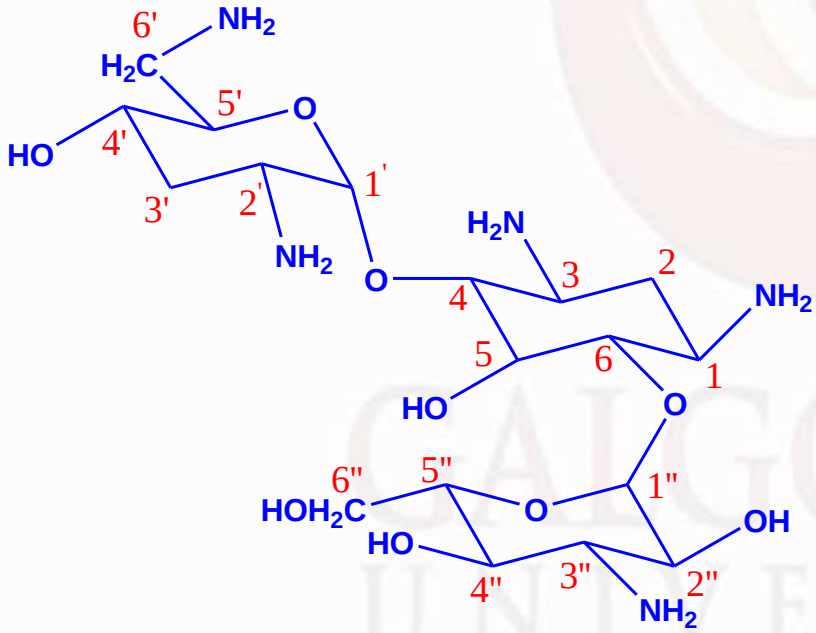
Aminoglycoside

Disclaimer

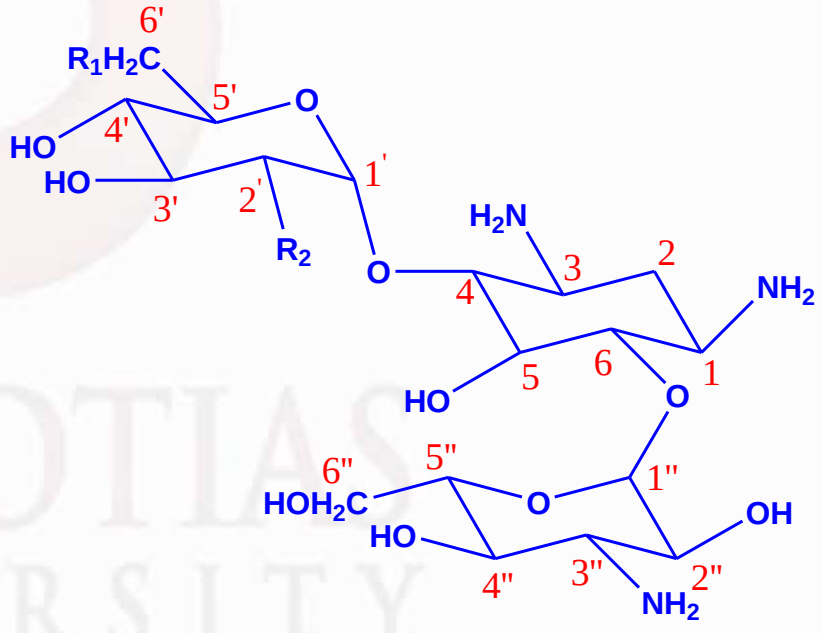
All the content material provided here is only for teaching purpose.

Introduction

- ✓Antibiotics contain an aminocyclitol moiety to which aminosugars are glycosidically linked.
- ✓They may be more correctly called aminocyclitol antibiotics.



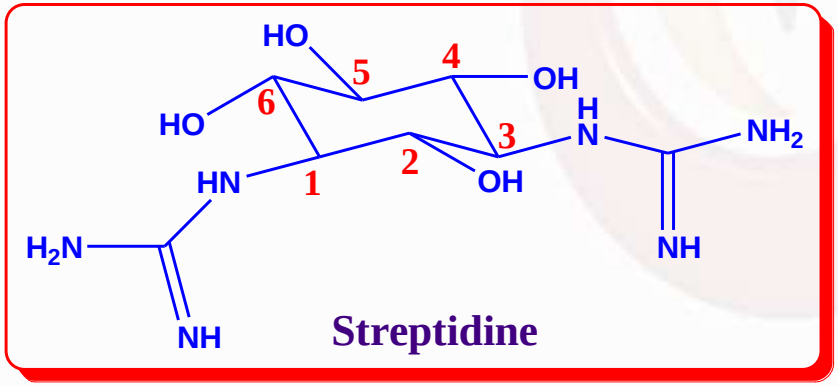
Tobramycin

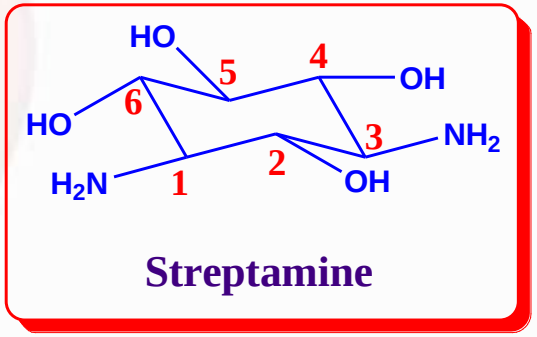


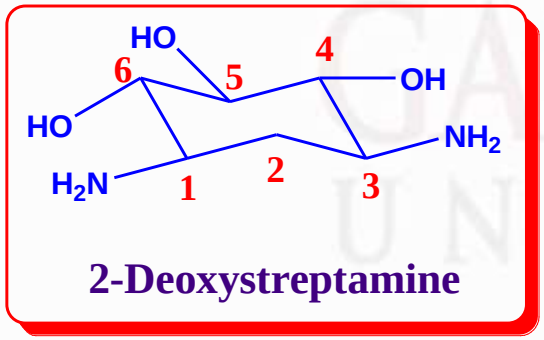
Kanamycins

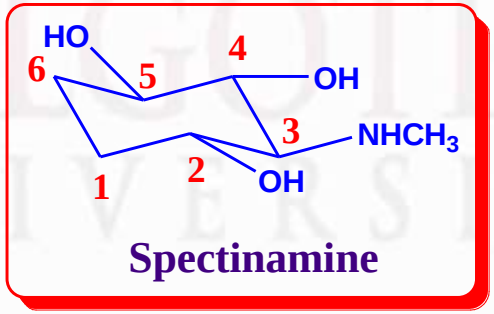
Aminocyclitols???

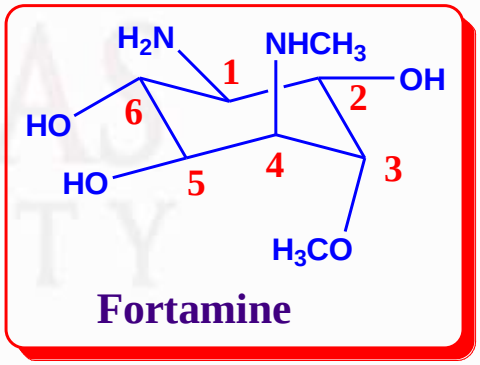
- ✓Cyclohexanes with several substituted or unsubstituted amino and hydroxyl groups which bring them high water solubility.
- ✓Streptidine and Streptamine can be called 1,3-diguanidino and 1,3-diamino inositol, respectively.



