Chapter 1

INTRODUCTION

1.1 Peptides and Peptidomimetics

Peptides are naturally occurring biological molecules. They are short chains of amino acid monomers linked by peptide bonds. The covalent chemical bonds are formed when the carboxyl group of one amino acid reacts with the amino group of another. Amino acids that have been incorporated into peptides are termed "residues" due to the release of either a hydrogen ion from the amine end or a hydroxyl ion from the carboxyl end, or both, as a water molecule is released during the formation of each amide bond. Peptides have become instrumental in mass spectrometry allowing the identification of proteins of interest based on peptide masses and sequence. Peptides have recently been used in the study of protein structure and function. For example, synthetic peptides can be used as probes to see where protein-peptide interactions occur. [4]

Peptides are ubiquitous in nature and play a key role in various biological and physiological processes in living organisms. A peptide is a large molecule made of amino acids that are linked with peptide bonds. They are involved as hormones and neurotransmitters in intercellular communication, antibodies in the immune system, and also in the transport of various substances through biological membranes. The unique features of the amide backbone are utilized for effective bonding with receptors to accomplish drug action. However, natural peptides possess a few drawbacks such as poor solubility and low potency to pass through cell membranes which are detrimental for their use as drugs effectively. The focus on improving the utility of peptides as drugs by modifying the peptide backbone and introducing unnatural linkages has lead to a variety of peptidomimetics as shown in Fig 1.1.

Peptides are a rich source of pharmacophores from which medicinal chemists are developing new useful therapeutic drugs. After binding to an enzyme, or a membrane receptor, peptide-based inhibitors, neurotransmitters, immunomodulators (the active agents of immunotherapy are collectively called immunomodulators). These are the agents that augment or diminish immune responses and hormones influencing cell to cell

communications and control a variety of vital functions such as metabolism, immune defence, digestion, respiration, *etc*.

Though naturally occurring peptides based on coded amino acids have been widely used as drugs, there are problems with the use of peptides as therapeutic agents. The problems mainly arise from their rapid metabolism by proteolysis and their interactions at multiple receptors. As a result, peptide researchers have sought modifications of peptide structures to create more stable molecules.

Peptides have found wide applications as bio-stable, bio-available, and often potent surrogates of naturally-occurring peptides. They form the basis of important families of enzyme inhibitors and act as receptor agonists and antagonists.

A peptidomimetic is a compound that is designed to mimic a biologically-active peptide, but has structural differences that give greater advantages for its function as a drug. For instance, a peptidomimetic that is designed to mimic a hormone would have greater stability and be more available to its target receptor to transmit signals. Peptidomimetics may have unnatural amino acids or other unusual compounds to stabilize their structure or alter their biological activity.

The reason for the interest in peptides is that many have significant biological activity. This means they can act as hormones and signal molecules for the central nervous system and the immune system. Peptides can affect a wide range of cellular activity, among them digestion, reproduction, and sensitivity to pain. Cellular and biological activities of many peptides are of interest as targets for drugs, but it can be difficult for them to cross the membrane to enter a cell. Also, peptides that do make it into a cell are frequently unstable.

A peptidomimetic is a small protein-like chain designed to mimic a peptide. They typically arise either from the modification of an existing peptide or by designing similar systems that mimic peptides such as peptoids and β-peptides. Irrespective of the approach, the altered chemical structure is designed to advantageously adjust the molecular properties such as stability or biological activity. This can have a role in the development of drug-like compounds from existing peptides. These modifications involve changes to the peptide that do not occur naturally (such as altered backbones and the incorporation of non-natural amino acids).

Peptidomimetics are molecules predicted to exert a similar biological activity as natural peptides but with additional advantages such as good oral absorption and metabolic stability. They are molecules in which one or more peptide bonds are replaced

by diverse kinds of unnatural linkages such as ureas, carbamates, sulfonamides, azatides, thioureas, acetals, phosphones, and heterocycles like tetrazoles, triazoles, thiazoles, oxazoles, *etc*. and have gained remarkable significance in synthetic and medicinal chemistry as substitutes to the native peptide bond.

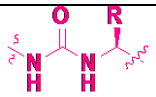
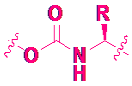
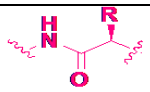
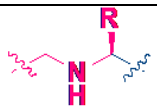
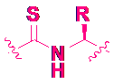
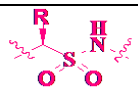
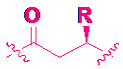
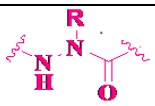
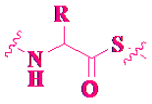
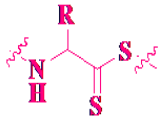
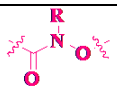
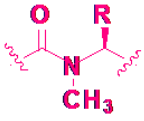
Sl. No.	Structure	Name
1		Ureidopeptide
2		Peptidyl carbamate
3		Retro-inverso peptide
4		Reduced amide peptide
5		Thiopeptide
6		Sulfonamide peptide
7		Ketomethylene peptide
8		Azapeptide
9		Thioester peptide
10		Dithioester peptide
11		Amidoxy peptide
12		*N*-Methyl peptide

Figure 1.1 Selected examples of peptide backbone modifications

1.2 Diazomethyl ketone

Diazomethyl ketones are known as versatile and useful substitutes for a wide range of chemical modifications, and their chemistry continues to be of interest because of their extensive use in different areas of organic synthesis. They have applications in organic syntheses, inhibition of multidrug resistance of certain types of lymphoblasts, antifungal, antibacterial, antimicrobial, and antitubercular activities. They also find application in agrochemical industries.

N-protected diazomethyl ketone is an intermediate in the preparation of bromomethyl ketone. They are widely employed for the synthesis of irreversible enzyme inhibitors. In fact, since diazo compounds are precursors of pharmaceutically interesting scaffolds such as chloromethylketones and diazomethane, diazomethyl ketone continues to be extensively used in the synthesis of HIV protease inhibitors such as squinavir, nelfinavir, palinavir, and amprenavir.