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PEPTIDOMIMETICS AS A CUTTING EDGE TOOL FOR ADVANCED HEALTHCARE

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ABSTRACT: With exponential advancements in healthcare and pharmaceutical sciences, Peptidomimetics have emerged as essential tools in the designing and development of novel and improvised therapeutics. The peptidomimetic based drugs are designed with the aim of overcoming the shortcomings of natural peptides and proteins. Thus, peptidomimetic therapeutics possesses increased efficiency, stability and overall better pharmacokinetic properties. This review paper outlines the applications and the underlying principles of peptidomimetic based therapeutics in various diseases and issues related to healthcare. Recent advancements in the development of peptidomimetics for Cancer therapy, Renin inhibition, HIV drugs, Analgesics, anti microbials and anti viral drugs have been discussed. Additionally, the applications of peptidomimetics in anti oxidants, anti malarial drugs, blood filtration membranes and as fibrinogen antagonists have also been included.

INTRODUCTION: Proteins, along with the nucleic acids in a cell form the molecular basis of life itself [1]. Proteins are the backbones of almost all the metabolic reactions occurring in any organism. The importance of Peptides to life is evident from the most primitive organism to man. Ranging from the way the hair is curled to the way DNA is coiled; a myriad of roles are filled by Peptides [2]. Thus, they hold the key to solving deepest mysteries of diagnosis and treatment of diseases and disorders [3]. Therefore, from a past few decades there have been extensive research in designing synthetic peptides and proteins for health care [4- 5]. The greatest impediment to this scientific endeavor is the complexity in the structure of Proteins and thus, its synthesis [6]. Peptidomimetics is a state-of-the-art technique that helps in overcoming this barrier [7].

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In 1970, Hughes *et al*., made a striking discovery that laid foundations of a revolutionary branch f Protein Engineering: Peptidomimetics. He observed that the structure of a naturally occurring Opioid molecule: Morphine was similar to N-terminal structure of endogenous opioid peptides, Enkephalins and β-endorphin. The resemblance in the Morphine Phenol system and N-Terminal tyrosine residue in the opioid receptors implied that these molecules also interacted with the opioid receptors in a similar manner and cause similar responses [8-9].

Intrigued by the fact that a non-peptide natural product was having the same effect as that of a natural peptide effector, Farmer hypothesized that other compounds might be discovered which will be non-Peptidic in nature but will "copy" or "mimic" naturally occurring proteins. He introduced the concept of "peptide mimicking" which is now referred to as "Peptidomimetics" [10-11].

Peptidomimetics: Definition and Designing: In the broadest sense, Peptidomimetics are organic molecules which mimic some properties of natural peptide ligands. They are designed by either

making changes in an existing peptide or by designing similar molecules that functional equivalence to peptides [12]. Farmer was the first to define Peptidomimetics as "designing of novel scaffolds to replace the entire peptide backbone while retaining isosteric topography topography of the enzyme-bound peptide confirmation" [13].

Josef Vagner *et al.*, defined Peptidomimetics as "compounds whose essential elements (pharmacophore) mimic a natural peptide or protein in 3D space and which retain the ability to interact with the biological target and produce the same biological effect" [14].

Peptidomimetics are designed to overcome the barriers posed by natural peptides such as premature proteolysis, low availability and less receptor selectivity [15]. This process of designing is initiated by forging structure-activity relationships (SAR) which tell about a minimal active sequence or the chief pharmacophore elements; also they recognize those essential residues responsible for a biological effect. After this, the 3-D arrangements of these features are studied by applying structural constraints. By doing so the peptide complexity reduces and the native pharmacophore model is expressed in 3-D space. This way of modeling keeps up with the re-assembly of critical elements and the non peptide entities on a new modified platform that has the improved pharmacophore attached to the receptor [16-18].

Peptidomimetics have found numerous applications in the fields of drug designing, drug delivery, synthetic hormones, growth factors and many other such aspects of health care where physiology encounters its limits[19-20].

Peptidomimetics: Classification: The various types of peptidomimetics have been classified as below:

Type-I peptidomimetics or pseudopeptides: Type-I peptidomimetics were the first class of peptide based mimics to be invented. They are amide bond isosteres; compounds that contain one or more mimics of molecules near the amide bond [21]. Technically, they are classified as pseudopetides as they contain amino acids that are not found in natural polypeptides. Conventionally, the molecules that mimic the peptide back bone are classified under Type-I peptidomimetics [22]. These compounds have a backbone analogous to the peptide backbone and also retain functional properties so that binding and contact sites remain intact. Type-I peptidomimetics are used to identify targets and make lead compounds for drug design and development [23]. Designing of protease inhibitors for understanding the reaction mechanism of enzyme catalyzed reactions also uses Type-I peptidomimetics [24]. One example of these types of peptidomimetics is Pyrrolinones. They contain side chains similar to peptides that bind to active sites of most peptidases but unlike normal peptides, are resistant to proteolysis [25].

