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Peptide Chemistry's Contribution to the Treatment of the Majority of Serious Illnesses: Peptide Antitumors

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Abstract

Cancer is still considered one of the most serious diseases threatening human life. In the past three decades, there enormous efforts have been undertaken to confront cancer diseases. Within such efforts, many therapeutic agents have been developed to treat cancer patients in their early, as well as late cancer-developing stages. These agents vary from antibiotics, chemically synthesized compounds, and natural products-based drugs. Proteins, peptides, and amino acids have been implicated in preventing the development of different types of cancer. For this, this review focuses on the reports regarding peptide compounds showing their biological activity especially as anti-cancer agents.For example: Bleomycin, Cryptophycin and its analogues, Bombesin, Bradykinin and prophyrin family.

Keywords: Peptide Chemistry; Illnesses; Peptide Antitumors

1. Introduction

Cancer is one of the biggest public health concerns (worldwide) due to the ever-increasing incidence of cancer. It is worth noting that one of the most important causes of cancer is that it results from changing people's living habits and increasing environmental pollution [1]. According to the WHO International Cancer Research Institute (International Agency for Research on Cancer, IARC), in China, there were 4.292 million new cancer patients and the number of cancer deaths reached 2.841 million in 2015. That is, the average number of new cancer patients per minute has exceeded 8 people. In 2017, lung cancer and cancers of the digestive system were the top five cancers with high mortality rates. The World Health Organization predicts that the number of new cancer cases in the world will reach 20 million, and 12 million people will die of cancer by 2020 [1 - 3].

Therapeutic peptides have many advantages towards proteins or antibodies such as small size, easy to synthesis and have the ability to penetrate the cell membranes. They also have high activity, specificity and affinity; low drug-drug interaction; and biological and chemical diversity. Peptides are used in treatment because they do not accumulate in specific organs (e.g. kidney or liver), which help in decreasing their toxic side effects [4]. They can also be rapidly synthesized, easily modified [5] and are less immunogenic than recombinant antibodies or proteins [6]. By the time, peptides have been evolved as promising therapeutic agents in the treatment of cancer, and application of peptides in a variety of other therapeutic areas is growing rapidly. Currently there are about 60 approved peptide drugs in the market generating an annual sale of more than $13 billion [7]. Out of four peptide drugs in the market which have reached global sales over $1 billion, three peptides are used in treating cancer directly or in the treatment of episodes associated with certain tumors (leuprolide, goserelin, and octreotide). The number of peptide drugs entering clinical trials is increasing steadily; it was 1.2 per year in the 1970s, 4.6 per year in the 1980s, 9.7 per year in the 1990s, and 16.8 per in 2000s [8]. There are many peptide derivatives in the clinic and preclinic development.Recently Peptides were most frequently for indications of cancer (18%) and metabolic disorders (17%) [9].

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Although medical methods are constantly improving, and Anticancer Peptides (ACPs) are frequently being developed, these traditional methods of treatment still have some worrisome defects and drawbacks, such as severe side effects and drug resistance [10, 11]. The emergence of drug-resistant cancer cells brings not only obstacles to chemotherapy, but also new challenges for the development of anti-tumor drugs. Therefore, the development of ACPs with high selectivity and the ability to withstand or delay drug resistance has recently become a focus of anticancer research [1].

Peptides are bioactive substances that perform various cellular functions in the body, and they also play essential roles in the body to complete various complex physiological activities [12 - 16]. In general, it has been observed during our recent articles, that the synthetic organic and peptide chemistry are promising as biologically activate [17-48]. Peptides are generally small proteins formed by the dehydration condensation of 10 to 100 acids and are widely distributed in the body. Peptides are widely utilized in the endocrine, cardiovascular, and digestive systems, [49, 50]. Polypeptide drugs are peptides which have specific therapeutic effects, formed by chemical synthesis, gene recombination, or are derived from animals, plants, bacteria, and fungi [51]. They are a specific application of peptides in the field of medicine. Compared with other small-molecule drugs, peptide drugs have stronger specificity to cancer cells and may be safer for the body. They can also increase the sensitivity of cancer cells to other clinical treatment methods. Antimicrobial peptides are easy to synthesize and make into medicine [52]. With the advent of drug development to combat antibiotic resistance, ACPs have become a popular area of drug research in China, which is at the forefront of this wave current [53-57]. Although the progress in biochemical processes associated with carcinogenesis, the successful treatment of cancer remains a challenge because of the general toxicity associated with the clinical use of traditional cancer chemotherapeutic agents. So, synthesis of new drugs for cancer treatment is considered an important and challenging task for medicinal chemists worldwide [58].

2. Peptide Antitumors

2.1. Some selected examples of peptide antibiotics:-

There has been a tremendous interest in the field of peptides as antitumor, over the past few years:

2.1.1. Bleomycin:

Bleomycin, figure 1, was discovered as shown in the references [59-60]. It is on the World Health Organization's List of Essential Medicines [61]. It is available as a generic medication [62]. It is made by the bacterium *Streptomyces verticillus* [62]. Bleomycins, are a family of glycopeptide antitumor antibiotis and were clinically used in combination chemotherapy against several types of cancer [63, 64]. Liren Huang, et al. [65], synthesized functional models for bleomycin, which are composed of a simple analog of the metal-complexing moiety of bleomycin and oligo- N-methyl pyrrole peptide DNA-binding moieties. These arise the therapeutic effect of bleomycin.

