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Pseudo-peptides in drug discovery: A newer technology

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Abstract

Drug discovery is devoted to the topic and draws together knowledge gained on different types of peptidomimetics and other pseudo-peptides with drug properties. It includes peptoides (N-substituted oligo-glycines) beta-peptides, gamma-peptides, pyrrole-imidazole polyamides, DNA-like peptide nucleic acids, Alpha-helical peptide nucleic acids, DNA-cleaving pseudo-peptides in DNA binders as well as peptide nucleic acids. Peptides are among the most versatile bioactive molecules, yet they do not make good drugs, because they are quickly degraded or modified in the body. Thus, drug discovery has turned to the novel field of peptidomimetics to design non-peptide compounds mimicking the pharmacophore and thus the activity of the original peptide. These novel compounds open up new perspectives in drug design by providing an entire range of highly specific pharmaceuticals that have a high bioavailability. Peptides are among the most versatile bioactive molecules, yet the do not make good drugs, because they are quickly degraded or modified in the body. To overcome this problem, stable and at the same time biologically active pseudo-peptides have been developed. These novel compounds open up new perspectives in drug design by providing an entire range of highly specific and non-toxic pharmaceuticals. This is the first work devoted to the topic and draws together knowledge gained on different types of Peptidomimetics and other pseudo-peptides with drug properties. As such, it includes peptoids, beta-peptides, polyamide DNA binders as well as peptide nucleic acids. The experts in the field of cheminformatics, chemogenomics, proteomics and genomics discuss chemical properties and stability, biological activity and reactivity, as well as practical aspects of synthesis, making this a prime resource for drug developers and bioorganic chemists working with these compounds**.**

Key Words: Peptidomimetics, PKC Isozyme, Gamma glutamyltransferase

Introduction

Peptides are among the most versatile bioactive molecules, but they are quickly degraded or modified in the body. The novel field of Peptidomimetics deals in designing non-peptide compounds that mimics the Pharmacophore and thus has the activity of the original peptide. These novel compounds open up new perspectives in drug design by providing an entire range of highly specific pharmaceuticals that have a high bioavailability[1].

Example of Pseudopeptide:

Binding of activated PKC Isozyme (Protein Kinase C) to their RACKs determines the functional specificity of PKC:

PKC Isozyme translocate from one cell compartment to another when activated by the appropriate signal with each isozyme translocating to a unique subcellular site[2]. We suggested that this unique localization is mediated by binding of each of the activated isozymes to their corresponding isozyme-specific anchoring proteins, termed RACKs (for Receptors for Activated C-Kinase).

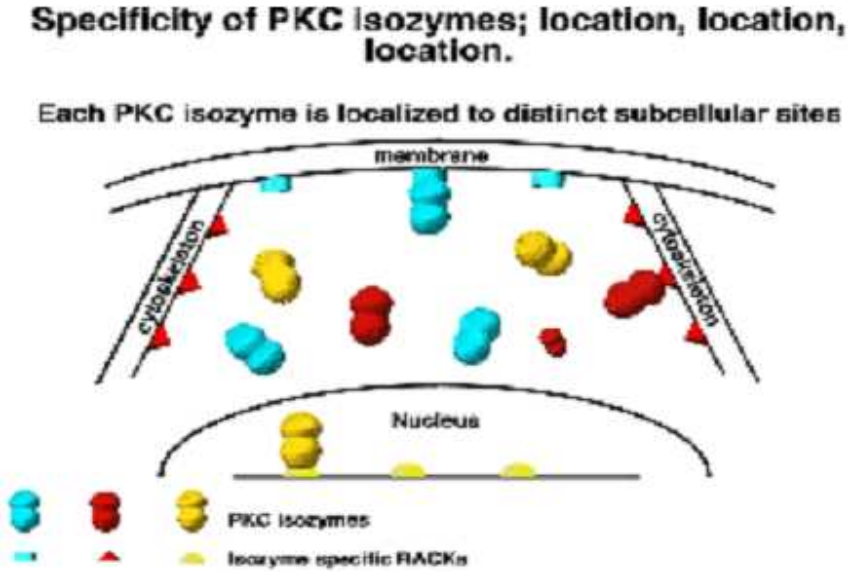

Fig 1: Location of Pseudopeptides

Binding of activated PKC isozymes (protein kinase C) to their RACKs determines the functional specificity of PKC:-

PKC isozymes translocate from one cell compartment to another when activated by the appropriates singal with each Isozyme translocating to a unique sub cellular site[3].

