

# Pharmaceutical Chemistry

## Antibacterial Antibiotics

# AMINOGLYCOSIDES

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AL-Mustaqbal University

College of Pharmacy

**Lecture 2**

# Aminoglycosides

**Streptomycin**, first aminoglycoside antibiotic used in chemotherapy isolated from the actinomycetes and, particularly, from the genus *Streptomyces*.

Among the many antibiotics isolated from that genus, several compounds closely related in structure to streptomycin. Six of them—

**kanamycin, neomycin, paromomycin, gentamicin, tobramycin, and netilmicin** are marketed in the United States.

# Amikacin

a semisynthetic derivative of kanamycin A, has been added, and it is possible that additional aminoglycosides will be introduced in the future.

All aminoglycoside antibiotics are absorbed very poorly following oral administration, and some of them (kanamycin, neomycin, and paromomycin) are administered by that route for the treatment of GI infections. Because of their potent broadspectrum antimicrobial activity,

## Chemistry

- ❖ Aminoglycosides are so named because their structures consist of amino sugars linked glycosidically.
- ❖ All have at least one aminohexose, and some have a pentose lacking an amino group (e.g., streptomycin, neomycin, and paromomycin).
- ❖ Additionally, each of the clinically useful aminoglycosides contains a highly substituted 1,3-diaminocyclohexane central ring; in kanamycin, neomycin, gentamicin, and tobramycin, it is deoxystreptamine, in streptomycin, it is streptadine.

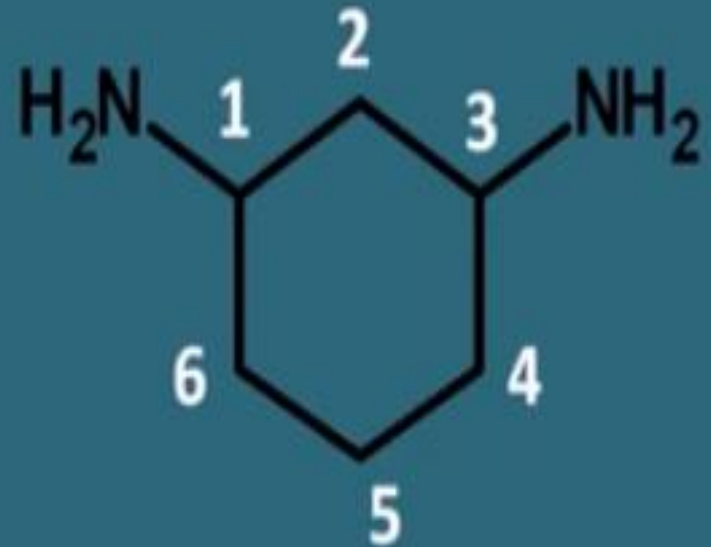
# Structural features

Suggested: Natural drugs || Along with synthetic analogues || Part-2



✓ Central ring

**1,3-Diaminocyclohexane**



✓ Amino sugar

Hexose or Pentose

- ❖ The aminoglycosides are thus strongly basic compounds that exist as **polycations at physiological pH**
- ❖ Aminoglycosides are apparently **not metabolized in vivo**.
- ❖ Their inorganic acid salts are **very soluble in water**.
- ❖ All are available **as sulfates**.
- ❖ Solutions of the aminoglycoside salts are stable to autoclaving.
- ❖ The high water solubility of the aminoglycosides no doubt contributes to their pharmacokinetic properties.
- ❖ They distribute well into most body fluids but not into the central nervous system, bone, or fatty or connective tissues.

# Spectrum of Activity

Although the aminoglycosides are classified as **broad spectrum antibiotics**, their greatest usefulness lies in the treatment of serious systemic infections caused by **aerobic Gram-negative bacilli**.

# Mechanism of Action

The aminoglycosides act directly on the bacterial ribosome to **inhibit the initiation of protein synthesis**.

- Gram Negative Aerobic Bacilli

- E. Coli
- Klebsiella
- Proteus



- *Pseudomonas*

- *Tobramycin > Gentamicin*

- *Mycobacteria*

- *Streptomycin*



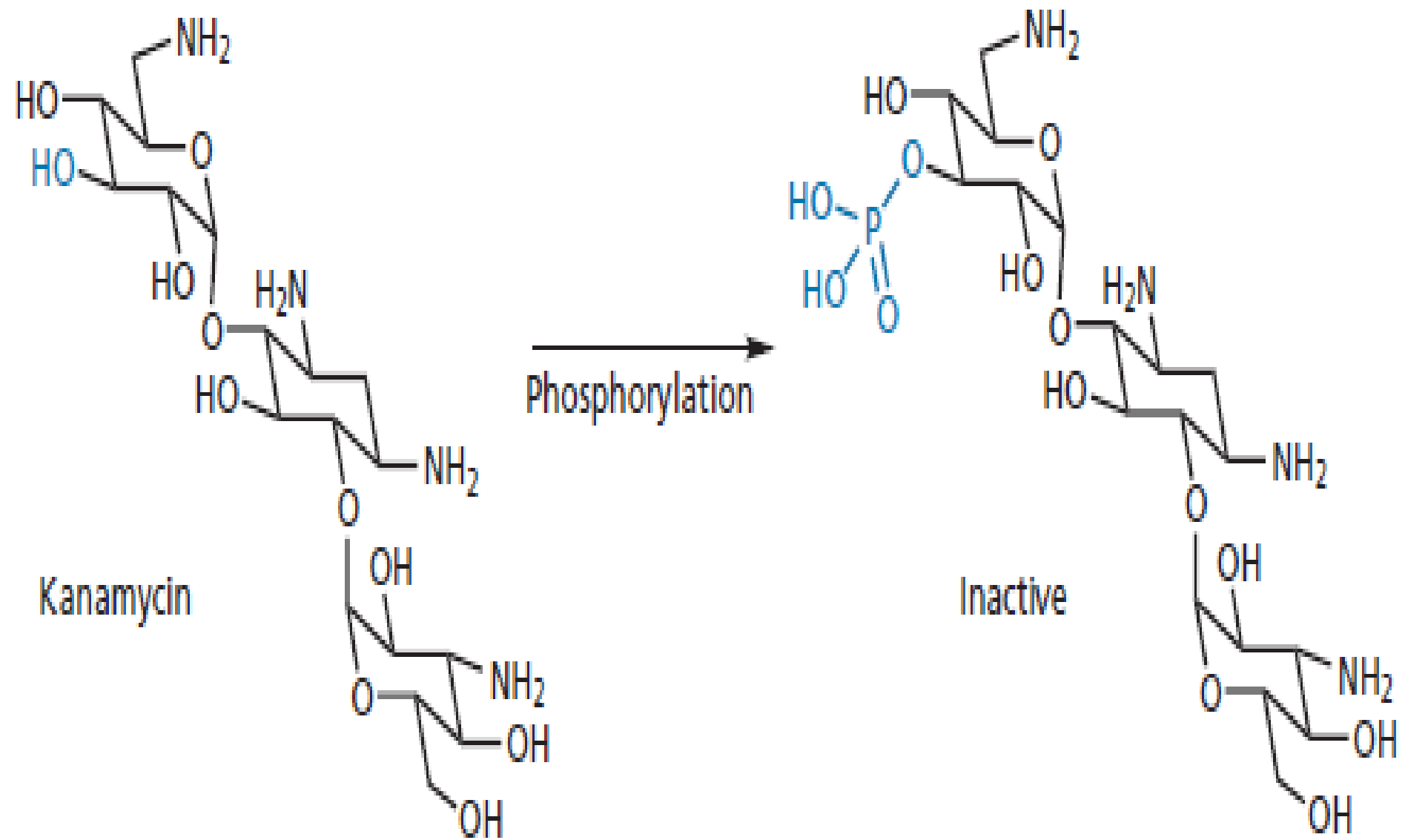
- Not used for Gram Positive Aerobes
- Not useful against anaerobes



