Chapter

1

INTRODUCTION TO MEDICINAL CHEMISTRY

Medicinal and Pharmaceutical Chemistry is a chemistry-based scientific discipline, with an interaction of chemistry and pharmacology. Medicinal Chemistry also involves the aspects of biological, medical and pharmaceutical sciences. It is concerned with the invention, discovery, design, identification and preparation of biologically active compounds, the study of their metabolism, the interpretation of their mode of action at the molecular level and the construction of structure-activity relationships.

The process of drug discovery involves the identification of candidates, synthesis, characterization, screening and assays for therapeutic activity. Once a compound has shown its value in these tests, it will begin the process of drug development prior to clinical trials. Pharmaceutical chemistry is focused on quality aspects of medicines and aims to assure fitness for the purpose of medicinal products. The science of medicinal chemistry involves the design and synthesis of novel drugs based on an understanding of how drugs work in the body at the molecular level. Medicinal Chemistry is a multifaceted discipline that encompasses synthetic organic chemistry, natural products chemistry, enzymology, chemical biology, structural biology and computational methods, all of which is aimed at the discovery and development of new therapeutic agents. 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).

In 1948 the term **'Division of Pharmaceutical Chemistry'** founded by the American Chemical Society was renamed as 'Division of Medicinal Chemistry.' A new discipline was born, but it took quite a time before it was accepted as such. Medicinal chemistry meanwhile found a place within the pharmaceutical industry and at universities. In 1970 a Section Medicinal Chemistry was started by the Organic Chemistry Division of the IUPAC, followed by the founding of the European Federation of Medicinal Chemistry in 1972. These

developments in the framework and the organizational structures have not helped to arrive an internationally accepted definition for this branch of science and also difficulty in deciding the name of the field: Medicinal chemistry (English), Chimie therapeutique (French), Wikstofforschung (German), Chimica Farmaceutica (Italian), and Farmacochemie (Dutch). The use of the term 'Pharmaceutical Chemistry' when medicinal chemistry is meant is especially confusing as Pharmaceutical Chemistry is the established term for chemistry related to finished medicinal products.

In textbooks dating from the early 1970s several definitions could be found and IUPAC published a comprehensive definition of Medicinal chemistry as

"Medicinal Chemistry concerns the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds at the molecular level. Emphasis is put on drugs, but the interest of the medicinal chemist is not restricted to drugs but include bioactive compounds in general. Medicinal chemistry is also concerned with the study, identification and synthesis of the metabolic products of these drugs and related compounds"

Medicinal chemistry includes:

- The process of drug discovery: The process of drug discovery includes the identification and production of new active compounds. 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 obtained from either natural products or synthetic compounds generated by computational chemistry, like screening of chemical libraries, combinatorial chemistry, pharmaceutical biotechnology etc.
- Optimization process: The "hit" compound is improved for its pharmacologic, pharmacodynamic and pharmacokinetic properties by chemical or functional group modifications, transforming it into a more effective, selective and less toxic lead compound. The pharmacokinetic phase is usually identified with the ADME

(absorption, distribution, metabolism, elimination), while the safety of a drug is a matter of toxicology: both are crucial for a bioactive molecule to be used as a drug.

- Development process: Optimization of synthetic lead compound molecule for mass production and modification of its pharmacokinetic properties so that it is safe to use in human clinical trials.
- Evaluation of the properties of existing drugs is also part of medicinal chemistry.

Modern drug research and development (R&D) has experienced remarkable changes as technological and scientific developments in the past years have dramatically changed the pharmaceutical innovation process. Well-established strategies, such as high-throughput screening (HTS), have progressively been applied in association with novel techniques founded on genomics, molecular and structural biology and molecular modeling. More efficient organic synthesis methods, chemical biology approaches and bio- and chemo informatics strategies have intensely changed the process by which an initial hit is converted into a marketable drug. In fact, this endeavor has become more challenging and more complex. In part, this can be attributed to the expansion of the field towards novel therapeutic areas that are at the limits of the science and technology available today.

Chapter

2

HISTORY OF MEDICINAL CHEMISTRY

The ancient folk medicine and early natural-product emerged the field of medicinal chemistry about 150 years ago. The oldest record (~ 5100 years ago) of the use of medicinal plants are from the ancient civilization of the Greek, the Romans, Galenic medicine in Europe, Chinese, Mayans of Central America and Ayurvedic Medicine in India. The therapeutic uses of plants are recorded in the writings of Hippocrates, Dioscorides, Pliny and Galenus by the Ancient Greeks and Romans. Some of these herbal drugs are still in use today; for example, Coca leaves containing Cocaine and Mushroom containing Methylated tryptamine were chewed by South American for hallucination; Ipecacuanha containing emetine for the treatment of dysentery was used by ancient people of Brazil; the ancient Greeks used opium, squill, hyoscyamus, reserpine and ephedrine. In the Middle Age various "Materia Medica" and "Pharmacopoeias" brought together traditional uses of plants. The Pharmaceutical years before 1800s are called the age of botanicals.