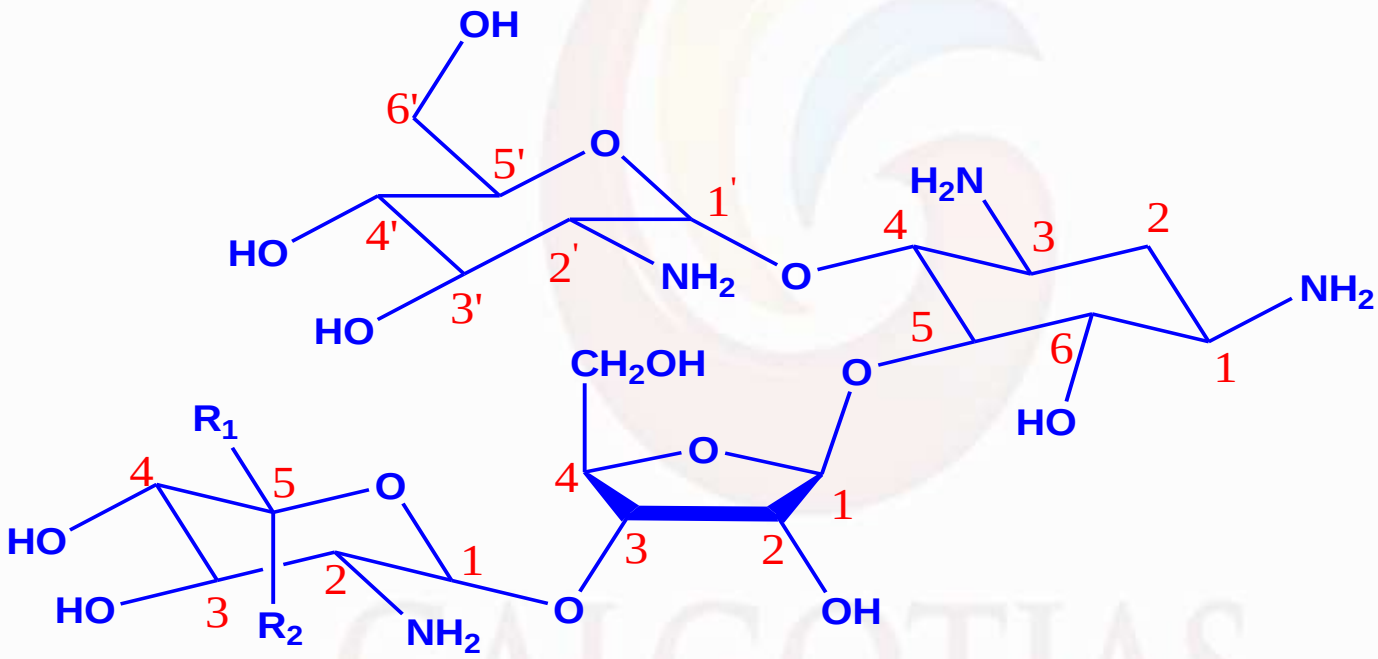








✓All have an aminohexose as the amino sugar and some have a pentose as an extra sugar.



Paromomycin I: R_1= H; R_2= CH_2NH_2
Paromomycin II: R_1= CH_2NH_2; R_2= H

Spectrum of Antimicrobial Activity

- ✓ Aminoglycosides are broad-spectrum antibiotics effective in:

1. Systemic Infections caused by aerobic G(-) bacillus (klebsiella, proteus, enterobacters).
2. Tuberculosis, Brucellusis, Tularaemia and yersinia infections.
3. Amoebic dysentery, shigellosis and salmonellosis.
4. Pneumonia and urinary infections caused by *Pseudomona aeroginosa.*

- ✓ G(+) and G(-) aerobic cocci except staphylococci and anaerobic bacteria are less susceptible.

Microbial Resistance against Aminoglycosides

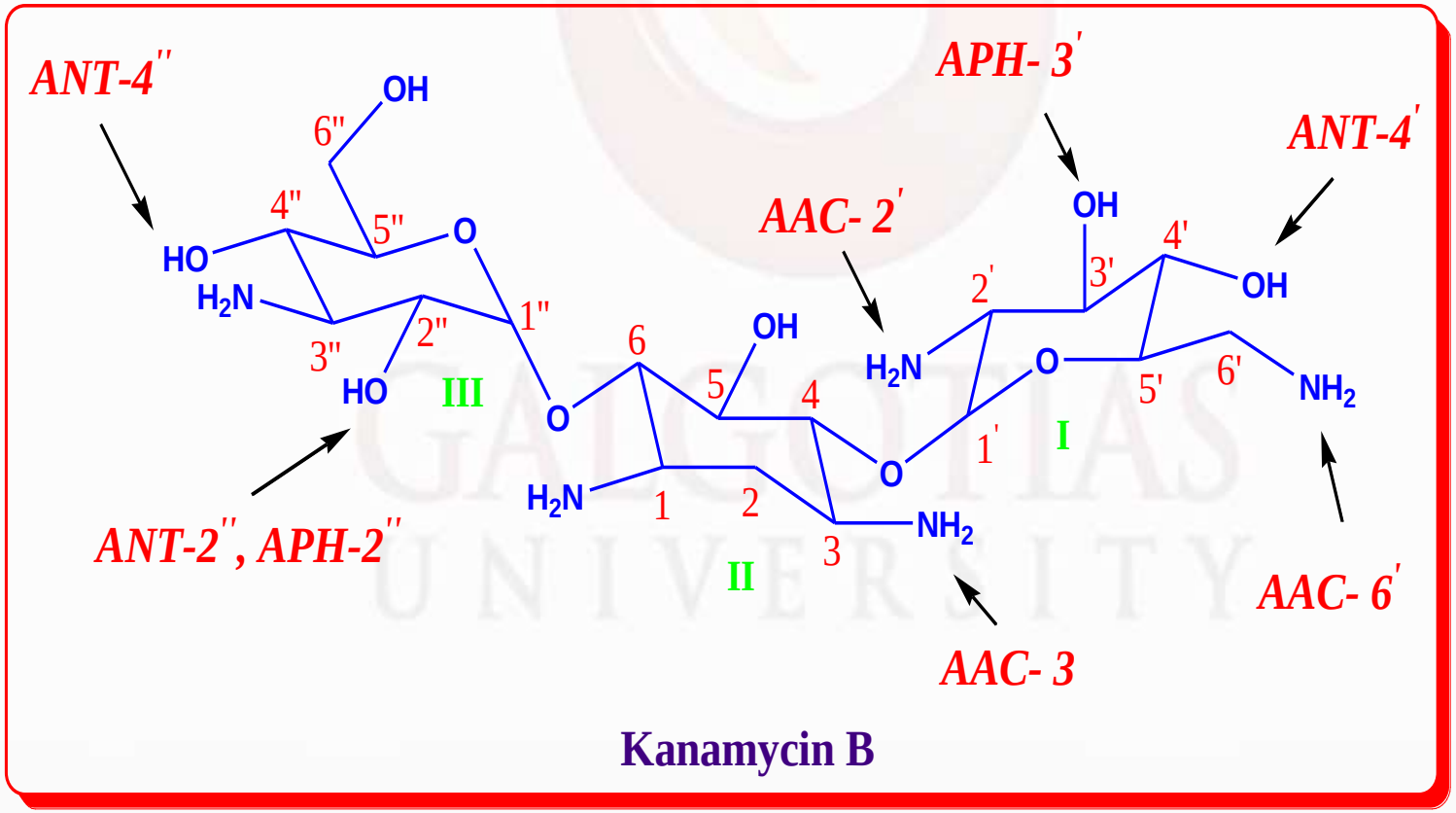
- ✓ Resistant strains have emerged against streptomycin, kanamycin and gentamycin in clinic.
- ✓ R factor is resposible for the production of aminoglycoside deactivating enzymes:

1) Acetyl transferases (AAC)
2) Phosphotransferases (APH),
3) Nucleotidyl transferases (ANT)

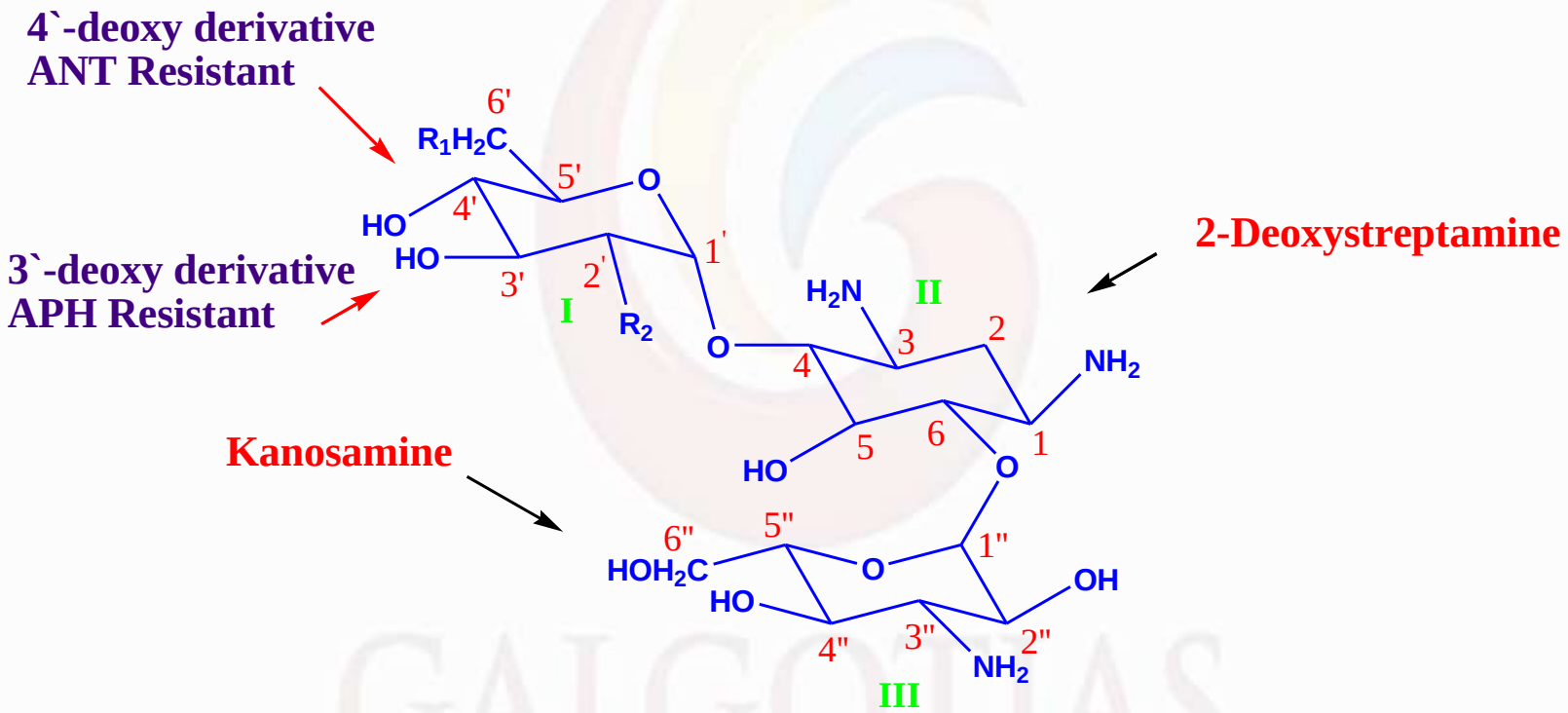
- ✓ These enzymes transfer to hydroxyl and amino groups of the drug.

