CHAPTER 1

INTRODUCTION TO MEDICINAL CHEMISTRY

Medicinal Chemistry is a science that deals with the discovery or design of new therapeutic chemicals and the development of these chemicals into useful medicine. It blends synthetic chemistry, molecular modeling, computational biology, structural genomics and pharmacology to discover and design new drugs and investigate their interaction at the cellular, molecular and animal level. Medicinal chemistry combines structure-function relationships of known drugs with rational designs, optimize the physicochemical properties of drug molecules and improve the efficacy of the drug particularly with respect to stability and bioavailability. Out of every 5,000 new compounds identified during the discovery process, approximately five are considered safe for testing in human volunteers after preclinical evaluations. After three to six years of further clinical testing in patients, only one of these compounds on an average is ultimately approved as a marketed drug for treatment. Two major phases are involved in creating new drugs are the discovery phase and clinical testing phase.

The discovery phase: The earliest drug discoveries were made by random sampling of higher plants. 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. Some examples are Ephedrine isolated from the Chinese drug *Ma Huang* used for the treatment of hay fevers and respiratory ailments, Morphine isolated from opium poppy used as narcotic analgesics and Quinine isolated from cinchona species has antimalarial activity.

New discovery often begins with target identification-choosing a biochemical mechanism involved in a disease condition. Up to 5,000 to 10,000 molecules for each potential drug candidate are subjected to a rigorous screening process and one or more lead compounds are chosen. The molecule size, shape, strengths and weaknesses,

preferred conditions for maintaining function, toxicity, bioactivity and bioavailability are characterized for the chosen molecules. In the preclinical stage of drug development, an investigational drug must be tested extensively in the laboratory to ensure whether it will be safe to administer to humans. Testing at this stage can take from one to five years and must provide information about the pharmaceutical composition of the drug, its safety, how the drug will be formulated and manufactured and how it will be administered to the first human subjects. Preclinical testing analyzes the bioactivity, safety and efficacy of the formulated drug product. This testing is critical to a drug's eventual success and as such, is scrutinized by many regulatory entities. During the preclinical stage of the development process, plans for clinical trials and an Investigational New Drug (IND) application are prepared.

Clinical testing is usually described as consisting of Phase-I, Phase-II, Phase-III and Phase-IV clinical studies. Phase-I studies are designed to verify safety and tolerability of the candidate drug in humans and typically take six to nine months. These are the first studies conducted in humans. A small number of subjects, usually from 20 to 100 healthy volunteers, take the investigational drug for short periods of time. Testing includes observation and careful documentation of how the drug acts in the body, how it is absorbed, distributed, metabolized and excreted.

Phase-II studies are designed to determine effectiveness and further study the safety of the candidate drug in humans. Depending upon the type of investigational drug and the condition it treats, this phase of development generally takes from six months up to three years. Testing is conducted with up to several hundred patients suffering from the condition the investigational drug is designed to treat. This testing determines safety and effectiveness of the drug in treating the condition and establishes the minimum and maximum effective dose. Most Phase-II clinical trials are randomized or randomly divided into groups, one of which receives the investigational drug, one of which gets a placebo containing no medication and sometimes a third group that receives a current standard treatment to which the new investigational drug will be compared.

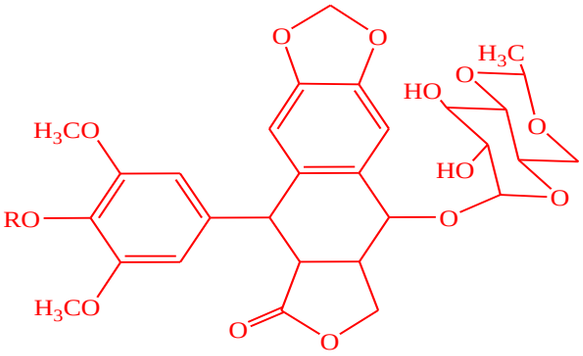
Phase-III studies provide expanded testing of effectiveness and safety of an investigational drug, usually in randomized and blinded clinical trials. It is conducted with several hundred to thousands of volunteer patients suffering from the condition the investigational drug treats and requires 1 to 4 years of testing. Medicines which have completed research and development processes and which have undergone successful

screening in clinical trials must apply for a product license. The application for license must be submitted to the appropriate regulatory body for the country where the medicine will be sold. Each regulatory body has their own submissions and approval processes

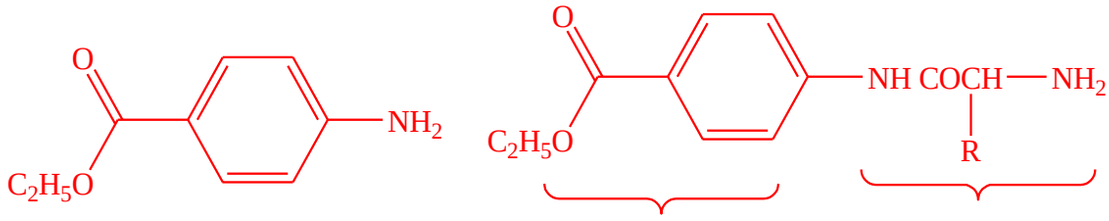
Phase - IV is long-term human studies carried out once a drug has been licensed. They continue to investigate longer term side effects, risks, benefits and the optimal use of the drug. Rare side-effects are frequently identified during these trials and if identified on risk-benefit analysis the drug is withdrawn.

Even though research in new drug discovery rescues the humanity-

"***Natural Forces within Us Are the True Healers of Diseases***"

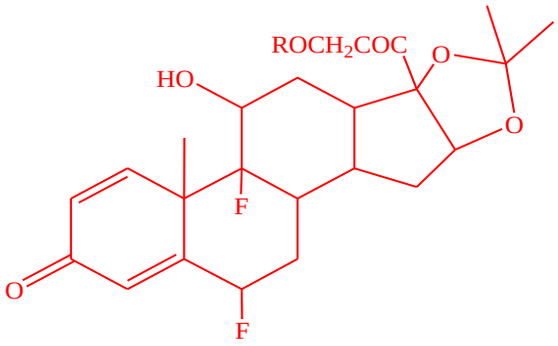


The local anesthetic Benzocaine has been converted into water soluble amide prodrug form with various amino acids; amidase-catalyzed hydrolysis in human serum occurs rapidly.



(ii) **Dermal Absorption**

The skin is designed to maintain the body fluids and prevent absorption of xenobiotics into the general circulation. Consequently, drugs applied to the skin are poorly absorbed. Corticosteroids for the topical treatment of inflammatory, allergic and pruritic skin conditions can be made more suitable for topical absorption by esterification or acetonidation. For example, both Fluocinolone acetonide and Fluocinonide are prodrugs used for inflammatory and pruritic manifestations.



(iii) Ocular Absorption

A major problem in ocular therapeutic is the attainment of an optional drug concentration at the site of action. The difficulty is largely due to the fact that all the