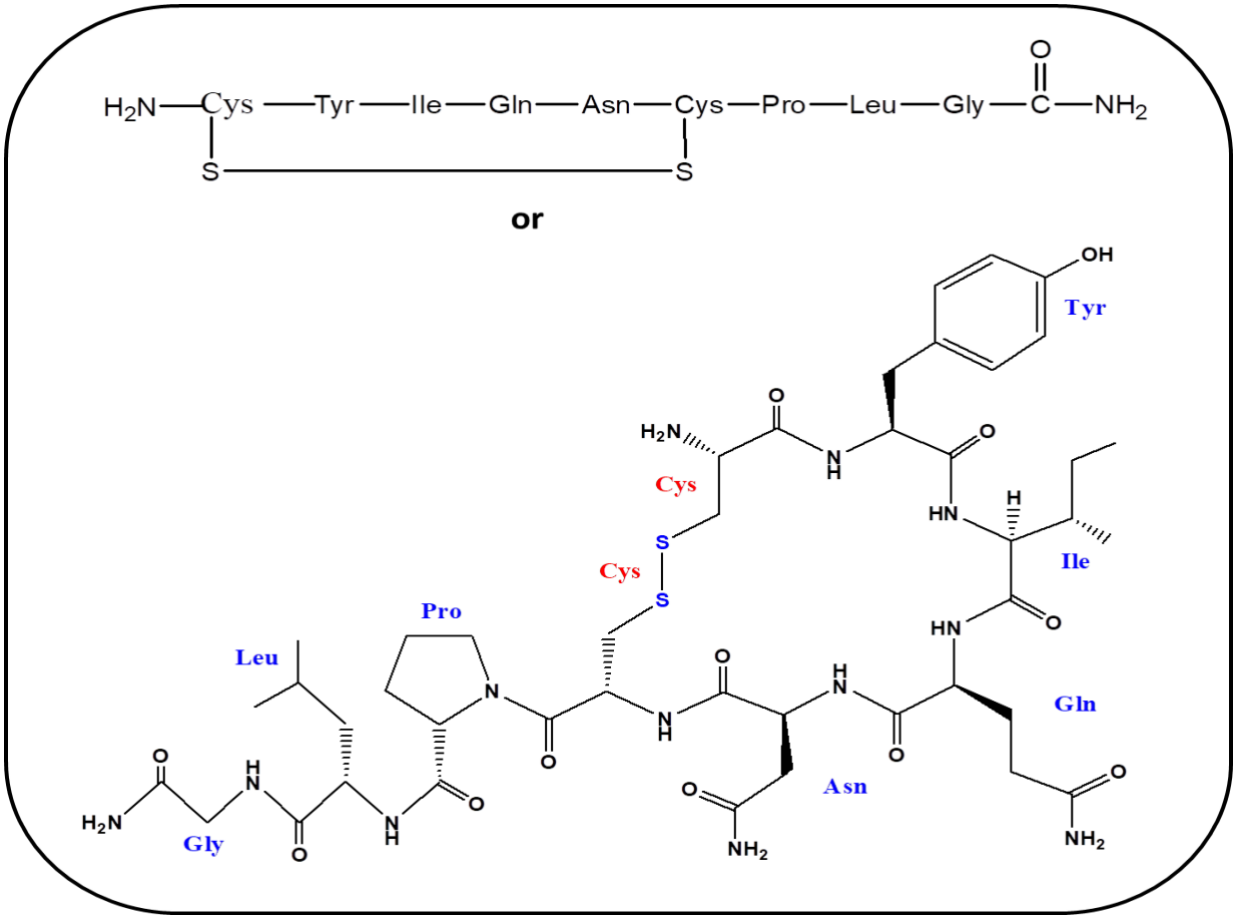
Course Name: Proteins and Lipids
Paper Number: 4202
Section: A
Course Instructor: Prof. Shrikant Kukreti
Study Material (name of Topic/Chapter): Peptides