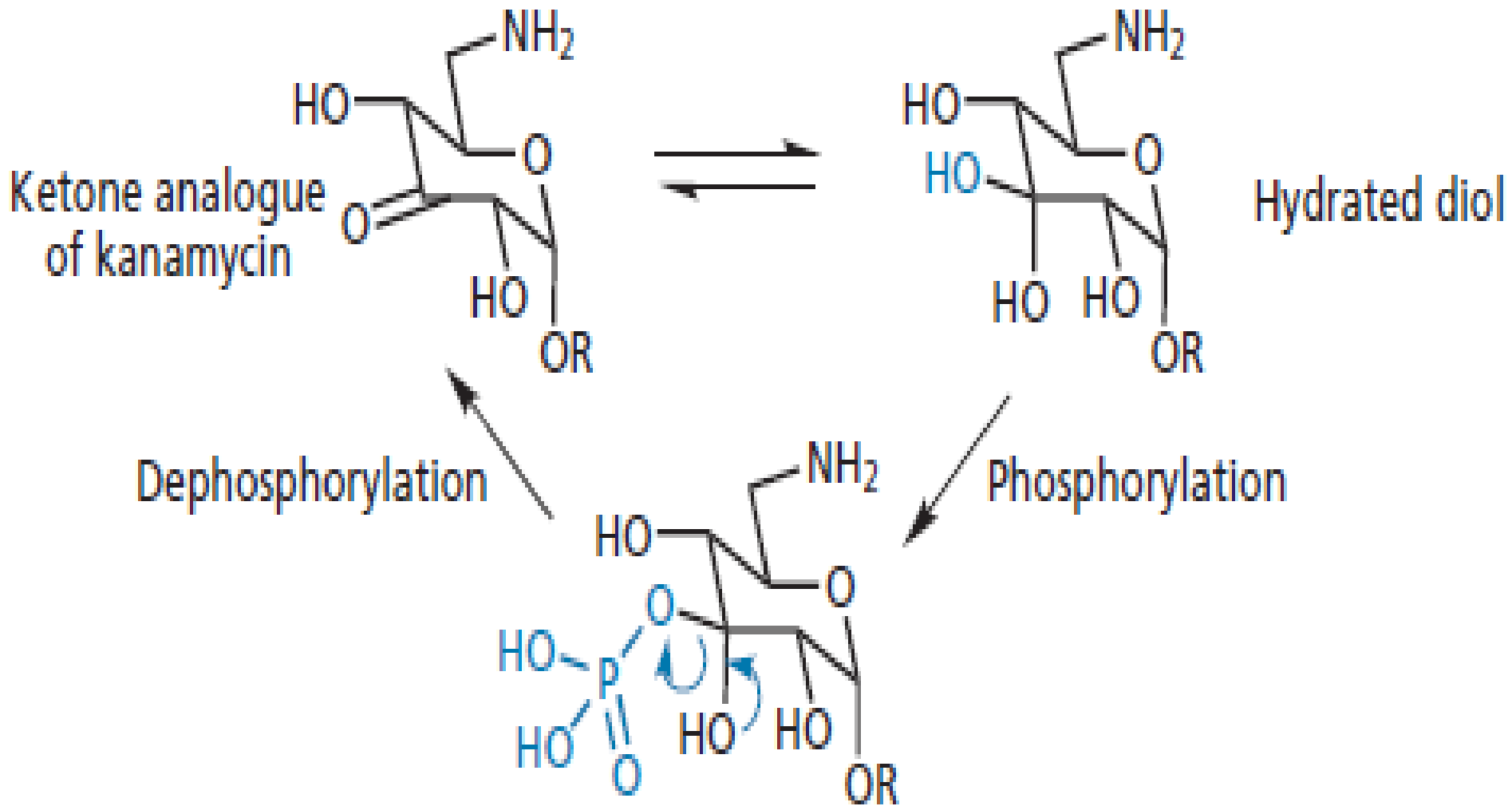
Resistance of individual aminoglycosides to specific inactivating enzymes can be understood, in large measure, by using chemical principles.

**First**, one can assume that if the target **functional group is absent** in a position of the structure normally attacked by an inactivating enzyme, then the antibiotic will be resistant to the enzyme.

**Second**, **steric factors** may confer resistance to attack at functionalities otherwise susceptible to enzymatic attack.



The phosphorylation reaction causing resistance to kanamycin.



Analogue of kanamycin which is resistant to phosphorylation.

# Structure–Activity Relationships (SAR)

It is convenient to discuss sequentially aminoglycoside SARs in terms of substituents in rings I, II, and III.

Ring I is crucially important for characteristic broad spectrum antibacterial activity, and it is the primary target for bacterial inactivating enzymes.

❖ Amino functions at 6' and 2' are particularly important as kanamycin B (6'-amino, 2'-amino) is more active than kanamycin A (6'-amino, 2'-hydroxyl), which in turn is more active than kanamycin C (6'-hydroxyl, 2'-amino).

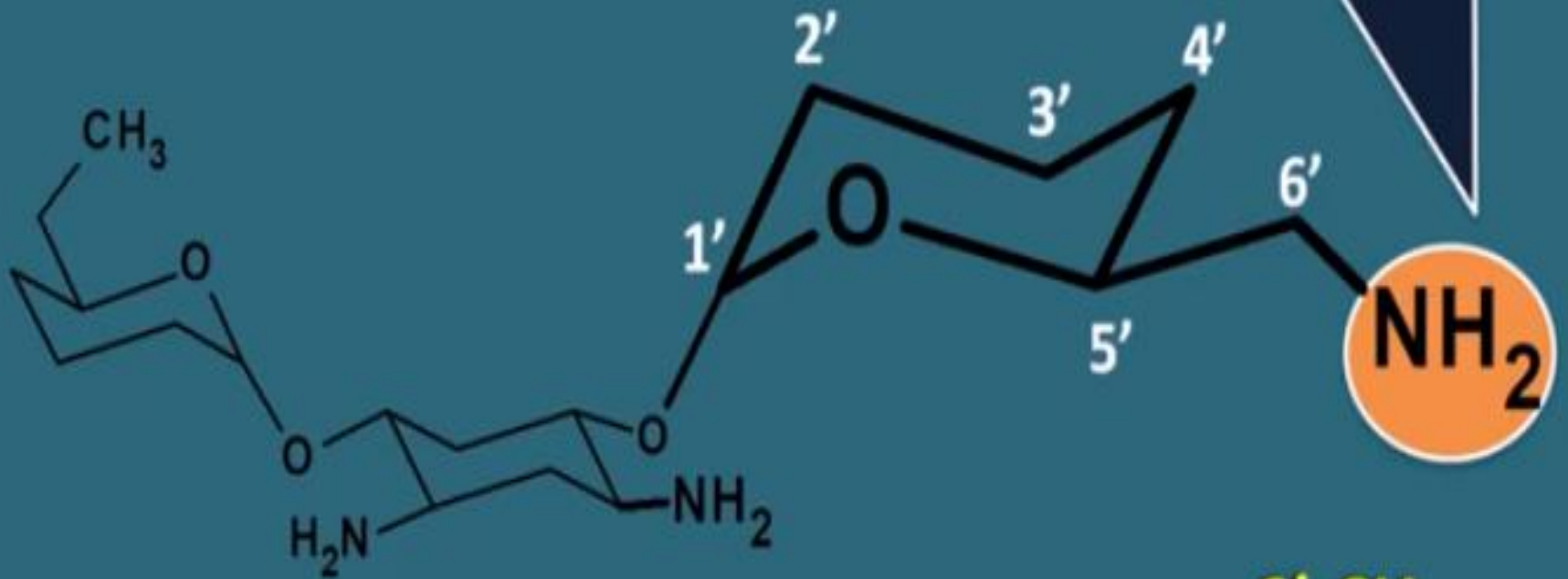
- ❖ **Methylation** at either the 6'-carbon or the 6'-amino positions does not lower appreciably antibacterial activity and confers resistance to enzymatic acetylation of the 6'-amino group.
- ❖ **Removal** of the 3'-hydroxyl or the 4'-hydroxyl group or both in the kanamycins (e.g., 3',4'-dideoxykanamycin B or **dibekacin**) does not reduce antibacterial potency.
- ❖ The gentamicins also **lack oxygen functions** at these positions, as do sisomicin and netilmicin, which also have a **4'5'-double bond**.

