Polypeptide antibiotics (polyenes)

Cyclicpeptides

The usual physiologically significant peptides are linear. Several bacterial species, however produce antibiotic mixtures of cyclic peptides, some with uncommon amino acids & some with common amino acids but with the D-absolute stereochemistry.

→ Posses unique characteristics.

(a) Frequently consists of several structurally similar but chemically distinct entities isolated from a single source.

(b) most of them are cyclic, with few exceptions. (e.g. gramicidins)

(c) Frequently contain D-amino acids and/or un-natural amino acids not found in higher plants or animals.

(d) many of them contain non-aminoacid moieties such as heterocycles, fatty acids, sugars etc.

→ Polypeptide antibiotics may be acidic, basic, Zwitterionic or neutral depending on the number of free carboxyl and amino or guanidino groups in their structures.

These glycopeptide agents are not readily metabolized.

→ usually are water soluble and are highly lethal to susceptible bacteria, because they attach themselves to the bacterial membranes and interfere with their semipermiability so that essential metabolites leak out and undesirable substances pass in.

→ Unfortunately, they are also highly toxic in humans, so there use is reserved for serious situations in which there are few alternatives or to topical uses.

Bacteria rarely are able to develop significant resistance to this group of antibiotics.

→ They generally are unstable, so solutions are protected from heat, light & extremes of pH

→ A chief source of medicinally important members of this class is "Bacillus spp."

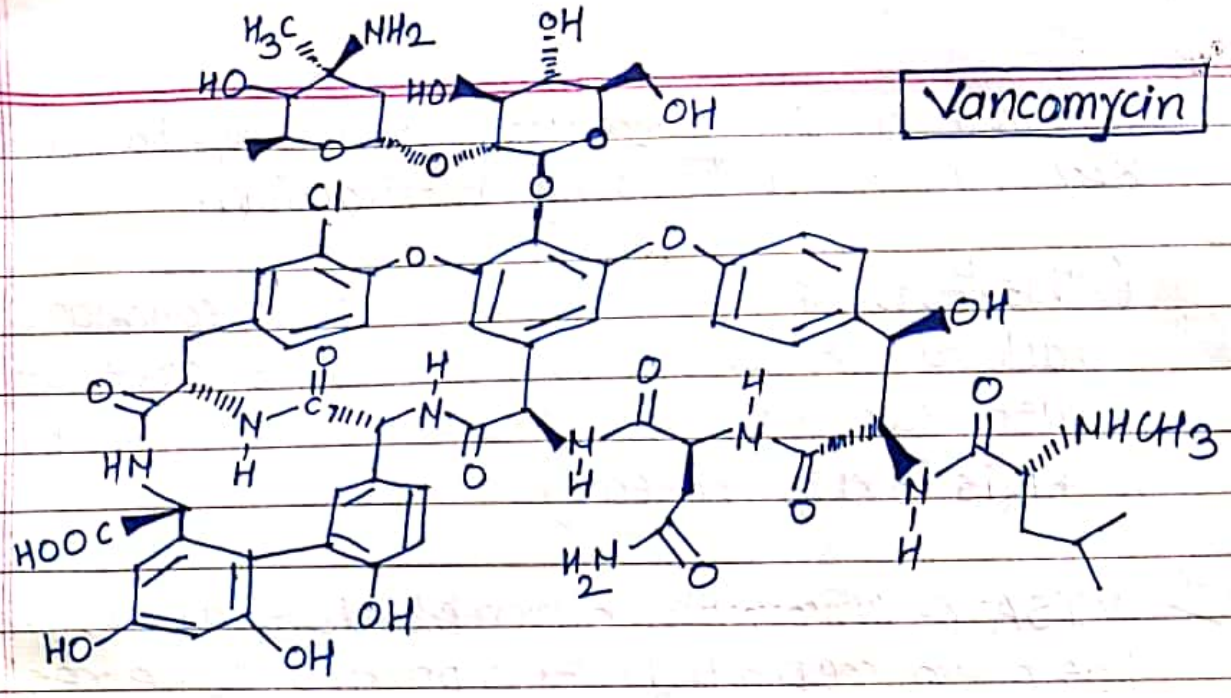
→ The antitumor-antibiotics actinomycin and bleomycin are peptides isolated from "streptomyces spp."
(The antitubercular antibiotics capreomycin & viomycin)