Aminoglycoside Deactivating Enzymes

- AAC acetylates 3-NH_2 of the ring II, and 2`, 6`- NH_2 of the ring I.
- APH phosphorylates 3`-OH of the ring I and 2``-OH of the ring III.
- ANT adenylates 2``,4``-OH of the ring III and 4`-OH of the ring I.



Kanamycin and Deactivatig Enzymes



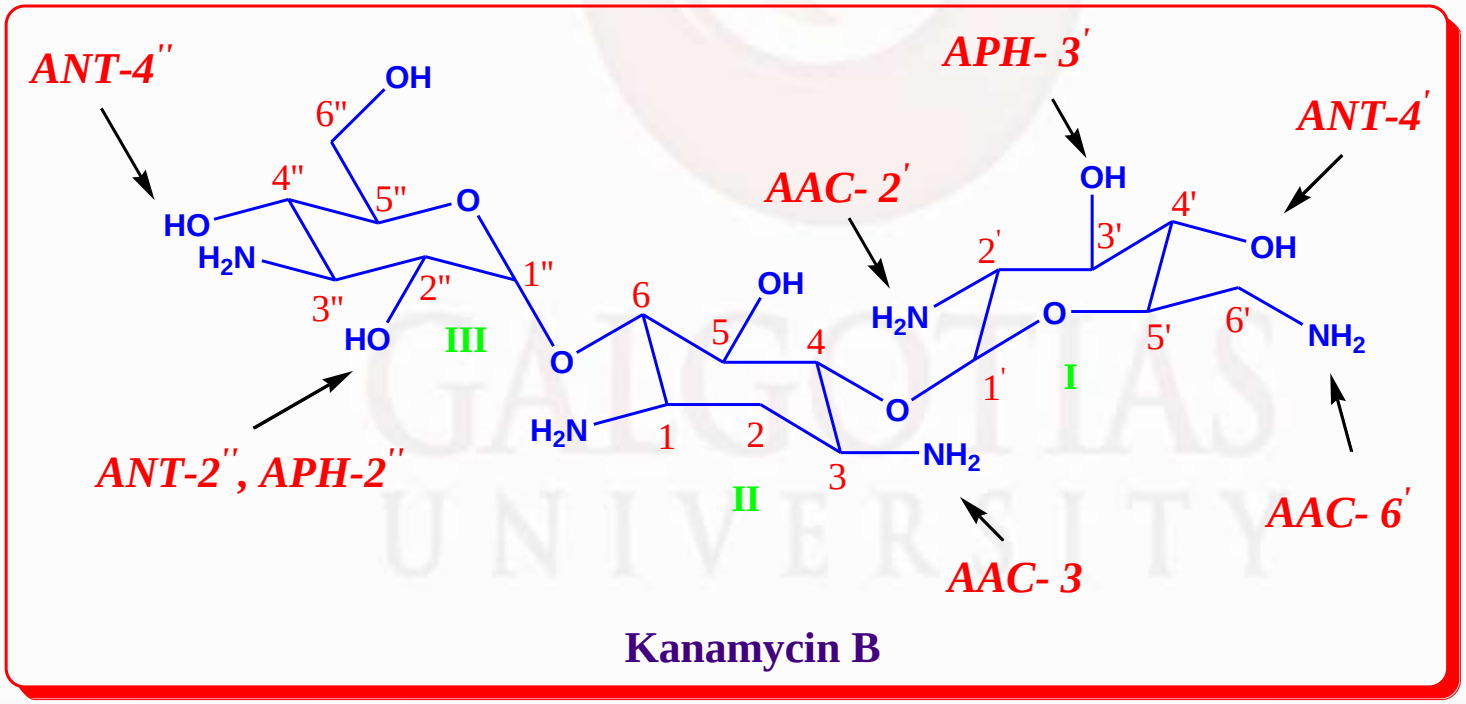
Kanamycin A: R_1= NH_2 ; R_2 = OH
Kanamycin B: R_1 = NH_2 ; R_2 = NH_2
Kanamycin C: R_1= OH; R_2 = NH_2

The Minor Mechanism for Microbial Resistance

- ✓Decreased uptake of the drug in some strains of *p. aeroginosa* in hospital infections because of blockade in the active transport of aminoglycosides.
- ✓Aminoglycoside molecules attach through their cationic groups to anionic portions of membrane phospholipids of bacteria. Upon this attachment the the ATP-dependent uptake occurs.
- ✓Bivalent cations such as Ca^{2+} and Mg^{2+} compete with the drug in this process and antagonise them.
- ✓Anaerobic bacteria lack the ATP-dependent uptake process, so they are resistant to aminoglycosides.

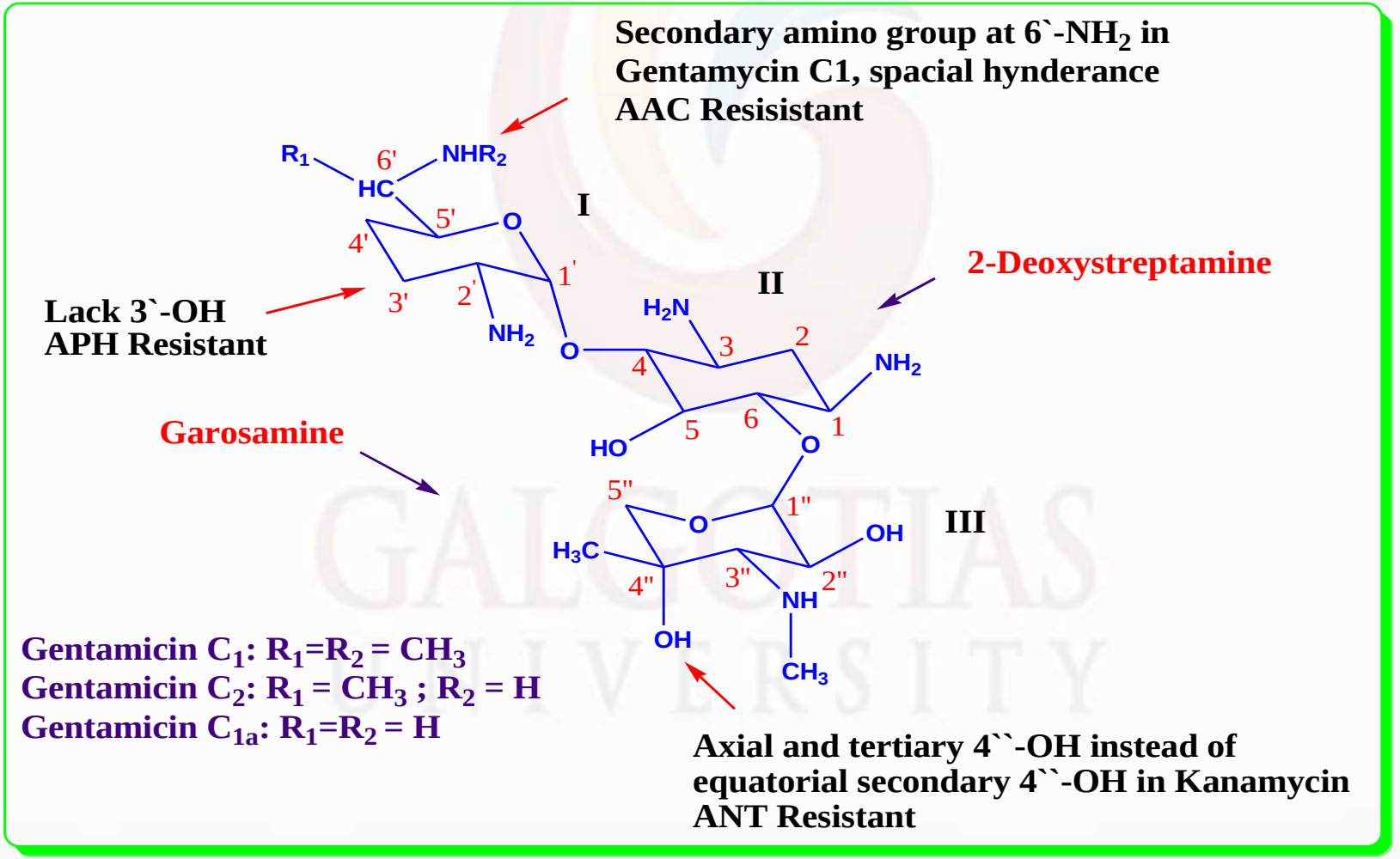
SAR of Aminoglycosides

- ✓ Ring I is very necessary for broad-spectrum antibacterial activity.
- ✓ 2` and 6`-NH_2 groups are specially important. Exchanging of one of them in kanamycin B with hydroxyl group decreases the activity (kanamycin A, C)