# Common structure



Ring I: At 6<sup>th</sup> position:

Target for inactivation by  
AAC



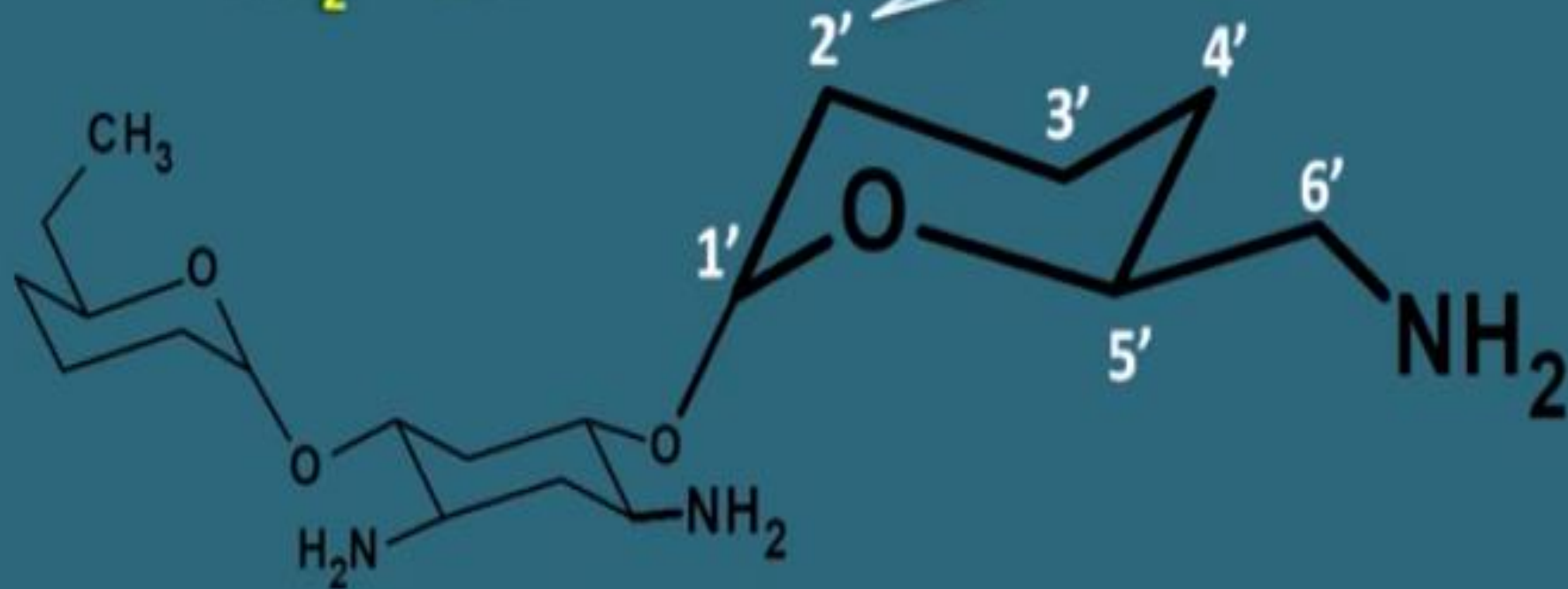
-CH<sub>3</sub> substitution  ↓ *Inactivation*

6'-CH<sub>3</sub>  
6'-NHCH<sub>3</sub>

Ring I: At 2<sup>nd</sup> position:

