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Therapeutic importance of peptidomimetics in medicinal chemistry

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ABSTRACT

Today there is a highly elevated demand for synthesis and screening of nature-like biopolymers and their more stable modified derivatives like peptidomimetics because availability of huge amounts of genomic and proteomic data can contribute for research in this area. The design and synthesis of peptidomimetics are most important because of the dominant position peptide and protein-protein interactions play in molecular recognition and signaling, especially in living systems. The design of peptide mimetics can be viewed from several different perspectives and peptidomimetics can be categorized in a number of different ways. Study of the vast literature would suggest that medicinal and organic chemists, who deal with peptide mimics, utilize these methods in many different ways. This manuscript is an endeavor to discuss a variety of methodologies and strategies to develop and establish systematic tools for transformation of peptides into peptidomimetics or further into small drug-like molecules and their pharmacological activities having significance in modern drug design.

Keywords: Peptidomimetics, synthesis, pharmacological activities, drug design.

INTRODUCTION

Advancement of drug discovery methods in medicinal chemistry has enabled the medicinal chemists to design and develop novel drug molecules which can be used effectively in the treatment of various human diseases. A brief introduction of some of the recent techniques of drug design like molecular docking, quantitative structure activity relationship, chemogenomics

and marine pharmacology with special emphasis on peptidomimetics has been mentioned here as given below:

Molecular docking: It is routinely used for understanding the drug-receptor interactions in modern drug design and it is considered to be a significant technique which holds great promise in the field of computer based drug design by screening small molecules by orienting and using them in binding site of a protein receptor [1].

Quantitative structure-activity relationship (QSAR): It is an important method in research for rational drug design and the mechanism of drug actions. In addition, it is useful in areas like the design of virtual compound libraries and the computational chemical optimization of compounds. QSAR studies can express the biological activities of compounds as a function of their various structural parameters and also explains that the variation in biological activity depends on changes in the chemical structure [2].

Chemogenomics: It represents a new approach for target receptor identification and drug development. Chemogenomics combines the latest tools of genomics and chemistry including chemical libraries by screening large chemical libraries quickly and efficiently against selected target receptors which can create new treatments for many human diseases [3].

Marine Pharmacology: Natural drug discovery from marine organisms has indicated that these are novel and promising sources of biologically active compounds. They produce a variety of metabolites, some of which can be used for drug development. In past few years, significant numbers of novel metabolites with potent pharmacological properties have been discovered from the marine organisms and at present time also several novel compounds derived from marine natural products are now in the drug design pipeline with more scope of clinical development [4].

Peptidomimetics: Use of peptidomimetics is one of the most recent methods of drug design and development in medicinal chemistry. These are small protein-like chains which are designed to mimic a peptide. They typically arise either from modification of an existing peptide, or by designing similar systems that mimic peptides, such as peptoids and β-peptides [5]. The altered chemical structure is designed to advantageously adjust the molecular properties such as, stability or biological activity [6]. This can have a role in the development of drug-like compounds from existing peptides. These modifications involve changes to the peptide that will not occur naturally (such as altered backbones and the incorporation of nonnatural amino acids) [7]. For example anticancer peptidomimetics can bind to target proteins in order to induce cancer cells into a form of programmed cell death called apoptosis by mimicking key interactions that activate apoptotic pathway in the specified cells. This shows that peptidomimetics can play vital role in the treatment of various types of cancers [8].

Classification

The various types of peptidomimetics have been classified as below:

Type-I peptidomimetics or pseudopeptides: These are synthesized by structure based drug design. These peptidomimetics are closely similar to peptide backbone while retaining functional groups that makes important contacts with binding sites of the receptors. Some units mimic short

portions of secondary structure of peptide for example p-turns and have been used to generate lead compounds. Many early protease inhibitors were designed from substrate/product mimetics of the peptide bond in a transition state or product state for the enzyme-catalyzed reaction. For example Pyrrolinones contains peptide-like side-chains that fit the active sites of most peptidases and also these are resistant to normal proteolysis because they replace amide bonds with metabolically stable units on amino acid unit of parent peptides.

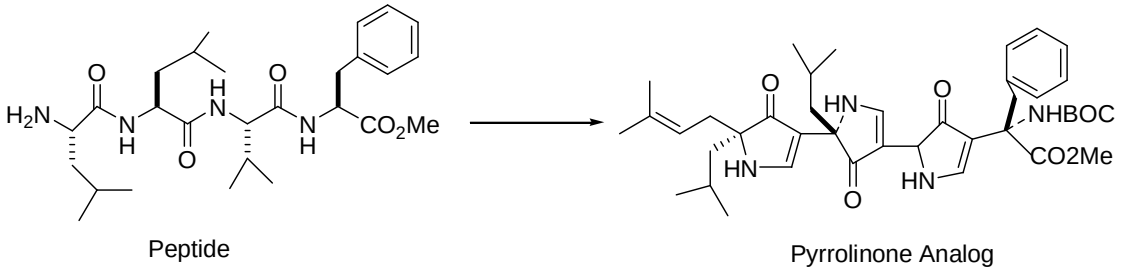

Fig. (1): Correlation of pyrrolinone-based peptidomimetics and the parent peptide.

