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Peptide Chemistry's Role in Treating Most Serious Diseases: Peptide Antibiotics.

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Abstract

The study of antimicrobial peptides is a rapidly growing field. Antibacterial peptides were first considered rather species-specific. Therefore, we focused our review of peptide antibiotics, although the peptide antibiotics are composed of amino acids, they often show little similarity to gene-encoded polypeptides in terms of structure and mechanism of their biosynthesis. Alternatively, an extensive reference survey was conducted for the peptides used as antibiotics, and some examples of antibiotics that are chemically composed of various amino acids and peptides were studied. Moreover, we focused in this review some selected examples of important peptide antibiotics, for example, bacitracin (I), gramicidin (II), monamycins, alafosfalin and albomycisn.

Keywords: Amino Acid; Peptide Chemistry; Diseases; Peptide Antibiotics.

1. Introduction

Antimicrobial peptides (AMPs) are components recognized in the past from various immune systems, especially innate and found in living organisms in general, and eukaryotic organisms in particular, worldwide. AMPs possess a strong diversified biological activity against a wide range of all types of bacteria, viruses, fungi and parasites [1, 2]. This distinct biological activity also includes membrane interaction [3, 4]. Alternatively; AMPs is increasingly found and post-translational modifications (PTMs) play an important role in improving the efficacy of various peptides and the specificity of these mechanisms of action [5-9]. The authors also note that most PTMs that have been biologically tested as AMPs are considered rare [6], typically phosphorylation of residues [1, 6, 10] and helical inversion of residues to produce various D amino acids [11–13]. However, only two types of PTMs are found ubiquitously among the AMPs of eukaryotic organisms [6] of which the first is the oxidation of an amino acid residue (cysteine) to form disulfide bridges [14]. Scientists have observed that disulfide bridges play an important and major architectural role in the antimicrobial effect of AMPs [6], mainly by maintaining the amphipathic topography of the biologically studied molecules and thus their ability to interact with target membranes and kill Host cells [5, 15]. This form of structural stabilization is critical for the therapeutic development of AMPs and furthermore is demonstrated by the cysteine knot architectures of cyclotides from plants [2, 16]. The exceptional stability of these peptides (linear and cyclic) coupled with their high tolerance to residue substitutions [17] make them potential candidates to serve as lead compounds in scenarios ranging from tumor imaging [18] to the prevention of contact transmission of HIV sexual [19]. The second most common type of PTM found in AMPs is the insertion of all C-terminal slits, which are mostly identified in all amphibians [6]. This falls into only two main categories: the presence of either a ranabox [20] or an amide group [21]. Moreover, the RNA box is found in most rancid frogs and consists of a C-terminal circular hepeptide with a conserved disulfide bond [20, 22, 23]. This PTM occurs in AMPs such as gaegurins and palustrins and appears to play an important role in facilitating membrane affinity for these peptides by stabilizing their C-terminal structure [20, 24]. Alternatively, the importance of the C-terminal medium in the antimicrobial effect of

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various amphibians, as well as other amplifier AMPs is far from clear understanding [25]. Recently, a group of homologous AMPs, maximin H1 to maximin H55, was identified in frogs (genus Bombina only). Moreover, all of these amplifiers exhibited a central C-terminal, which clearly indicates the functional relevance [26-28]. Recent studies conducted on synthetic AMP compounds have shown that the C-terminal Midation can enhance efficacy as distinct antibacterials without increasing the hydrolytic capacity and thus increase the therapeutic potential of these peptides [29]. Given that maximin H5 from Bombina maxima has strong, narrow-spectrum and antibacterial activity [30].

2. Some selected examples of peptide antibiotics:-

2.1. bacitracin and gramicidin:

Since the discovery of bacitracin, figure (1), and gramicidin, figure (1), [31], many peptide antibiotics have been synthesized.

Lee, J.H., *et al*. [32] studied bacitracin A which is useful antibiotics obtained from bacterial cultures. bacitracin A is a cyclic polypeptide containing a bridging D-Lysine residue. It is active against wide variety of gram-positive organisms.

Bacitracin [33] is a mixture of related cyclic peptides produced by organisms of the licheniformis group of *Bacillus subtilis var* Tracy, first isolated in 1945. These peptides disrupt Gram-positive bacteria by interfering with cell wall and peptidoglycan synthesis. Bacitracin is primarily used as a topical preparation, as it can cause kidney damage when used internally. Antibiotics such as bacitracin have been shown to act as dermatological irritants and may slow healing in otherwise sterile wounds [34, 35].

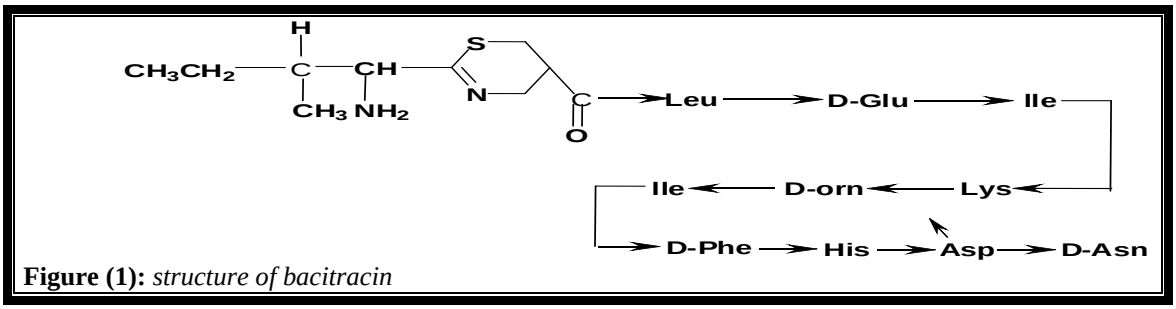


Figure (1): *structure of bacitracin*

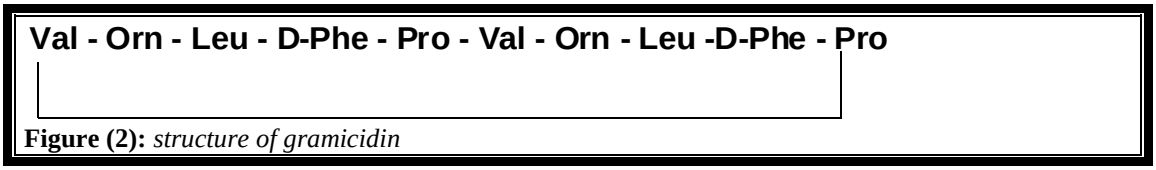


Figure (2): *structure of gramicidin*

2.2. Monamycins:

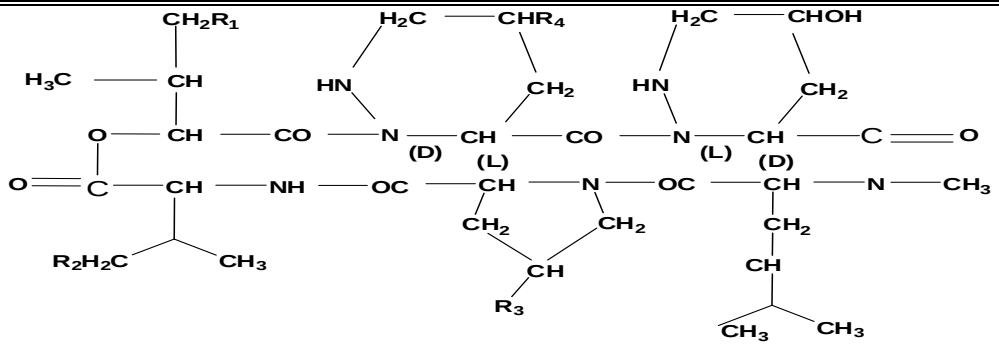
Generally peptide antibiotics vary in their action mechanisms e.g. inhibition of cell-wall synthesis, increased permeability of the cell wall, or influence on nucleic acid synthesis. The presence of D-amino acids and unusual non-proteinogenic amino acids is characteristic. Monamycins, figure (3), a family of 15 hexapeptide members, which as ionophores, induce the passage of ions through biological membranes, have hexahydropyridazine-l-carboxylic acid as their characteristic basic unit and exhibit antibacterial properties. Their structural formula will as shown in figure (3), [36].