It is suggested that this unique localization is medicated by binding of each of the activated isozymes to their corresponding Isozyme specific anchoring proteins, termed RACKs (for receptors for activated protein kinase[4].

Isozyme-selective inhibitory peptides:-
For all the PKC isozymes when the translocation inhibitors are 6-8 amino acids long and they selectively inhibit translocation and function of their corresponding isozymes at intracellular concentrations of 3-10 nm[5-6].

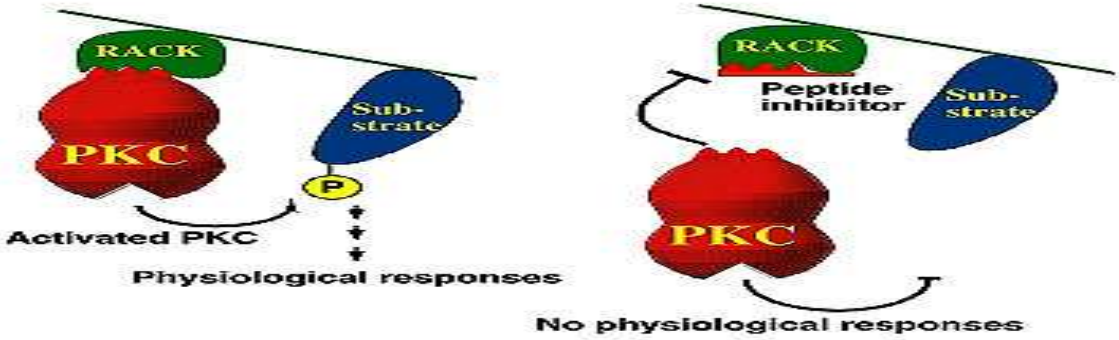

Fig 2: Isozyme-selective inhibitory peptides

Translocation activators:-
These are short peptides that induce translocation of PKC by mimicking the action of the RACK on the enzyme[7]. These peptides are called pseudo-RACK peptides.