SAR of ring I *continued*

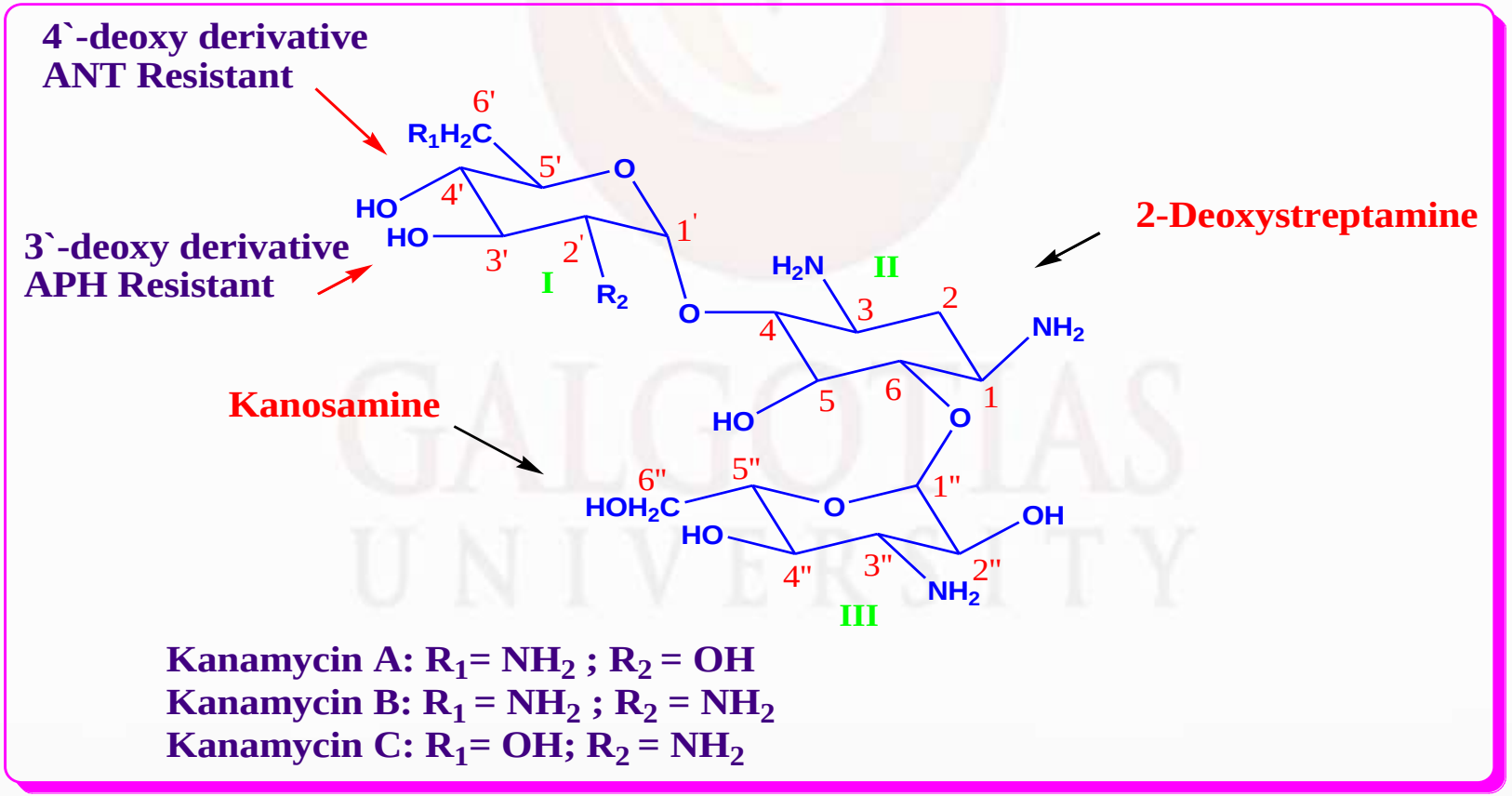
- ✓Methylation of C-6` or 6`- NH_2 doesn't alter the antibacterial activity, but increases the resistance against AAC.



SAR of ring I *continued*

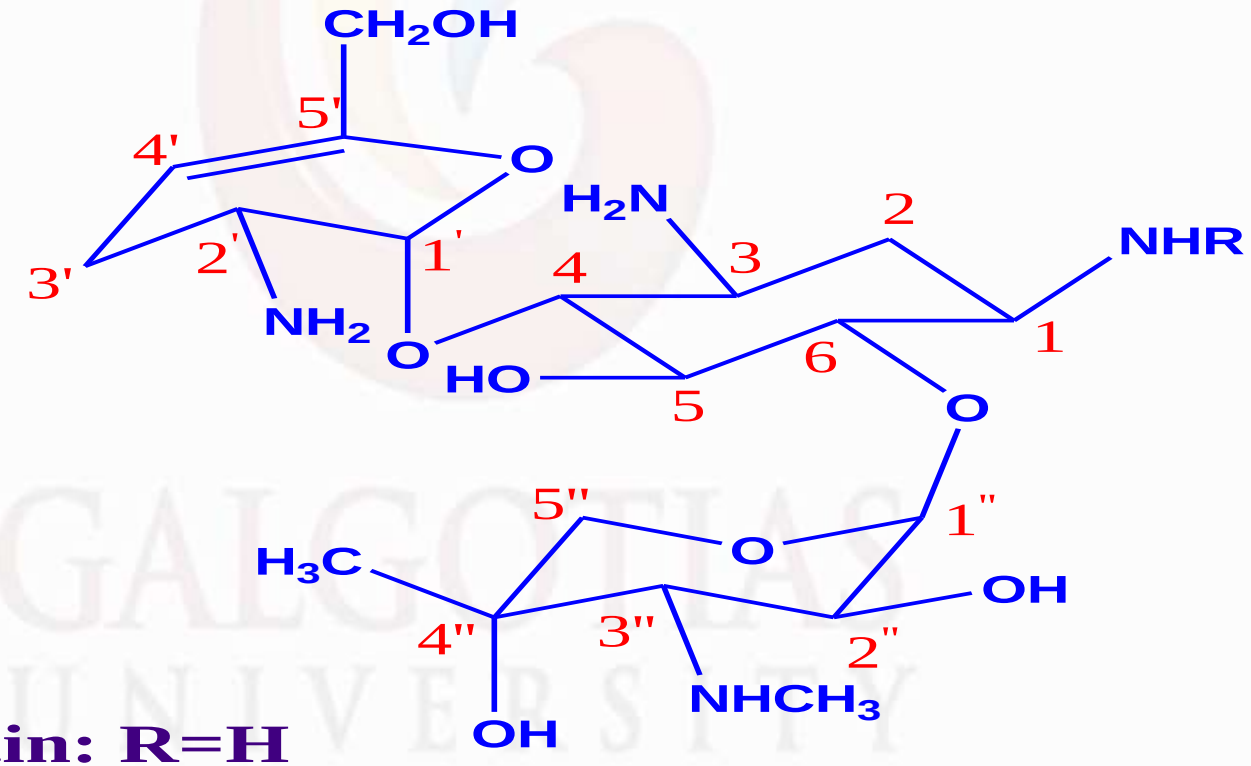
- ✓Omitting the 3`-OH and/or 4`-OH in kanamycin doesn't decrease the antibacterial activity but increases the resistance against AAC: 3`,4`-dideoxykanamycin B: Dibekacin.

The same is true for gentamicin.



