Studies:

- Studies using synthetic aperture radiation (SAR) can shed light on how medications work. Medicinal chemists can determine which structural elements are necessary for a specific mode of action by analyzing the SAR of several molecules.

E. Specific Activities:

- Creating and evaluating a number of compounds with different structural characteristics in order to carry out SAR research.
- Finding structural motifs that correlate with higher or lower activity by analyzing the data on biological activity.
- Creating SAR models to forecast novel compound activity through statistical and computational techniques.
- Creating novel medication candidates with enhanced qualities by utilizing SAR data.

Taking everything considered, SAR research is essential to medicinal chemistry because it offers a methodical way to comprehend how drug structure and biological activity are related. Medicinal chemists can create and improve medications with higher efficacy, safety, and selectivity thanks to this information.

4.6 Medicinal Chemistry in Drug Development:

Medicinal chemistry is a fundamental component of drug discovery, which is the process of discovering and developing novel drugs to treat a wide variety of illnesses. Medicinal chemists create, synthesis, and assess novel drug candidates using their expertise in chemistry, biology, and pharmacology.

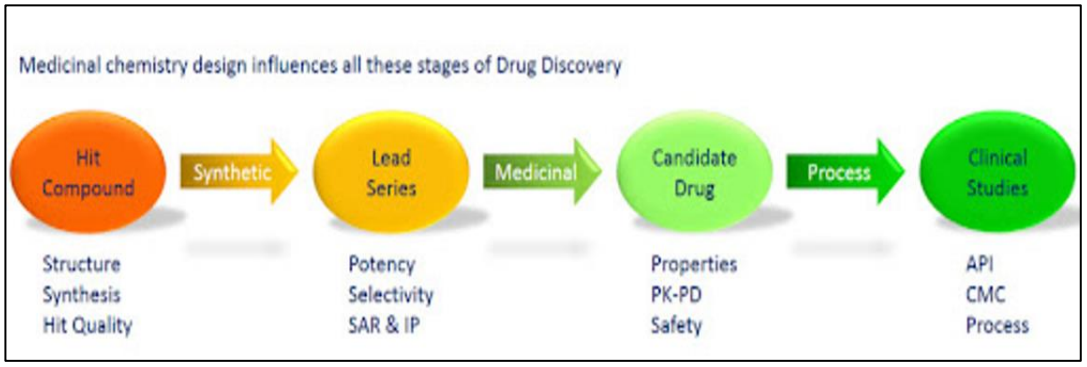


Figure 4.1: Medicinal Chemistry Design Influences All These Stages of Drug Discovery

A. Target Identification and Validation:

- Pharmacologists and biologists work along with medicinal chemists to discover and verify novel therapeutic targets, which are chemicals or pathways implicated in the pathophysiology of disease.

B. Lead Generation:

- Small compounds with the ability to interact and regulate the indicated therapeutic targets are designed and synthesized by medicinal chemists. Lead compounds are the name assigned to these substances.

C. Lead Optimization:

- To increase the lead compounds' potency, selectivity, and pharmacokinetic (i.e., absorption, distribution, metabolism, and excretion) qualities, medicinal chemists modify their structure and characteristics.

D. Drug Synthesis and Characterization:

- Synthetic techniques are created by medicinal chemists to generate the best possible medication candidates in greater quantities. They also describe the medications' solubility, stability, and purity, among other physicochemical characteristics.

E. Preclinical Development:

- Preclinical research is carried out by medicinal chemists collaborating with biologists and pharmacologists to assess the safety and effectiveness of potential drugs in animal models.

F. Specific Activities:

- Developing and creating new chemical entities (NCEs) in accordance with knowledge of pharmacological targets and disease mechanisms.
- Screening NCEs for biological activity against specific targets using in vitro and in vivo assays.
- NCEs can have their structures modified to enhance their pharmacokinetic, potent, and selective qualities.
- Developing structure-activity relationships (SARs) to understand the relationship between molecular structure and biological activity.
- Working along with biologists, pharmacologists, and toxicologists to assess the safety and effectiveness of potential medications.

All things considered, medicinal chemistry plays a critical role in the discovery and development of novel medications that are efficacious in treating a variety of illnesses.

4.7 Applications of Medicinal Chemistry:

A. Drug Discovery and Development:

- Determining and evaluating novel therapeutic targets for a broad spectrum of ailments
- Improving drug delivery methods to reduce adverse effects and increase bioavailability.
- Identifying and validating new drug targets for a wide range of diseases.
- Improving drug delivery methods to reduce negative effects and increase bioavailability.

B. Preclinical Development:

- Evaluating the safety and effectiveness of novel therapeutic candidates through in vivo and in vitro research.
- Determining the pharmacokinetic and pharmacodynamic properties of drugs.
- Recognizing possible side effects and pharmacological interactions.

C. Clinical Trials:

- Developing and carrying out clinical studies to assess new medications' effectiveness and safety in people.
- Analysing side effects in patients and gathering information on the effectiveness of medications.

D. D. Drug Metabolism and Pharmacokinetics:

- Investigating the body's processes for medication absorption, distribution, metabolism, and excretion.
- Maximizing medication dosage schedules to produce the intended therapeutic outcomes.

