CHAPTER

INTRODUCTION TO MEDICINAL CHEMISTRY

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1.1 INTRODUCTION

Medicinal Chemistry is a science discipline, at the intersection of Chemistry and Pharmacy involved with designing, synthesizing and developing pharmaceutical drugs. It is a multidisciplinary subject involving Organic Chemistry, Biochemistry, Physiology, Microbiology, Pharmacology, Toxicology, Genetics and Computer modeling. It explains the design and production of compounds, which can be used for prevention and treatment of human or animal diseases. It also includes the study of existing drugs, their biological properties and Quantitative Structure Activity Relationship (QSAR).

The earliest drug discoveries were made by random sampling of higher plants. Many of the drugs in use, in the last fifty years or more have been of synthetic or semi-synthetic origin, prior to that period were of natural origin. The folklore medicines have found their root in the daily life of individuals. Beginning with AD 1800 there was a continuous activity in this area and many of the well known medicinal plants were analyzed and their active principle characterized. In the latter part of the 19^{th} century, biologically-active organic molecules began to be isolated in relatively pure form for medicinal use. For example, Salicyclic acid from willow bark, Morphine and Codeine from the opium poppy, Ephedrine from the Chinese herb Ma Huang, anti-malarial agent Quinine from cinchona bark, leaves of the purple foxglove plant provided an excellent source of Digitoxin etc.,

Although synthesis of the first synthetic drug, Aspirin, occurred in the latter half of the 19^{th} century, it was not until the early 1900s that the recognition of Aspirin as an universal pain reliever was realized and this discovery spawned the era of therapeutic agents. The chemical knowledge of isolated compounds gave a way for many synthetic substances.

In 1930s and 1940s, synthetic sulfa drugs, the natural antibiotic penicillin from *Penicillium notatum*, the semi-synthetic antibiotic Tetracycline, produced from *Streptomyces aureofaciens* and the anti-tubercular aminoglycoside Streptomycin, from *Streptomyces griseus*, were all landmark discoveries.

Hundreds and thousands of new organic compounds are prepared annually throughout the world and many of them are entered into pharmacological screens to determine whether they have useful biological activity or not. This process of random screening has been considered inefficient, but it has resulted in the identification of new "lead compounds" whose structure has been optimized to produce clinical agents. During the next several decades advances in spectroscopy (NMR, Mass), X-ray crystallography, electrophoresis, ultracentrifugation, HPLC, PTLC, LCMS and other technologies contributed to the discovery of additional chemical entities with therapeutic activities and to the development of some vaccines. Selected examples include tranquilizers, oral contraceptives and poliomyelitis vaccines.

The seeds for the concept of rational drug design were laid in 1940s and 1950s by G.Hitchings and G.Elion in their work on DNA-based antimetabolites, which led to the discovery of modified purines with antineoplatic activity. The discovery in DNA replication, transcription and translation led to a much better understanding of viral replication, laid the foundation for antiviral drug discovery. In 1971, isolation of natural product Taxol from *Taxus brevifolia* represents an excellent example of the combination of phytoconstituent and organic synthesis in the development of an anticancer agent. Developments in molecular biology and virology had a major impact in the scientific understanding of the replication of the retrovirus (HIV) in the 1980s and early 1990s.

The modern drug research owes its rationality to Paul Ehlrich, who coined intellectual tools of Medical Sciences, such as receptor for drugs. The antibacterial agent Prontosil laid the foundation of the concept of biochemical metabolites and stearic analogues. This enabled the Medicinal Chemists to "drug design". The drug design was based on modification of the structure of a "lead" compound. The lead compound was suffering from some therapeutically undesirable side effect. The efficiency of its increased recently, by high-throughput screening

(HTPS) system utilizing cell line culture systems with enzyme linked immune system assay (ELISA) and receptor molecules derived from gene cloning. The techniques of molecular graphics and computational chemistry have provided novel chemical structures that have led to new drugs with potent medicinal activities.

1.2 Drug Design

Computational drug discovery has created many opportunities to accelerate and rationalize the multidisciplinary drug discovery process and has generated an array of new approaches to design drugs. Drug design involves the following four phases

i) Discovery and research
ii) Development
iii) Regulatory review and approval
iv) Marketing

It takes approximately 10 to 12 years from the initiation and identification of the drug target to bring the drug into the market.

1.2.1 Discovery and Research

The first step in the drug discovery process is "target identification". Target may be a either molecule or a protein receptor that is associated with a disease condition or pathology. For this purpose, it is important to understand how the disease occurs at the molecular, cellular, and genetic levels. Once a target is identified, the next step involves understanding how the target plays a role in the disease process. This is followed by testing of the target against different known and new compounds to identify either one or several "lead compounds" which interact with the target and show the potential to either neutralize or slow the disease process. After careful review, one or more lead compounds are chosen.

1.2.2 Drug Development

Once researchers identify a promising compound for development they conduct experiments on the selected compounds, such as metabolism (pharmacodynamics and pharmacokinetics), safety, toxicity, dosage and efficacy, potential benefits, mechanisms of

action, route of administration, its effects on different groups of people (such as by gender, race or ethnicity), drug-drug interaction and its effectiveness as compared with similar drugs The candidate drug is thoroughly investigated, optimized and prepared for testing in animals is referred as "preclinical phase" and the efficacy and safety of a drug candidate in human is being referred as "clinical testing" and it involves phase I, II, III and IV.

1.2.3 Regulatory Review and Approval

Clinical trial results establish whether there is a proof to support the safety and efficacy of the drug candidate to treat various disorders. At this stage, applications with all the necessary information, including quality, preclinical and clinical data collected during development of the product, are submitted to the relevant regulatory authorities in order to obtain approval to market the drug in their jurisdictions e.g. New Drug Application (NDA) in US and a Marketing Authorization Application (MAA) in the EU and CDSCO (Central Drugs Standard Control Organization) approval for Indian market. Regulatory agencies exist in most territories to oversee the development, approval and marketing of drugs.

1.2.4. Marketing

Once the drug has been approved, marketing or commercialization of the drug is the last phase in the drug development. The drug manufacturer must submit marketing authorization applications in every country or territory in which it wants to sell the drug. Phase IV clinical trials are conducted by the manufacturer to evaluate the safety and efficacy of the marketed drug, for further development and such post-marketing clinical studies are mandatory in some territories.