2.3. Alafosfalin

Alafosfalin, figure (4), is peptide antibiotics, having an aminophosphonic acid at the C-terminal end of a peptide chain, have been synthesized by Roche Products Ltd /U.K. [37]. Alafosfalin, which inhibits the biosynthesis of the bacterial cell wall, is effective against gram-positive and gram-negative microorganisms.

2.4. Albomycins:

Benz, G. [38] isolated albomycins from the strain streptomyces spec. WS/116, are nucleoside peptides that exert antibiotic effects and have iron-complexing properties, structural formula as shown in figure (5).



(R^x=R^2=R^4=H, R^3=CH_3), which form strong complexes with K^+, Rb^+ and CS^+

Figure (3): *structure of Monamycins*

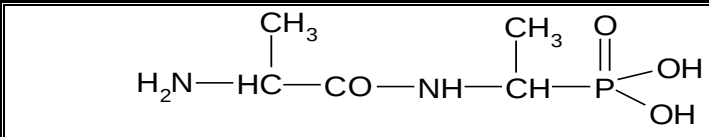
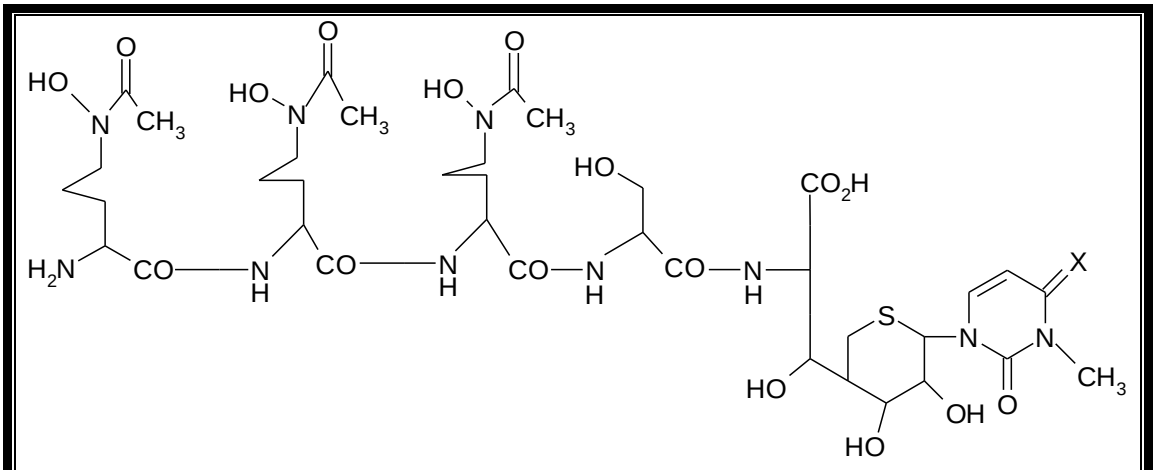


Figure (4): *structure of alafosfalin*



X = N-CO-NH_2, X = O, X = NH

Figure (5): *structure of desferriforms of albomycisn*

2.5. Cecropins:

Cecropins are antimicrobial peptides [39, 40]. They have three analogues, cecropin A, cecropin B, and cecropin P1 figures (6-8), respectively. Cecropins were first isolated from the hemolymph of Hyalophora cecropia, whence the term cecropin was derived. Cecropins lyse bacterial cell membranes; they also inhibit proline uptake and cause leaky membranes. Cecropins [41-43] constitute a main part of the innate immune system of insects. Cecropins are small proteins anywhere from 31 - 37 amino acids long and are active against both gram-positive and gram-negative bacteria. Cecropins isolated from insects other than Hyalophora cecropia (Cecropia moth) have been given various names, such as bactericidin, lepidopterin, and sarcotoxin. All of these peptides are structurally related.

Anticancer activities of cecropin B, and cecropin P1 were first demonstrated with *in vitro* studies of mammalian leukemia and lymphoma cell lines, where cells were sensitive to peptide concentrations on the order of 10^{-6} M [44]. Two multidrug-resistant breast and ovarian cancer cell lines also showed sensitivity to the peptides [44]. Further, peptide anticancer activity is reported as being complete within one hour of treatment [44]. *In vivo* studies of murine ascitic colon adenocarcinoma cells showed a similar trend, where mice treated with cecropin B exhibited increased survival time compared to untreated mice [44].

Ceeropins [45] are produced in insects on account of the lack of lymphocytes and immunoglobulins by a humoral immune reaction, and have a broad spectrum of antibacterial activity. Cecropin A analogs have been synthesized by Andreu *et al*. [46] by the solid-phase method. Amino acid sequences of cecropin A analogs will be as shown in figure (6). A derivative of Cecropin B is an anticancer polypeptide (L). Structure consists of mainly alpha helixes, determined by solution NMR. Protein molecular weight = 4203.4g/mol [47]. Some of the cecropins (e.g. cecropin A, and cecropin B) have anticancer properties and are called anticancer peptides (ACPs) [48]. Hybrid ACPs based on Cecropin A have been studied for anticancer properties [48].

2.6. Alamethicins:

Alamethicins peptide antibiotics were synthesized by Jones, R. N. *et al*. [51] with the following sequences as shown in figure (9). Alamethicins exerts bacteriostatic, fungicidal, cytostatic, and hemolytic effects. Altogether a quadricyclic structure containing 19 amino acids is formed. In fact, this structure is also active in the cell plaque forming test which has been used to identify the thymopoietine activity: the stimulation of maturation of T lymphocytes.

2.7. Ramoplanin:

Ramoplanin [52], figure (10), is a new glycolipodesipeptide antibiotic, derived from strain ATCC 33076 of *Actinoplanes* [53], it is active against a broad range of Gram-positive bacteria. Its development has been fast-tracked by the U.S. Food and Drug Administration as a treatment for multiple antibiotic-resistant *Clostridium difficile* infection of the gastrointestinal tract [54], Unlike vancomycin, it is absorbed in the gastrointestinal tract, although it is unstable in the bloodstream, so can be taken only orally against *Clostridium difficile* infections of the gastrointestinal tract [55-57].

2.8. Thiazolyl peptide (GE-2270A):

Selva, E. *et al.* synthesized a novel thiazolyl peptide antibiotic isolated from *Amycolatopsis fastidiosa* [58], and known as GE-2270A, nocathiacin and thiazomycin has good activity against aerobic and anaerobic Gram-positive bacteria and anaerobic Gram-negative bacteria, figures [59] (11-13), respectively.