Late 18th or early 19th centuries may be viewed as the birth period of modern medicinal chemistry with the introduction of side chain theory of drug action in 1885 by Berlin immunologist Ehrlich, who coined the term chemotherapy and defined it as "the chemical entities exhibiting selective toxicities against particular infectious agent". At the beginning of the 19th century, the development of modern organic chemistry and medicinal chemistry focused on finding active ingredients present in medicinal plants and certain animals. The isolation of pure substances from plants namely Morphine, Quinine, Atropine, Emetine, Caffeine, Colchicines etc., from crude medicinal plant extracts contributed to the increased use of pure substance as therapeutic agents.

Many of the developments after 1860s arose from the synthesis of compounds specifically for their medicinal properties. For example, even though the use of willow bark as a pain-killer was known, the analgesic activity of its constituent Salicin and salicylic acid were developed in the 1860s and 1870s; Paracetamol and Phenacetin (1886) were also known as pain-killers. The end of the 19^{th} century also saw the development of several important vaccines, including those for tetanus and diphtheria. As a result of these discoveries and the progress made in organic chemistry, the pharmaceutical industry came into existence at the end of the nineteenth century.

At the turn of the 20th century, Medicinal Chemist Paul Ehrlich (who synthesized Salvarsan, the first chemical treatment for syphilis) initiated the transition from the study of plants or their extracts with specified therapeutic activities towards the synthesis of a specific drug substance in the laboratory. Antibacterial sulphonamides were developed, after the identification of antibacterial activity of Prontosil red by Domagk in 1930s. The activity of these compounds as inhibitors of folic acid biosynthesis and as anti-metabolites of p-aminobenzoic acid was identified later by Woods (1940). The synthesis of the first synthetic pharmaceutical drug, Aspirin, occurred in this period which was later on recognized as universal pain reliever and this discovery spawned the era of therapeutic agents

Together with the discovery of Penicillin in 1929 by Sir Alexander Fleming and its subsequent examination by Florey and Chain in 1941 led to a water-soluble powder of much higher antibacterial potency and lower toxicity than those of previously known synthetic chemotherapeutic agents. It is the best example of serendipitous discovery which is called as Golden Age of Antibiotics a new era in medicine. The relatively easy bio-assays for anti-bacterial and anti-fungal activity led to the isolation of a number of antibiotics including Streptomycin (1944), Chloramphenicol (1949) and the Tetracyclines such as Aureomycin (1949).

The middle third of the 20th century witnessed a blossoming of pharmaceutical invention, with breakthroughs in the development of synthetic vitamins, hormones (Thyroxine, Oxytocin, Corticosteroids etc.,) anticonvulsant, psychotropics, antihistamines and new vaccines. Several of these constituted entirely new classes of medicines. Illness such as tuberculosis, diphtheria and pneumonia could be treated and cured for the first time in human history. The structures of the steroid hormones were established in the 1930s and 1940s. The discovery of Cortisone as anti-inflammatory agent in 1949 motivated the synthesis of number of anti-inflammatory semi-synthetic steroids such as Prednisolone, Betamethasone, Triamcinolone, Ethinylestradiol and Progestogens. Problems associated with separating the anti-inflammatory activity from the mineralocorticoid activity of the cortical steroids led to interest in the development of non-steroidal anti-inflammatory agents (NSAIDs). Major innovations were made in cardiovascular drugs starting with anti-hypertensive and β-blockers in the 1960s, followed by calcium-channel blockers, ACE inhibitors and cholesterol-reducing drugs. The successes of 1950s and 1960s were leading light by the work of Gertrude Elion and George Hitchings (1988 Nobel Laureates) who

introduced Azathioprine, the first immunosuppressive agent, Allopurinol for gout, Acyclovir the first useful antiviral compound against herpes and other DNA viruses.