Bleomycin is a medication used to treat cancer [62]. This includes Hodgkin's lymphoma, non-Hodgkin's lymphoma, testicular cancer, ovarian cancer, and cervical cancer among others [62]. Typically used with other cancer medications [62], it can be given intravenously, by injection into a muscle or under the skin [62]. It may also be administered inside the chest to help prevent the recurrence of a fluid around the lung due to cancer; however talc is better for this [62, 66].

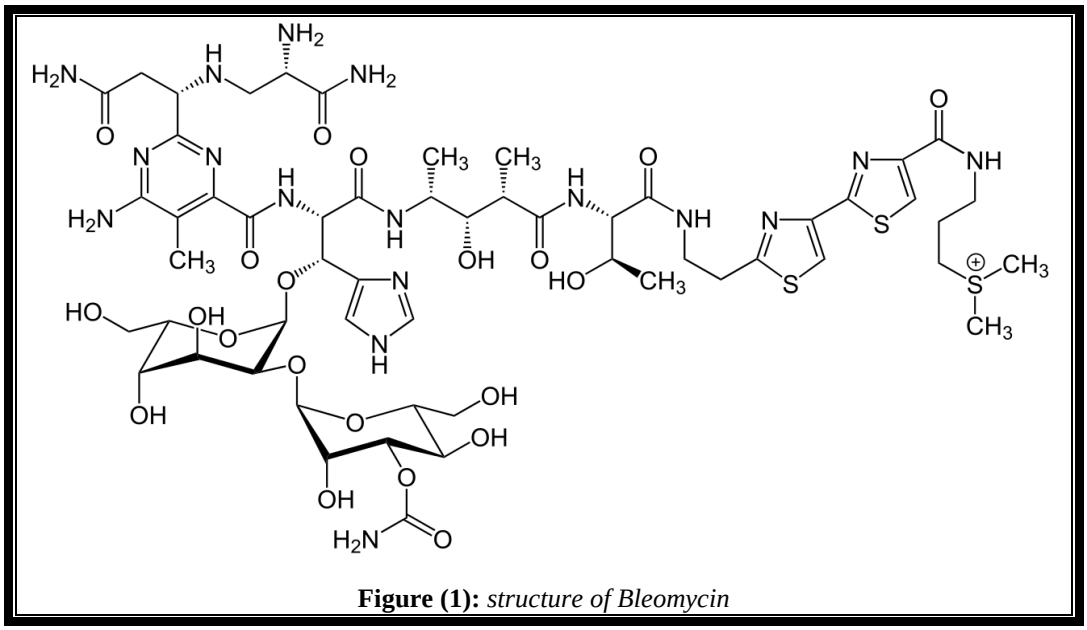


Figure (1): *structure of Bleomycin*

2.1.2. Cryptophycin:

Schwartz and Co-wrokers [67], reported the isolation of a novel depsipeptide from a nostoc cyanobacterium that was extremely active against filamentous fungi and yeast of the genus cryptococcus. Subsequently, Moore and co-workers [68], determined the structure of crvptophycin as shown in figure 2. They found that it was a member of a family of macrolides that could be isolated from Nostoc and that these compounds exhibited extraordinary activity against a variety of tumor cell lines [69].

The cryptophycins are a family of potent antimitotic depsipeptides isolated in the early 1990s from both *Nostoc* sp. ATCC 53789 [70] and *N.* sp. GSV 224 [71]. The correct structures of the cryptophycins were determined via total synthesis [72]. Although initially identified as antifungal agents, these depsipeptides also inhibit mitosis by binding at the peptide site within the vinca domain and are active against a number of human cancer cell lines, including cell lines resistant to other agents, with IC_{50} values in the low picomolar range [73-76]. The extraordinary potency of the cryptophycins resulted in intense efforts to generate therapeutic analogs from both total and semisynthesis [77-82]. An overview of the resulting SAR is depicted in figure 3.