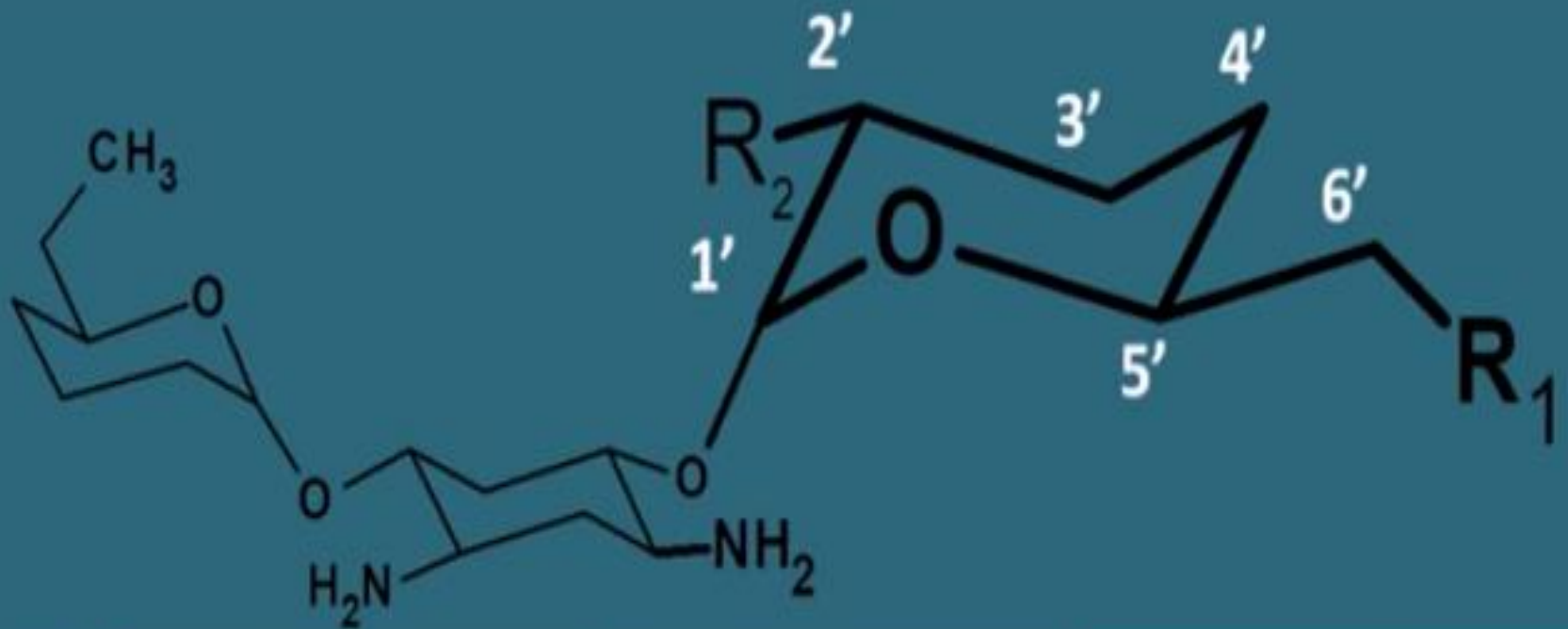
**-NH<sub>2</sub> > -OH**

2-Amino group increases activity



*-NH<sub>2</sub> both at 2' and 6' further increases activity*

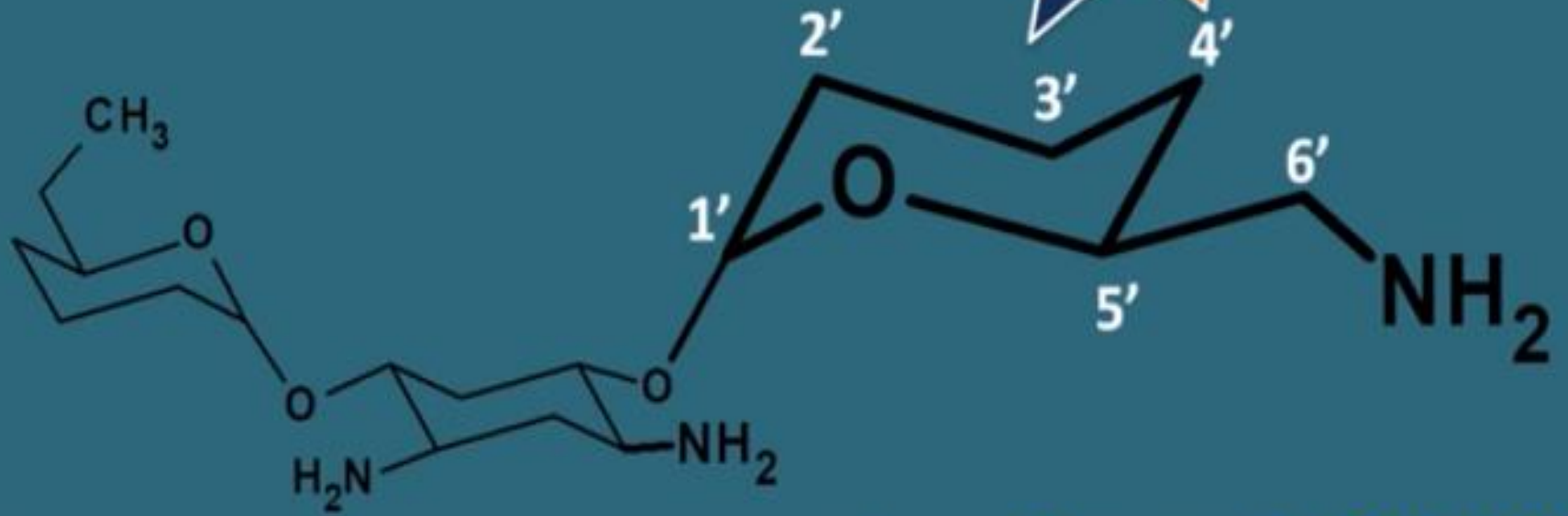




| Drug        | 6 <sup>th</sup> position ( $R_1$ ) | 2 <sup>nd</sup> position ( $R_2$ ) |
|-------------|------------------------------------|------------------------------------|
| Kanamycin B | $-NH_2$                            | $-NH_2$                            |
| Kanamycin A | $-NH_2$                            | $-OH$                              |
| Kanamycin C | $-OH$                              | $-NH_2$                            |

Ring I: At 3<sup>rd</sup> & 4<sup>th</sup> positions:

-OH is not essential



3'-OH is inactivated by phosphorylation



*Removal of 3'-OH decreases inactivation*

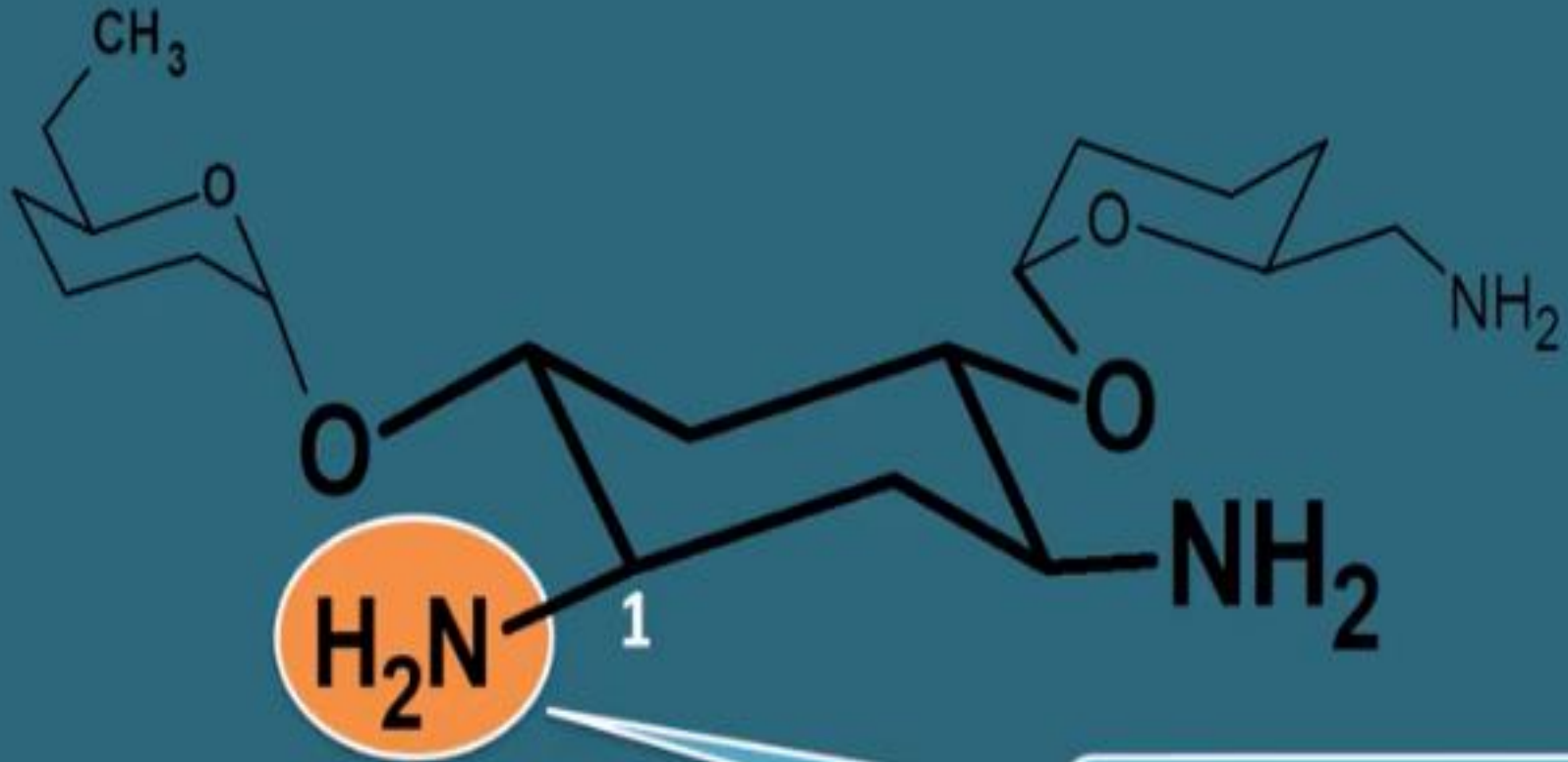
❖ None of these derivatives is inactivated by phosphotransferase enzymes that phosphorylate the 3 hydroxyl group.