I. Vancomycin (hydrochloride)
II. Bacitracin
III. Polymixin B (sulfate)

Vancomycin

→ is produced by fermentation of Amycolatopsis orientalis (formerly Nocardia orientalis)

→ Chemically, vancomycin has glycosylated hexapeptide chain that is rich in unusual amino acids, many of which contain aromatic rings cross linked by aryl ether bonds into a rigid molecular frameworks.



Vancomycin

MOA

→ vancomycin is bacterial cell wall synthesis inhibitor
→ active species is homodimer of two vancomycin units
→ The binding site for it's target is peptide-lined cleft having high affinity for acetyl-D-alanyl-D-alanine & related peptides through five hydrogen bonds.
→ It inhibits both transglycosylases (inhibiting the linking bet.ⁿ muramic acid & acetyl glucosamine units) & transpeptidase (inhibiting peptide cross linking) activities in bacterial cell wall biosynthesis.

Resistance

Vancomycin-resistant bacteria are emerged as VRE & VRSA
VRE (vancomycin resistant enterococcus)
VRSA (vancomycin resistant staphylococcus aureus)
The mechanism of resistant appears to be alteration of the target D-alanyl-D-alanine units on the peptidoglycan cell wall precursors to D-alanyl-D-lactate. Results in

MRSA → methicillin Resistant Staphylococcus aureus.

lowered affinity for vancomycin due to lack of a key hydrogen bonding interaction.

(This form of resistance will become common in the bacteria for which vancomycin is presently the last sure hope for successful chemotherapy →
→ This is a great fear)

✓ VISA (vancomycin-intermediate S. aureus), also has been reported. It appears to be resistant because of a thickened peptidoglycan layer.

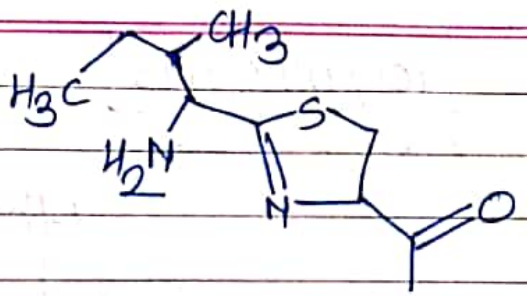
Therapeutic Applications

The useful spectrum is restricted to Gram positive pathogens. → multiply resistant, coagulase-negative staphylococci and 'MRSA' which causes septicemias, endocarditis, skin & soft tissue infections. & infections associated with venous catheters.

→ Adverse effects

clinical use has been limited due to renal toxicity
→ rapid infusion rate has been shown to cause anaphylactoid reactions → hypotension, wheezing, dyspnea, urticaria & pruritis.
→ significant drug rash. (red man syndrome)
(These adverse effects → much less frequent with slower infusion rate)