Type-II peptidomimetics or functional mimetics: These are non peptide molecules that bind to a peptide receptor. They are identified and designed by methods like High Throughput Screening and Molecular modelling [26]. A classic example of this class of peptidomimetics is Morphine. Morphine showed responses similar to natural peptides like enkephalins and β-endorphines while binding with endogenous opoid receptors [27]. It is still uncertain if these peptidomimetics mimic the structure of the parent protein and whether they bind to the same subsites as that of parent protein. Despite these gray areas, they have found numerous applications in drug development and lead target identification [28]. Many GPCR antagonists have been developed using this concept [29].

Type-III peptidomimetics or topographical mimetics: This class of peptidomimetics is in accordance with Farmer's original definition of peptidomimetics. They contain a novel non peptide scaffold on which additional functional groups are attached and thus, they are also called topographical mimetics [30]. X-ray structural determining methods are used to compare both the peptide derived compound and non peptide mimic [31]. Several protease inhibitors have been designed based on this concept. This class of peptidomimetics has proved that molecules with alternate scaffolds and side chains can behave in a similar way as that of natural peptides [32].

Type-IV peptidomimetics or non-peptide mimetics: This class of peptidomimetics has been recently discovered. They are called GRAB-peptidomimetic (group replacement-assisted

binding) [33]. They possess certain functional features similar to Type-I peptidomimetics and can participate in certain unique enzyme interactions. An example of this class of peptidomimetics is Piperidine inhibitors. They are used to make non peptidic rennin inhibitors which are more conformationaly stable than natural protein inhibitors [34].

Peptidomimetics for Cancer therapy: Protein peptide interactions (PPI) are the backbone of all cellular signaling peptides. Metabolic diseases, especially cancer, hack into these PPIs and form a complex network of modified interactions. Understanding these PPIs and concocting methods to counteract them is a fundamental application of Peptidomimetics [35]. Peptidomimetics can be employed, with sufficient efficacy to interfere, inhibit or augment such interactions to engender a normal, homeostatic response [36].

The typical characteristics of a Cancerous cell include decreased cell apoptosis, rapid cell proliferation, and prolonged cell life. Traditional Chemotherapy, Radiotherapy and other non-specific use of therapeutic agents encounter their short comings due to poor specificity and severe side effects which often leads to exacerbation of the situation [37]. Peptidomimetics provides a more target specific approach in dealing with the intricacies of PPIs.

This can be better understood by some potential targets for Peptidomimetic modulation in common carcinogenic pathways. For example, the JAK/STAT pathway has EGF receptor as its target protein and results in head, neck, breast, lung cancer. Peptidomimetics can be used to elicit a desired signaling effect of STAT-STAT homodimer disruption or decreased STAT mediated gene activation [38-39]. Another example is that of Notch pathway which leads to breast, melanoma and medulloblastoma. Peptidomimetics can be employed to disrupt Notch cofactor complex and decreased ERα signalling [40]. The Wnt pathway has Tcf-Lef target proteins which cause intestinal adenocarcinomas, myeloid leukemia and prostate cancer. Peptidomimetics are capable of β-Catenin/Tcf Lef complex disruption, decreased Tcf-Lef mediated gene activation [41].

Interleukin - 1β converting enzyme is an enzyme that converts pro IL-1β to biologically active cytokine IL-1β. This enzyme plays an important role in regulating certain apoptotic pathways that are key to understanding mechanisms of diseases like malaria and even HIV. A class of peptidomimetic has been developed which has exceptionally high affinity for the enzyme. These are called Pyridazinodiazeines and are made by replacing with Val-Ala unit (P3-P2 residues) by a pyrimidineacetic acid surrogate [42-43].

Disruptions of Apoptotic pathways are the key mechanism in many diseases including Cancer. Cancerous cells undergo uninterrupted mitosis as they are capable of evading the Apoptotic machineries. BCL-2 family proteins play a major role in the regulation of apoptosis [44]. Amphipathic α-helical BH3 segment is a "death domain" which mediates the interaction between BCL-2 members. Exploiting this pathway, BH3 peptidomimetics have been designed with "hydrocarbon stapling" method which are protease resistant, have better cell permeability and also increased affinity for BCL-2 proteins [45].