## ❖ Ring II

❖ Few modifications of ring II (deoxystreptamine) functional groups are possible without appreciable loss of activity in most of the aminoglycosides.

The 1-amino group of kanamycin A can be acylated (e.g., **Amikacin**), however, with activity largely retained. Netilmicin (1-N-ethylsisomicin) retains the antibacterial potency of sisomicin and is resistant to several additional bacteria-inactivating enzymes.

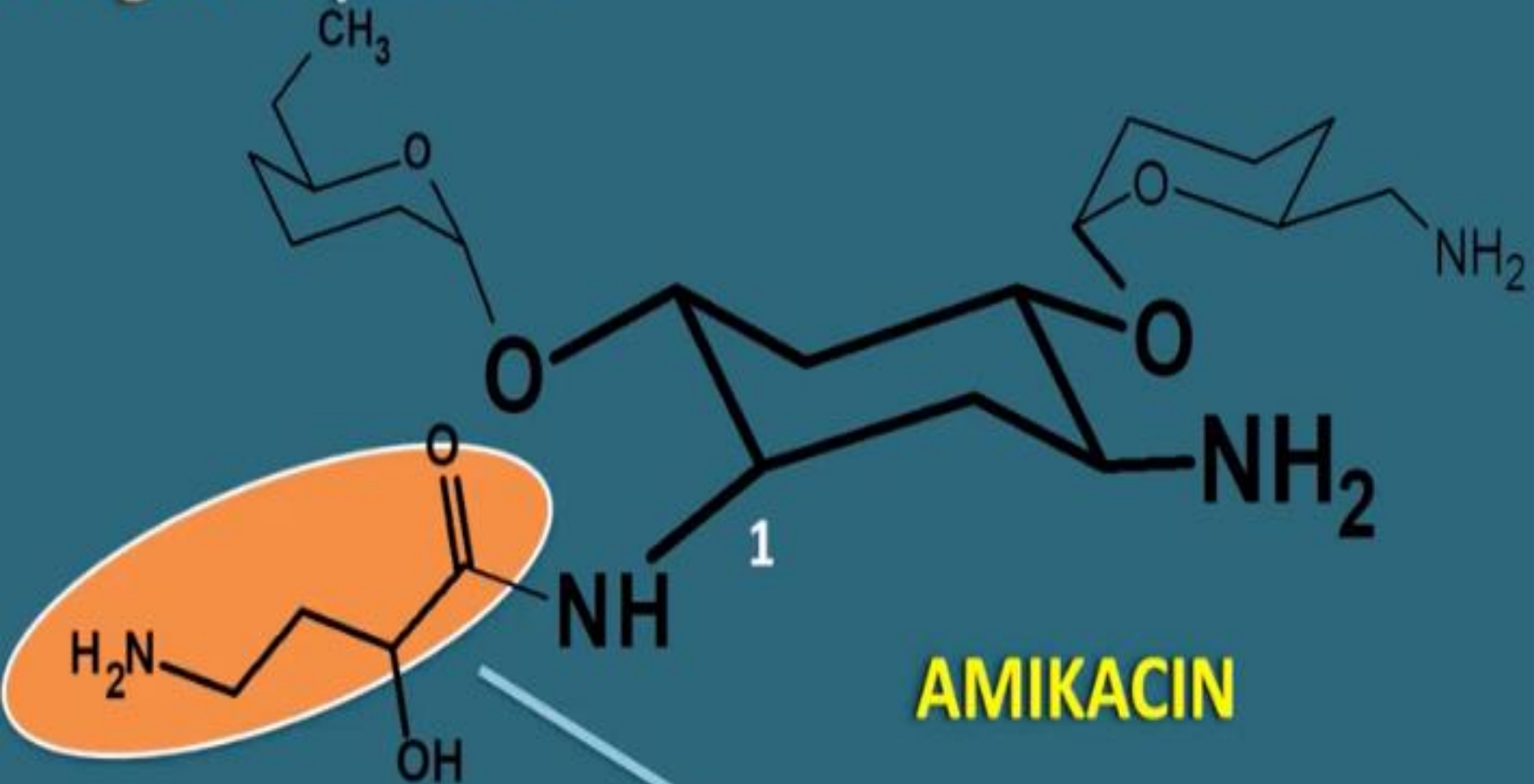
# Ring II: 1<sup>st</sup> position



$-\text{C}_2\text{H}_5$   *Resistance for inactivation*