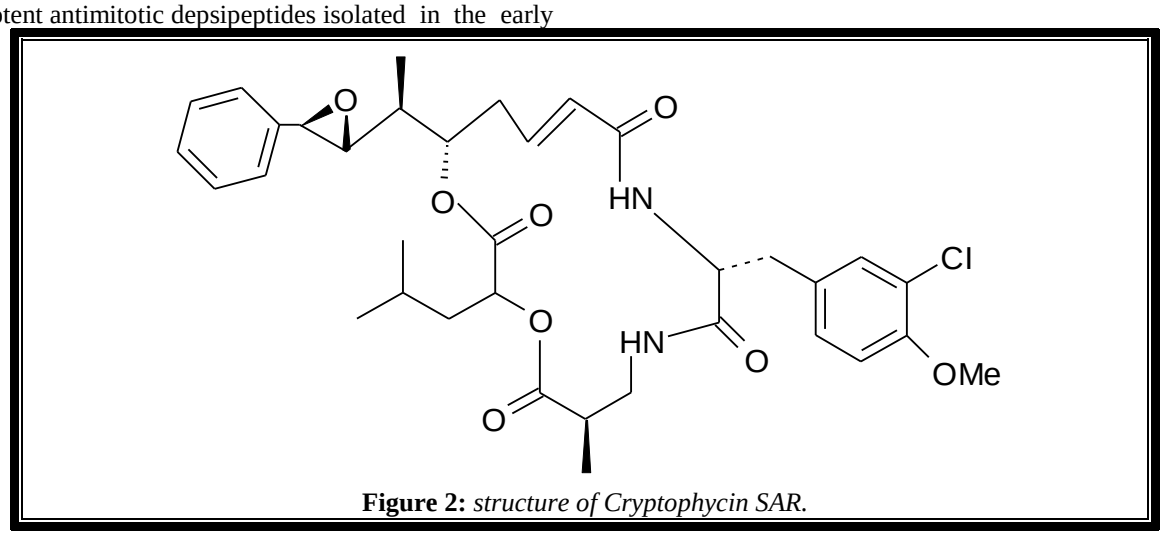


Figure 2: *structure of Cryptophycin SAR.*

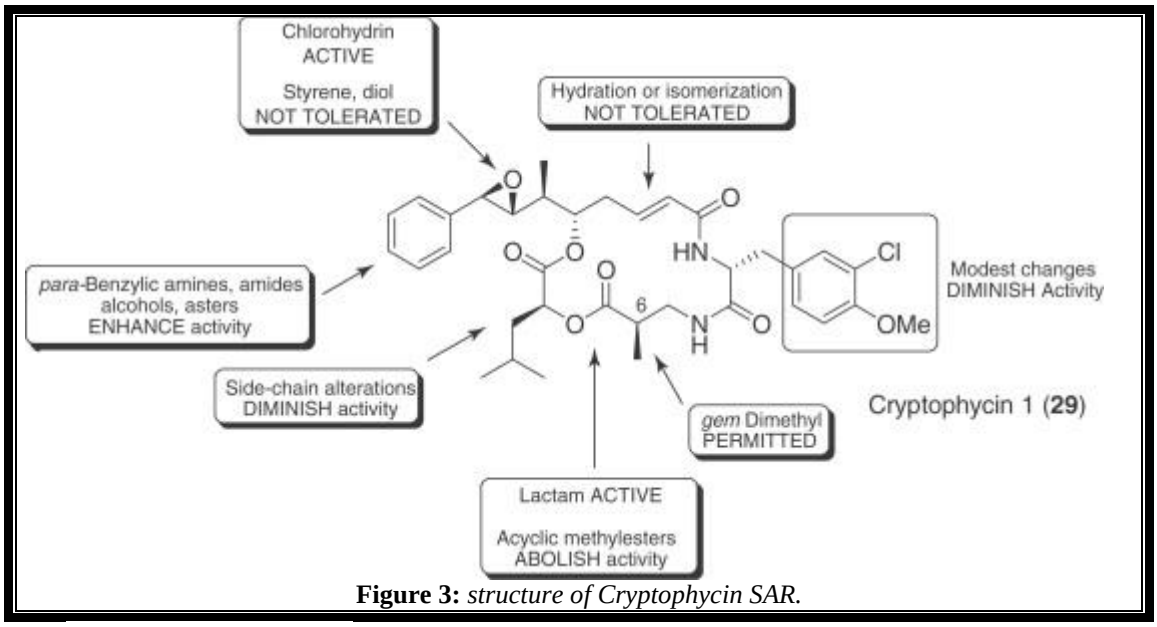
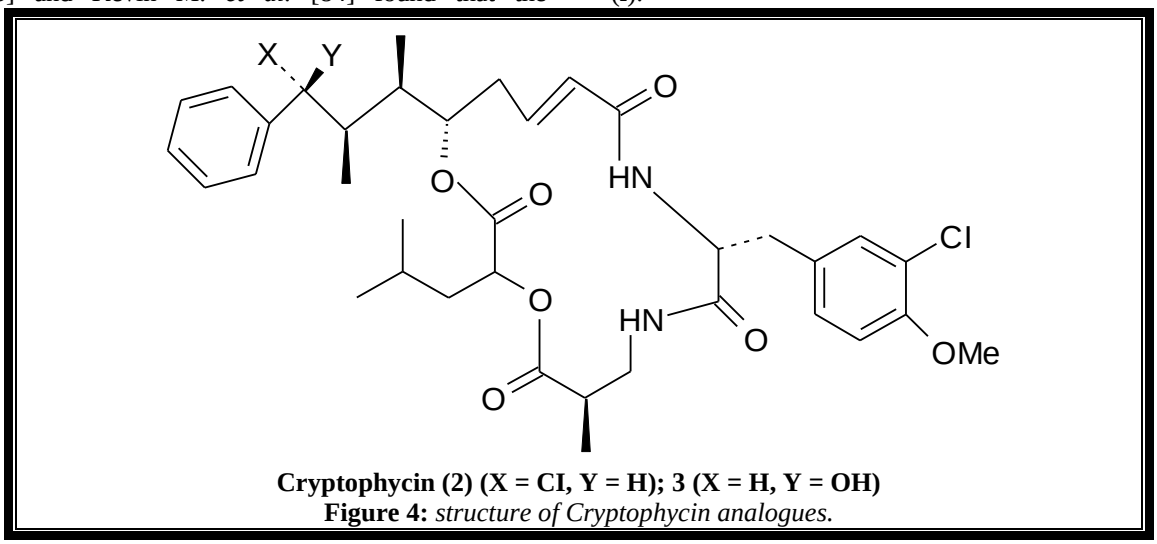


Figure 3: *structure of Cryptophycin SAR.*

2.1.3. Cryptophycin analogues:

In addition to the natural cryptophycins, Golakoti, T. [83] and Kevin M. *et al.* [84] found that the synthetically derived cryptophycin (**2, 3**), as shown in figure 4, was more active in vivo than cryptophycin (**1**):



Cryptophycin (2) (X = CI, Y = H); 3 (X = H, Y = OH)