Type-II peptidomimetics or functional mimetics: These peptidomimetics are synthesized by molecular modeling and high throughput screening (HTS) etc. These are small non-peptide molecule that binds to a peptide receptor. Morphine was the first well-characterized example of this type of peptidomimetic. Initially, type I1 mimetics were considered to be direct structural analogs of the natural peptide, but characterization of both the endogenous peptide and antagonist's binding sites by site-directed mutagenesis indicate that antagonists for a large number of receptors seem to bind to receptor subsites different than those used by the parent peptide. Consequently, functional mimetics may not mimic the structure of the parent peptide. Despite this uncertainty, the approach has been quite successful and produced a number of potential drug lead structures. For example G-protein coupled receptor (GPCR) antagonists.

Type-III peptidomimetics or topographical mimetics: These are synthesized by structure based drug design which represents that they possess novel templates, which appear unrelated to the original peptides but contain the essential groups, positioned on a novel non-peptide scaffold to serve as topographical mimetics. Several type III peptidomimetic protease inhibitors have been characterized where direct X-ray structural determination of both the peptide-derived inhibitor and the heterocyclic non-peptide inhibitor complexes have been compared. These examples demonstrate that alternate scaffolds can display side-chains so that they interact with proteins in fashion closely related to that of the parent peptide for example non-peptide protease inhibitors.

Type-IV peptidomimetics or non-peptide mimetics: These are synthesized by Group Replacement Assisted Binding (GRAB) technique of drug design. These structures might share structural functional features of type I peptidomimetics, but they bind to an enzyme form not accessible with type I peptidomimetics for example piperidine inhibitors [9].

Methods of synthesis

Several approaches which have been used for the synthesis of peptidomimetics are discussed as below:

1. Synthesis of N,N′-orthogonally protected trithiocarbonate-linked dipeptidomimetics: N-Protected amino alkyl thiols were treated with carbon disulphide in the presence of triethylamine (TEA) to generate trithiocarbonate salt, which upon reaction with appropriate halides afforded dipeptidomimetics in good yields. Further, the procedure was extended for the synthesis of *N*,*N*′-orthogonally protected trithiocarbonate-linked dipeptidomimetics [10].

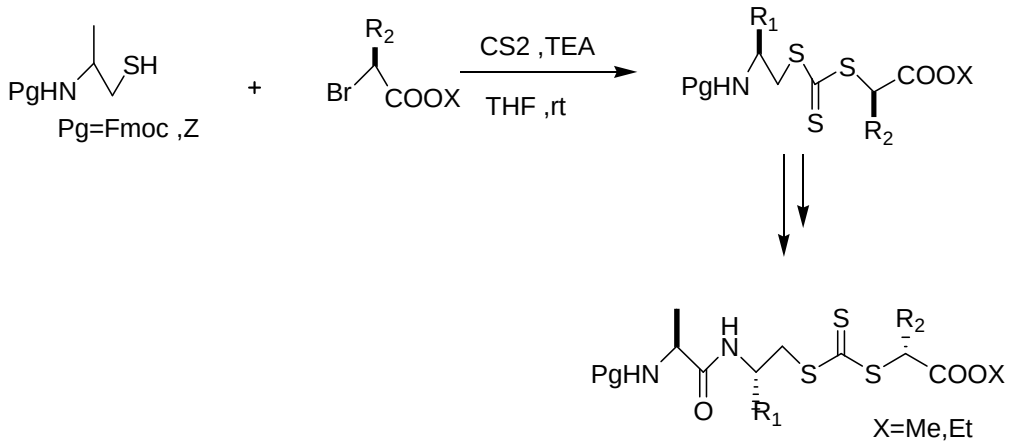

Fig. (2): Synthesis of N,N-orthogonally protected trithiocarbonate-linked dipeptidomimetics.

2. Synthesis of pyrrolidinones and pyrrolidines peptidomimetics: Protected diaminoalcohols obtained through allyl addition to α-amino acid-derived imines and subsequent hydroboration were used for the preparation of pyrrolidinones and pyrrolidines. Pyrrolidinones were synthesized with moderate yields by oxidation of the hydroxy function with tetrapropylammonium perruthenate/*N*-methylmorpholine-*N*-oxide and concomitant cyclization while pyrrolidines were synthesized in good yields by tosylation of the hydroxy group and subsequent intramolecular nucleophilic substitution. Thus accessible substrates were transferred into peptidomimetics by attachment of amino acid moieties at both termini using conventional peptide coupling strategies [11].

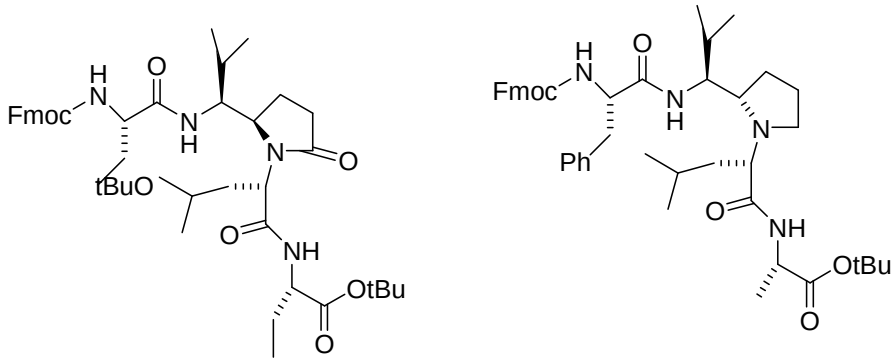

Fig. (3): Synthesis of pyrrolidinones and pyrrolidines peptidomimetics.