Acylation retains activity

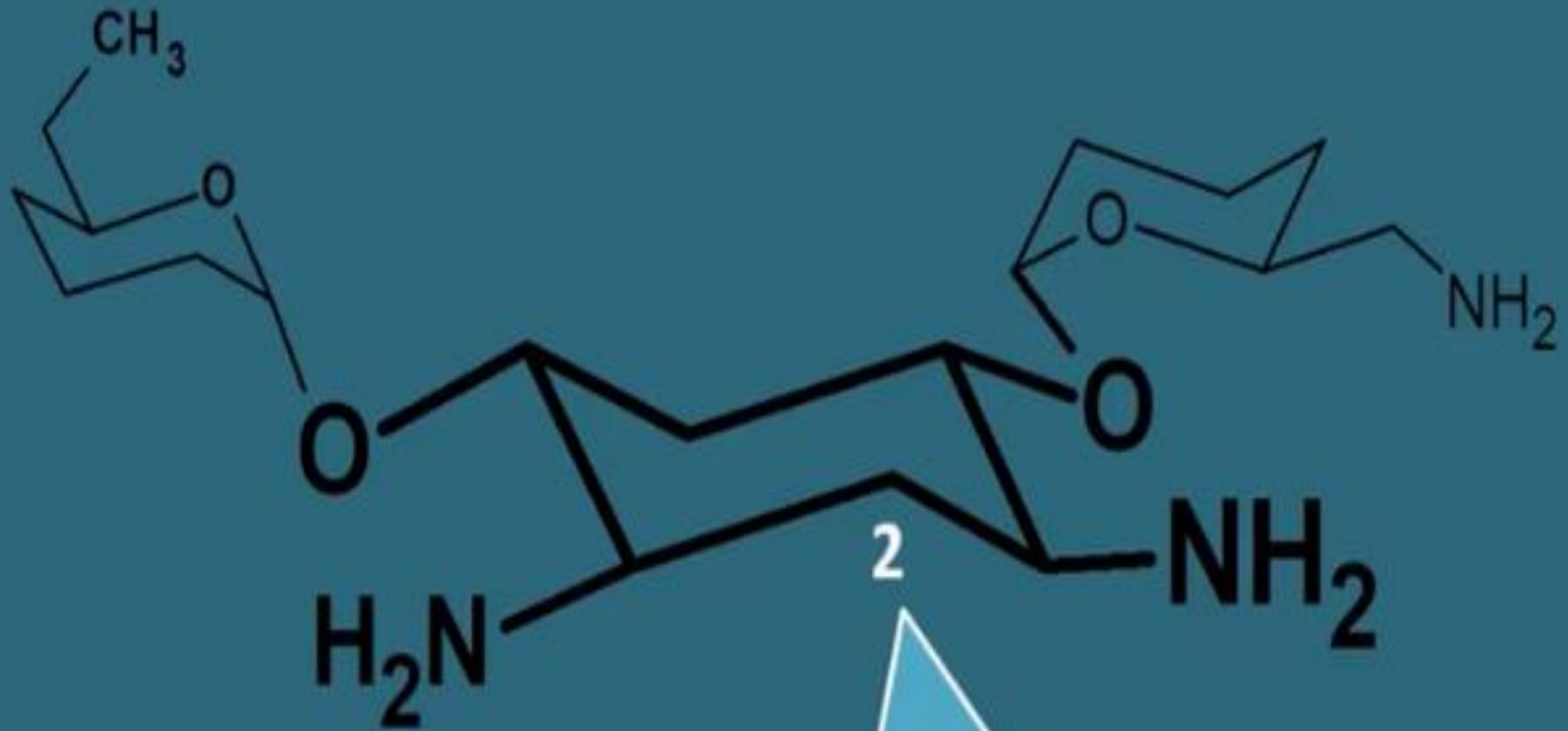
# Ring II: 1<sup>st</sup> position



**AMIKACIN**

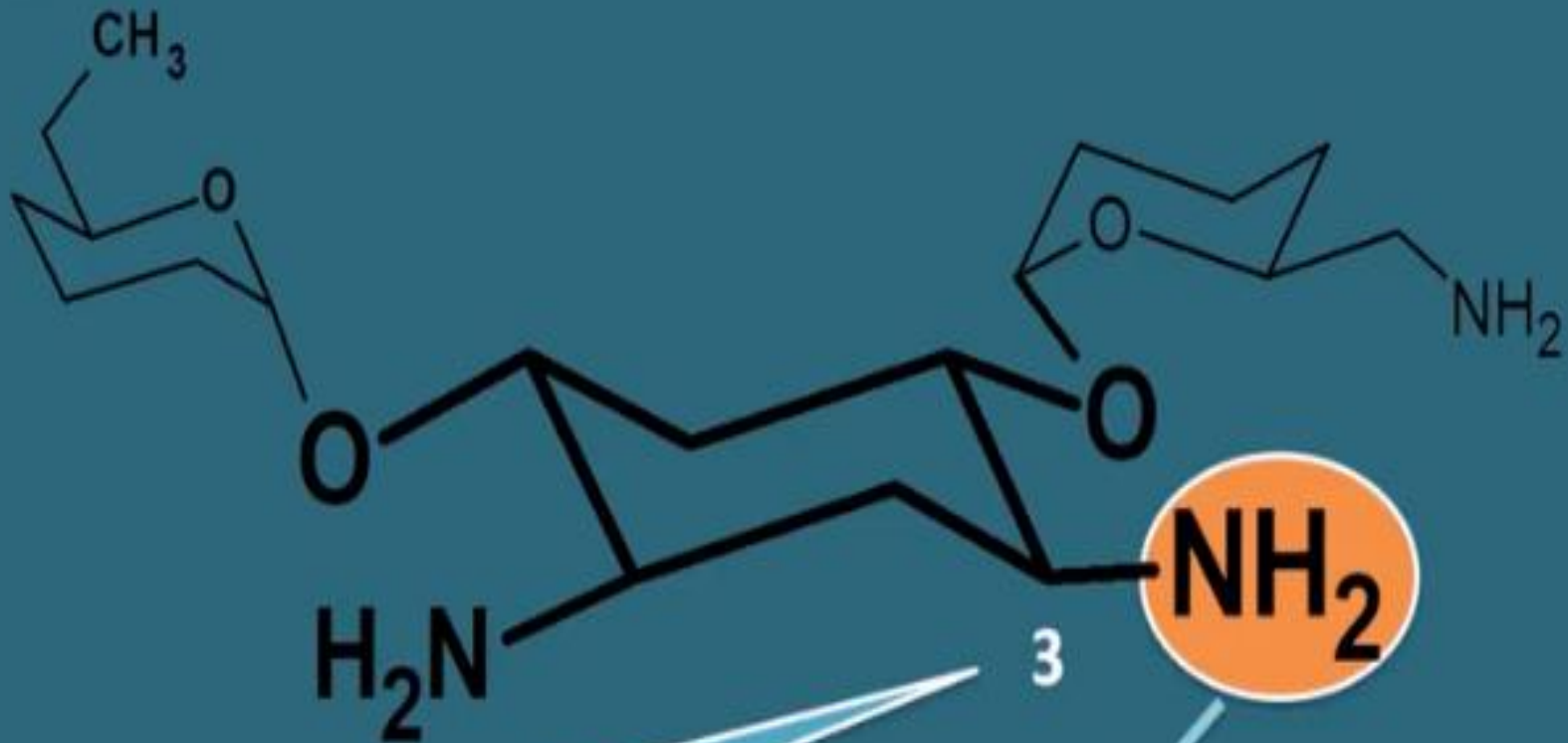
*4-Amino-2-hydroxybutanoyl*

## Ring II: 2<sup>nd</sup> position



-OH group increases  
resistance

## Ring II: 3<sup>rd</sup> position



Removal of  $-\text{NH}_2$   
increases resistance

Target for acylation  
thereby inactivated

**Ring III** functional groups appear to be somewhat less sensitive to structural changes than those of either ring I or ring II.