In Hydrocarbon stapling, there is a synthetic brace attached to it which enhances its pharmacological properties. These peptidomimetics are called SAHBS (Stabilized alpha-helix of BCL-2 domains). This technique was tested *in vivo* and the results were promising on human leukemia xenografts [46].

TABLE 1: PETIDOMIMETICS FOR CANCER THERAPY

Peptidomimetic Backbone	Homologous natural Peptide	Advantage	Principle of Design	Reference
β Peptides	α amino acids	a) Confirmational Versatality b) Greater *in-vivo* stability	14 β3 helices utilized to support the p53 side chain responsible for interaction with HDM-2	47
β Hairpins	HDMM-2 bound p53 α Helix	a)Display localized group of amino acids b) Recognize partner	The intermolecular separation between Cα atoms of F-19 and W-23 on the surface of an α Helix attached to a HDM-2 attached to p53 is	48

		proteins c) Conformationally constrained peptides	similar to the separation between the C atoms of 2 amino acids in the hairpin.	
Chlorofusin Peptidomimetic	9 residue cyclic peptide of a fungal metabolite	High affinity and selective binding	An ester system attached to a chromophore which is responsible for the identification of HDM2.	49
Terphenyls	α Helix	Mimic side chains amino acids which are not adjoining but are a site for active protein peptide interactions	Phenyl rings have structural properties similar to α helices when they possess a staggered confirmation. In addition, alkyl substituents are attached at regular intervals to make their structure mimic α helices.	50
Tryptophan based Peptidomimetic	Multiple residues	Low molecular weight and high binding affinity	Acyltryptophanylpiperazides and indole-substituted) tryptophan peptidomimetic. a) phenoxy moiety mimics a side chain of p53. b) W23 is mimicked by a Tryptophan substituted on C5 or C6 position.	51

Peptidomimetics for Renin Inhibitors: Renin inhibitors refer to a type of pharmaceutical drugs used essentially in the treatment hypertension. The mechanism of these drugs is based on inhibiting the first step of the renin–angiotensin–aldosterone system (RAAS). This is a rate limiting step which involves the conversion of angiotensinogen toangiotensin I. As a consequence, there is a complete absence of Angiotensin II. This is based on the fact that renin only acts to inhibit this step unlike Angiotensin converting Enzyme which is also involved in other metabolic reactions [52]. The first attempts to make potential inhibitors acceptable oral bioavailability were made in 1970s. The process was arduous and time consuming. The first and second generations faced hindrances such as poor bioavailability and less efficiency. The third generation of these drugs lead to a drastic improvement.

These compounds were non peptidic renin inhibitors. They had sufficient oral bioavailability were fairly potent for clinical use. The first drug of this type to get a market approval; Aliskiren, was the only available Renin inhibitor till 2012 [53].

A novel strategy has recently been developed for these Peptidomimetic Renin Inhibotors. They use Bioactive Hydroxythelene Dipeptide Isoesters with Hydrophobic P3-P1 moieties [54].

The synthesis of novel truncated -amino-hydroxyethylene dipeptide isosteres lacks the P4-P2 peptide backbone. Also, a hydrophobic P3 moiety is covalently linked to either the P1 sec-butyl side chain or P1 cyclohexylmethyl of the of a transition state mimic via an alkyl spacer. This peptidomimetic was successful in inhibiting human renin at the sub-micromolar level. This showed that the use of peptidomimetic lead to a significant increase in binding affinity to the enzyme as compared to the previous classes of drugs which were based on isoesters[55].

Peptidomimetics to combat HIV: Peptidomimetics are also being researched upon for applications against the HIV virus. HIV virus initiates it's infection by the interaction of its capsid envelope glycoprotein gp120 and human CD4. This results in gp120 binding with a coreceptor like CCR5 and CXC4. The present approach for clinical anti HIV drugs inhibit viral replication after infection [56].

This approach has failed to develop a full proof cure due to high mutation rate of HIV and drug resistance. To overcome this drawbacks an entirely different approach involving peptidomimetics has been developed. A peptidomimetic has been developed from the CD4 binding natural peptide NMWQKVGTPL.

All the amino acids not contributing to binding like Aspargine, Glutamine and Methionine were eliminated and the two hydrophobic amino acids tryptophane and leucine were replaced by synthetic hydrophobic non amino acid residues. Other additional non-peptide linkages have also been introduced. The resulting mimetic showed 170 times higher binding affinity to CD4 and 5 times higher proteolytic stability compared to the original peptide. The additional advantage of possessing a lower molecular weight also added to its better pharmacological properties [57 - 58].