Lys^{1} - Trp^{2} - Lys^{3} - Leu^{4} - Phe^{5} - Lys^{6} - Lys^{7} - lle^{8} - Glu^{9} - Lys^{10} - Val^{11} - Gly^{12} - Gln^{13} - Asn^{14} - Ile^{15} - Arg^{16} - Asp^{17} - Gly^{18} - Ile^{19} - lie^{20} - Lys^{21} - Ala^{22} - Gly^{23} - Pro^{24} - Ala^{25} - Val^{26} - Ala^{27} - Val^{28} - Val^{29} - Gly^{30} - Gln^{31} - Ala^{32} - Thr^{33} - Gln^{34} - Ile^{35} - Ala^{36} - Lys^{37} - NH$_2$
Figure (6): *structure of cecropin A analogs* [49]

Lys^{1} - Trp^{2} - Lys^{3} - Val ^{4} - Phe^{5} - Lys^{6} - Lys^{7} - lle^{8} - Glu^{9} - Lys^{10} - Met^{11} - Gly^{12} - Arg^{13} - Asn^{14} - Ile^{15} - Arg^{16} - Asn^{17} - Gly^{18} - Ile^{19} - Val^{20} - Lys^{21} - Ala^{22} - Gly^{23} - Pro^{24} - Ala^{25} - Ilu^{26} - Ala^{27} - Val^{28} - Leu^{29} - Gly^{30} - Glu^{31} - Ala^{32} - Lys^{33} - Ala^{34} - Leu^{35} - NH$_2$
Figure (7): *structure of cecropin B analogs* [48]

Ser^{1} – Trp^{2} – Leu^{3} – Ser^{4} – Lys^{5} – Thr^{6} – Ala^{7} – Lys^{8} – Lys^{9} – Leu^{10} – Glu^{11} – Asn^{12} – Ser^{13} – Ala^{14} – Lys^{15} – Lys^{16} – Arg^{17} – Ile^{18} – Ser^{19} – Glu^{20} – Gly^{21} – Ile^{22} – Ala^{23} – Ile^{24} – Ala^{25} – Ile^{26} – Gln^{27} – Gly^{28} – Gly^{29} – Pro^{30} – Arg^{31} – NH$_2$
Figure (8): *structure of Cecropin P1 analogs* [50]

AC - Aib^{1} - Pro^{2} - Aib^{3} - Ala^{4} - Aib^{5} - Ala^{6} - Gln^{7} - Aib^{8} - Val^{9} - Aib^{10} - Gly^{11} - Leu^{12} - Aib^{13} - Pro^{14} - Val^{15} - Aib^{16} - Aib^{17} - GIu^{18} - Gln^{19} - PhI^{20}
Ac = *acetyl*, **Phl** = *phenylalaninol*, **Aib** = *2-Aminoisobutyric acid*
Figure (9): *structure of alamethicins peptide*

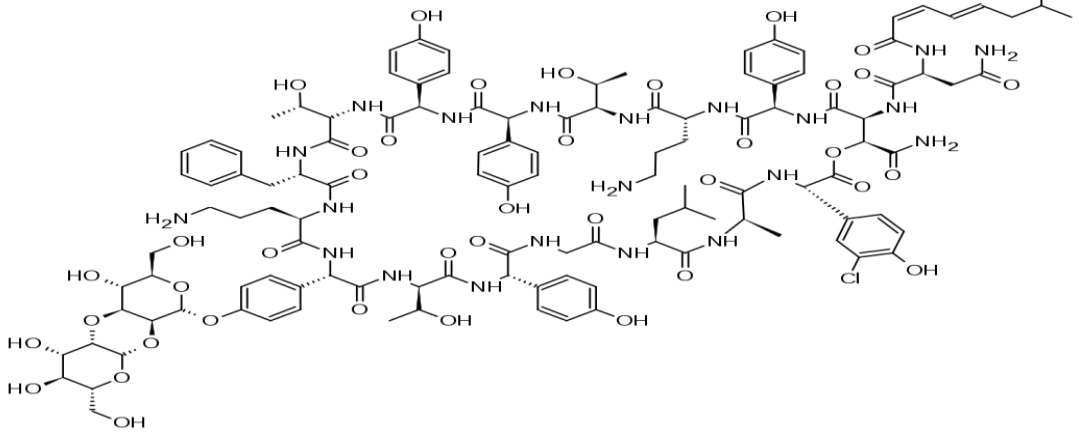


Figure (10): *structure of ramoplanin*

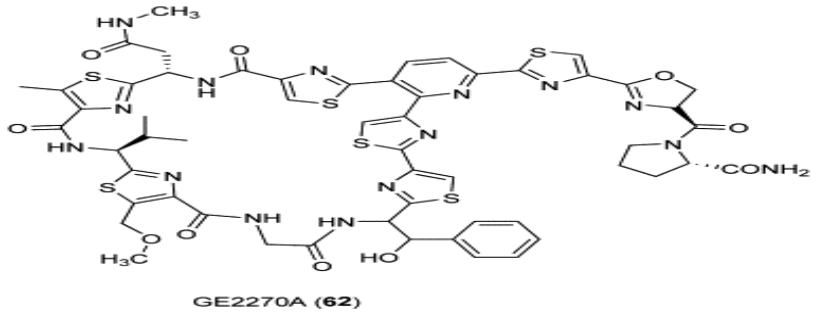


Figure (11): *structure of GE-2270A*

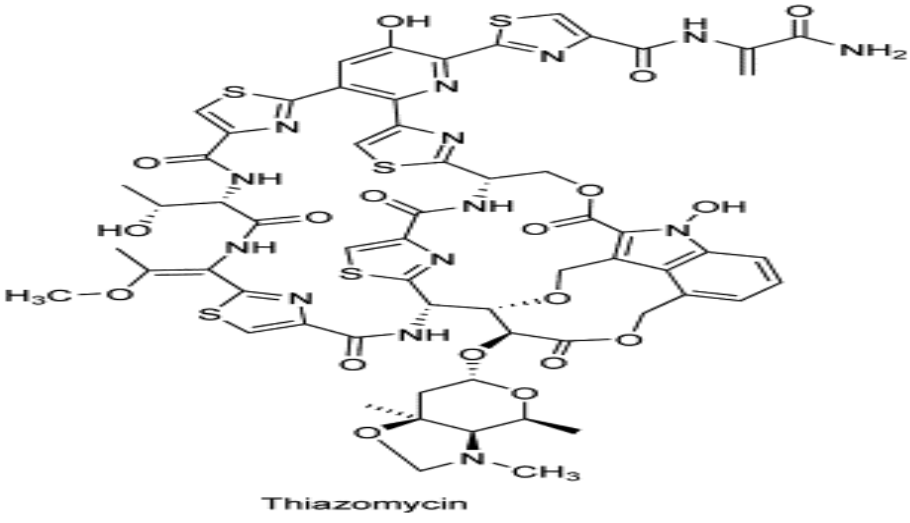


Figure (12): *structure of nocathiacin*

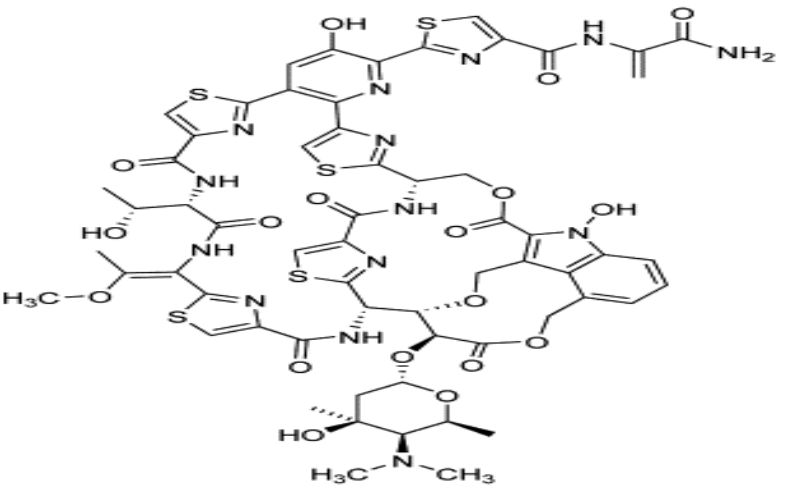


Figure (13): *structure of thiazomycin*

2.9. Vancomvcin:

Vancomvcin, figure (14), [60] is a glycopeptides (peptides with sugar) has been used for the treatment of infections due to Gram-Positive bacteria. Vancomycin is an antibiotic medication used to treat a number of bacterial infections [61]. It is recommended intravenously as a treatment for complicated skin infections, bloodstream infections, endocarditic, bone and joint infections, and meningitis caused by methicillin-resistant *Staphylococcus aureus* [62]. Blood levels may be measured to determine the correct dose [63]. Vancomycin is also recommended by mouth as a treatment for severe *Clostridium difficile* colitis [61]. When taken by mouth it is very poorly absorbed [61].