Bacitracin



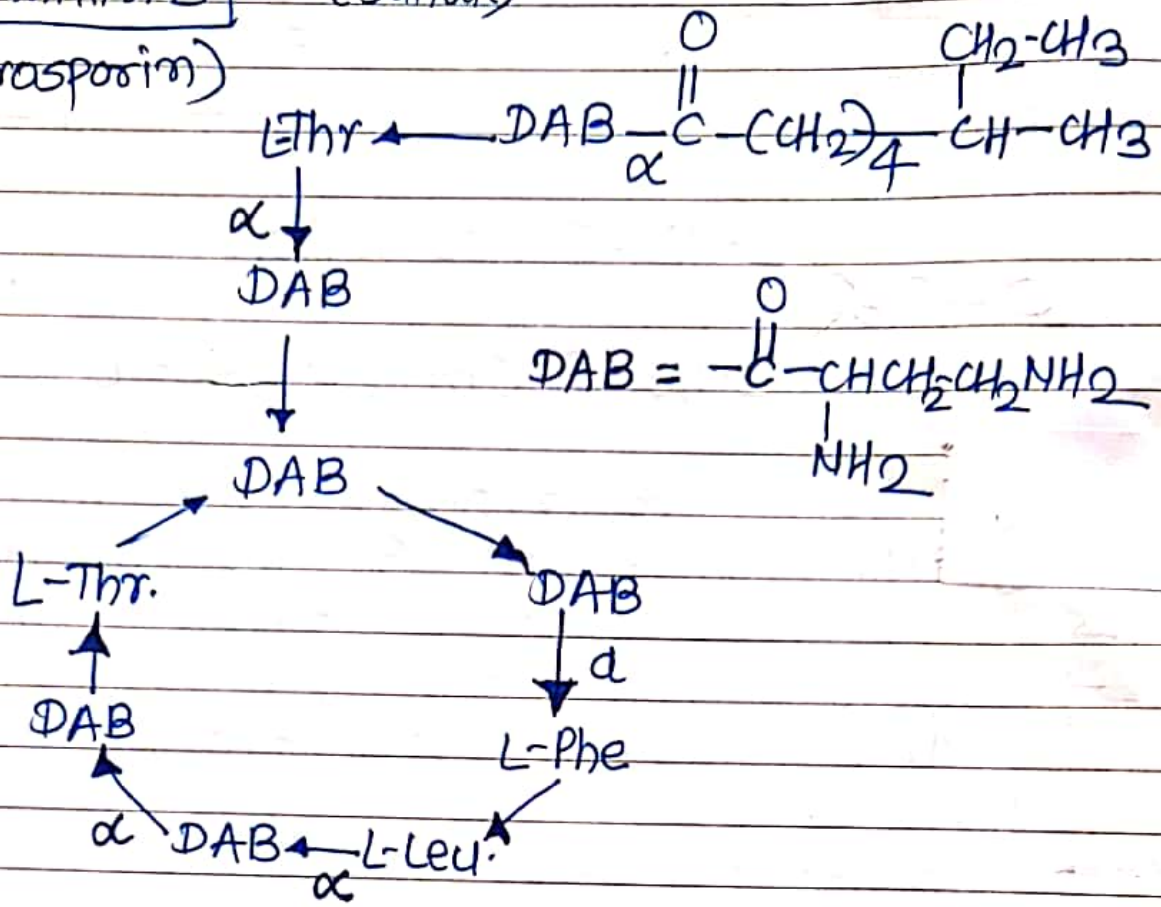
Bacitracin A

D-Phe — L-His - D-Asp - L-Asn — L-Leu — L-Ile - D-Orn - L-Lys - L-Ile - D-Glu

→ Mixture of similar peptides produced by fermentation of the bacterium Bacillus subtilis
→ The A-type component predominates.
→ Action is to inhibit both peptidoglycan biosynthesis at the last stage. & disruption of plasma membrane function.
→ complex mixture of polypeptides
10 polypeptides have been isolated by counter current distribution techniques.
A, A', B, C, D, E, F_1, F_2, F_3 & G.
→ commercial pdt. known as bacitracin is a mix. of principally A with smaller amounts of B, D, E & F_1, F_2 & F_3.

Polymixin B (sulfate)

(Aerosporin)



→ Discovered in 1947 in almost simultaneously in three seperate laboratories in the U.S. & Great Britain.

→ Basillus polymyxa & Bacillus aerosporus were found to be identide species, the name B. polymyxa is used to refer to all the strains that produce closely related polypeptides called "**polymyxins**"

→ polymyxins identified so far, are → polymyxins A, B_1, B_2, C, D_1, D_2, M, colistin A (polymyxin E_1), colistin B (polymyxin E_2), circulins A & B, and polypeptin.

→ Polymyxin B as the sulfate is usually used in medicine, when used systemically it causes less kidney damage.