TABLE 2: PEPTIDOMIMETIC DRUGS FOR HIV

Name of Peptidomimetic	Design Criteria	Special Groups added	Features	References
Saquinavir	HIV-1 Protease acts on sites containing specific pairs of amino acids. Saquinavir is designed to be equivalent to those sites.	Decahydrosoquioline (DIQ)	i) Aqueous solubility ii) Limited conformational freedom of inhibitor	59
Ritonavir	Inhibits HIV-1 protease by blocking its binding site.	Pyridyl groups instead of terminal phenyl residues	i) Strong inhibitor of cytochrome P450 enzyme ii) used only in a combination therapy	60
Indinavir	Designed to be an analogue of the cleavage site of HIV protease.	Terminal Phenyl groups	i) Hydroxy ethelene backbone ii) Increased potency	61
Nelfinavir (non peptidomimetic)				62
Amprenavir	N,N-disubstituted amino-sulfonamide non peptide	One end has tetrahydofuran carbamte and other end has isobutylphenyl sulphonamide	i) Fewer ciral centers: ease of synthesis ii) Enhanced aqueous solubility	63
Lopinavir	Forms a complex with the enzyme that cripples its activity.	Phenoxyacetyl group and modified Valine with 6 membered cyclic urea ring	i) Greater bioavailability ii) Core similar to Ritnovir	64
Fosamprenavir	Phosphoester pro drug of amprenavir		i) Better solubility ii) Better bioavailability (than amprenavir)	65
Atazanvir	Similar to Ritunavir	Azapeptides	i)Better resistance profiles than previous inhibitors ii) Can only be absorbed under acidic environment	66
Tiranvir	Non peptidic Coumarin template	Sulfonamide containing a hydroxyl and a pyrone group	i) Broader anti-viral activity ii) Discovered by high throughput screening	66
Darunavir	Non peptide analogue of Amprenavir	Bis-THF moiety	i) Has the ability to form a complex with proteases that have become resistant to Amprenavir	67

Analgesic Peptidomimetics: Peptidomimetics have also found applications in the making of Analgesics. The analgesic peptidomimetics mimic Leu-Enkephalin. Leu-enkephalin is an endogenous opioidpeptide neurotransmitter with the amino acid sequence Tyr-Gly-Gly-Phe-Leu. This is commonly found sequence in the central nervous system of many animals, including humans. It is one of the two forms of enkephalin; the other is met-enkephalin. The tyrosine residue at position 1 is found to be equivalent to the 3-hydroxyl group on morphine. Leu-enkephalin has agonistic actions at both the μ- and δ-opioid receptors. A peptidomimetic called TP11879-26 has been made which has an Opoid receptor and thus acts as an analgesic [68]. Another approach is targeting the neuronal voltage-gated N-type calcium channel ($Ca_v2.2$).

Peptidomimetics have been made which belong to the library of anthranilamide-derived ω-Conotoxin GVIA mimetics. They have the diphenylmethyl piperazine moiety which works for Calcium channel blockade. This imparts analgesic property to that Peptidomimetic [69].

Peptidomimetic Anti-microbial drugs: Resistance of microbes to different antibiotics is a growing health concern in various parts of the world. Antimicrobial peptide molecules are what have been in use for defense against microbes. But, they have intrinsic drawbacks, such as susceptibility to enzymatic degradation, toxicity, and high production cost [70]. Peptidomimetic methods for creating Antimicrobial peptides have been recently discovered that help in resistance against multi-drug resistant bacteria, while overcoming the drawbacks of the already in use, Antimicrobial peptides. Hu *et al.,* [71] and Niu *et al.,* [72] reported the development of a new class of peptidomimetics termed "AApeptides", and depending on the position of the side, they have been divided into two subclasses: α-AApeptides and γ-AApeptides[73].

Peptidomimetics as Fibrinogen Antagonist: Platelet aggregation is a crucial step in mechanisms like blood clotting and has implications in many cardio-vascular diseases like myocardial infarction, ischemic attacks and strokes. In the process of blood clotting and platelet aggregation, the last step involves the binding of fibrinogen to receptor - glycoprotein IIb / IIIa (GP IIb / IIIa) on the surface of activated platelets. This mechanism is being targeted in recent years to develop fibrinogen antagonists for application in preventing Thrombosis[74]. Fragments of RGD (Arg-Gly-Asp) sequence have been mimicked which are responsible for the binding of Fibrinogen to GP IIb/IIIa.