3. Synthesis of glyoxylamide peptidomimetics: Novel mono- and bis-glyoxylamide peptidomimetics were prepared via the facile ring-opening of *N*-acylisatins with amino acids and peptide derivatives. The ring-opening of *N*-acylisatins with dipeptides and tripeptides was

discovered to be the most efficient strategy for the synthesis of second and third generation glyoxylamides [12].

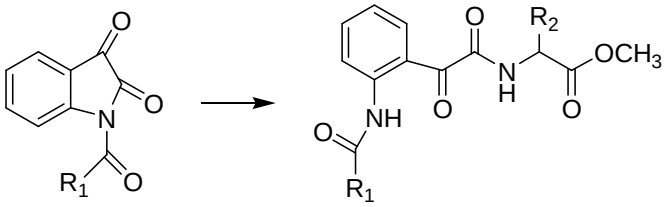

Fig. (4): Synthesis of glyoxylamide peptidomimetics.

4. Synthesis of peptidosulfonamides: Peptidosulfonamides can be synthesized by solid-phase synthesis methods using either a Merrifield or a Tentagel® resin. The possibility to prepare cyclic peptidosulfonamides was illustrated by the synthesis of cyclo-phenylalanyl[$CH_2S(O)_2N$]-glycine. However, translation of synthesis of peptidosulfonamides in solution to a solid-phase method was rather laborious and still requires careful optimization [13].

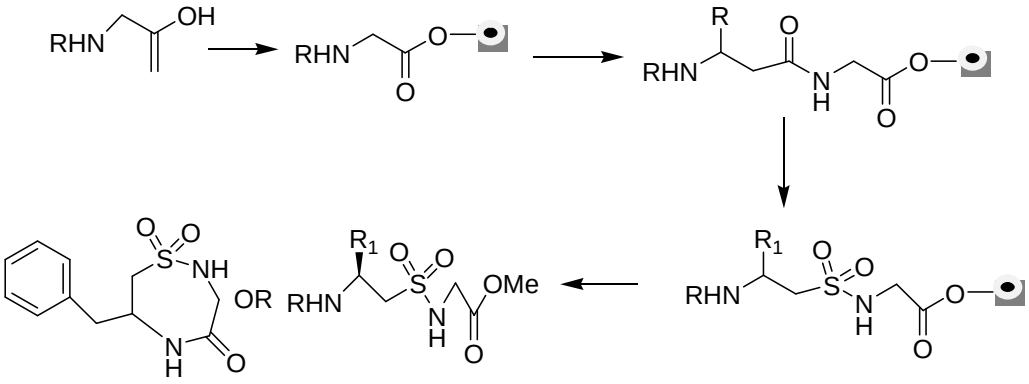

Fig. (5): Synthesis of peptidosulfonamides.

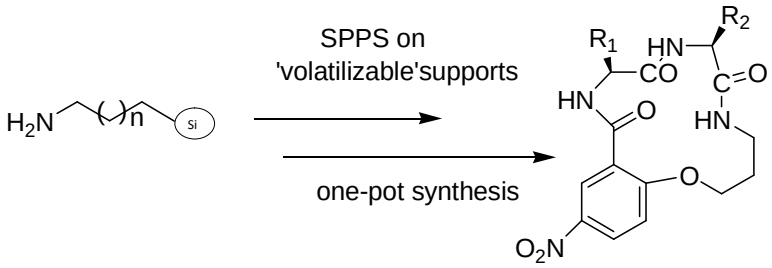

Fig. (6): Synthesis of C-hydroxyalkylamido peptidomimetics.

5. Synthesis of C-hydroxyalkylamido peptidomimetics: A promising method for the high-throughput synthesis of linear C-hydroxyalkylamido peptidomimetics and beta-turn cyclic peptidomimetics via "volatilizable" aminoalkyl functionalized silica gels is presented. Boc amino acids and carboxylic acids were coupled on functionalized aminoalkyl silica gels using a standard DIC/HOBt coupling protocol. After peptide synthesis, the resin bound peptide was cleaved using a two-step process to obtain the linear C-hydroxyalkylamido peptidomimetics.

Beta-turn cyclic peptidomimetics were generated by intramolecular S(N)Ar cyclization in an aqueous solution. Both the linear and the cyclic peptidomimetics were obtained with good to excellent yields and purities through a "one-pot" reaction [14].

6. Synthesis of sulfamate peptidomimetics: Sulfamoylation in the solid phase using sulfamoyl chloride followed by the acylation of the corresponding sulfamoylated product. The presence of protected amino functions on the building blocks opens the possibility of the addition of more diversity. This approach,which is compatible with Fmoc/Boc/Alloc protection, provides a useful and efficient tool for the preparation of new sulfamate peptidomimetics [15].