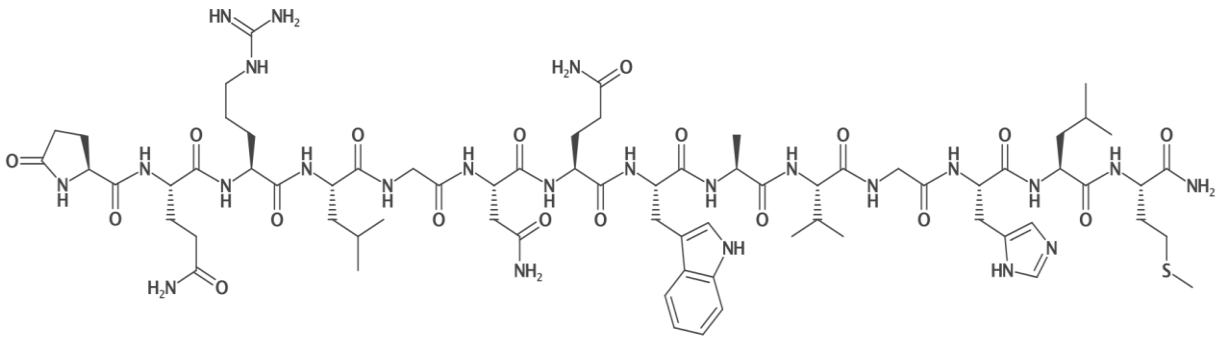
Figure 4: *structure of Cryptophycin analogues.*

2.1.4. Bombesin:

Schally, Andrew W., *et al.* [85] prepared polypeptide with antitumor activity, bombesin antaganists, figure 5, using solid-phase method. It was found that this peptide inhibited I - Tyr^4-bombesin binding to swiss 3T3 cells with Ki = 0.078 nM. This compound at 25 µg / day in mice reduced tumor volume of estrogen dependent MXT mouse mammary cancer by half after 10 days.

Bombesin is a 14-amino acid peptide [86] originally isolated from the skin of the European fire-bellied toad (*Bombina bombina*) [87]. It has two known homologs in mammals called neuromedin B and gastrin-releasing peptide. It stimulates gastrin release from G cells. It activates three different G-protein-coupled receptors known as BBR1, -2, and -3 [88]. It also activates these receptors in the brain. Together with cholecystokinin, it is the second major source of negative feedback signals that stop eating behavior [89].

Bombesin is also a tumor marker for small cell carcinoma of lung, gastric cancer, pancreatic cancer, and neuroblastoma [90].



Other names: *Pyr-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH₂*
Figure 5: *structure of bombesin.*

2.1.5. Pentapeptide analogues:

Kulikov, S.V., *et al.* [91] prepared a pentapeptide with the sequence:

Glp[1]-Glu[2]-Asp[3]-Cys[4]-Lys[5]-OH

It was synthesized via the solid-phase method. The stabilized peptide inhibits proliferation of bone marrow cells of patients with chronic myeloleukemia 5-to 20- fold and has a less pronounced effect on peripheral blood cells. Thus its use in therapy for hemoblastoses is promising.

Synthetic peptide analogs [92] of the [Arg-Gly-Asp-Ser] (RGDS), sequence of fibronection in which the amino acid of Gly was substituted with another one, i.e. [Arg-X-Asp-Ser] (RXDs), and N-terminal modified (RXDs) analogs were prepared to examine their antimetastatic effects in murine lung or liver metastasis models, as well as the inhibitory effect on tumor cell invasion, migration and adhesion in vitro. Peptides RXDs (X = L-Leu, D-Leu), as well as RGDs at a high dose of 3000 fig, significantly reduced the number of lung tumor colonies. At a dose of 1000 µg/mouse, N-terminal modified RXDs analogs, i.e. AC-DRXDs [AC-Asp-Arg-X-Asp-Ser] (X = Gly, L-Leu, D-Leu), showed a more potent inhibitory effect on the lung or liver metastasis. It is of great interest that RXDs (X = L-Leu, D-Leu) was able to regulate tumor cell adhesion, migration and invasion mediated by laminin as well as by fibronection differently than RXDs (X - Gly).

2.1.6. Peptide as inhibitors of tumor necrosis factor:

Doehring, Elena *et al.* [93] synthesized the following peptide as inhibitors of tumor necrosis factor -an activity:

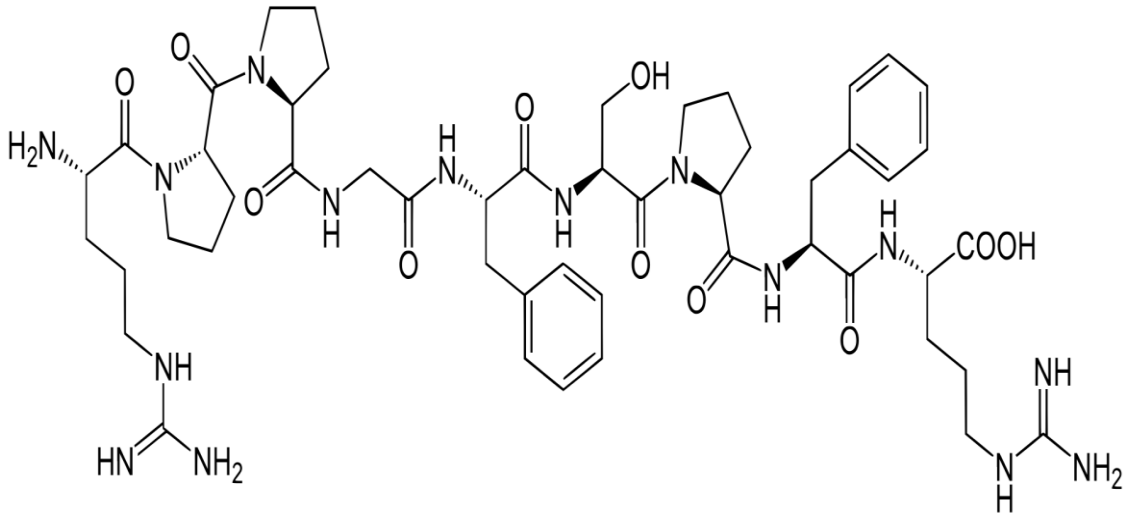
[H - Ile[1] - Thr[2] - Cys[3] - Thr[4] - Ala[5] - Ser[6] - Gln[7] - Ser[8] - Val[9] - Ser[10] – Asiin[11] - Asp[12] - Val[13] - Val[14] - Trp[15] - OH].