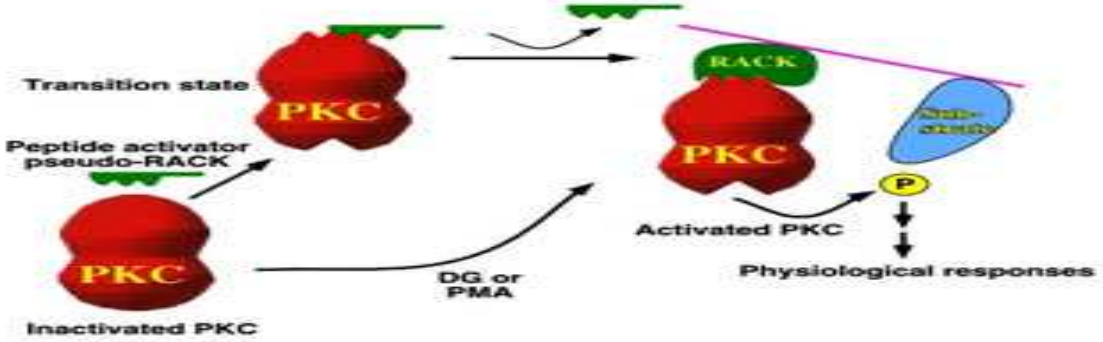

Fig 3: Translocation activators

Chemistry of Pseudopeptides[8-9]:-

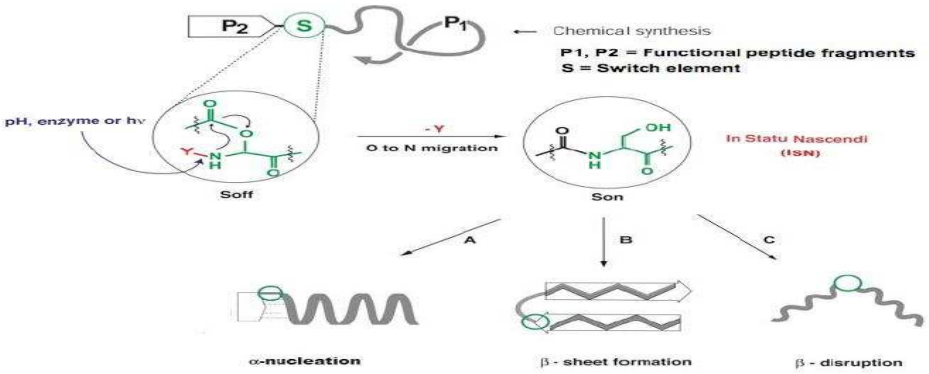

Fig 4: Chemistry of Pseudopeptides

Penetration of Pseudopeptides:-

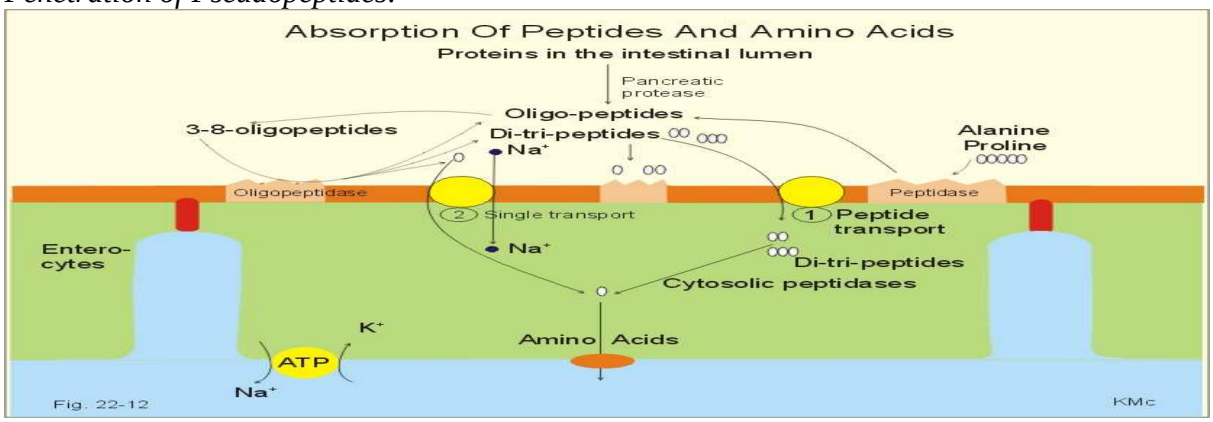

Fig 5: Penetration of Pseudopeptides

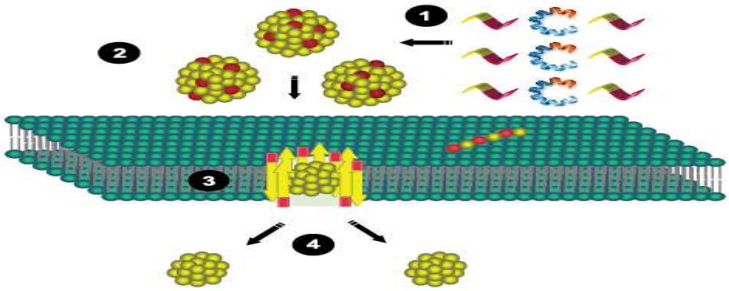

Fig 6: Penetration of Pseudopeptides

GGT(Gamma glutamyltransferase) is involved in the transfer of amino acids across the cellular membrane [10-11].

Classes of Pseudo-peptides:-

With respect to their chemical properties, Pharmacological activity, as well as practical aspects of synthesis:

1) Oligo-glycines: Versatile Oligo N-Substituted Glycines.
2) Beta-peptides: *ß*-Peptides, *y*-Peptides and Isosteric Backbones: New Scaffolds with Controlled Shapes for Mimicking Protein Secondary Structure Elements[12].
3) Gamma-peptides: Regulation of Gene Expression with Pyrrole-Imidazole Polyamides.DNA-like peptide nucleic acids Alpha-helical peptide nucleic acids α-Helical Peptide Nucleic Acids (α-PNAs).DNA-cleaving pseudo-peptides DNA and RNA-cleaving Pseudo-peptides[13].