Rajagopalan, *et al*. [64] found that, the complexes of vancomycin group antibiotics with peptides are stabilized by hydrogen bonding and hydrophobic interactions. Their complex with the bacterial cell-wall mimetic peptides, figure (15), has been carried out in methanol at low temperature:

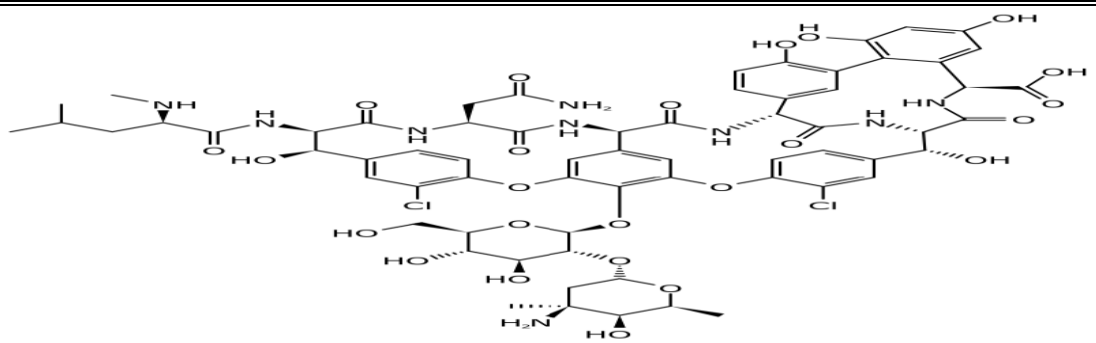


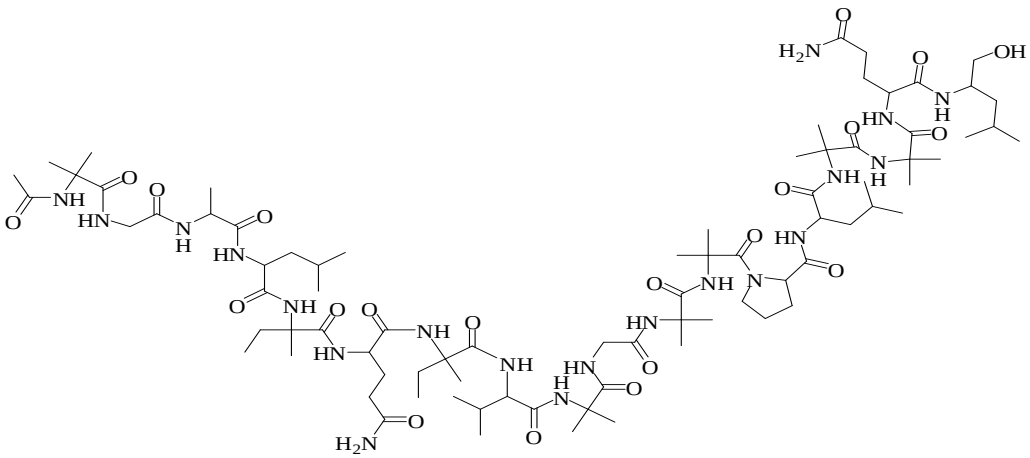
Figure (14): *structure of Vancomycin*

AC-D-Ala-D-Ala-OH, Me Succinyl-D-Ala-D-Ala-OH and AC-L- Lys (AC)-D-Ala-D-Ala-OH
Figure (15): *structure of vancomycin complexes with the bacterial cell-wall mimetic peptides*

2.10. Trichobrachin:

Brücker, H. *et al*. [65] reported the rapid and sensitive detection of a particular group of fungal peptide antibiotics of the "Peptaibol" family. Screening procedure detected the characteristics, non-protein amino acids of this group of peptides, namely α-aminoisobutyric Acid (Aib) and, in many cases, isovaline (IVa). Application of the method to filamentous fungi revealed that many species and strains of some microorganisms are capable of producing peptaibol antibiotics. Bruckner, H. *et al*. [66] reported on the isolation and sequence determination of the poly peptide antibiotics Trichobrachin, and Trichovirin I. They reported on the total synthesis of one component of the Trichovirin complex namely Trichovirin I, figure (16).

AC - Aib[1] - Asn[2] - Leu[3] - Aib[4] - Pro[5] - Ala[6] - Val[7] - Aib[8] - Pro[9] - Aib[10] - Leu[11] - Aib[12] - Pro[13] – Leu - OH[14]



N-acetyl-alpha-methyl-alanyl-glycyl-DL-alanyl-DL-leucyl-DL-isovalyl-DL-glutaminyl-DL-isovalyl-DL-valyl-alpha-methyl-alanyl-glycyl-alpha-methyl-alanyl-alpha-methyl-alanyl-DL-prolyl-DL-leucyl-alpha-methyl-alanyl-alpha-methyl-alanyl-DL-glutaminyl-DL-leucinol

Figure (16): *structure of trichovirin I.*

2.11. Lactoferrin (Lfcin):

Bellamy *et al*. [67] have shown that gastric cleavage of bovine lactoferrin, an antibacterial protein, by pepsin produces a peptide fragment, bovine lactoferricin 17-41, which possesses all of the antibacterial activity of the native protein. This 25 residues longpeptide (17-41) can further be reduced by ten residues at the c-terminal and to give a peptide fragment, bovine lactoferricin 17-31, without any loss of antibacterial activity.

Lactoferrin (Lfcin), figures (17-22): also known as lactotransferrin (Ltfcin), is a multifunctional protein of the transferring family. Lfcin is a globular glycoprotein with a molecular mass of about 80 kDa that is widely represented in various secretory fluids, such as milk, saliva, tears, and nasal secretions. Lfcin is also present in secondary granules of PMNs and is secreted by some acinar cells. Lfcin can be purified from milk or produced recombinantly. Human colostrum (*"first milk"*) has the highest concentration, followed by human milk, then cow milk (150 mg/L) [68]. Lfcin is one of the components of the immune system of the body; it has antimicrobial activity (bacteriocide, fungicide) and is part of the innate defense, mainly at mucoses [68]. In particular, Lfcin provides antibacterial activity to human infants [69, 70]. Lfcin interacts with DNA and RNA, polysaccharides and heparin, and shows some of its biological functions in complexes with these ligands. Lfcin belongs to the innate immune system. Apart from its main biological function, namely binding and transport of iron ions, Lfcin also has antibacterial, antiviral, antiparasitic, catalytic, anti-cancer, and anti-allergic functions and properties [71].

Morten Bohmer *et al*. [72] synthesized similar human, murin, caprin and porcine lactoferricin analogues of bovine lactoferricin 17-31 using solid-phase peptide synthesis and compared their antibacterial activity and they also improved their antibacterial activity. Lactoferrin prevents the attachment of *H. pylori* in the stomach, which in turn, aids in reducing digestive system disorders. Bovine lactoferrin has more activity against *H. pylori* than human lactoferrin [73].

The anticancer activity of bovine lactoferrin (bLF) has been demonstrated in experimental lung, bladder, tongue, colon, and liver carcinogeneses on rats, possibly by suppression of phase I enzymes, such as cytochrome P450 1A2 (CYP1A2) [74]. Also, in another experiment done on hamsters, bovine lactoferrin decreased the incidence of oral cancer by 50% [75]. Currently, bLF is used as an ingredient in yogurt, chewing gums, infant formulas, and cosmetics [75].