Early 20th century also proposed that drugs might elicit therapeutic and pharmacological actions via interactions with discrete membrane-associated recognition sites, on target organs called receptor turned out as new target in the field of drug research. The pharmacological characterization of receptors in almost all organs, including the brain, provided the basis for a large number of benzodiazepines, β-blockers γ -amino butyric acid and introduction of monoclonal antibodies, which block receptors of growth on tumor cells. The enhancement of instrumentation and the introduction of powerful technology also facilitated laboratory automation and aided the discovery and development of new drugs. Drug companies attempted to develop more useful tools to facilitate the drug discovery process. This caused a significant shift away from the serendipitous approach towards rational drug design. The development of *in vitro* assays using animal tissues became an essential support tool for tracking Structure Activity Relationship (SAR) and allowing chemist to optimize structures before animal testing. This allowed a wide range of compounds to be made around a SAR hypothesis. Rational design of drugs based on knowledge of the biological system being investigated allowed highly specific selective antagonists and agonists to be developed

Other notable advancements in drug design made in the mid to late 20th century include: intervention of charge transfer (Kosower, 1955); induced-fit theory of drug action (Koshland, 1958); concepts of drug latentiation (Harper, 1959) and prodrug (Albert, 1960); concepts of isosterism and bioisosterism (Grimm's and Erlenmeyer's, 1929-1931) had a tremendous impact on the understanding of structure activity relationship (SAR) of drugs ;application of mathematical methods to medicinal chemistry and transformation of SAR studies into quantitative SAR (QSAR) (Hansch and others, 1960s); and application of artificial intelligence to drug research (Chu, 1974). Significant advancements in the discovery process were seen with the advances in molecular and cellular biology. This technology allowed *in vitro* optimization of lead molecules against the human version of receptor or enzyme and allowed a deeper analysis of their physiological nature.

Simultaneous advances in analytical technology viz. detection systems and data capture systems, laboratory automation etc., and in molecular biology viz. *in vitro*

introduction of bioassay design techniques and microplate technology etc., allowed biological targets to be screened that had proven to be intractable before. With all these essential technology ingredients in place, the pharmaceutical laboratory in the early 1990s was set for the first real version of High Throughput Screening (HTS). HTS is a highly automated robotic system that tests small amounts of large numbers of compounds against potential targets. In 1990s, when Combinatorial chemistry mushroomed it provides very large numbers of new chemical entities to be screened for biological activity through HTS. It is a novel approach to chemical synthesis that enables the creation of large numbers of organic compounds by linking chemical building blocks in all possible combinations. The objective of both approaches is to provide very large numbers of new chemical entities to be screened for biological activity *in vitro*. Since the mid-1980s, the geometrical aspects of molecular structures were also taken into account leading to the development of the 3D-QSAR, which exploits information on the molecular geometry.

In spite of the significant advances in biological screening of large number of compounds by using HTS techniques, the screening of many millions of chemicals against hundreds of biological targets are too expensive. Virtual screening of chemical libraries has emerged as a complementary approach to HTS. Molecular graphics added a new dimension to computational chemistry and opened up the field of molecular modeling. Advances in the field of NMR and X-ray crystallography gave scientists the means for determining the three-dimensional (3-D) structure of larger and more complicated protein structures. Molecular modeling advanced beyond the capabilities of physical molecular models and it became possible to develop sophisticated molecular graphics for the use in chemical design and computer-aided drug discovery (CADD). In this new world, Medicinal Chemists identify and optimize lead compounds not only for potency, but also with a strong emphasis on avoiding potential side effects (for drug safety) and on controlling *in vivo* absorption, distribution, metabolism and excretion properties.

During the early stages of medicinal chemistry development, Chemists were primarily concerned with the isolation of medicinal agents found in plants. Presently, the advent of genomics, proteomics, bioinformatics and efficient technologies like, combinatorial chemistry, high throughput screening (HTS), virtual screening, *de novo* design, *in vitro*, *in silico,* ADMET screening and structure-based drug design has revolutionized the process of modern drug discovery. Genomic technology also brings the potential to clone and express

human receptors for HTS. Availability of huge database of drugs from drug bank, protein data bank coupled with recent advances in technology further fuel the use of *in silico* techniques to increase the chance of success in many stages of the discovery process.

Despite so many advances, the therapeutic treasury is still lacking of drugs and there remains an increasing need for novel, innovative therapeutic agents not only in area that are historically well served, but also for the diseases associated with environmental, occupational, aging and lifestyle factors for which there is no effective medicine available and considerable demand exists in market. Therefore, the quest for newer and potent therapeutic agents is never ending. Medicinal chemistry continues to play a major role in drug research and development, taking advantage of newer techniques and increased knowledge of different branches of related sciences.