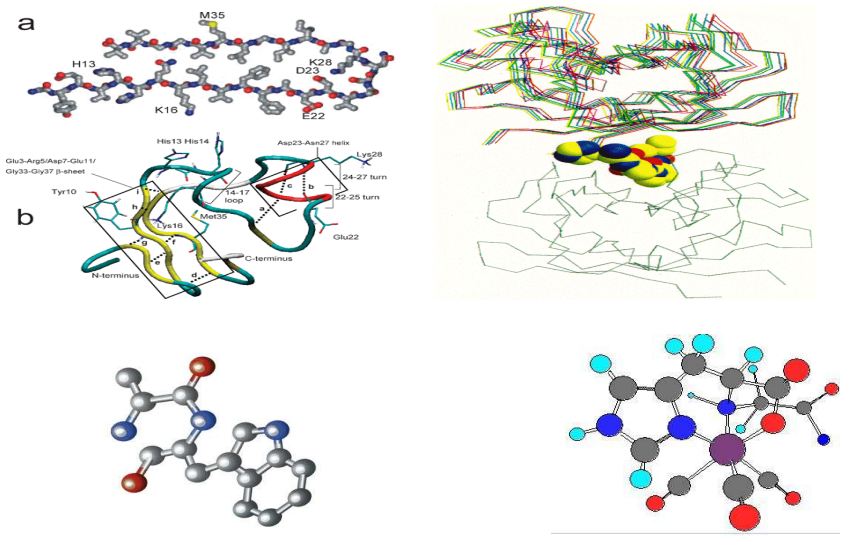

Fig 7: Gamma peptides

Types of Pseudopeptides:-

Beta Amyloid Peptide:-

Beta-amyloid is a peptide that forms amyloid plaques in the brains of Alzheimer's disease (AD) patients[14]. Beta amyloid peptide consists of 43 amino acids. It is created via the enzymatic digestion of amyloid precursor protein (APP) by beta secretase and gamma secretase. Amyloid beta (Aβ or Abeta) is a peptide of 39–43 amino acids that appear to be the main constituent of amyloid plaques in the brains of Alzheimer's disease patients[15].

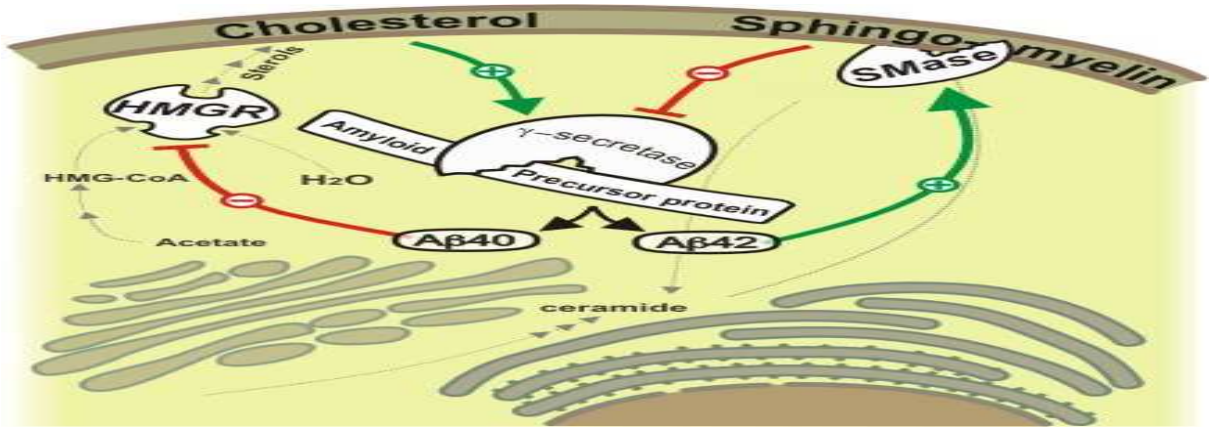

Fig 8: Beta amyloid peptides

Fig 9: Structure of alanine

BACE1 is a vertebrate-specific enzyme, which, together with presenilin-dependent γ-secretase, cleaves APP to generate the neurotoxic amyloid-β peptide (Aβ) [16].