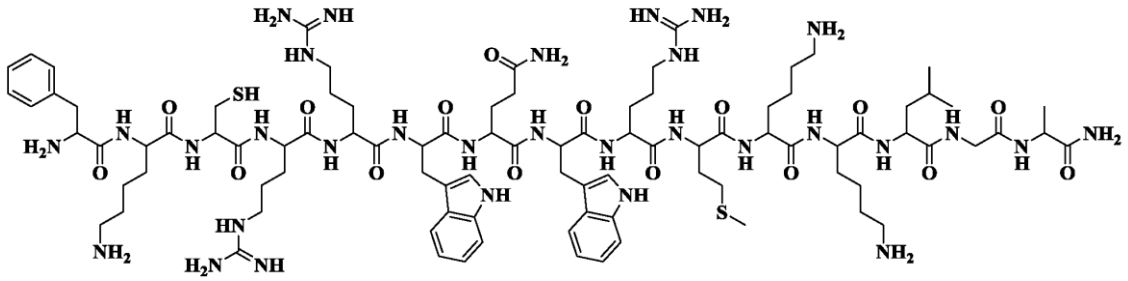


Figure (17): *structure of Lactoferrin B 17-31*

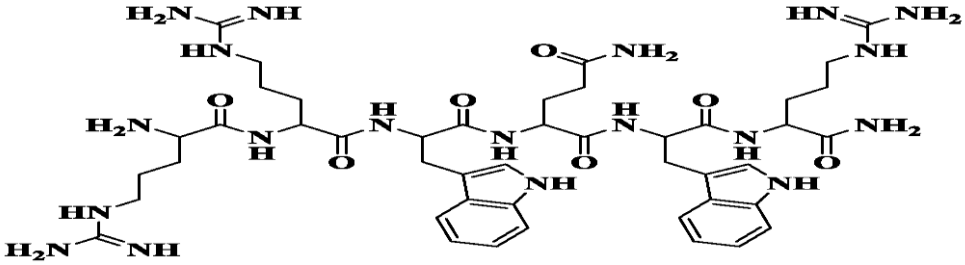


Figure (18): *structure of Lactoferrin B 20-25*

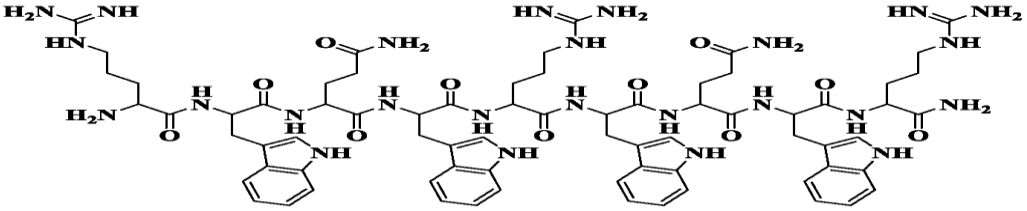


Figure (19): *structure of Lactoferrin B (21-25)$_{pal}$*

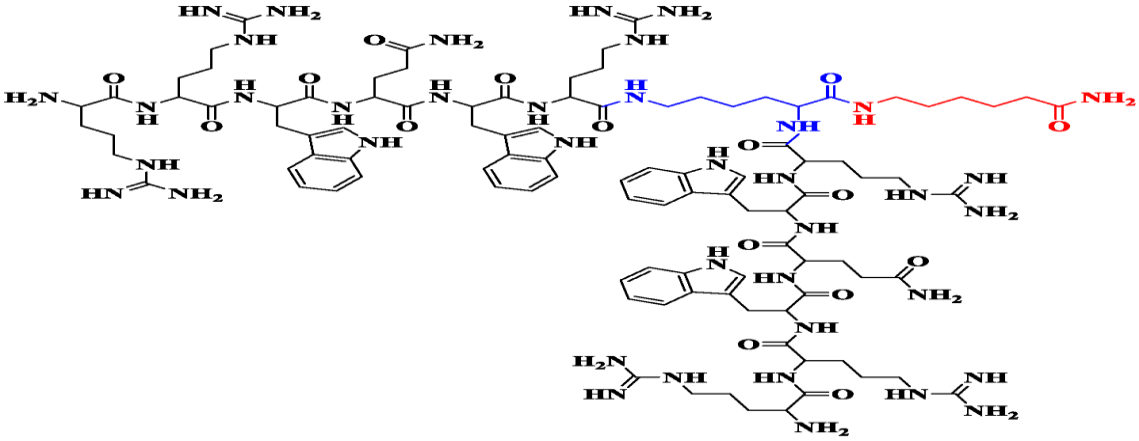


Figure (20): *structure of Lactoferrin B (20-25)$_2$*

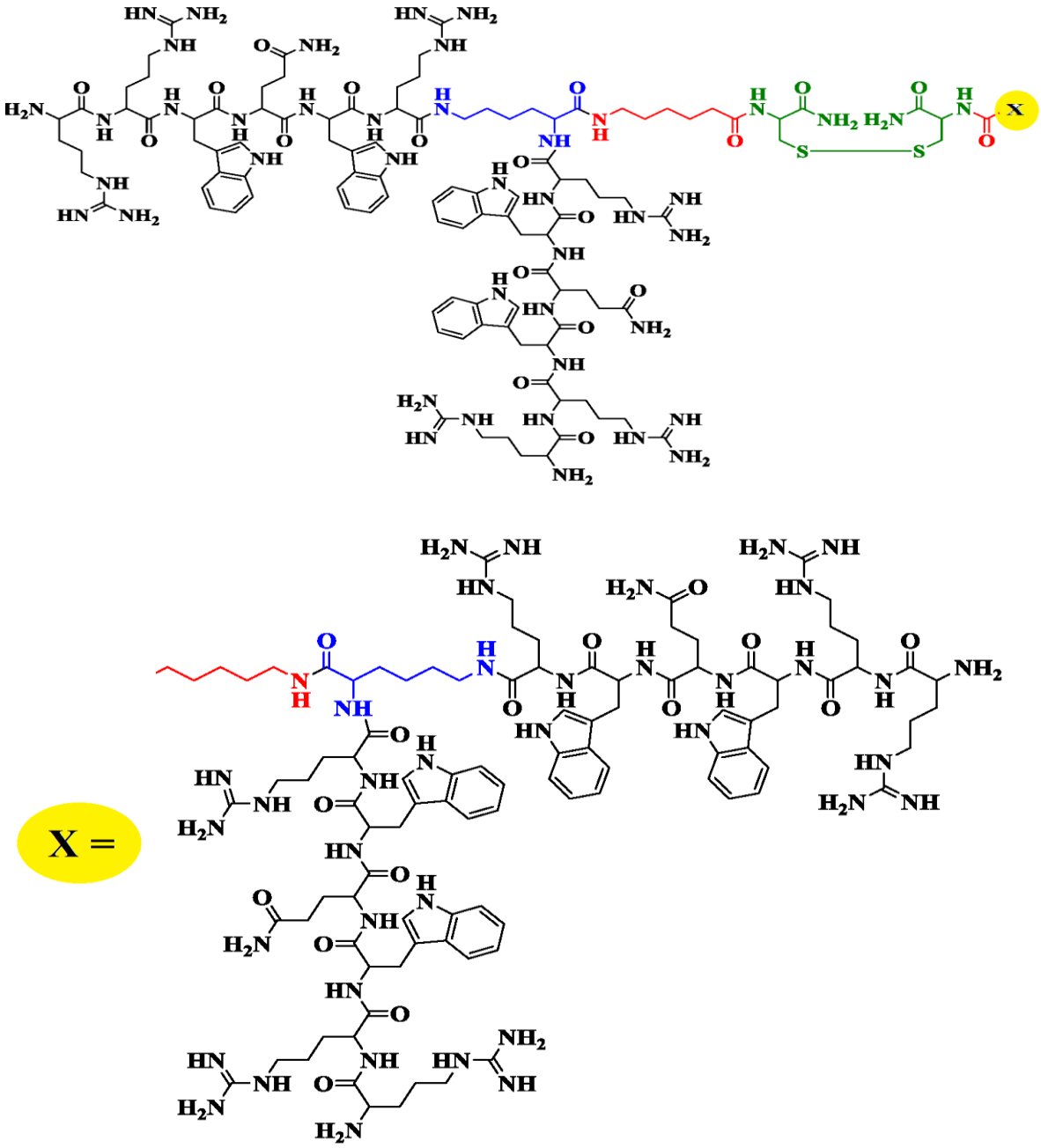


Figure (22): *structure of Lactoferrin B (20-25)4*

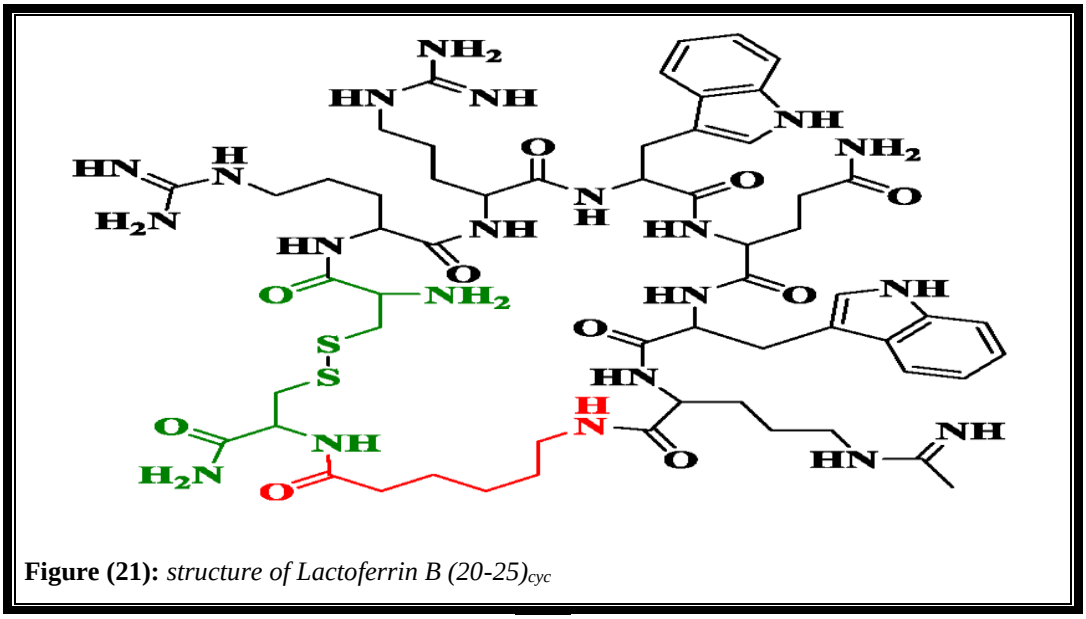


Figure (21): *structure of Lactoferrin B (20-25)$_{cyc}$*

2.12. Teicoplanin:

Teicoplanin 1 [76] is a glycopeptide related to vancomycin, is an antibiotic, it has recently been introduced into clinical practice for treatment of infections caused by methicillin-resistant and Gram-positive organisms. *in vitro* and *in vivo* studies have shown that teicoplanin is superior to vancomycine, having lower toxicity and higher activity. The antibacterial activity of this family of antibiotics arised from specific binding of the glycopeptide to bacterial cell wall precursors terminating in the sequence D-Ala-D-Ala. Jieping *et al*. [76] synthesized 14-membered macrocycles related to ring of teicoplanin 1.

Teicoplanin is an antibiotic used in the prophylaxis and treatment of serious infections caused by Gram-positive bacteria, including methicillin resistant *Staphylococcus aureus* and *Enterococcus faecalis*. It is a semisynthetic glycopeptide antibiotic with a spectrum of activity similar to vancomycin. Its mechanism of action is to inhibit bacterial cell wall synthesis [77]. Teicoplanin is marketed by sanofi-Aventis under the trade name targocid. Other trade names include ticocin marketed by Cipla (India). Oral teicoplanin has been demonstrated to be effective in the treatment of pseudomembranous colitis and *Clostridium difficile*-associated diarrhoea, with comparable efficacy with vancomycin [78]. Its strength is considered to be due to the length of the hydrocarbon chain [79]. Teicoplanin (TARGOCID, marketed by Sanofi Aventis Ltd) is actually a mixture of several compounds, five major (named teicoplanin A2-1 through A_2-5) and four minor (named teicoplanin R_S-1 through R_S-4) [80]. All teicoplanins share a same glycopeptide core, termed teicoplanin A_3-1, a fused ring