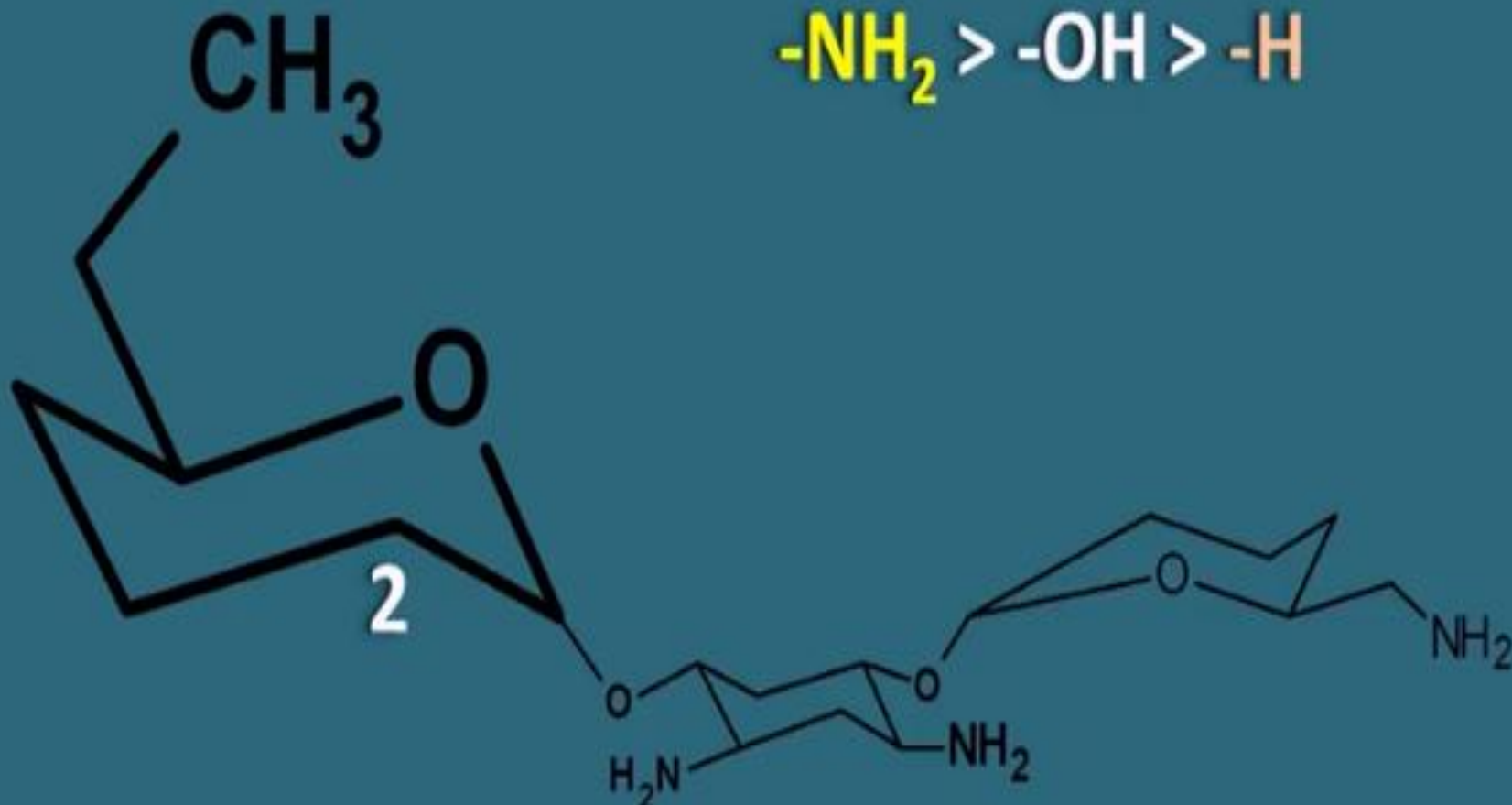
Although the 2''-deoxygentamicins are significantly less active than their 2''-hydroxyl counterparts, the 2''-amino derivatives (seldomycins) are highly active.

The 3''-amino group of gentamicins may be primary or secondary with high antibacterial potency. Furthermore, the 4''-hydroxyl group may be axial or equatorial with little change in potency.