2.1.7. Bradykinin:

Bradykinin (BK) is a 9-amino acid peptide chain, as shown in figure 6, [94] [Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg], has a broad range of activities in normal physiology and pathophsiology. It also acts as an autocrine growth factor for pulmonary epithelial cells and human lung cancers, especially small cell lung carcinoma (SCLC) which has neuro endocrine features.

Bradykinin is a potent endothelium-dependent vasodilator and mild diuretic, which may cause a lowering of the blood pressure. It also causes contraction of non-vascular smooth muscle in the bronchus and gut, increases vascular permeability and is also involved in the mechanism of pain [95]. During inflammation, it is released locally from mast cells and basophils during tissue damage [96]. Specifically in relation to pain, bradykinin has been shown to sensitize TRPV1 receptors, thus lowering the temperature threshold at which they activate, thus presumably contributing to allodynia [97]. Bradykinins have been implicated in a number of cancer progression processes [98]. Increased levels of bradykinins resulting from ACE inhibitor use have been associated with increased lung cancer risks [99]. Bradykinins have been implicated in cell proliferation and migration in gastric cancers [100], and bradykinin antagonists have been investigated as anti-cancer agents [101].

Bradykinin has been proposed as an explanation for many symptoms associated with COVID-19, including dry coughs, myalgia, fatigue, nausea, vomiting, diarrhea, anorexia, headaches, decreased cognitive function, arrhythmia and sudden cardiac death [102]. Overactivation of bradykinin is thought to play a role in a rare disease called hereditary angioedema [103].



Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg

IUPAC name: *(2S)-2-{(1²S,3²S,9S,12S,14²S,17S)-1¹-[(2S)-2-Amino-5-(carbamimidoylamino) pentanoyl]-9-benzyl-12-(hydroxymethyl)-2,4,7,10,13,15-hexaoxo-5,8,11,16-tetraaza-1(2),3,14 (1,2) - tripyrrolidina-19-benzenanonadecaphane-17-carboxamido}-5-(carbamimidoylamino)pentanoic acid*

Figure 6: *structure of bradykinin (BK).*

2.1.8. Therapeutic agents as prophyrin into cells:

Surprisingly, when the highly potent Bi and B2 receptor antagonist monomer [B9430; D-Arg-Arg-Pro-Hyp-Gly-Igl-Ser-DIgl-Oic-Arg], was dimerized with appropriate cross-linkers such as suberimidyl, these novel dimers [104, 105] were able to inhibit selectively the growth of SCLS. These dimers or short chain mimetics may have opened a new route for the development of highly potent agent for the treatment of human lung cancer.

Laurent Chaloin, *et al.* [106] designed a new family of carrier peptides to improve the efficiency of cellular uptake of drugs. These carrier peptides based on two sequences, (a nuclear localization sequence and a signal peptide) [107] in order to deliver therapeutic agents such as prophyrin into cells.

Porphyrin is a double-strand DNA cleaving agent with antitumoral properties which has limited membrane permeability.

The antitumor activity of the hormone somatostatin has long been known as several analogs of it are already in clinical practice and antisecretory drugs [108], but their lack of selectivity is a main disadvantage to use them as antitumor agents, the following heptapeptide was synthesized and developed as tumorselective somatostain analog: **[D-Phe-Cys-Tyr-D-Trp- Lys-Cys-Thr-NH_2]**. This peptide has very strong antitumor activity both in vitro and in vivo without showing endocrine side effects, several analogs of heptapepted were synthesized by systematic substitutions of all amino acids (but the cys residues) and measured their antiproliferative and colony formation inhibitory effect on different tumor cell lines. The biological activity of the new analogs was tested on human colon carcinoma cell lines, melanoma and human leukaemia cell lines and on colony formation on human breast carcinoma cell line. The synthesized peptide analogs show antitumor activities.

HGA [human GnRH analogs] [109] with the formula as shown in figure 7. HGA exhibit antitumor activity on human breast, prostatic and endometrium cancer cell lines. Binding HGA to poly (N-vinyl pyrolidone-Co-maleic acid) yields conjugates of more favorable biological properties. The peptide hormone conjugates have remarkably increased life time in the circulation while there in vitro and in vivo anticancer effects are enhanced. Also Radio labeled conjugates containing I in the backbone or in the GnRH moiety have been synthesized. This conjugates show much longer life time than the parent HGA or the polyacid.