Non peptide selective inhibitors like derivatives of benzodiazepines, aminobenzamidino succinyles, isoxazolines, isoquinolines have been made [75]. Further amelioration to these class of drugs was made by a series of RGD-mimetics. They are based 4-oxo-(piperazine-1-yl)butyric acid as Argmimetic and β-aryl-β-alanines as Asp-Phe-mimetics. To modify the natural structure of the fibrinogen receptors, various approaches like cyclization of RGD containing peptides, substitution of major pharmacophores of RGD sequence and designing of peptidomimetics that are conformationally constrained are being used. These peptidomimetic drugs have higher oral bioavailability and potency[76].

Peptidomimetics for Blood Filtration Membranes: Most of the mammalian cells use Integrins, which are trans membrane proteins for cell to cell adhesion by the Extra Cellular Matrix. As far as non peptide mimetics are concerned, covalent surface grafting technique has been developed for blood filtration membrane. It has potential applications for depletion of leukocyte from blood products [77]. The $\alpha_4\beta_1$ integrin plays an important role in the transport of mononuclear leukocytes to sites of inflammation. This integrin binds to ECM fibronectin via the LDV (Leu-Asp-Val) sequence. The sequence is contained in an alternatively spliced segment (CS-1). Due to the role of $\alpha_4\beta_1$ in the inflammatory response, the LDV motif became the key factor in the discovery of (non-peptide) small molecule antagonists. The LDV (Leu-Asp-Val) motif is mimicked and a spacer arm is added to it. To increase leukocyte retention, the essential bioactive molecules were fixed to a blood filtration membrane covalently [78].

Peptidomimetic Antiviral drugs: One major application of peptidomimetic anti viral drugs is against Hepatisis C virus. The present treatments for Hepatitis C have several drawbacks like less efficiency and increased side effects. To overcome these shortcomings, a new strategy involving peptidomimetics has been developed. The HCV (Hepatisis C virus) produces a protein called NS3 Serine protease. This protein is essential for the replication of the virus. This makes it is a perfect target for anti viral therapeutics. BILN-2061 is a peptidomimetic created which acts as an inhibitor of NS3 Serine protease. This drug has shown promising results and showed lower levels of serum HCV RNA content [79].

Similarly, peptidomimetic drugs are also being designed against HERES simplex viruses (HSV). HSV produces ribonucleotide reductase enzyme which converts to deoxyribo-nucleotides. This enzyme is formed by the binding of two subunits. BILD 1263 is a peptidomimetic designed which inhibits the binding of these units. BILD 1263

mimics the C terminal amino sequence on the smaller subunit. Thus, it competes with the larger subunit in binding with the smaller subunit [80].

Peptidomimetics for Anti-Malarial Drugs: Malaria is a highly threatening wide spreading disease in the tropical countries. Treatment options have slowly started to fail due to the evolution of drug resistance in Plasmodium organisms. Alternate methods are being researched upon and one such example is the peptidomimetic inhibitors of the protein farnesyl transferase wherein Chakrabarthi *et al.*, reported that FTase inhibitor showed inhibition activity against the growth of P. falciparum in human red blood cells. These findings suggested that protein farnesylation in P. falciparum could be a new target for antimalarial agents [81-82].

Antioxidant activity of peptidomimetic drugs: Among peptidomimetics, DOPA derivatives play an important role in the therapy of Parkinson disease (PD). PD is one of the most important neurodegenerative disorder, characterized by dopamine (DA) depletion in dopaminergic neurons of the striatum of the brain. DOPA peptides are able to increase the capacity of DOPA in penetration of the blood brain barrier (BBB)5 by specific peptide-mediated carrier transport systems (PMCTS). Thus, adequate DA concentration is restored which leads to inhibition of cell damage due to oxidation. These mimetics also act as supportive molecules for drugs. They protect the drug from fast metabolism and also prevent side effects [83].

Other examples of peptidomimetic antioxidant are β-alanylhistamine and L-prolylhistamine which possess resistance to enzymatic hydrolysis. Natural peptides like L-carnosine have proven to be ineffective due to hydrolytic enzymes [84].

CONCLUSION: There is a wide range of diseases that require treatments based on proteins and peptides. As described, in this review, considerable research and development has been done to enhance and improvise protein based therapeutics using peptidomimetics. A number of examples cited in this review support the fact that peptidomimetics have proven to be advantageous over conventional drugs and have opened new gateways for pharmaceutical sciences and drug therapies in not only one, but many diseases and healthcare issues. However, further research is required for improvising designing techniques for peptidomimetics. A major impediment in the field of peptidomimetics is that there are thousands of natural peptides available but due to complexities in structures, only a few can be mimicked to form useful drugs. Thus, further advancements are required in identifying protein sequences and metabolic pathways which can be exploited to design peptidomimetics. Hence, a lot of work needs to be done to completely replace conventional protein therapeutics with a new class of peptidomimetic drugs.

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