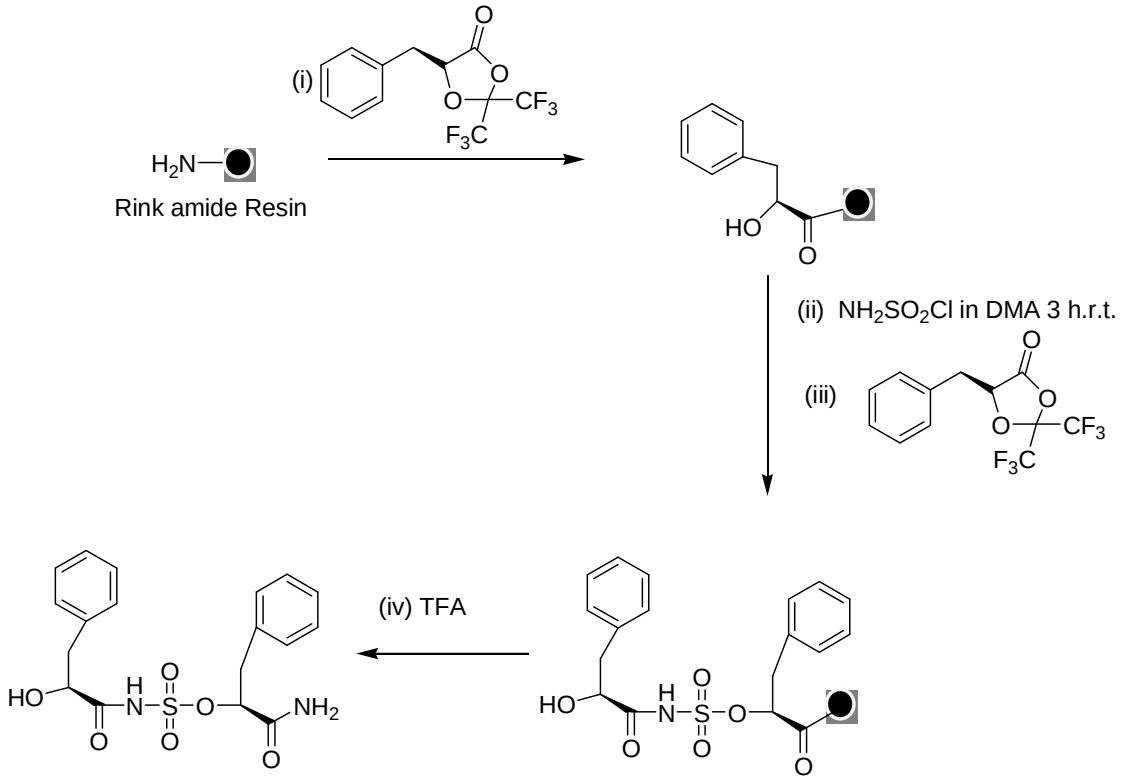

Fig. (7): Synthesis of sulfamate peptidomimetics.

Pharmacological activities

The various types of pharmacological activities displayed by peptidomimetics have been discussed as below:

1. Anti-microbial activity

Srinivas *et al.* developed some novel peptidomimetic antibiotics based on the antimicrobial peptide protegrin I to combat the growing health threat posed by resistant pathogenic microorganisms. Several rounds of optimization gave a lead compound that was active in the nanomolar range against Gram-negative *Pseudomonas* species. Biochemical and genetic studies showed that the peptidomimetics had a non-membrane-lytic mechanism of action and identified a homolog of the beta-barrel protein LptD (Imp/OstA), which functions in outer-membrane

biogenesis, as a cellular target. The peptidomimetic showed potent antimicrobial activity against *Pseudomonas aeruginosa* in a mouse septicemia infection model [16].

Gram-positive bacteria utilize surface protein virulence factors such as the MSCRAMMs (microbial surface components recognizing adhesive matrix molecules) to aid the initiation and propagation of infection through adherence to host endothelial tissue and immune system evasion. These virulence-associated proteins generally contain a C-terminal LPXTG motif that becomes covalently anchored to the peptidoglycan biosynthesis intermediate lipid II. In *Staphylococcus aureus*, deletion of the sortase isoform SrtA results in marked reduction in virulence and infection potential, making it an important antivirulence target. The chemical synthesis and kinetic characterization of a nonhydrolyzable phosphinic peptidomimetic inhibitor of SrtA derived from the LPXTG substrate sequence was demonstrated by Kruger *et al*. This phosphinic peptidomimetic inhibitor of SrtA showed significant anti-microbial activity [17].