E. Drug Formulation and Delivery:

- Designing medication formulations with increased bioavailability, solubility, and stability.
- Developing medication delivery systems with a focus on particular cells or tissues.
- Formulating drugs in controlled-release forms to prolong their effects.

F. Quality Control and Assurance:

- Establishing analytical techniques to guarantee the potency, purity, and identification of medicinal products.
- Implementing into effect quality control measures to guarantee pharmaceutical products' effectiveness and safety.

G. Regulatory Affairs:

- Setting up regulatory filings to get new medications and medicinal goods approved.
- Consulting with regulatory organizations to guarantee adherence to safety and efficacy requirements.

H. Biotechnology:

- Development and production of biomolecules for use in medicine, such as proteins, peptides, and nucleic acids.
- Generating RNA-based medicines and gene treatments to treat cancer and hereditary illnesses.
- Developing bioconjugates for improved drug delivery by combining therapeutic compounds with ligands that target specific targets.

I. Agriculture:

- Producing insecticides and herbicides to minimize their negative effects on the environment while controlling pests and weeds.
- Creating animal health products to cure and prevent illnesses in pets and livestock.
- Developing crop protection chemicals to increase yield and disease resistance.

J. Cosmetics and Personal Care:

- Designing skincare products that enhance appearance, health, and aging of the skin.
- Developing hair care products that improve the look and quality of hair.
- Creating perfumes and additional personal hygiene items

K. Environmental Science:

- Creating bioremediation plans to break down environmental pollutants.
- Producing adsorbents and catalysts to remove toxins from air and water.
- Developing sensors to identify and track environmental threats.

L. Forensic Science:

- Developing methods for DNA fingerprinting and other forensic applications.
- Analyzing explosives and other hazardous materials.
- Assessing and recognizing drugs in biological samples for legal purposes.

M. Chemical Education: Students are taught about drug design, molecular interactions, and chemical synthesis procedures through the integration of medicinal chemistry ideas into their educational curricula.

N. Other Applications:

- Creating synthetic vaccinations to prevent infectious diseases.
- Investigating the application of concepts from medicinal chemistry to disciplines like tissue engineering and nanotechnology.
- Developing pharmaceuticals for animal use.
- Creating novel materials for medical equipment and implants.

4.8 Several Exciting Trends and New Fields are Anticipated to Influence Medicinal Chemistry in The Future:

A. Precision Medicine: The field of medicinal chemistry is heading toward customized treatments that take into account each patient's unique genetic, molecular, and lifestyle characteristics. The goal of this strategy is to minimize side effects while optimizing therapeutic efficacy.

B. Targeted Drug Delivery: Drug potency and side effects can be decreased and medications can be precisely targeted to particular tissues or cells due to advancements in drug delivery technologies. Researchers in medicinal chemistry are creating new delivery systems such hydrogels, liposomes, and nanoparticles.

C. Biological Therapeutics: The field of medicinal chemistry is broadening to encompass biological treatments including peptides, proteins, antibodies, and nucleic acids, in addition to small molecule medications. These biologics present new opportunities for highly effective and selective disease treatment.

D. Computational Drug Design: Medicinal chemists are able to speed up drug discovery by predicting drug-target interactions, improving molecular structures, and screening virtual compound libraries due to the growing capabilities of artificial intelligence and computational approaches.

E. Fragment-Based Drug Discovery: In drug development, fragment-based strategies screen small, low molecular weight molecules to find fragments that attach to a target. Then, using medicinal chemistry, these fragments are optimized to create lead molecules, which provides a more successful and economical method of drug development.

F. Natural Product Drug Discovery: Medicinal chemists are investigating novel approaches such as synthetic biology, genome mining, and metabolomics to find and optimize medications derived from natural products. Natural products remain a rich source of therapeutic leads.

G. Multi-Target Drug Design: Numerous targets and intricate molecular pathways are involved in many illnesses. Drugs that can modulate several targets at once are being

created by medicinal chemists, which should improve therapeutic outcomes and lower drug resistance.

H. **Drug Repurposing and Combination Therapies:** Medicinal chemists are creating combination medicines to increase efficacy and overcome resistance in a variety of disorders, as well as investigating novel uses for already-approved medications through drug repurposing.
I. **Nanomedicine:** Developing drug delivery methods with improved efficacy and fewer adverse effects that can target particular cells or regions. Creating nanomaterials for biosensing, regenerative medicine, and diagnostic imaging.
J. **Bioconjugation:** Creating bioconjugates that combine therapeutic compounds with ligands that target specific disease cells in order to deliver medication.
K. **Natural Product Discovery:** Investigating the natural world for new therapeutic candidates and bioactive substances by looking into plants, marine life, and microorganisms. Creating methods for the extraction, purification, and characterization of natural compounds having possible medical uses.
L. **Immunotherapy:** Creating and manufacturing immunomodulatory medications that strengthen the immune system's defenses against illnesses like cancer. Creating drug-antibody combinations that specifically target cancer cell antigens.
M. **Sustainability and Green Chemistry:** Reducing the influence on the environment by using sustainable approaches in medication development and discovery. Creating ecologically friendly synthetic processes and synthesizing drugs with renewable materials.

In general, innovation, the fusion of multidisciplinary methods, and an emphasis on precision and customized medicine to address the increasing complexity of human health and disease will characterize the future of medicinal chemistry.