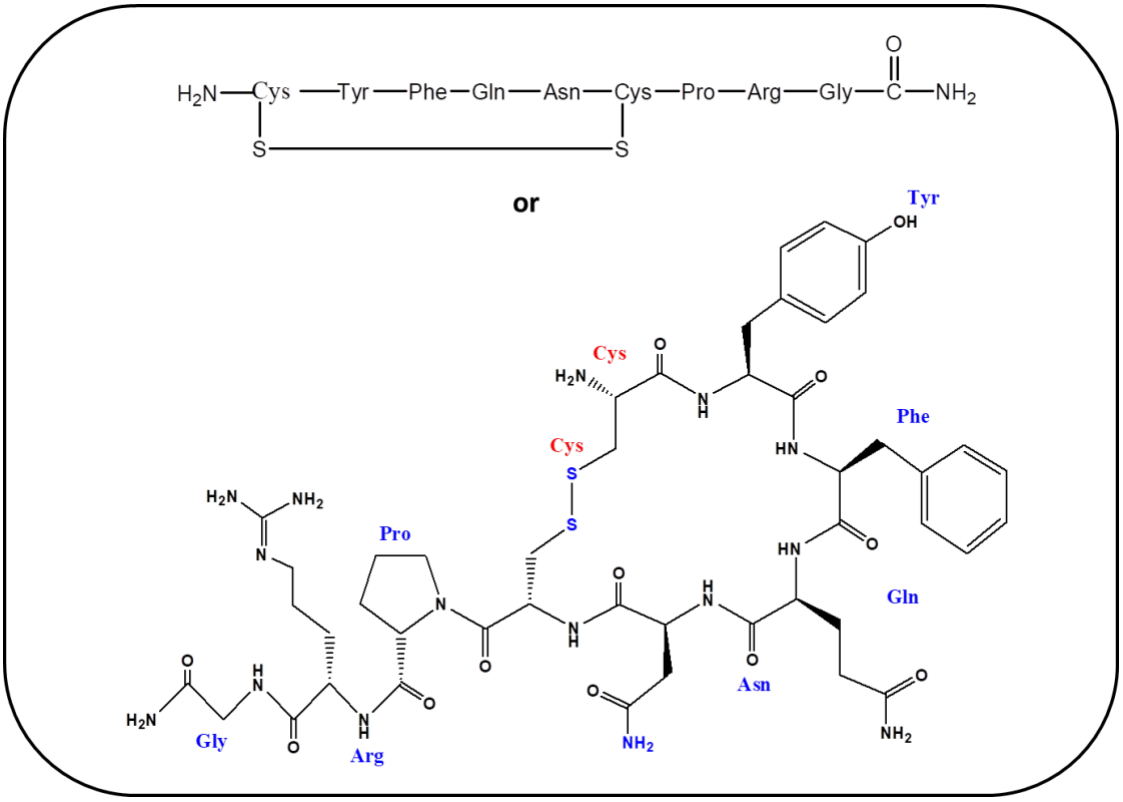
Oxytocin and **Vasopressin** (each nonapeptide with a disulphide bridge) are derived from proteins called proneurophysins that are about 160 and 215 amino acids long, respectively. The structure of **Oxytocin** is similar to **Vasopressin.** The two genes are located on the same chromosome separated by relatively small distance of less than 15000 bases, in most of species.
Posterior pituitary serves as a storage and secretory organ for these two peptide hormones. They are synthesized by specific hypothalamic cells and are subsequently transported in specialized vesicles along axonal pathways directly into the posterior lobe of the pituitary.

Oxytocin:



Structure of Human Oxytocin

Vasopressin:



Structure of Human Vasopressin

Oxytocin and Vasopressin were isolated and purified from pituitary glands of slaughter house animals, and their total synthesis was reported in 1954 by an American biochemist Vincent du Vigneaud. For this work Vigneaud was awarded Nobel prize in Chemistry in 1955. Both the peptide hormones contain one intra-chain disulphide linkage. Each has Cys residue at one and six positions. With seven of the nine amino acids in common the 3D structure of Oxytocin and anti-diuretic Vasopressin must be important for each to be specifically recognized by their receptors. The disulphide bridge which closes the ring and intramolecular hydrogen bonds, make it rigid. Oxytocin has a half life of about 6 minutes whereas Vasopressin has half-life of 18-20 minutes.