SAR of ring I *continued*

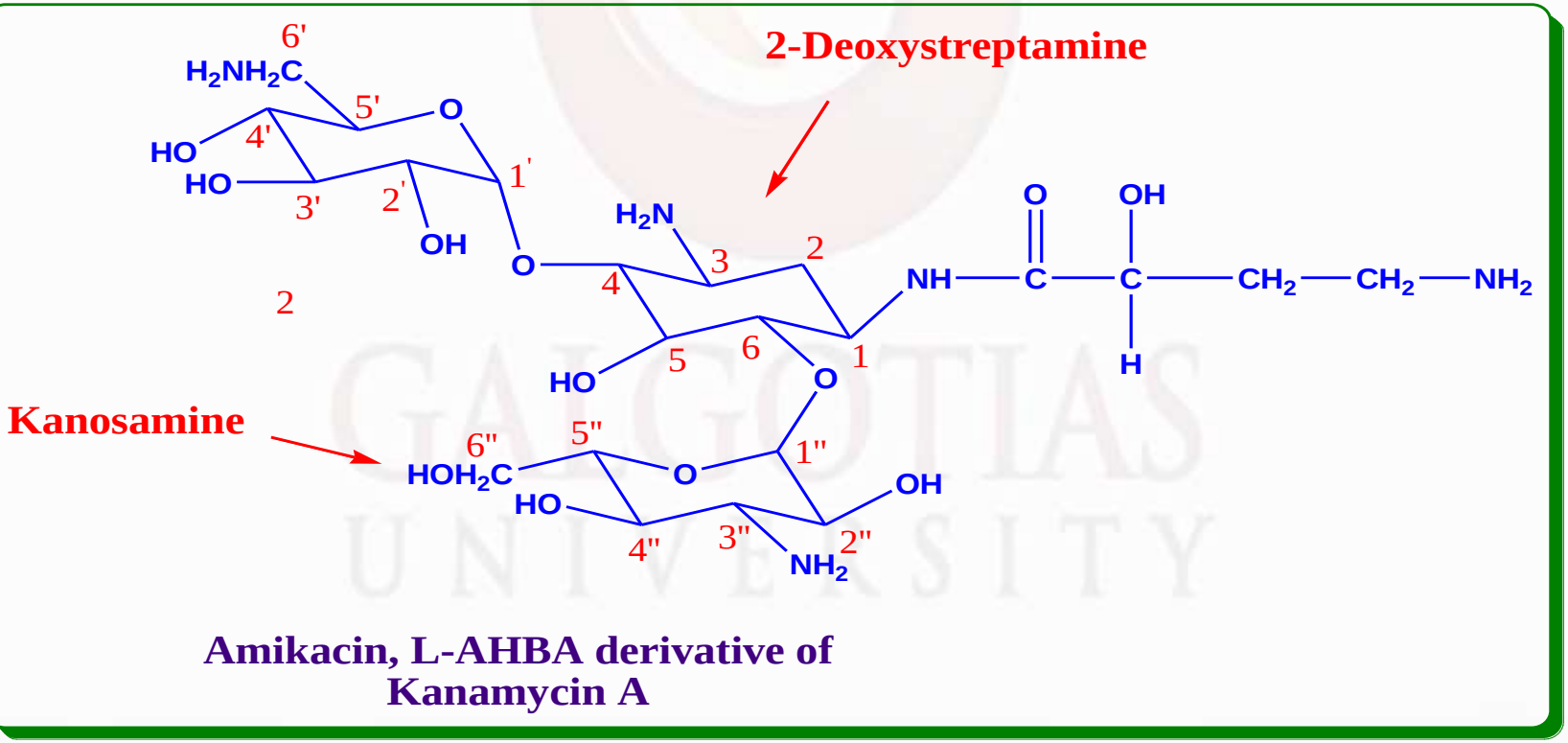
- ✓Omitting the 3`-OH and 4`-OH and the addition of a double bond between C-4` and C-5`has the same effect.



Sisomicin: R=H
Netilmicin: R=C_2H_5

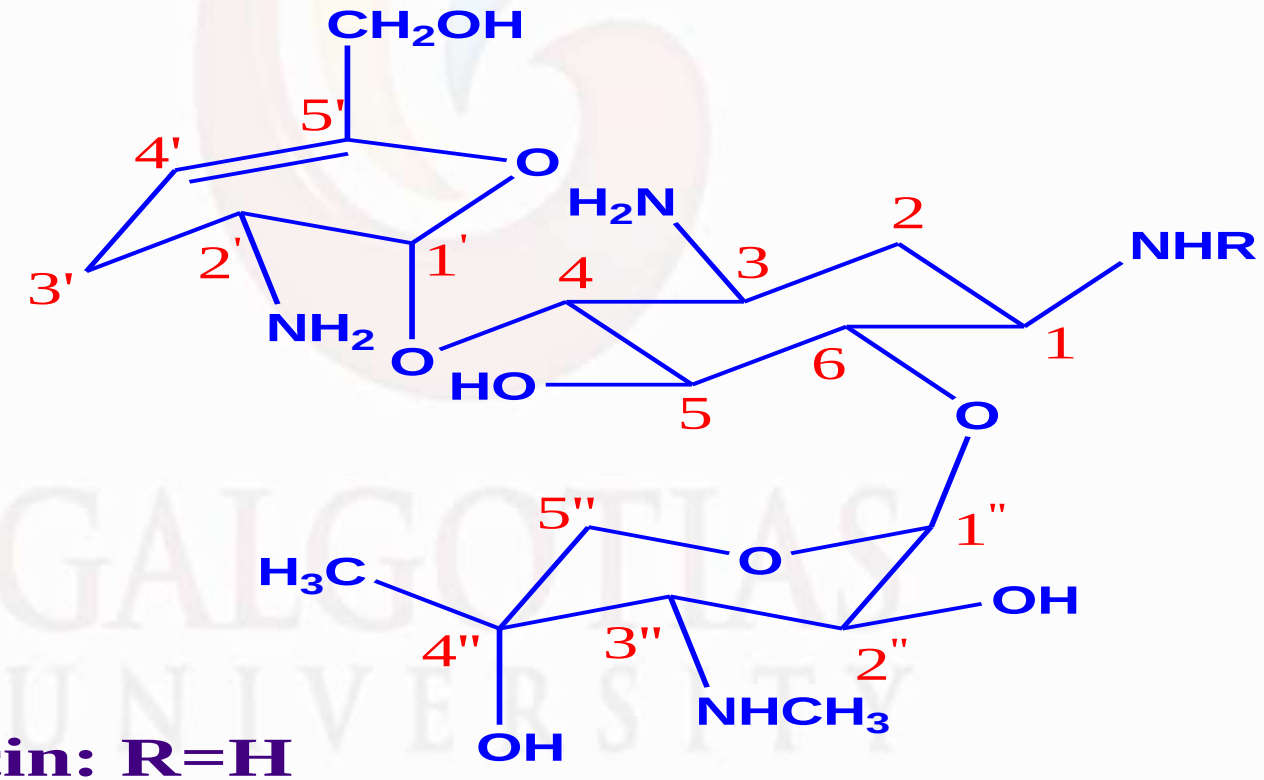
SAR of Aminoglycosides *continued*

- ✓Ring II is flexible toward changes. 1-NH_2 in kanamycin can be acylated and the antibacterial activity remains almost unchanged , but resistance against deactivating enzymes increases: Amikacin



SAR of ring II *continued*

- ✓1-NH_2 ethylation of sisomycin saves the antibacterial activity and increases the enzymatic resistance: Netilmycin