AC- D– Trp– D– Cpa– D– Trp– Ser– Tyr- D- Lys- Leu- Arg- Pro- D- Ala- NH_2

Figure 7: *human GnRH analogs (HGA).*

3. Plasma Kinins:

Plasma kinins are tissue hormones liberated from a-globulins of the blood plasma by kallikrein, (kallikrein is the term used to designate the group of proteolytic enzymes that catalyze the hydrolysis of blood globulin). Bradykinin and kallidin, are short polypeptides, as shown in figure 7, they are smooth

muscle hypotensive agents liberated from specific plasma proteins exposed to snake venom or trypsin. Since they are derived from proteins, these peptides contain only protein amino acids. They have the formula, as shown in figure 8.

Arg^{I}-Pro^{2}-Pro^{3}-Gly^{4}-Phe^{5}-Ser^{6}-Pro^{7}-Phe^{8}-Arg^{9}	**Lys^{1}-Arg^{2}-Pro^{3}-Pro^{4}-Gly^{5}-Phe^{6}-Ser^{7}-Pro^{8}-Phe^{9}-Arg^{10}**
Bradykinin	**Kallidin**

Figure 8: *Comparison of the chemical structure of bradykinin and kallidin*

Bradykinin, was first synthesized by Boissonnas *et al.* [109]. The most important effect of the kinins (Bradykinin and Kallidin) is a dilation of the peripheral vessels, which leads to an improved blood flow, in the kidneys for example, and therefore increases dieresis. Also, kinins can contribute to the regulation of blood pressure. Moreover, kinins cause a contraction of the bronchial muscle.

J. Knolle, *et* al. [110] stated that, the Nonapeptide Bradykinin (BK) **(Arg^{1}-Pro^{2}-Pro^{3}-Gly^{4}-Phe^{5}-Ser^{6}-Pro^{7}-Phe^{8}-Arg^{9})** is one of the main mediators which are released when the body responds to traumata and injury. Bradykinin influence vascular tone and permeability, decreases blood pressure and initiates or enhances the release of mediators from leukocytes. BK is involved in pain, inflammation and certain allergic reactions. It is considered to be a new therapeutic principle for the treatment of such diseases. By replacing Pro^{7} by D-Phe^{7} yields antagonists of BK. The bradykinin antagonists emerging from their synthetic efforts e.g. D-Arg [$Hyp^{2,}$ $Thi^{5, 8,}$ D-Phe^{7}] BK, have been used widely as pharmacological tools to evalute the role of BK in many biological processes.

J. Knolle, *et al*. [110], modified several positions of the peptide sequence by introduction of unnatural amino acids. First they replaced D-Phe^{7} by the imino acid D-Tic. This increase the potency to some extent. Also they replaced aromatic amino acid in position 8 (Phe) by Pro, we observed in addition an approximately 10-fold enhanced biological activity. D-Arg° [$Hyp^{3,}$ $Thi^{5'}$ D-Tic^{7}, Oic^{8}] BK with the code name HOE 140 for further development. All data of this peptide obtained so far confirm the high potency of this compound and also it blocks the BK-induced release of histamine. Also the antiinflammatory effect was demonstrated. Also this compound gives more active biological data which suggest its use in the therapy of allergic rhinits, common cold, asthma, etc. HOE 140 has the structure, as shown in figure 9.

[H-D-Arg°-Arg^{1}-Pro^{2}-Hyp^{3}-Gly^{4}-Thi^{5}-Ser^{6}-D-Tic^{7}-Oic^{8}-Arg^{9}-OH]

Figure 9: *structure of HOE 140*

Gobbo, Marina *et* al. [111] synthesized of two bradykinines-like kinins isolated from vespa analis and vespa tropica, as shown in figures 10 and 11, respectively, and of their cyclic analogs, but it was found that the cyclic kinins were less potent than their linear analogs.

[H-$Gly^{1}$$Arg^{2}$$Pro^{3}$-$Pro^{4}$-$Gly^{5}$-$Phe^{6}$- Ser^{7}-Pro^{8}-Phe^{9}-Arg^{10}-Val^{11}-lle^{12}-OH, VSK-A]

Figure 10: *structure of bradykinines-like kinins isolated from vespa analis*

[Gly^{1}-Arg^{2}-Pro^{3}-Hyp^{4}-Gly^{5}-Phe^{6}-Ser^{7}-Pro^{8}-Phe^{9}-Arg^{10}-Val^{11}-Val^{12}-OH, VSK-T]

Figure 11: *structure of bradykinines-like kinins isolated from vespa tropica*

M. Amblard [112] replacing the dipeptide [D-Tic-Oic] in the potent bradykinin receptor antagonist HOE 140, mentioned before. By various constrained dipeptide mimics produced unexpectedly very potent bradykinin Bi and B_2 receptor agonists with enhanced stability towards enzymatic cleavage.

Katrin Krause, *et al*. [113], developed bradykinin antagoists as potential therapeutic agents against pain and inflammation. The synthesized cyclic peptides with the aim of introducing a conformational constraint into the N-terminal part of the molecule

4. Peptides as Antithrombotic

It was found that certain peptide sequences have anti-thrombotic activity. They inhibited platelet aggregation and thrombus formation.

Abelman, Matthew Mark, *et al.* [114], prepared peptide a-ketoamide derivatives as antithrombotics and for imaging thrombi. The prepared peptides inhibited thrombin and were superior to hirulog-1 in preventing venous thrombus in the rat venous stasis model.

Chu-Biao Xue, *et al.* [115], synthesized an antithrombotic cyclic peptide antagonist of glycoprotein IIb/IIIa, figure12, which is a membrane-bound protein that projects from the surface of platelets where it plays an important role in hemeostasis. They synthesized and developed.