Functions: Oxytocin causes ejection of milk from the mammary glands (neuroendorine reflex) and contraction of uterine smooth muscle, causing expulsion of fetus. Human Vasopressin increases blood pressure

(vascoconstriction) and helps in retention of water (antidiuretic) by acting on kidneys (facultative reabsorption).

Endomorphins:

These are natural painkillers, usually alkaloids from the opium poppy. These substances are oligopeptides containing 5-50 amino acids. The two known endomorphins, endomorphin-1 and endomorphin-2, are tetrapeptides consisting of Tyr-Pro-Trp-Phe and Tyr-Pro-Phe-Phe amino acids sequences respectively. These sequences fold into tertiary structures with high specificity and affinity for the μ opioid receptor binding it exclusively and strongly. The two pentapeptide examples are called **Enkephalins.** These are endogenous opioid pentapeptides that are produced mainly in the central nervous system, chromaffin cells of adrenal medulla and other peripheral tissues. Both are products of the proenkephalin gene. Four of the five amino acids present in pentapeptide enkephalins are identical.

Tyr-Gly-Gly-Phe-Leu is called Leu-enkaphalin, while the other terminating in methionine, represented as Tyr-Gly-Gly-Phe-Met is called Met-enkaphalin.

Enkephalins possess virtually all the properties of the morphine opiates. Enkephalin peptides preferentially bind to **δ** opioid receptor. Regrettably, both are readily hydrolysed by the body's peptidase enzymes. The search is on for a way to stabilize these compounds while retaining their activity [*Ishida, T. et al. Biochemical J. (1984) 218, 677-689. X-ray diffraction studies Enkeaphalins*]

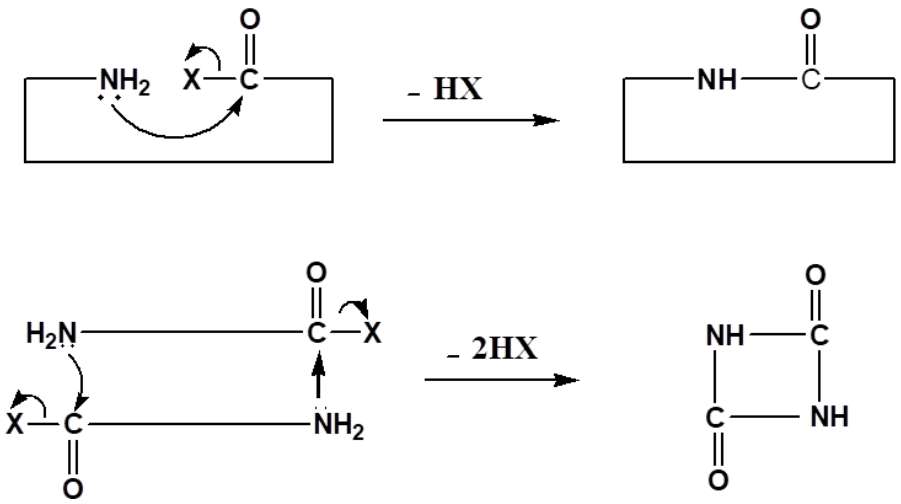
Cyclic Peptides:

Peptides can form two kinds of cyclic structures.

Homodetic cyclic peptides: Here, only the peptide bonds participate in ring formation.