Infectious disease is a critically important global healthcare issue. Gregory *et al.* attempted to bridge the research areas of natural host defense peptides (HDPs), a component of the innate immune system, and biocidal cationic polymers. Recently discovered peptidomimetics and other synthetic mimics of HDPs, that can be short oligomers as well as polymeric macromolecules, provide a unique link between these two areas. An emerging class of these mimics are the facially amphiphilic polymers that aim to emulate the physicochemical properties of HDPs but take advantage of the synthetic ease of polymers. These mimics have been designed with antimicrobial activity and, importantly, selectivity that rivals natural HDPs. In addition to providing some perspective on HDPs, selective mimics, and biocidal polymers, focus is given to the arsenal of biophysical techniques available to study their mode of action and interactions with phospholipid membranes. The issue of lipid type is highlighted and the important role of negative curvature lipids is illustrated. Finally, materials applications (for instance, in the development of permanently antibacterial surfaces) are discussed as this is an important part of controlling the spread of infectious disease [18].

2. Anti-cancer activity

Yung-Feng *et al.* synthesized some novel unnatural amino acid-substituted (Hydroxyethyl)urea peptidomimetics which inhibited secretase, the neuronal differentiation of neuroblastoma cells and also interfered with tumorigenesis and the malignancy of neuroblastomas. Which shows that these peptidomimetics can be used as lead compounds for further development of novel anticancer drugs [19].

Epidermal growth factor receptor (EGFR) kinase and the related human epidermal growth factor receptor-2 (HER2, ErbB2) are two growth factor receptors that have implications in cancer. The over expression or activation of HER2 occurs frequently in breast, ovarian, and lung cancers, making it an important therapeutic target in the treatment of cancer. Blocking HER2-mediated signaling with antibodies or small molecules has been shown to be effective in inhibiting cell growth. After analyzing the crystal structure of the HER2-herceptin complex, several peptidomimetics (HERP5, 6 & 7) were designed by Satyanarayanajois *et al.* to inhibit HER2-mediated signaling for cell growth.. Two of the compounds (HERP5 and HERP7) exhibited antiproliferative activity, with IC_{50} values of 0.396 μM and 0.143 μM, respectively, against SKBR-3 cell lines (breast cancer cell lines) that overexpress HER2 protein [20].

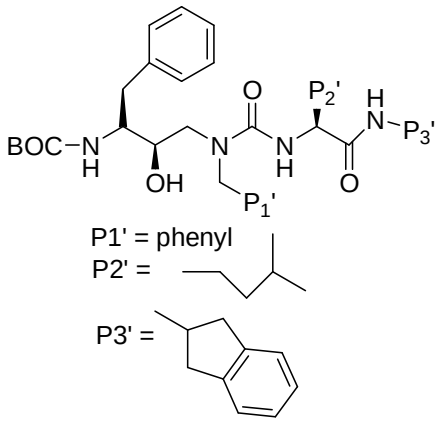

Fig. (8): Chemical structure of unnatural amino acid-substituted (Hydroxyethyl)urea peptidomimetics

Gastrin is a trophic factor in gastrointestinal tumors, including pancreatic cancer, which makes it an interesting target for development of therapeutic antibodies. Screening of microarrays containing bicyclic peptidomimetics by Timmerman *et al*. identified a high number of gastrin binders. A strong correlation was observed between gastrin binding and overall charge of the peptidomimetic. Most of the best gastrin binders proceeded from CDRs containing charged residues. In contrast, CDRs from high affinity antibodies containing mostly neutral residues failed to yield good binders. Our experiments revealed essential differences in the mode of antigen binding between CDR-derived peptidomimetics (K_d values in micromolar range) and the parental monoclonal antibodies (K_d values in nanomolar range). However, chemically derived peptidomimetics from gastrin binders were very effective in gastrin neutralization studies using cell-based assays, yielding a neutralizing activity in pancreatic tumoral cell lines comparable with that of gastrin-specific monoclonal antibodies. These data support the use of combinatorial CDR-peptide microarrays as a tool for the development of a new generation of chemically synthesized cyclic peptidomimetics with functional activity [21].

Lapis demonstrated that host defence peptides (HDP) produced by almost all species of living organisms and widely recognized as antimicrobial antibiotics have also proved to be capable of killing a wide variety of cancer cells. They have many advantages over conventional cytotoxic chemotherapeutic agents. They seem to kill cancer cells by effects on plasma membranes and/or the membranes of mitochondria. They are often effective against multidrug-resistant cells. They have a broad spectrum of activity in that their killing effects are not restricted to particular kinds of cancer. Above all they commonly have few side effects in that they do not have the same detrimental effects on normal cells as they do on cancer cells. It has been demonstrated that HDP and peptidomimetics can be used as effective adjuvants to conventional chemotherapeutic agents. In addition they have effects on neo-angiogenesis which is important in relation to tumour growth. HDP have been shown to be powerful immunomodulators in a number of circumstances and in this respect they are believed to be instrumental in strengthening immunological host defence against cancer cells. Importantly it has also been shown that certain HDP have the capability to alter the capacity of cells to import Ca ions by affecting the location and thus function of calreticulin. Such changes it has been argued are significant in facilitating

the killing of tumour cells by immunogical means. HDP constitute a novel class of anticancer agents [22].