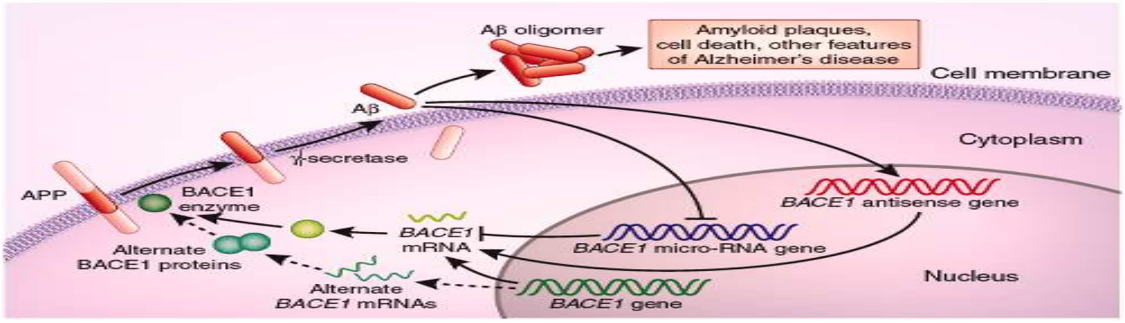

Fig 10: Mechanism of peptides

Application in Alzheimer Disease: - β Amyloid Control can help to control Alzheimer Disease

- β-Secretase inhibitors. These work to block the first cleavage of APP outside of the cell.

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- γ-Secretase inhibitors (e. g. Semagacestat). These work to block the second cleavage of APP in the cell membrane and would then stop the subsequent formation of Aβ and its toxic fragments.

- Selective Aβ42 lowering agents (e. g. Tarenflurbil). These modulate γ-secretase to reduce Aβ42 production in favor of other (shorter) Aβ versions.

- Immunotherapies: These stimulate the host immune system to recognize and attack Aβ or provide antibodies that either prevent plaque deposition or enhance clearance of plaques.

- Anti-aggregation agents: These prevent Aβ fragments from aggregating or clear aggregates once they are formed.

- Amyloid beta (Aβ or Abeta) is a peptide of 39–43 amino acids that appear to be the main constituent of amyloid plaques in the brains of Alzheimer's disease patients.

Gamma peptides:

Pyrrole-imidazole polyamides :Pyrrole-imidazole polyamide (PIP) is a nuclease-resistant novel compound that inhibits gene expression through binding to the minor groove of DNA. Human aurora kinase-A (AURKA) and -B (AURKB) are important regulators in mitosis during the cell cycle. It also Inhibits Expression of the Human Transforming Growth Factor- B1 Gene. A pyrrole–imidazole polyamide targeting transforming growth factor-β1 inhibits restenosis and preserves endothelialization in the injured artery.

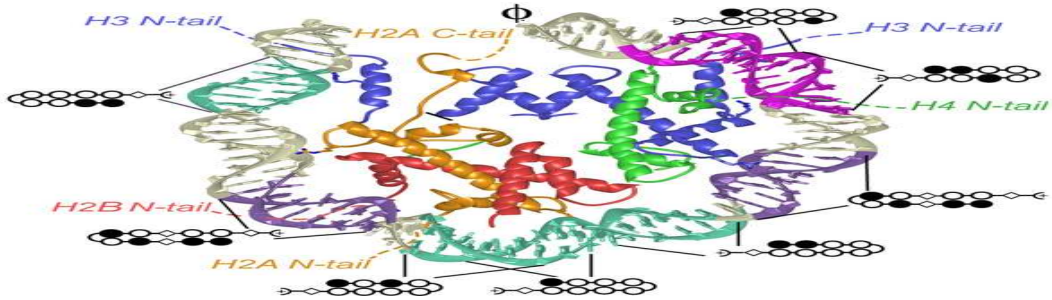

Fig 11: Gamma peptides

Peptide Nucleic Acids:

- Peptide nucleic acids (PNA's), a new, completely artificial DNA/RNA analog. The most impressive property of PNA's are their ability to form extremely stable complexes with complementary DNA oligomers.

- The PNA monomer is 2-aminoethyl glycine linked by a methylenecarbonyl linkage to one of the four bases (adenine, guanine, thymine, or cytosine) found in DNA. Like amino acids, PNA monomers have amino and carboxyl termini. Unlike nucleotides, PNA's lack pentose sugar phosphate groups.

- PNA monomers are linked by peptide bonds into a single chain oligomer. By convention, the PNA oligomer is depicted like a peptide with its N-terminus at the first position. However, this end corresponds to the 3' end of a DNA or RNA strand. Hence, the N-terminus of a PNA hybridizes to the 5'-end of complementary single-stranded DNA.