IIb cyclo **[D- Abu- N^{α}- methyl- Arg- Gly- Asp- m- (aminomethyl)]**
IIIa cyclo **[D- Abu- N^{α}- methyl- Arg- Gly- Asp- m- (benzoic acid)]**
Figure 12: *structure of antithrombotic cyclic peptide antagonist of glycoprotein IIb/IIIa*

George Stavropoulos, et al, [116], stated that the property of peptides containing the sequence **Arg-Gly-Asp (RGD)** to inhibit platelet aggregation and thrombus formation in vitro has led to research for small peptides or mimtics to be used as antithrombotic drugs. They synthesized a series of salicyl-peptide amides and tested for their inhibitory activity.

5. Peptides of Immunological Importance:

Peptide chemists are becoming increasingly interested in the synthesis of immunosuppressive and immunostimulating peptides.

Hudecs, Ferenc et al. [117], synthesized branched polypeptides with polylysine backbone as macromolecules as shown in figure 13.

Poly [L-Lys-(DL-Ala_m)] **Poly [L-Lys-(Leu-DL-Ala_m)]**
AK **LAK**
Figure 13: *structure of branched polypeptides with polylysine backbone*

Carriers have been used for epitope mapping of the region of HSV-1 glycoprotein D and to investigate the effect of carrier in inducing epitope specific immune response relevent for vaccine design. It has been demonstrated that, branched polypeptide based conjugates of peptides are powerful tools for fine epitope structure and the induction of a protective, virus specific immune response is carrier dependent and can be manipulated by proper carrier selection.

(HSV-1 = Herpes virus simplex type 1 for fever blisters and it inactivated viruses). The following peptides were synthesized as shown in figure 14, and their conjugates with protein- type supports or macromol. When tested as the antigen against sera from both HIV-l-Pos. and -neg. (virus) as AIDS gave better results as immunodominant [118].

H-X-Tyr-Leu-Lys-Glu-Gln-Gln-Leu-Leu-Gly-lle-Trp-Gly-Cys-Ser-Gly-Lys-Leu-Y-NH_2
X, Y = bond, *Glu, Arg, Ile, Cys, Thr, Glu-Arg, lle-Cys-Thr*
Figure 14: *structure of Herpes virus (HSV-1).*

Bossus, Marc *et al.* [119], studied the resistance to enzymic degradation of conformationally constrained antigenic peptides. They synthesized a series of cyclic analog of a 20-residue peptide were designed and synthesized. They stated that, this cyclization dramatically increased the resistance to proteolytic digestion.

Evstigneeva, R.S. *et al.* [120], studied the synthesis and immunochemical properties of peptide fragments of the hepatitis C virus El, NS3, NS4 proteins. The 227-238 fragment of the El protein and the 1059-1070, 1207-1217, 1598-1602-GG, 1724-1731, and 1437-1448 Fragments of the NS3 and NS4 proteins of the hepatitis C virus were synthesized by known methods. Also immunological tests were described.

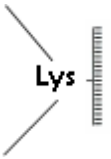
Cuichard, G. *et* al. [121], they synthesized and studied the antigenic properties of the reduced peptide bond pseudopeptide analogs of the C-terminal hexapeptide of histone H_3**,** as shown in figure 15. The resulting analogs were then examined, for their ability to bind polyclonal and monoclonal antibodies generated against the parent natural peptide and the protein. These results present the potent applicability of pseudopeptides in the immunol field.

(-lle^1-Arg^2- Gly^3-Glu^4-Arg^5-Ala^6-OH)
Figure 15: *structure of C-terminal hexapeptide of histone H_3*

Frank, R., *et al.* reported the synthesis of cellulose-bound bicystin peptides using the spot synthesis technique [122]. It was directed against the hing region of human IgG4 antibodies [123]. This hinge region is composed of two identical 20-mer peptides orientated in parallel manner via two disulphide bridges, figure 16. The orientation of the peptides on the cellulose is achieved by a lysine residue directly coupled to the cellulose [124].

Glu[1]-Ser[2]-Lys[3]-Tyr[4]-Gly[5]-Pro[6]-Pro[7]-**Cys[8]**-Pro[9]-Pro[10]-**Cys[11]**-Pro[12]-Ala[13]-Pro[14]-Glu[15]-Phe[16]-Leu[17]-Gly[18]-Gly[19]-**β-Ala[20]**

Disulphide Bridge



Glu[1]-Ser[2]-Lys[3]-Tyr[4]-Gly[5]-Pro[6]-Pro[7]-**Cys[8]**-Pro[9]-Pro[10]-**Cys[11]**-Pro[12]-Ala[13]-Pro[14]-Glu[15]-Phe[16]-Leu[17]-Gly[18]-Gly[19]-**βAla[20]**

Figure 16: *structure of disulphide bridges*

Proline rich protein (PRP) isolated from ovine clostrium possesses strong immunoregulatory properties. The hexapeptide fragment, **Tyr-Val-Pro-Leu-Phe-Pro,** has the similar immunological activity as PRP. Seeking for peptides with immunoregulatory properties, two analogs cyclic peptides of the hexapeptide were synthesized**,** figure 17 [125].

Cys-Val-Asp-Ser-Tyr-Val-Pro-Leu-Phe-Pro-Cys

AC-Asp-Tyr-Val-Pro-Leu-Phe-Pro-Lys-NH_2

Figure 17: *structure of* two analogs cyclic hexapeptides

Marc H.V. Van Regenmortel [126] stated that, synthetic peptides help in diagnosing viral infections, like monoclonal antibodies, can increase the specificity of diagnostic immunoassays. Synthetic peptides may be used as probes for detecting viral antibodies produced during infection. They also may be used for raising antibodies to detect viral antigens in biological materials.

