CHAPTER 1

GENERAL INTRODUCTION
Introduction:

The progress of drug design is extensively driven by the instincts, intuition and experience of pharmaceutical research scientists. It is often instructive to attempt to 'capture' these experiences by analyzing the historical record that is successful drug design projects to past. From this analysis the interference draw to play an important role in shaping our on current and future projects. Towards this region, we would like to analyze the structures of a large number of drugs.

The focus of drug design has switched from structure oriented to target oriented research, e.g. development of the antiulcer agent cimetidine. Histamine was the lead compound for the project and various strategies were used to find an analog that would prevent it fitting its receptor. Once an antagonist was developed, a theory was proposed on how it might interact with the histamine receptor at a molecular level. Further analogs were then synthesized to test theory and the theory was continuously modified as required.

In the nineteenth century, chemistry developed as a science, both in terms of experimental procedures and scientific theory. Scientist isolated and purified single compounds from natural extracts. Method of organic synthesis were developed that helped chemists altering structures in a predictable way.

A prerequisite for the design of safe drugs is knowledge about the various metabolic reactions that xenobiotics and endogenous compounds undergo in the organism. Because pharmacological activity depends on molecular structure, the medicinal chemist is restricted in the choice of functional groups for the design of new drugs. Often he finds or she encounters a situation where a structure has adequate pharmacologic activity but has an inadequate pharmacokinetic profile (i.e., absorption, distribution, metabolism and excretion). This is because pharmacology
and pharmacokinetic departments in the pharmaceutical industry often do not collaborate at the early stage of drug development. It is only late, when the synthesized entities is tested in animals or in humans, that pharmacokinetic disadvantages become obvious.

Modern drug discovery starts with the identification of a pharmacological target that is hypothetical and the primary cause of disease. Potential targets include host cell genes, receptors, signaling systems, organelles and biochemicals such as enzymes. Additionally, an element of a disease modifying process, such as an inflammatory mediator, may be a target. Biological processes required for propagation of infectious agents have also proven to be therapeutically useful targets; examples include protease and reverse transcriptase of the human immuno deficiency virus (HIV). Common to all targets selected as therapeutic opportunities is the hypothesis that some type of pathogenetic linkage exists to the disease-causing process, rather than to specific signs, symptoms, or effects.

Heterocyclic compounds have great applicability in pharmaceutics because they have specific chemical reactivity and provide false synthons in biosynthetic process or block the normal functioning of biological receptors. The inhibition of amide resonance resulting into more susceptibility of (3-lactam to nucleophile is considered at least in part responsible for antibacterial property, apparently by acetylating transpeptidase and thus inhibiting bacterial cell wall biosynthesis.

Most of the alkaloids which are nitrogenous bases occurring in plants and many antibiotics including penicillin and streptomycin have also heterocyclic ring system. Many natural pigments such as indigo, haemoglobin and anthocyanin are
heterocycles. Most of the sugars are their derivatives including Vitamin C for instance, exist largely in the form of five membered. Vitamin B6 (Pyridoxine) is a derivative of pyrimidine essential in aminoacid metabolism.

Important drugs, poisons and medicines (both natural and synthetic) such as sulphathiazole, pyrethrin, rotenmone, strychnine, reserpine, certain of the antihistamines, the ergot alkaloids caffeine, cocaine, barbiturates, etc. are heterocyclic compounds.

The ultimate product of a successful drug design effort. Our goal for this is to begin to deconvolute this information in order to apply it to design of new drugs.

Taking in view of the applicability of heterocyclic compounds, we have undertaken the preparation of heterocycles bearing pyrazole nucleus. The placement of a wide variety of substituents of these nuclei have been designed in order to evaluate the synthesized products for their pharmacological profile against several strains of bacteria and fungi.