Peptide Nucleic Acids:

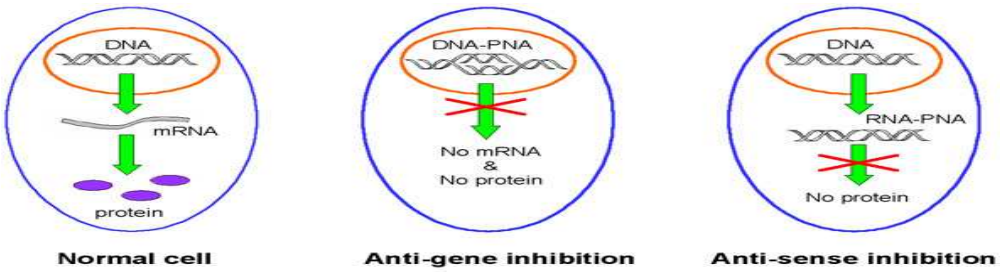

Fig 12: peptides nucleic acids

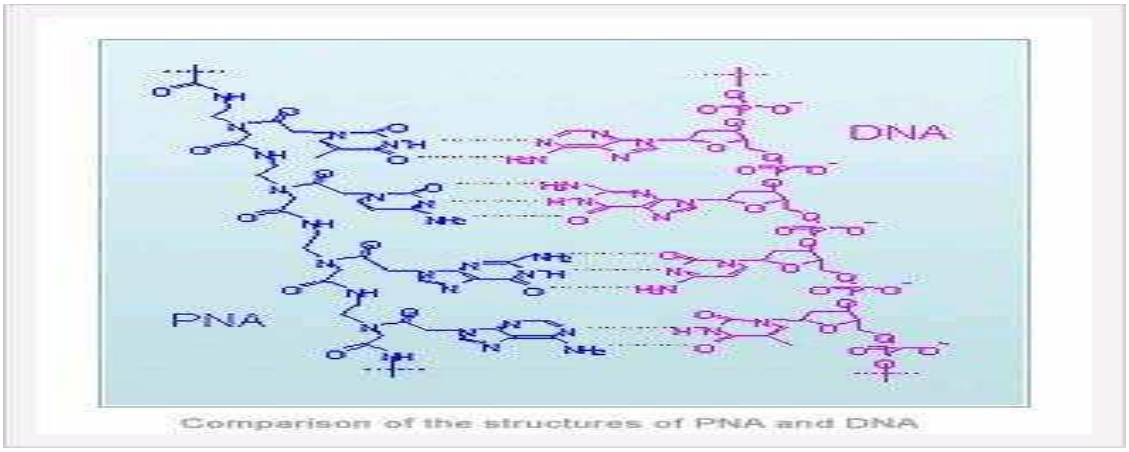

Fig 13: Structure of peptides nucleic acids

DNA Cleaving Pseudopeptides:

A synthetic 52-residue peptide based on the sequence-specific DNA-binding domain of Hin recombinase has been equipped with ethylenediaminetetraacetic acid (EDTA) at the amino terminus.
In the presence of Fe(II), this synthetic EDTA-peptide cleaves DNA at Hin recombination sites. The cleavage data reveal that the amino terminus of Hin is bound in the minor groove of DNA near the symmetry axis of Hin recombination sites. This work demonstrates the construction of a

hybrid peptide combining two functional domains: sequence-specific DNA binding and DNA cleavage.

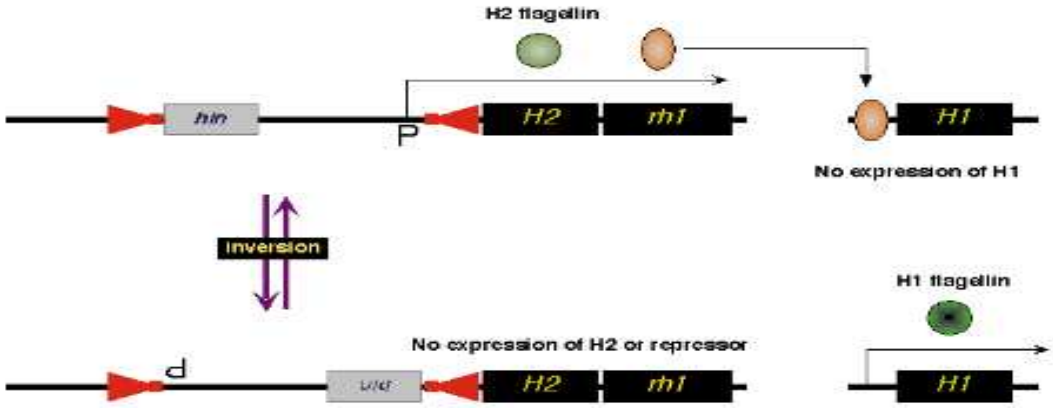

Fig 14: DNA Cleaving Pseudopeptides

Hin recombinase bound to DNA: the origin of specificity in major and minor groove interactions.