structure to which two carbohydrates (mannose and *N*-acetylglucosamine) are attached. The major and minor components also contain a third carbohydrate moiety, β-D-glucosamine, and differ only by the length and conformation of a side-chain attached to it. The structures of the teicoplanin core and the side-chains that characterize the five major teicoplanin compounds are shown in figure (23).

2.13. Amphipathic:

Zhong, Lingxia *et al*. [81] designed and synthesized of amphipathic antimicrobial peptides. A large proportion of antimicrobial peptides share a common structural feature that is critical to their antimicrobial activity, i.e., amphipathic α-helixes. Generally, antimicrobial peptides are characterized by high hydrophobic moment and low hydrophobicity values. Identification of putative amphipathic structures in proteins may provide a useful starting strategy in the design and synthesis of antimicrobial peptides [82].
On the other hand, in general, it has been observed during our recent articles, that the synthetic organic and peptide chemistry are promising as biologically activate [83-111]. Naturally occurring antimicrobial peptides are gene-encoded, ribosomally synthesized polypeptides [112]. These peptides are usually short (less than 100 amino acid residues), have a positive net charge, amphipathic nature, and often exhibit a broad spectrum of activity against bacteria, viruses, and fungi [113-115]. Because of the wide sequence and structural diversity, AMPs are traditionally classified based on secondary structure

conformations: α-helices, β-sheets, or random coil [116]. There are several well-known examples of antimicrobial peptides belonging to the families of the cathelicidins, defensins, thionins, cecropins, and magainins [117-120].

Indolicidin [121], a novel tryptophan-rich microbicidal tridecapeptide amide isolated originally from granules of bovine neutrophils [122]. Van Abel *et al*. [123] synthesized Indolicidin by solid-phase method. The antimicrobial potencies of natural and synthetic indolicidin, as determined by *in vitro* antibacterial, antiviral and antifungal assays, were identical. Further, the reactivities of natural and synthetic peptides with anti-indolicidin antibody were indistinguishable. Its primary structures as shown in figure (24).