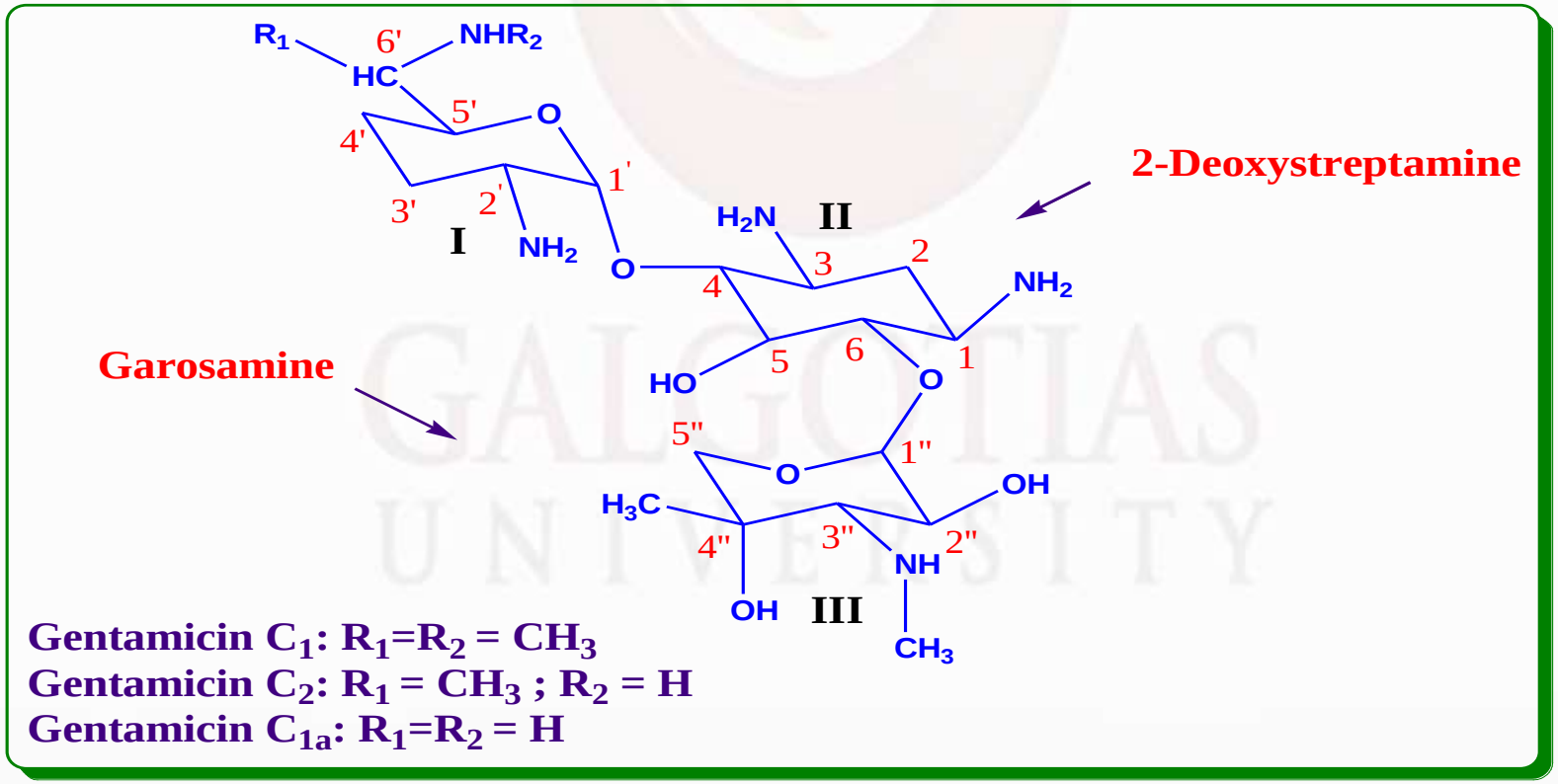


Sisomicin: R=H

Netilmicin: R=C_2H_5

SAR of Aminoglycosides *continued*

- ✓Ring III functional groups are less sensitive to modifications:
- ✓2``-deoxy gentamicins are less active than 2``-OH ones, but 2``-NH_2 derivative (seldomycin) are very active.
- ✓3``- NH_2 can be primary or secondary.
- ✓4``-OH can be axial or equatorial, the former is resistant against the deactivating enzymes (ANT).

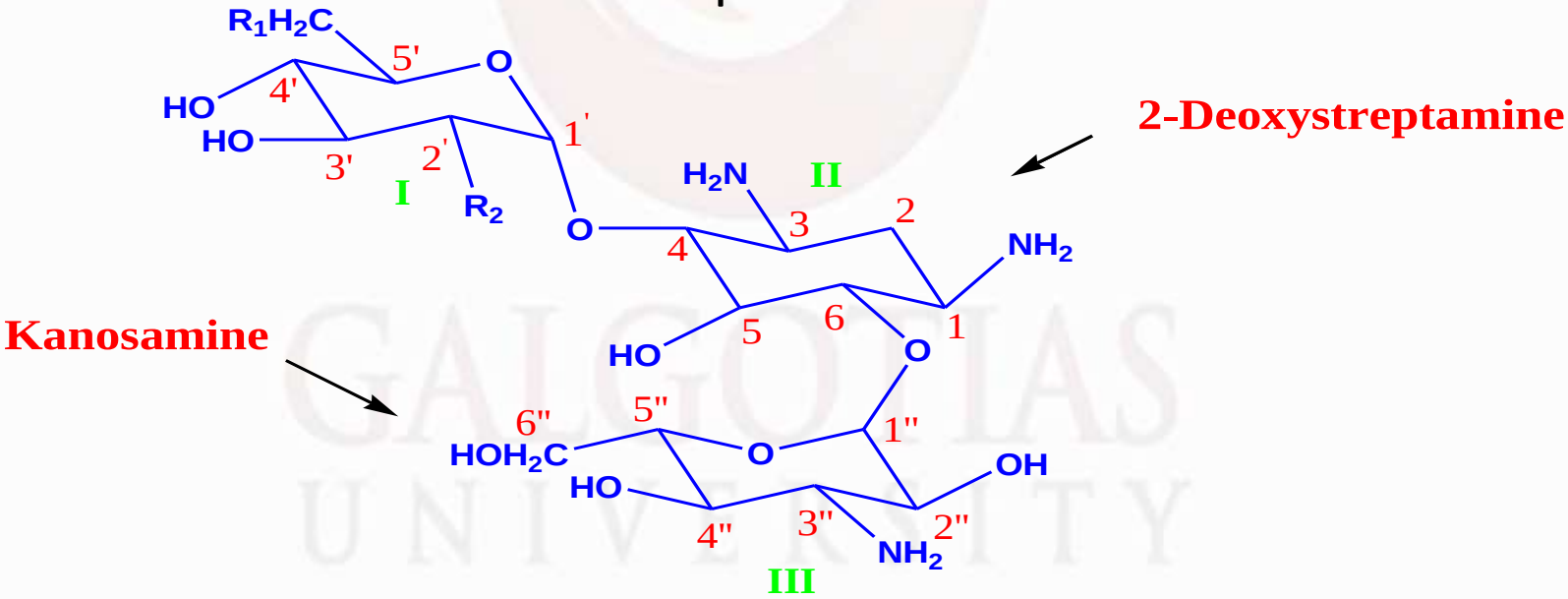


Mechanism of Action of Aminoglycosides

- ✓Inhibition of protein biosynthesis initiation upon attachment to 30s portion of ribosomes.
- ✓Misreading mutation of the genetic code and the synthesis of nonesense proteins which are not normal proteins so they cannot take part in cellular activities.
- ✓Nonesense proteins disturb the semipermeability of the bacterial cell and aminoglycoside molecules enter the cell easily and kill it.

Therapeutic Agents
Kanamycin

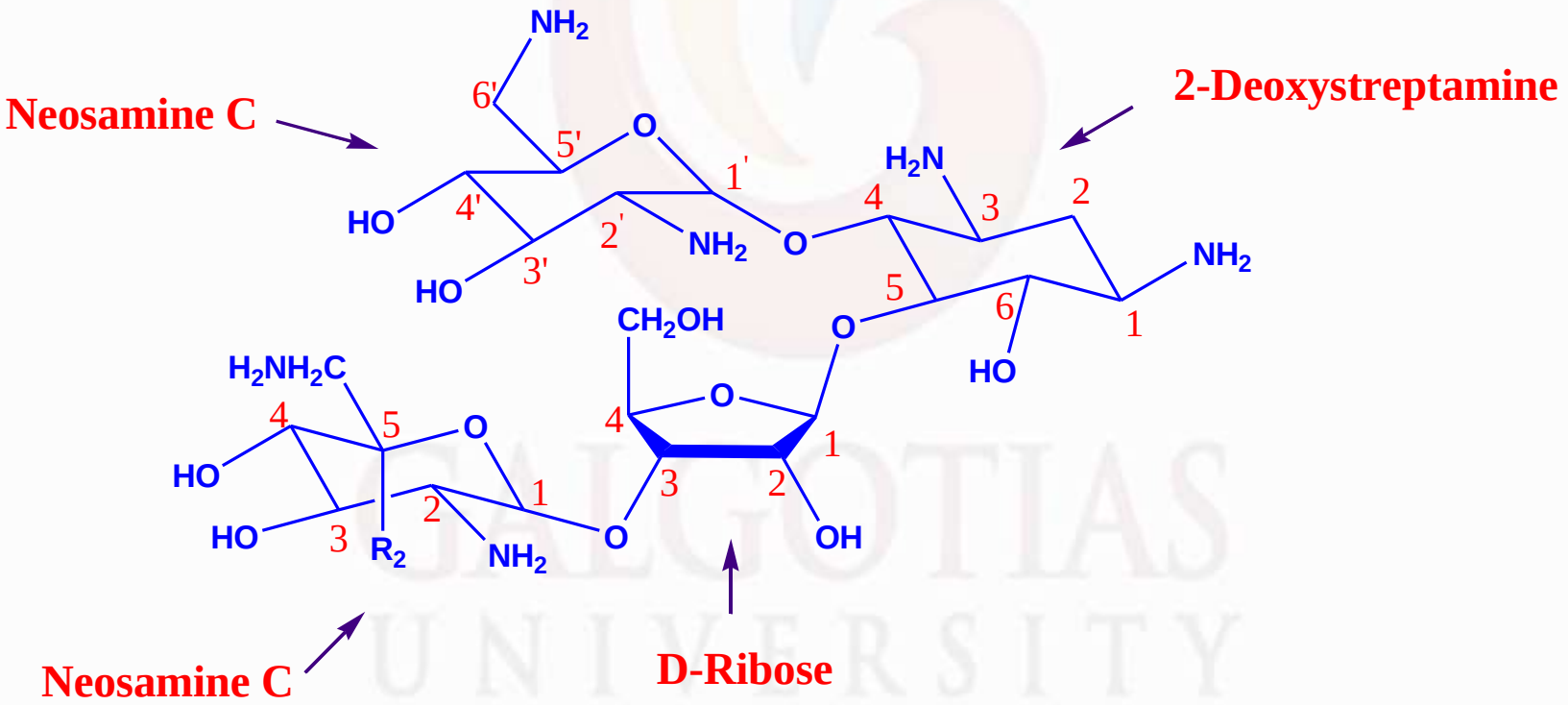
- ✓Isolated from cultures of *Streptomyces kanamyceticus*. The least toxic member in the market is kanamycin A.
- ✓It is used for the treatment of GI infections, such as dysentery and systemic G(-) bacillus infections caused by klebsiella, proteus, enterobacters.
- ✓For disinfection of GI before an operation.