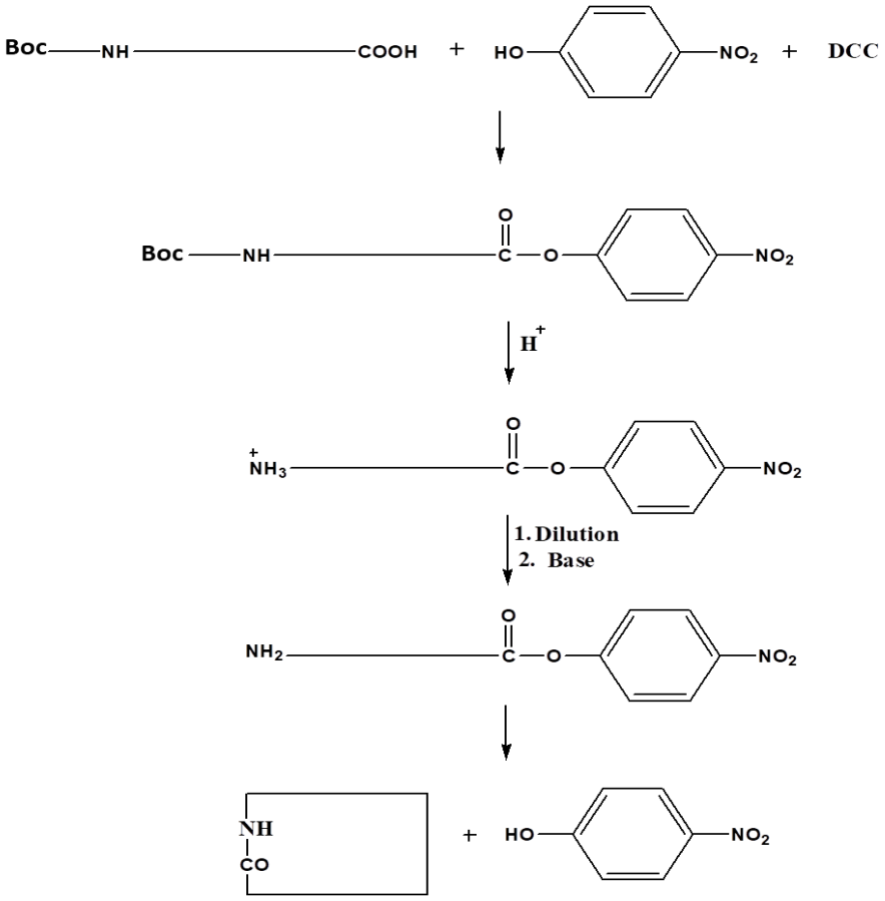
Heterodetic cyclic peptides: A disulphide bridge, an ester (lactone) linkage, or a thioester can play the role of the connecting piece between two points of the chain. In the synthesis of both classes of cyclic peptides, a general problem is encountered.

Cyclization requires two reactive groups within the same peptide chain and these can react intramolecularly or intermolecularly to yield dimers or polymers.



Production of larger rings can be more than a mere side chain reaction, when some interactions such as multiple H-bonds hold the two activated chains together in an antiparallel combination, then the main product of the reaction will be a dimer rather than the monomer. Such cyclodimerization was observed in synthesis of cyclic antibiotic Gramicidin -S.