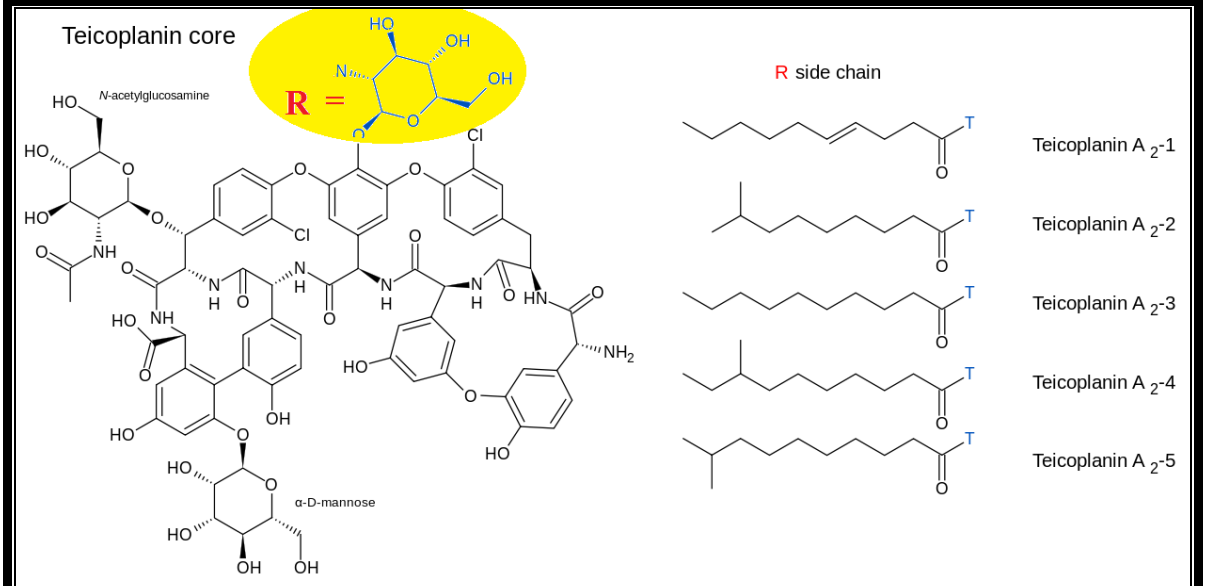


Figure (23): *structure of teicoplanin core (left, black) and side-chains that characterize teicoplanins A2-1 through A2-5 (right). In blue: β-D-glucosamine.*

2.14. Indolicidin:

Indolicidin, was isolated from cytoplasmic granules of bovine neutrophils [124]. It is one of the shortest known natural-occurring antimicrobial peptide [125], toxic to both prokaryotes and eukaryotes [125, 126]. The high percentage of proline and tryptophan residues makes indolicidin a unique antimicrobial. Unlike several other antimicrobial peptides, the structure of indolicidin upon membrane interaction is not a well-defined helix or a *β*-turn and does not display their characteristic amphipathic nature [126–129].

Yoshiki Uchida, *et al*. [130] prepared indolicidine and 22 analogs. They suggested that the C-terminal Arg-Arg-NH_2 structure is important for the expression of the potent antibacterial activity of indolicidine especially against gram-negative bacteria [131].

2.15. Cathelicidins:

Cathelicidins, are a family of precursors of antimicrobial peptides identified in mammalin myeloid Cathelicidin- derived peptides are 12-100 residues long and include α-helical, cys-rich, pro- and Arg-rich, and Trp-rich peptides.

Marco Scocchi *et al*. [132] have analysed the presence of cathelicideins in horse bone marrow cells, and identified three novel members as deduced from cDNA. They show putative antimicrobial domains of 26, 27 and 40 residues. These peptides which corresponding to these sequences have been synthesized and purified by RP-HPLC. The antimicrobial activity has been tested against gram - positive and gram-negative bacteria and showed good activities.

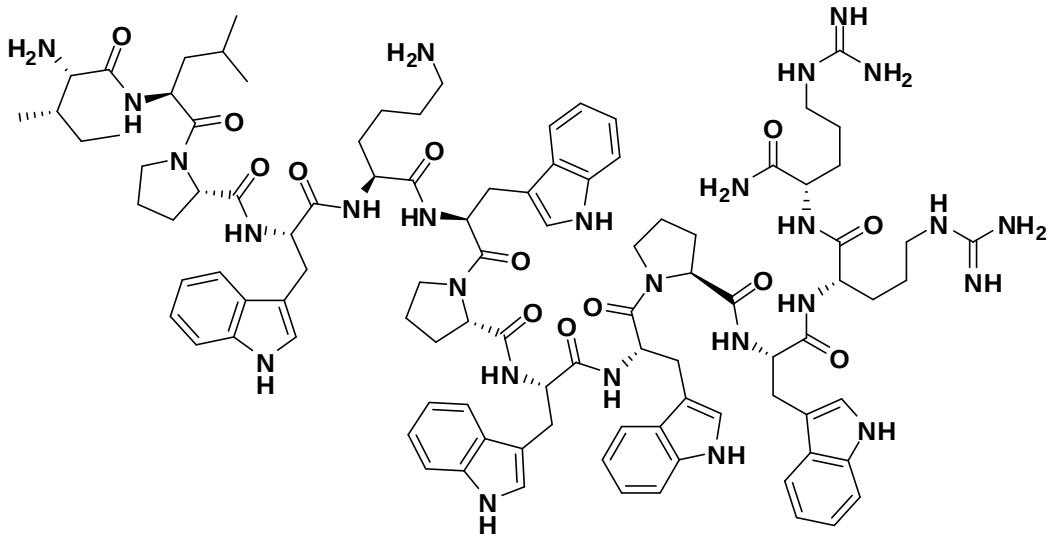
Microcin J 25, [133] a 21 - residue peptide antibiotic, microcins are a class of potent peptide antibiotics produced by Enterobacteriaceae, mainly E. coli, of faecal origin [134]. It inhibits the growth of E. coli and salmonella strains. The whole study reveald a 21-residue peptide consisting of natural amino acids.

The presence of thiazole or oxazole rings in microcin J 25 (MCC J 25) give rise to microcin B 17, [135] which have been supposed to be the structural motifs recognized by the inn- membrane protein sbma involved in the uptake of both microcins.

2.16. Macrolide

The macrolides are a class of natural products that consist of a large macrocyclic lactone ring to which one or more deoxy sugars, usually cladinose and desosamine, may be attached.

The lactone rings are usually 14-, 15-, or 16-membered. Macrolides belong to the polyketide class of natural products. Some macrolides have antibiotic or antifungal activity and are used as pharmaceutical drugs. Macrolides are bacteriostatic in that they suppress or inhibit bacterial growth rather than killing bacteria completely. Macrolides are protein synthesis inhibitors. The mechanism of action of macrolides is inhibition of bacterial protein biosynthesis, and they are thought to do this by preventing peptidyltransferase from adding the growing peptide attached to tRNA to the next amino acid [136] (similarly to chloramphenicol [137] as well as inhibiting bacterial ribosomal translation [136]. Another potential mechanism is premature dissociation of the peptidyl-tRNA from the ribosome [138]. Macrolide antibiotics do so by binding reversibly to the P site on the 50S subunit of the bacterial ribosome. This action is considered to be bacteriostatic. Macrolides are actively concentrated within leukocytes, and thus are transported into the site of infection [139].



(2S)-1-[(2S)-2-[[(2S)-6-amino-2-[[(2S)-2-[[(2S)-1-[(2S)-2-[[(2S,3S)-2-amino-3-methylpentanoyl] amino]-4-methylpentanoyl]pyrrolidine-2-carbonyl]amino]-3-(1H-indol-3-yl)propanoyl]amino] hexanoyl]amino]-3-(1H-indol-3-yl)propanoyl]-N-[(2S)-1-[[(2S)-1-[(2S)-2-[[(2S)-1-[[(2S)-1-[[(2S)-1-amino-5-carbamimidamido-1-oxopentan-2-yl]amino]-5-carbamimidamido-1-oxopentan-2-yl]amino]-3-(1H-indol-3-yl)-1-oxopropan-2-yl]carbamoyl]pyrrolidin-1-yl]-3-(1H-indol-3-yl)-1-oxopropan-2-yl]amino]-3-(1H-indol-3-yl)-1-oxopropan-2-yl]pyrrolidine-2-carboxamide

H-lIe^{1}-Leu^{2}-Pro^{3}-Trp^{4}-Lys^{5}-Trp^{6}-Pro^{7}-Trp^{8}-Trp^{9}-Pro^{10}-Trp^{11}- Arg^{12}-Arg^{13}-NH$_2$

Figure (24): *structure of indolicidin*

Some examples of antibiotic macrolides:

A. Azithromycin:

A zithromycin, figure (25): is an antibiotic medication used for the treatment of a number of bacterial infections [140]. This includes middle ear infections, strep throat, pneumonia, traveler's diarrhea, and certain other intestinal infections [140]. Along with other medications, it may also be used for malaria [140]. It can be taken by mouth or intravenously with doses once per day [140].