3. Anti-viral activity

In the search for new and effective prodrugs against the herpes simplex virus, a series of acyclovir analogues with a thiazole ring containing amino acids (glycine, alanine, valine, leucine) was investigated by Georgi *et al.* The chemical stability of some of the compounds containing different residues was studied at pH 1 and pH 7.4 at a temperature of 37°C. Some of the esters (Gly-thiazole, Ala-thiazole-acyclovir, Leu-thiazole-acyclovir) were rather unstable, especially under acidic conditions, and underwent rapid hydrolysis into the chemical precursor acyclovir. At pH 7.4, the stability of Valthiazole-acyclovir peptidomimetic was remarkable. At this pH, Val-thiazole-acyclovir peptidomimetic showed stability higher than that of valacyclovir (the first effective prodrug of acyclovir) [23].

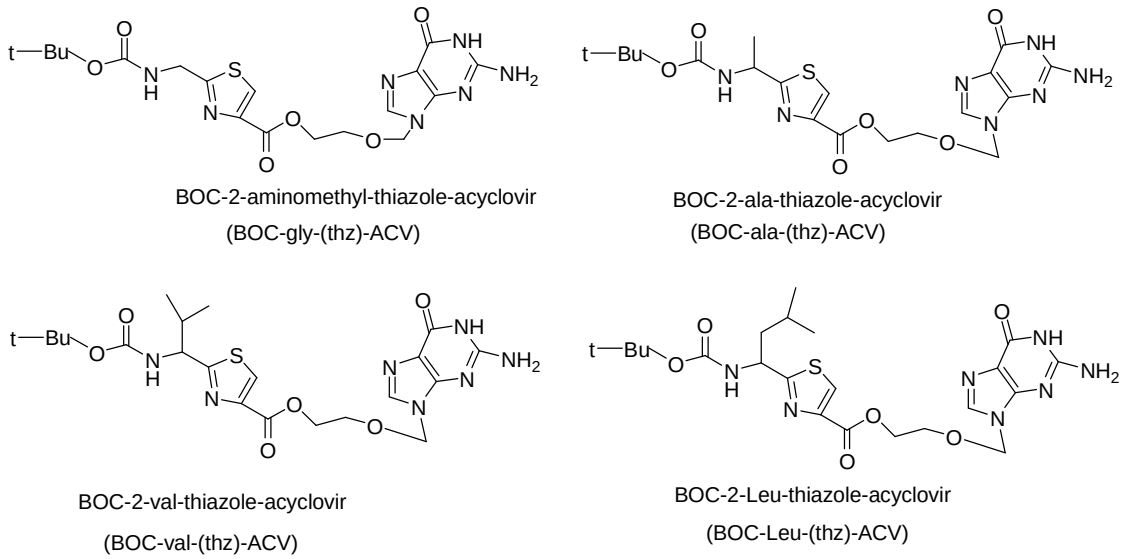

Fig. (9): Chemical structure of Acyclovir ester with peptidomimetics.

4. Immuno detection activity

Murali *et al.* disclosed the finding that antibody like binding peptidomimetics (ABiP) such as Anti-Her2/neu peptidomimetic (AHNP) which is a mimic of Herceptin, a mAb are used for advanced breast cancer therapy. The AHNP has been used as a defining tool to develop immunodetection probes that exemplify a general process application. AHNP has been expressed as an oligomeric fusion protein with streptavidin. These Herceptin like ABiPs were used to detect the Her2/neu antigen at extremely low concentrations using the immunodetection amplification technique (IDAT). A fully developed highly diverse library of ABiPs represents an alternative for panels of monoclonal antibodies and may also be useful for target validation, antigen detection, therapeutics and as a platform for drug development [24].

5. Selectivity for DNA receptors

A peptidomimetic template, consisting of a hydrophobic scaffold, a dansyl fluorophore, and an Arg-His recognition strand, was tested by Jeffrey *et al.* as a simple mimic of zinc finger of the

Zif268 protein. Association constants (K_A's) were on the order of 10^5 M^{-1} for complexes formed between the mimetic and duplexes d(CGGGAATTCCCG)$_2$ and d(AAAAAAAAATTTTTTTTT)$_2$. Modest selectivity was observed for the GC-rich DNA in a 0.5 M NaCl/buffer (0.1 M phosphate, pH 7.0) solution. Differences in K_A's along with observed CD profiles suggest that the mimetic associated with the duplexes using different binding modes. The DNA duplexes had weaker interactions with the free Arg-His recognition strand, the dansyl functional group, and a scaffold that contained only glycines as the recognition strand. The scaffold most likely provides for greater van der Waal's interactions, a larger hydrophobic effect upon association, and reduces the freedom of motion of the side chains. This last effect was confirmed by molecular mechanics calculations and by the fact that the mimetic suffered a smaller loss of entropic energy upon association than the free recognition strand. These studies show that the synthetic scaffold is a promising platform in which peptides can be attached to increase their affinity and possibly selectivity for DNA targets [25].