IKK beta Peptide:-

- IKK system for targeting NF-kB
- IKKβ is the most important component of IKK, hence IKKβ inhibitors are potentially suitable for treatment of inflammatory diseases.
- Attention should be paid to apoptosis which can be too much enhanced.
- IKKα is critical for antibody production.

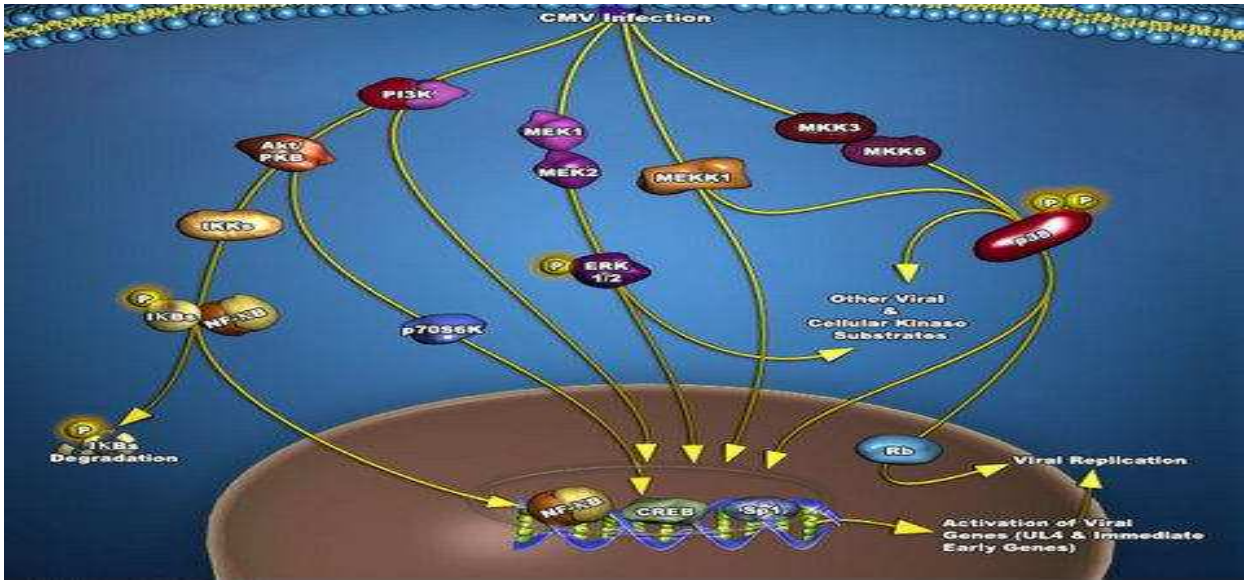

Fig 15: IKK beta Peptide

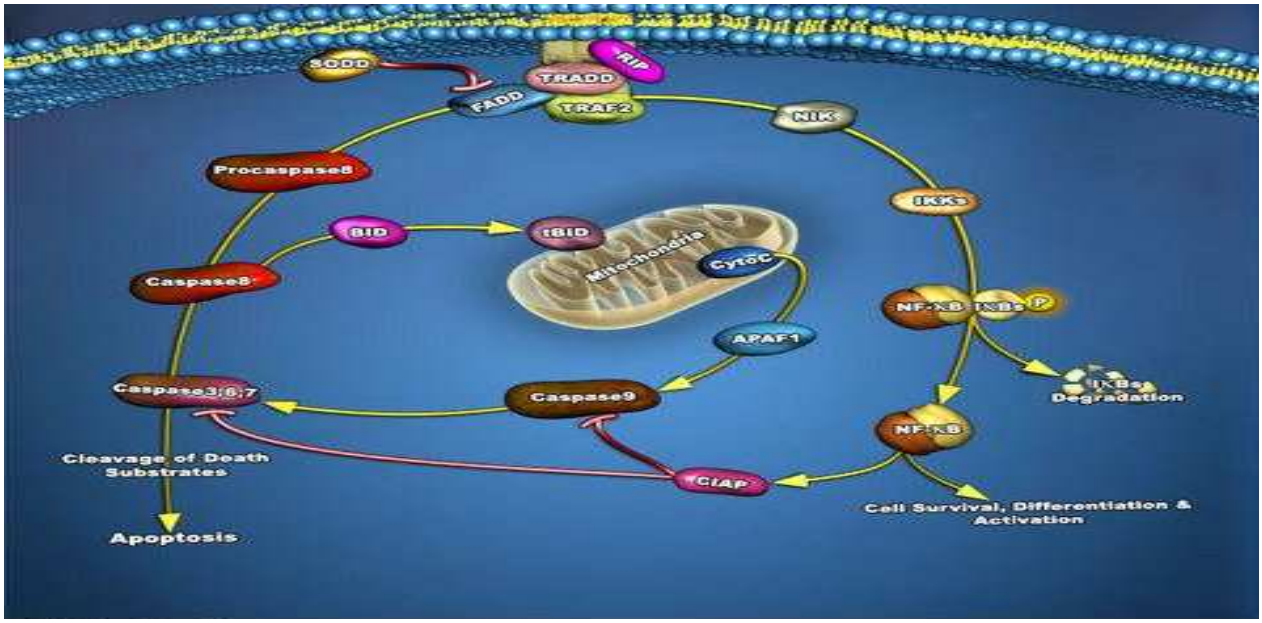

Fig 16: IKK beta Peptide

Examples of Novel Pseudopeptides and their Applications:-

pGlu-His-Amph,
pGlu-His-PEA,
pGlu-His-Amph-Cl,
pGlu-His-PEA-di-BzO,
pGlu-His-DA,
Pro-Leu-Amph
Pro-Leu-Amph-Cl,
Pro-Leu-PEA

- As a novel medicament for depletion of serotonin, an effective amount of a pseudopeptide of the class consisting of pGlu-His-Amph-NO2, pGlu-His-Amph-Cl, Pro-Leu-Amph NO2 and Pro-Leu-Amph-Cl together with a pharmaceutically acceptable carrier.
- As a novel medicament for antidepressive action, an effective amount of a pseudopeptide of the class consisting of pGlu-His-PPD.HCl, and Pro-Leu-PDD, together with a pharmaceutically acceptable carrier.
- As a novel medicament for tranquilizing effect, an effective amount of a pseudopeptide of the class consisting of pGlu-His-BD.HCl, pGlu-His-PP.HCl, Pro-Leu-BD and Pro-Leu-PP together with a pharmaceutically acceptable carrier.
- As a novel medicament for anti-epilepsy activity, an effective amount of a pseudopeptide of the class consisting of pGlu-His-AB and Pro-Leu-AB together with a pharmaceutically acceptable carrier.

- As a novel medicament for analgesic activity, an effective amount of a pseudopeptide of the class consisting of pGlu-His-PT, Pro-Leu-PT and Pro-Leu-NP together with a pharmaceutically acceptable carrier.