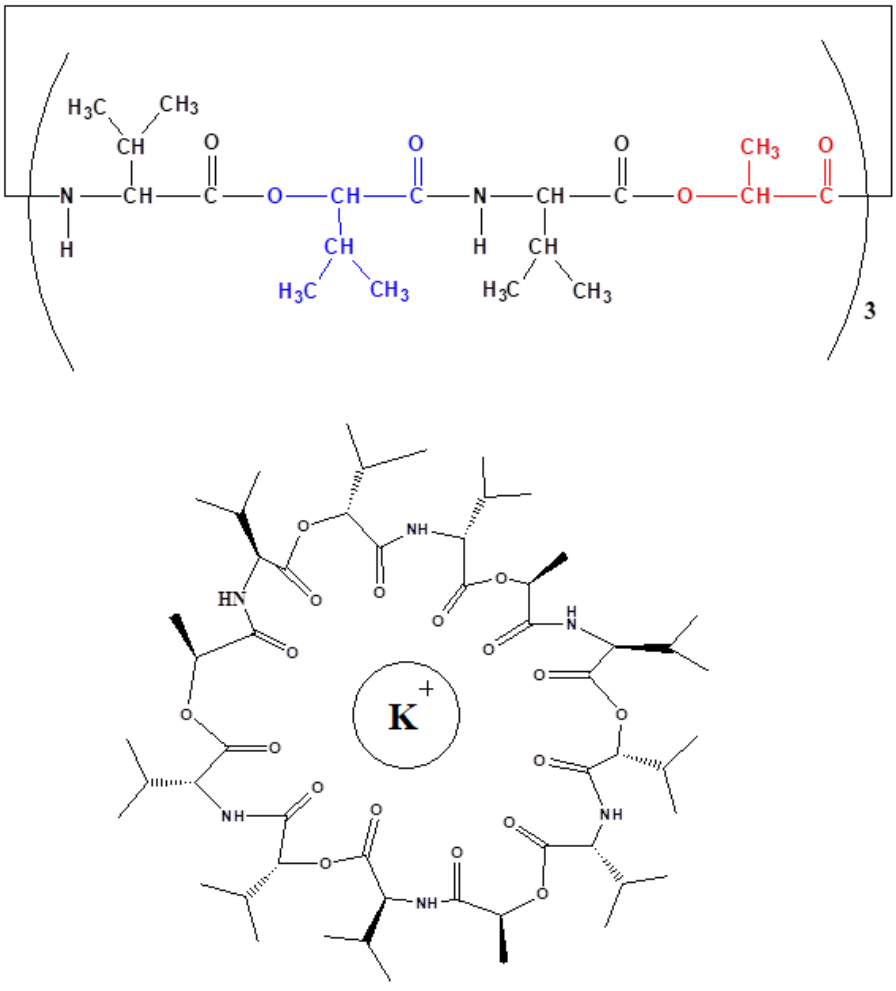
Dimerization and polymerization can be supressed by application of the ‘dilution principle’ (Karl Ziegler 1933). Accordingly, in dilute solution the rate of the biomolecular reaction is efficiently reduced, while that of simple cyclization a unimolecular process is uneffected. As the rule of thumb, cyclization should be carried out at a concentration not exceeding 10^{-3} M.



Reference: Miklos Bodanszky, Peptide Chemistry: A Practical Textbook (2nd Ed.) Springer-Verlag.

Valinomycin: A cyclododecadepsipeptide is a natural neutral ionophore produced by the cells of *Streptomyces fulvissimus*. It is an important member of the class depsipeptide, where one or more of its amides, -C(O)NHR- groups are replaced by the corresponding ester, -C(O)OR. Many depsipeptides have both peptide and ester linkages. They are mainly found in marine and microbial natural products. Valinomycin depsipeptide consists of 3 moles, each with L-valine, D-α-hydroxy isovaleric acid, D-valine and L-lactic acid linked alternately to form a 36-member ring from the 12 constituent molecules. Valinomycin has great flexibility in solution, but gains marked structure when it complexes K^+ with the six-carbonyl oxygen from acids, two additional oxygen

from water may coordinate with the K^+, to give a coordination no of 8. The 9 isopropyl groups and 3 methyl groups give this molecule low solubility in water but relatively high solubility in ether, benzene, chloroform and lipids. K+ ions bind to valinomycin and exchanges across the membrane. In the absence of a K^+ specific ionophore like valinomycin, K^+ solely seldom crosses a lipid bilayer. In the presence of valinomycin, K^+ is freely permeable. The stability constant K for the potassium-valinomycin complex is nearly 100,000 times larger than that of the sodium-valinomycin complex. This difference is important for maintaining the selectivity of valinomycin for the transport of potassium ions (and not sodium ions) in biological systems. The high affinity for K^+ gives this compound utility as antibiotic, insecticide and an ionophore in K^+ specific electrodes.



Structure of Valinomycin