The antigenic decapeptide hen egg lysozyme HEL [52-61], figure 18, the 52-61 segments are an immunogenic peptide for the murine major histocompatibility:

[Asp[52]-Tyr[53]-Gly[54]-IIe[55]-Leu[56]-Gln[57]-lle[58]-Asn[59]-Ser[60]-Arg[61]]

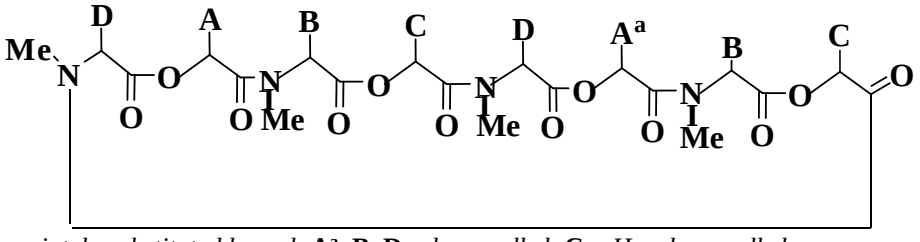
Figure 18: *structure of the antigenic decapeptide hen egg lysozyme HEL[52-61]*

It binds antigenic peptide and presents them to the surface of T-cells, thereby activating the immune response. In order to probe immunogenic conformation of this peptide we have used amino acids which constrain the space available to the Tyr[53] side chain. The results show that the side chain conformation, play a significant role in the recognition of the peptide by the T-cells [127-129].

6. Peptides of Various Importance:

Previously, we mentioned the role of different types of peptides to solve serious diseases e.g. central nervous system, antibiotics, antitumor, plasma kinins, antithrombotic and immunological field. Here we mentioned some other importance of peptides in other various diseases.

Nishiyama, *et al*. [130], synthesized cyclodepsipeptide compound as anthelmintic. A compound represented by general formula as shown in**,** figure 19, having an excellent helminthicidal activity as a vermicide for humans and animals, and is prepared.



A = *appropriately substituted benzyl*; **A[a], B, D** = *lower alkyl*; **C** = *H or lower alkyl*

Figure 19: *structure of cyclodepsipeptide compound as anthelmintic.*

Two new cyclic hepta peptides [131], mahafacyclines A**,** figure 20 and B**,** figure 21, were extracted from J. mahafalensis latex from Madagascar, their structure were:

Cyclo (- Gly^1 - Th^2 - lle^3 - Leu^4 - Gly^5 - Val^6 - Phe^7)
Figure 20*: structure of cyclic hepta peptides, Mahafacyclin A*

Cyclo (- Gly^1 - Thr^2 - Phe^3 - Phe^4 - Gly^5 - Phe^6 - Phe^7)
Figure 21: *structure of cyclic hepta peptides, Mahafacyclin B:*

The two peptides when screened for their antimalarial activity mahafcyclines A and B inhibited Plasmodium falciparum giving promising results.

P. Sikiric, *et al.* [132] synthesizes and measure pharmacological activity of the fragment of human Gastric Juice Protein (BPC). The N- terminal part of the protein (BPC) was sequenced and synthesized the fragment consisting of first 15 amino acid residues with the sequence as shown in**,** figure 22.

Gly^1 - Glu^2 - Pro^3 - Pro^4 - Pro^5 - Gly^6 - Lys^7 - Pro^8 - Ala^9 - Asp^{10} - Asp^{11} - Ala^{12} - Gly^{13} - Leu^{14} - Val^{15}
Figure 22: *structure of the protein human Gastric Juice Protein (BPC)*

This protein shows a wide range of biological activities in human organism, first of all the superior protection against different gastrointestinal and liver lesions, antiviral activity, antiinfalmmotory and analgesic activity.

This penta deca peptide was synthesized via the solid-phase method and was found to have high biological activity. It is nontoxic and high active also by peroral application. Therefore is very promising as a new medicine for the treatment of different inflammatory diseases and stress induced diseases.

Pseudopeptides containing isosteric replacements of the amide bond provide more stable analogs, which may even have enhanced biological activity towards influenza virus epitope [133]. Studies showed that this pseudopeptide modulates the ctytokine profile, also it is much more potent at low concentration, it has the following formula, as shown in figure 23.

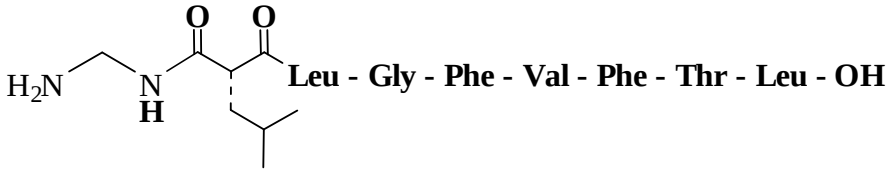


Figure 23: *pseudopeptides containing isosteric replacements of the amide bond*

Yuan, Zhuan Fang, *et al.* [134] synthesized and charcterized of new sweet dipeptide esters:**H-L-Asp-DL-AIa-OR** [R=cyclohexyl, 2, 6-dimethyl cyclohexyl]. The synthesized dipeptides were found sweetness over 100 and 200 times of that of sucrose; they appear to have sucrose-like taste and high stability.

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