Kanamycin A: R_1= NH_2 ; R_2 = OH
Kanamycin B: R_1 = NH_2 ; R_2 = NH_2
Kanamycin C: R_1= OH; R_2 = NH_2

Neomycin

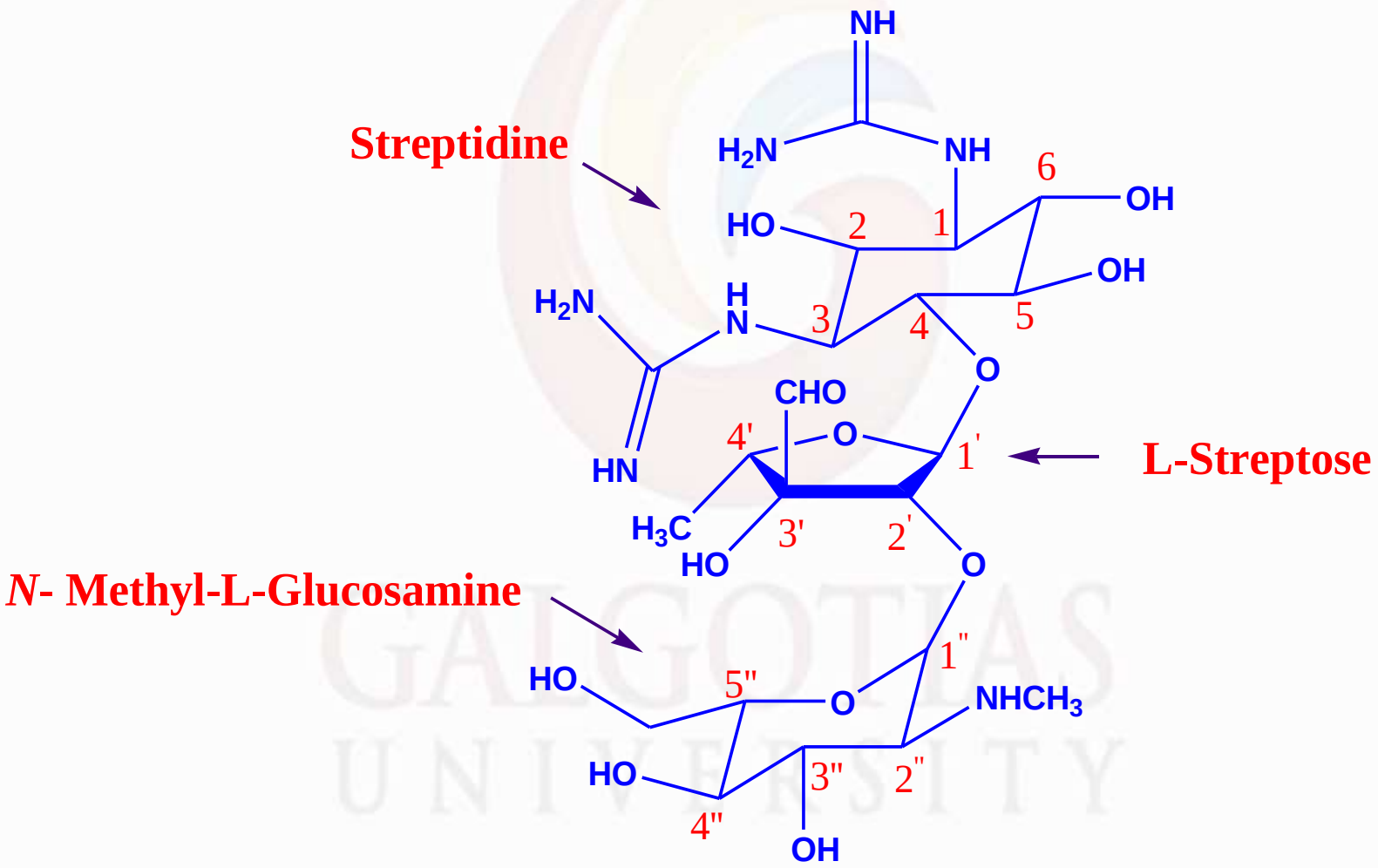
- ✓Isolated from cultures of *Streptomyces fradia* along with an antifungal subsance: Fradicin.
- ✓Effective against GI and dermal infections.



Neomycin

Streptomycin

✓Has a different aminocyclito (a 1,3-diguanidinoinositol).



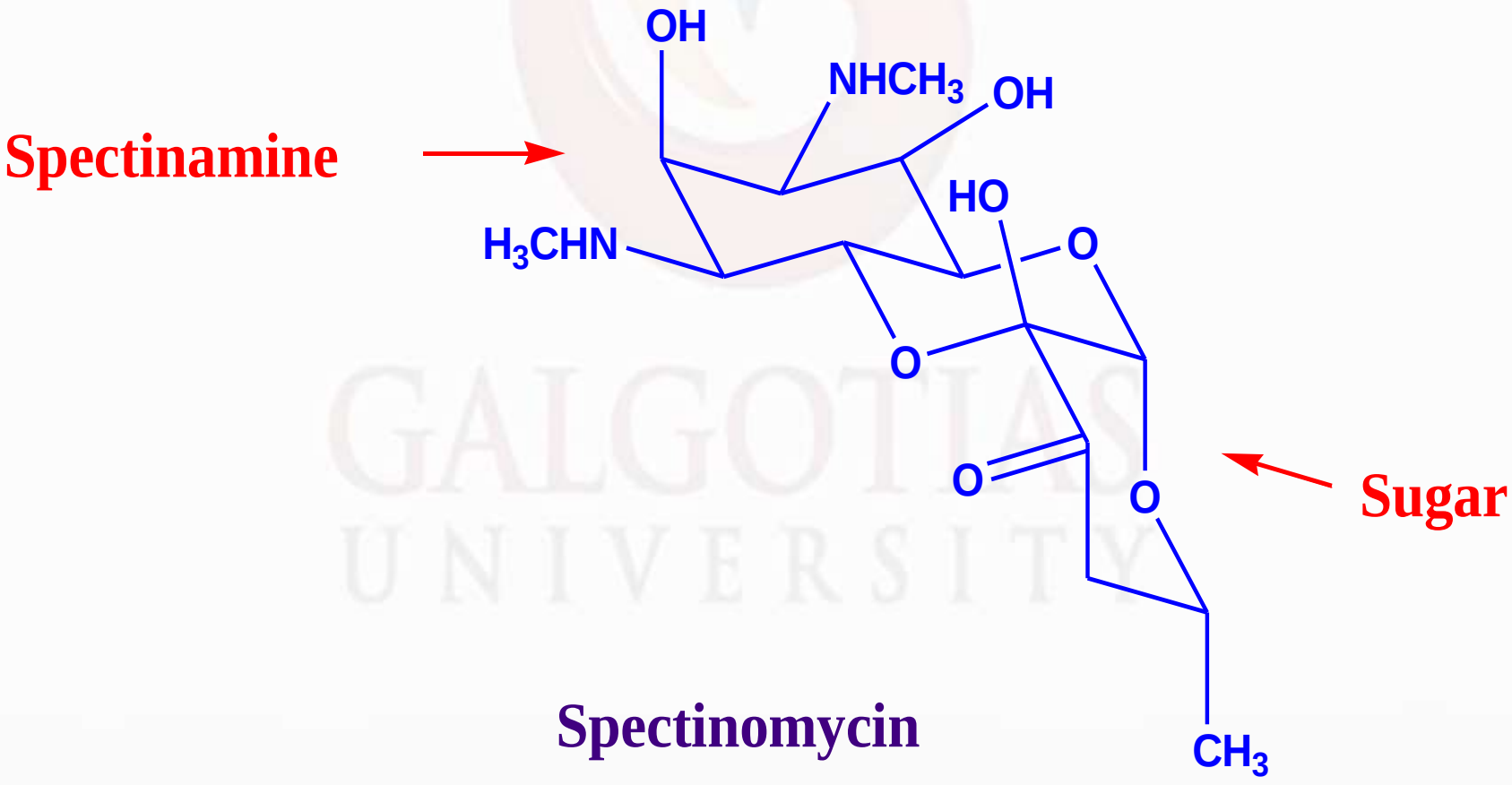
Streptomycin

Streptomycin *continued*

- ✓Isolated from cultures of *Streptomyces griseus.*
- ✓It was introduced against tuberculosis in 1943, kanamycin and amikacin are effective against tuberculosis, but not as much as streptomycin.
- ✓Streptomycin brought Waxman the Noble prize in 1952.

