CHAPTER 1

INTRODUCTION

1.1 GENERAL INTRODUCTION

An integrated and insightful look at successful drug synthesis depends upon the ability to identify new chemical entities that have potential to treat diseases in a safe and efficient manner. Many of the drugs in use, in the last fifty years or more have been of synthetic or semisynthetic origin. The pharmacopoeias prior to that period were of natural origin. Finding effective drugs is difficult. Many are discovered by chance observations, the scientific analysis of folk medicines or by noting the side effect of other drugs.

During the early stage of drug discovery the scientist’s were primarily concentrated with the isolation of medicinal agents found in plants. For example salicylic acid the precursor of Aspirin was isolated from Willow bark; Morphine a powerful pain killer from opium poppy, Quinine from cinchona bark; Digitalis from purple foxglove plants etc. Synthetic chemistry grew rapidly in sophistication during the first half of 20th century and first proved its value for pharma by enabling the discovery of Sulfad drugs [1].

Medicinal chemistry received further boost in 1940 as pharmacology, which until then had been dominated by physiology, became increasingly biochemical in character with new understanding of the role of enzymes and cell receptors. Medicinal chemistry is the application of chemical research technique used to identify, synthesize and develop chemical
entities for therapeutic use, which operates as an intersection of chemistry and pharmacology. It also includes the study of existing drug, their biological properties and quantitative structure activity relationship (QSAR).

The seeds for the concept of rational drug design were laid in the 1940s and 1950s by George Hitchings and Gertrude Elion in their work on DNA-based antimetabolites, which led to the discovery of modified purines with anticancer activity [2]. However, the era of DNA and medicine was largely stimulated by the elucidation of the double-helical structure of DNA by Watson and Crick in 1953 [3]. The ramifications of this discovery in DNA replication, transcription and translation led to a much better understanding of viral replication. This laid the foundation for antiviral drug discovery in subsequent decades as molecular targets in the viral replication cycle began to be identified. The 1950s also saw the discovery of Vancomycin, a glycopeptide which was developed much later for use against Methicillin-resistant staphylococci infections. The era of recombinant DNA technology and molecular cloning began around the mid-1970s. During the 1970s chemists turned increasingly to rational drug discovery based on structural knowledge of target and / or ligand, a movement that began a strategic shift away from natural products towards purely synthetic or natural based compounds. Rational drug design therefore requires significant knowledge of chemistry as well as biology, because chemical interaction between drugs and their target are what which determine whether a drug is biologically active or not.

The first drug developed using the rational approach was antiviral drug called Zanamivir [4]. This drug was designed to interact with a neuraminidase, a virus produced enzyme that is requested to release newly formed virus from the infected cells. Other rationally designed drugs include HIV drugs such as Ritonavir and Indinavir, both of which interact with viral proteins.
More recently automated high-throughput screening (HTS) system utilizing cell culture system with lined enzyme assays and receptor molecules derived from gene cloning have greatly increased the efficiency of random screening. It is now practical to screen enormous libraries of peptides and nucleic acid from combinatorial chemistry procedure. With significant advances in X-ray crystallography and NMR it’s possible to obtain a detailed representation of enzyme and other drug receptor. The techniques of molecular graphics and computational chemistry provide novel chemical structures that have lead to new drug with potent medicinal activities. Development of human immuno deficiency virus (HIV) protease and angiotensin converting enzyme inhibitors came from an understanding of the geometric and chemical character of the receptor enzyme active site [5]. Even if the receptor structure is not known in detail, rational approaches based on the physiochemical properties of a lead compound can provide new drug. Despite the progress there still remains an increasing need for novel innovative therapeutic agents. The aim is to improve the success in drug development by devising a better method for the synthesis of lead molecule from easily accessible, affordable and inexpensive raw material. The majority of drugs used today are distinct products of synthetic organic chemistry and most of them are heterocyclic derivatives.

1.2 NUCLEUS INTRODUCTION

Compounds classified as heterocycles probably constitute the largest and most varied family of organic compounds. They are rich sources of diverse physical, chemical and biological properties. In medicinal chemistry they are commonly used as template to design biologically active agents. A number of compounds having heterocyclic nucleus such as thiadiazole, triazole, benzthiazole, benzoaxazole, oxadiazole etc and their derivatives have been associated with broad spectrum of biological activities [7]. Synthesis of triazole fused with another heterocyclic ring has attracted widespread attention due to their diverse applications. Among them symmetrical triazole fused with