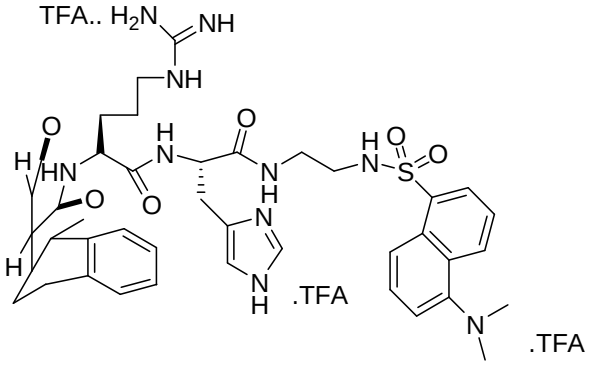

Fig. (10): Chemical structure of peptidomimetic template.

6. Anti-malarial activity

Ettari *et al.* synthesized some novel peptidomimetics bearing a protected aspartyl aldeyde warhead leading to the thioacylal and the acylal derivatives.Both Compounds proved to possess an increased antiplasmodial activity with respect to the parent molecule. Furthermore thioacylal can be considered as a promising trypanocidal agent [26].

7. Anti-oxidant activity

Mark proposed that l-carnosine-related peptidomimetics N-acetylcarnosine (N-acetyl-h-alanyl-l-histidine) (NAC) and carcinine (h-alanylhistamine) are metabolically related to l-carnosine and have been demonstrated to occur in tissues of many vertebrates, including humans, these compounds were shown resistant toward enzymatic hydrolysis. A series of related biocompatible imidazole-containing peptidomimetics were synthesized in order to confer resistance to enzymatic hydrolysis and ex vivo improvement of protective antioxidative properties related to l-carnosine. The included findings revealed a greater role of N-acetylcarnosine (NAC) and carcinine ex vivo in the prolongation and potentiation of physiological responses to the therapeutical and cosmetics treatments with l-carnosine as antioxidant. NAC can act as a time release (carrier) stable version of l-carnosine during application in ophthalmic pharmaceutical and cosmetics formulations which include lubricants [27].

8. Immunosuppressant activity

Dunehoo *et al*. found that RGD peptides/peptidomimetics have been marketed as anti-thrombic agents and are being investigated for inhibiting tumor angiogenesis. Other cell adhesion peptides derived from ICAM-1 and LFA-1 sequences were found to block T-cell adhesion to vascular endothelial cells and epithelial cells; these peptides are being investigated for treating autoimmune diseases. Recent findings suggest that cell adhesion receptors such as integrins can internalize their peptide ligands into the intracellular space. Thus, many cell adhesion peptides (i.e., RGD peptide) were used to target drugs, particles, and diagnostic agents to a specific cell that has increased expression of cell adhesion receptors. The utilization of cell adhesion peptides and receptors in specific targeted drug delivery, diagnostics, and tissue engineering. In the future, more information on the mechanism of internalization and intracellular trafficking of cell adhesion molecules will be exploited for delivering drug molecules to a specific type of cell or for diagnosis of cancer and heart and autoimmune diseases [28].

9. Aminopeptidase N inhibition activity

The biological characterization for the piperidinedione peptidomimetic analogues was performed by Qianbin *et al*. which revealed that most compounds displayed high inhibitory activity against aminopeptidase N (APN). In addition, they also displayed good activity in HL-60 cell assay and *in vivo* anti-metastasis assay. This interesting activity profile may also guide the design of new, specific inhibitors of target mammalian aminopeptidases with 'one-zinc' active site [29].

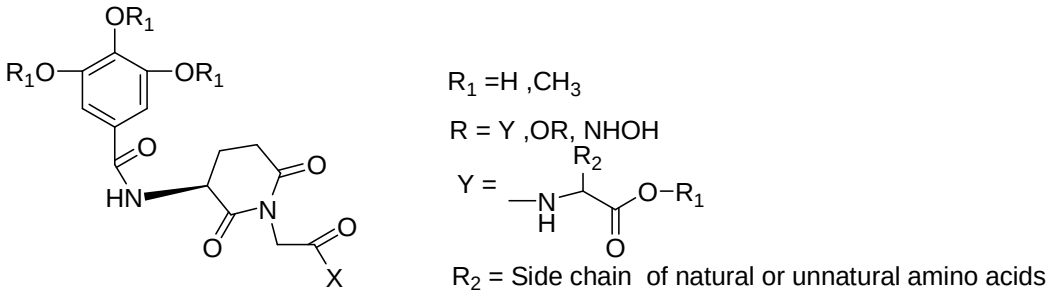

Fig. (11): Chemical structure of piperidinedione peptidomimetic.

10. Motilin Antagonistic activity

Naoki *et al*. successfully discovered two peptidomimetic motilin antagonists through the improvement of physicochemical properties of a tetrapeptide antagonist. Furthermore, with oral administration and based on motilin antagonistic activity, both compounds suppressed motilin-induced colonic and gastric motility in conscious dogs [30].

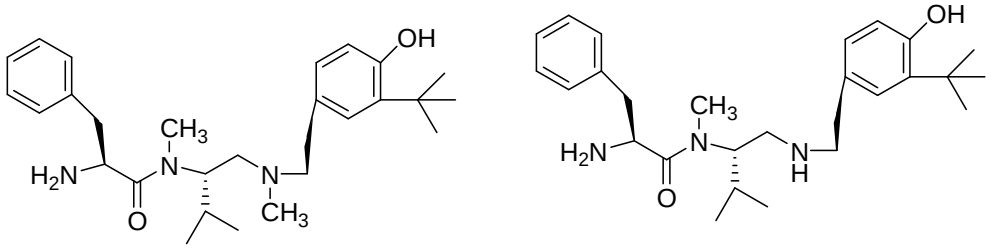

Fig. (12): Chemical strucures of peptidomimetic motilin antagonists.