Spectinomycin

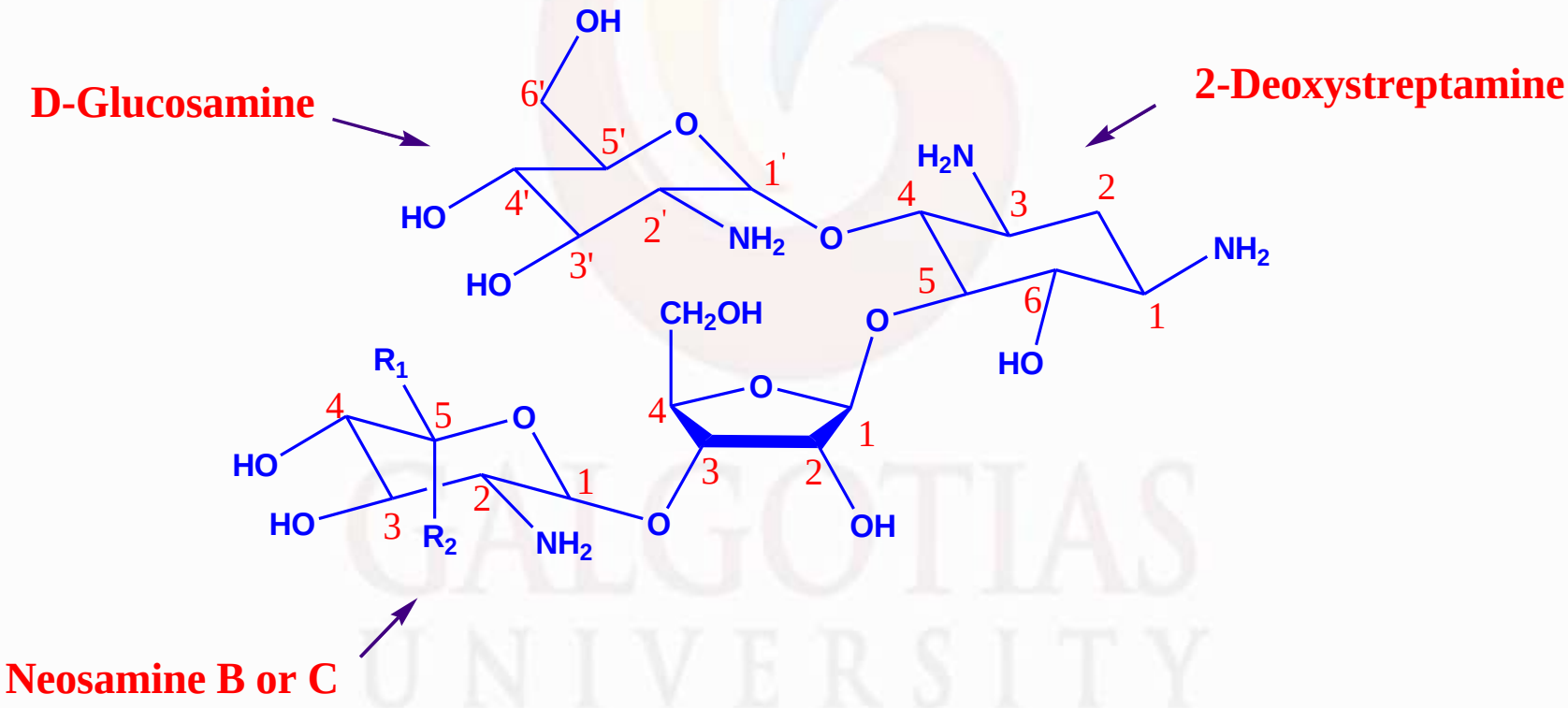
- ✓An unusual aminoglycoside isolated from cultures of *streptomyces spectabilis*.
- ✓The sugar portion has a carbonyl group and is fused through glycosidic bonds to the aminocyclitol portion, spectinamine.
- ✓It is used in a single dose against *Neisseria gonhorea*.



Spectinomycin

Paromomycin

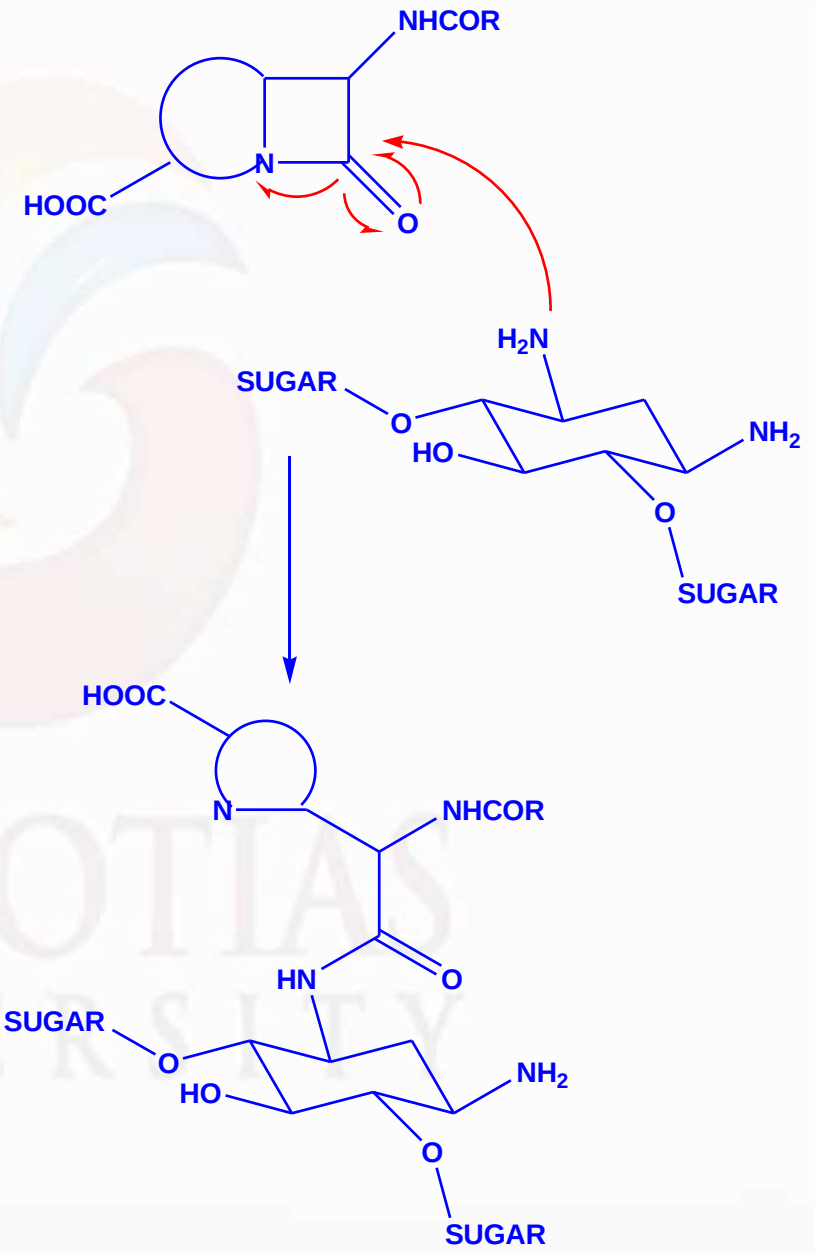
- ✓Isolated from *Streptomyces rimosus.*
- ✓In the tratment of GI infections caused by shigella, salmonella, *E.coli*, amoebas.



Paromomycin I: R_1= H; R_2= CH_2NH_2
Paromomycin II: R_1= CH_2NH_2; R_2= H

Mechanism of Chemical incompatility of Aminoglycosides with β-lactams

- ✓ Acylation of aminocyclitol portion by the β-lactam molecule.
- ✓ Begins with nucleophilic addition of the amino group to the carbonyl group of β-lactam ring.



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