- As a novel medicament for asthenia (weakness & loss of Strength), an effective amount of a pseudopeptide of the class consisting of pGlu-His-Amph and Pro-Leu-Amph together with a pharmaceutically acceptable carrier.
- As a novel medicament for sympathomimetric action, an effective amount of a pseudopeptide of the class consisting of pGlu-His-PEA and Pro-Leu-PEA together with a pharmaceutically acceptable carrier.
- As a novel medicament for the treatment of Parkinson's disease, an effective amount of a pseudopeptide of the class consisting of pGlu-His-DA and Pro-Leu-DA together with a pharmaceutically acceptable carrier.

Application:-

Anti-cancer

In cells, protein degradation is a key pathway for the destruction of abnormal or damaged proteins as well as for the elimination of proteins whose presence is no longer required. Among the various cell proteases, the proteasome, a multicatalytic macromolecular complex, is specifically required for the degradation of ubiquitinated proteins. In normal cells, the proteasome ensures the elimination of numerous proteins that play critical roles in cell functions throughout the cell cycle. Defects in the activity of this proteolytic machinery can lead to the disorders of cell function that is believed to be the root cause of certain diseases.

Moreover, because proteasome inhibitors can provoke cell death, it has been suggested that proteasomes must be continually degrading certain apoptotic factors.

For these reasons, proteasome inhibition has become a new and potentially significant strategy for the drug development in cancer treatment. The proteasome possesses three major peptidase activities that can individually be targeted by drugs. New pseudopeptides with the enriched nitrogen backbones bearing a side chain and a modified C-terminal position that inhibit proteasome activity.

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