B. Clarithromycin:

Clarithromycin, figure (26), sold under the brand name Biaxin among others, is an antibiotic used to treat various bacterial infections [142]. This includes strep throat, pneumonia, skin infections, H. pylori infection, and Lyme disease, among others [142]. Clarithromycin can be taken by mouth as a pill or liquid [142].

C. Erythromycin:

Erythromycin, figure (27), is an antibiotic used for the treatment of a number of bacterial infections [143]. This includes respiratory tract infections, skin infections, Chlamydia, pelvic inflammatory disease, and syphilis [143]. It may also be used during pregnancy to prevent Group B streptococcal infection in the newborn [143], as well as to improve delayed stomach emptying [144]. It can be given intravenously and by mouth [143]. An eye ointment is routinely recommended after delivery to prevent eye infections in the newborn [145].

Figure (25): *structure of zithromycin*
Other names: *9-deoxy-9α-aza-9α-methyl-9α-homoerythromycin A*
Trade names: *Zithromax, Azithrocin*, others [141]

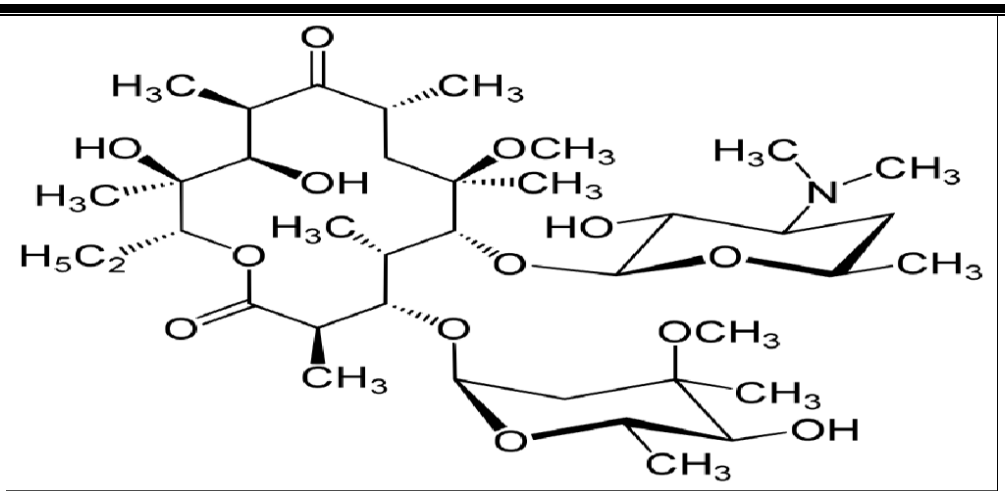


Figure (26): *structure of zithromycin*
Trade names: *Biaxin*

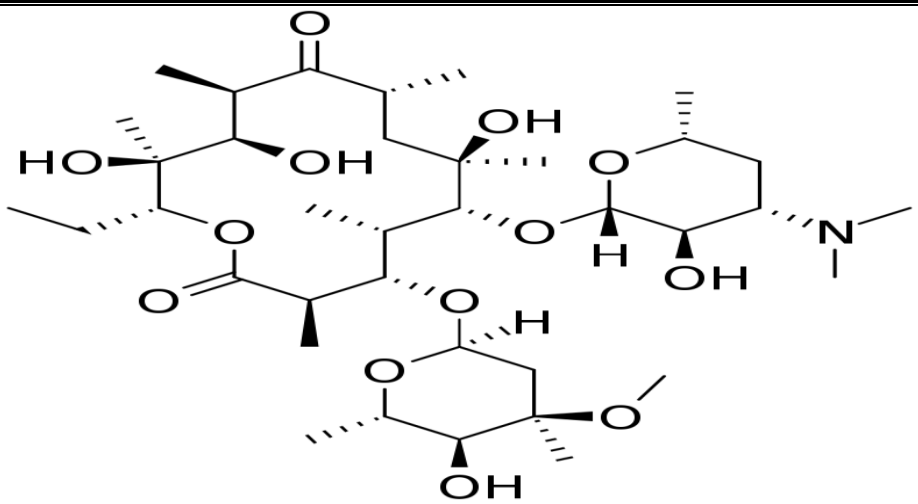


Figure (27): *structure of erythromycin*
Trade names: *Eryc, Erythrocin*, others [146]

D. Fidaxomicin:

Fidaxomicin, figure (28), sold under the brand name Dificid among others, is the first member of a class of narrow spectrum macrocyclic antibiotic drugs called tiacumicins [147]. It is a fermentation product obtained from the actinomycete *Dactylosporangium aurantiacum* subspecies *hamdenesis* [148, 149]. Fidaxomicin is minimally absorbed into the bloodstream when taken orally, is bactericidal, and selectively eradicates pathogenic *Clostridium difficile* with relatively little disruption to the multiple species of bacteria that make up the normal, healthy intestinal microbiota. The maintenance of normal physiological conditions in the colon may reduce the probability of recurrence of *Clostridium difficile* infection [150, 151].

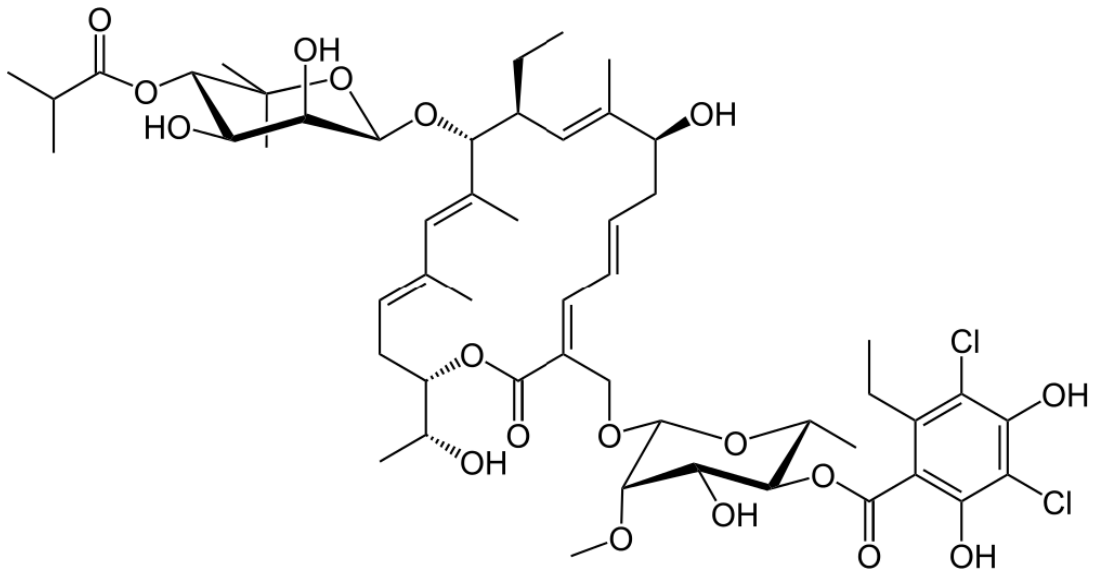


Figure (28): *structure of fidaxomicin*
Other names: *Clostomicin B1, lipiarmicin, lipiarmycin, lipiarmycin A3, OPT-80, PAR 01, PAR-101, tiacumicin B*
Trade names: *Dificid, Dificlir*

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