11. Analgesic activity

Duggan *et al.* reported the synthesis and biological activity of a low molecular weight non-peptidic mimic of the analgesic peptide ω-conotoxin GVIA. The molecular weight of this compound presents a reduction by 193 µg/mol compared to a previously reported lead. This compound exhibits an EC_{50} of 5.8 µM and is accessible in only six synthetic steps compared to the original lead (13 steps). They also report several improvements to the original synthetic route [31].

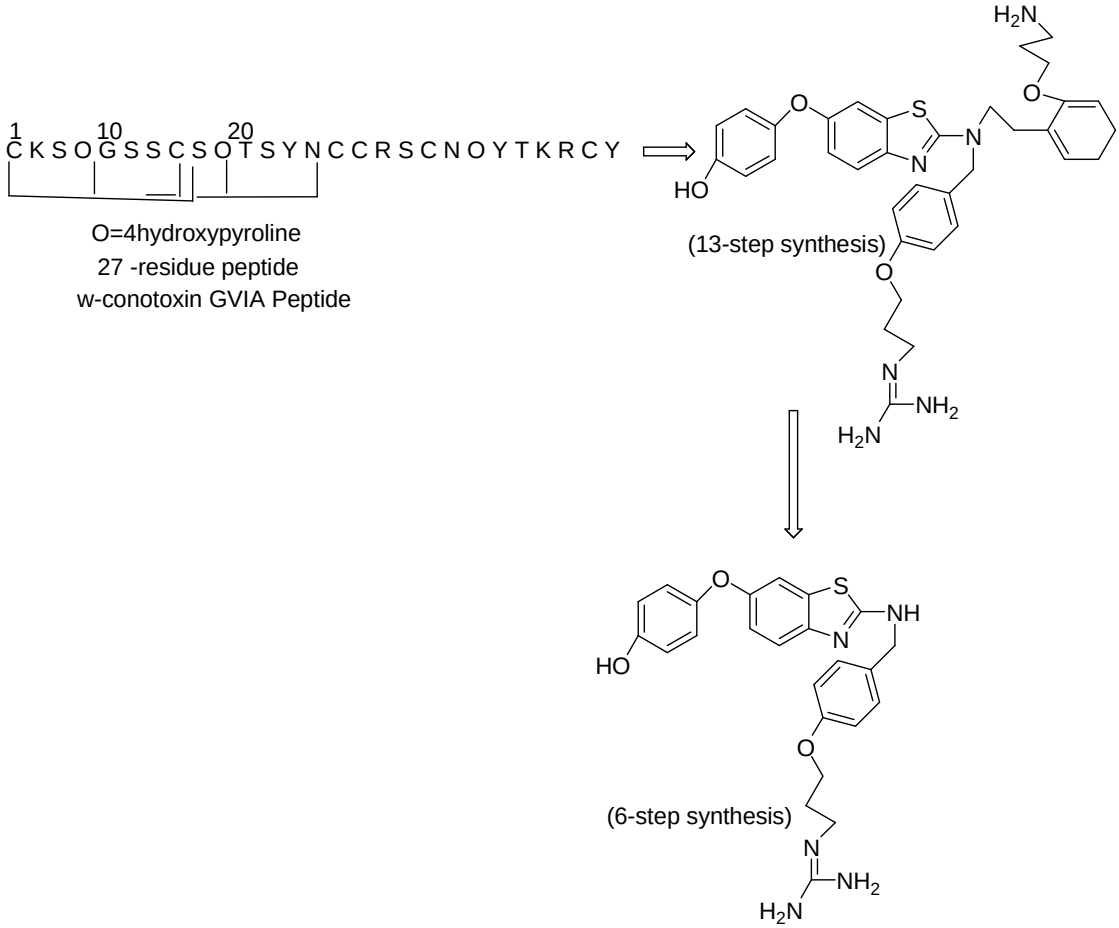

Fig. (13): Synthetic route of non-peptidic mimic of the peptide conotoxin GVIA.

CONCLUSION

In peptidomimetics, alterations to the side chain groups or the peptide backbone are used to improve the peptide's stability and/or biological activity. Since most linear peptides can easily be degraded by enzymatic proteolysis, altering the peptide backbone can help reduce their rate of degradation. The highly charged side chain groups on peptidomimetics provide greater binding affinity and selectivity of the receptors towards these peptidomimetics which will reduce unwanted side effects and improve the therapeutic effects. As a result of their properties, peptidomimetics are of high interest as bioactive agents and as drugs having pharmacological activities such as protease inhibition, antimicrobial, anticancer, analgesics, antiviral and antimalarial activities etc. This review highlights the synthesis, pharmacological activities and

contribution of peptidomimetics in further drug development of novel drugs which can be used effectively in the treatment of various diseases.

Acknowledgement
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