# Ring III: 2<sup>nd</sup> position

**-NH<sub>2</sub>** > **-OH** > **-H**

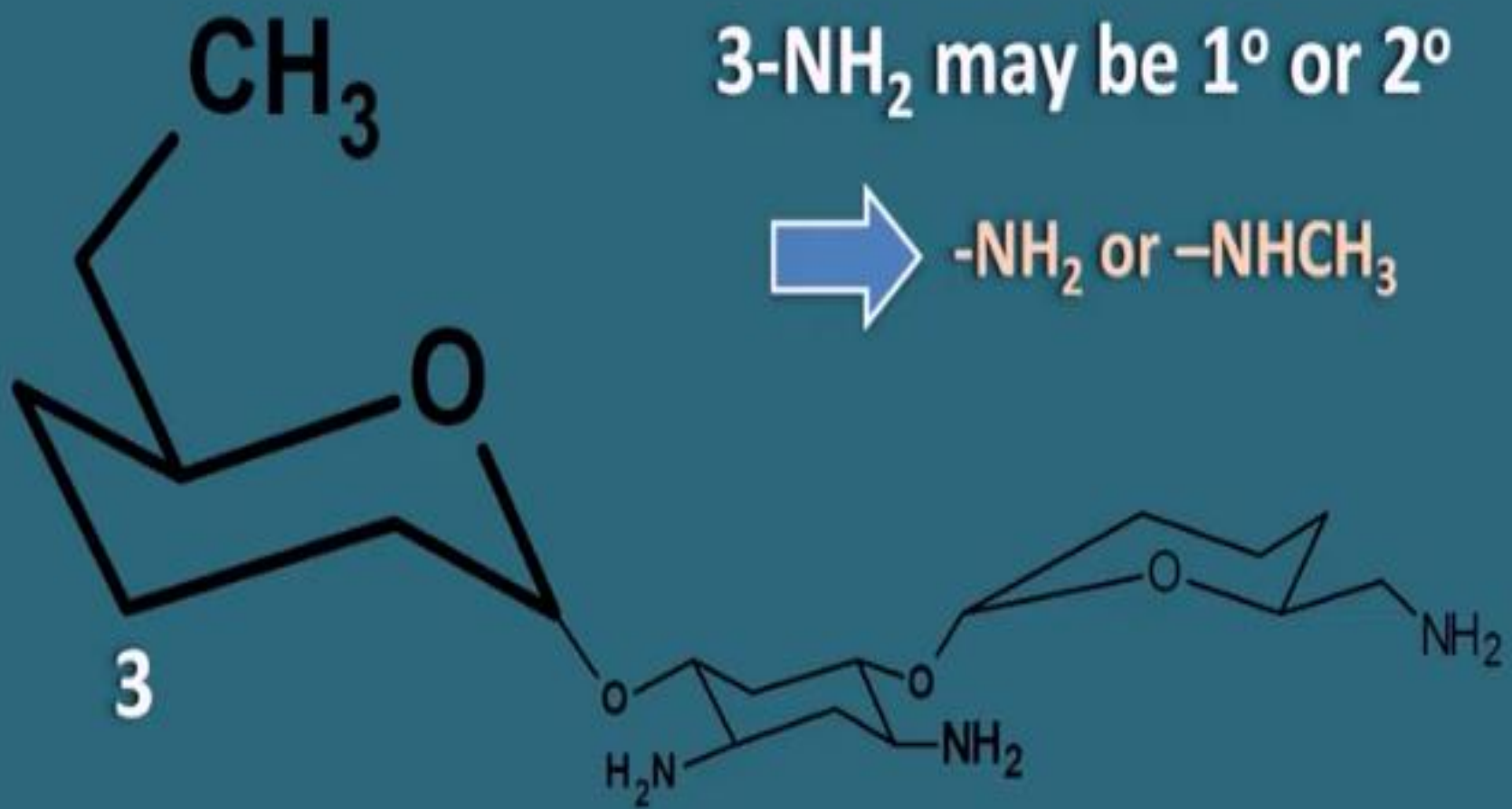


# Ring III: 3<sup>rd</sup> position

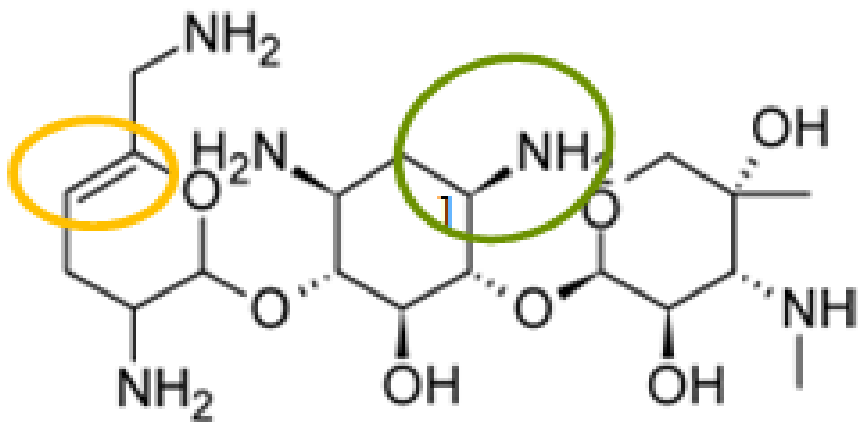
**3-NH<sub>2</sub>** increases activity

3-NH<sub>2</sub> may be 1° or 2°

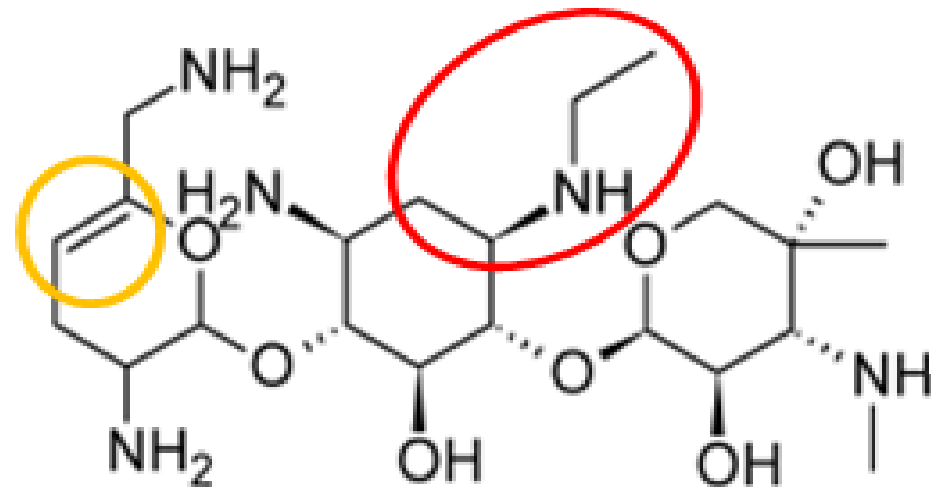
➡ -NH<sub>2</sub> or -NHCH<sub>3</sub>



**Netilmicin (1-N-ethylsisomicin)** semisynthetic derivative prepared by reductive ethylation of NH<sub>2</sub> of C1 in sisomicin retains the antibacterial potency of sisomicin and is resistant to several additional



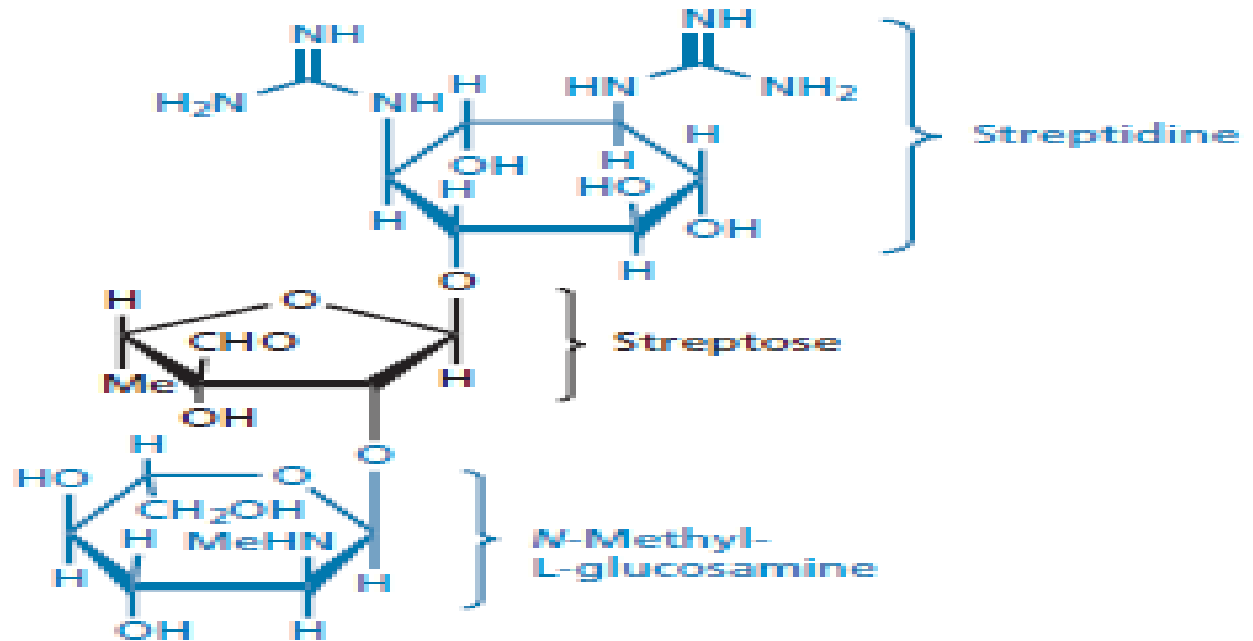
**sisomicin**



**Netilmicin**

# Products

**Streptomycin Sulfate**, Streptomycin acts as a **triacidic base** through the effect of its two strongly basic guanidino groups and the more weakly basic methylamino group



Streptomycin (from *Streptomyces griseus*)

**Acid hydrolysis yields streptidine and streptobiosamine,**

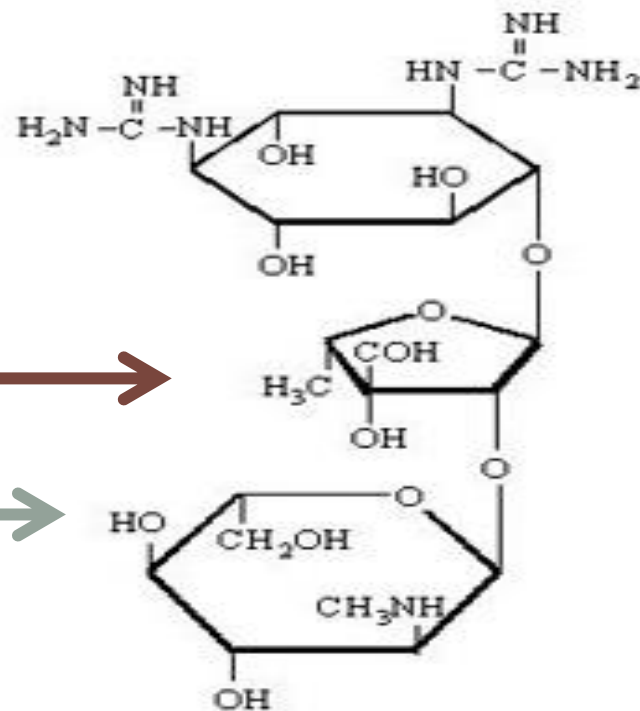
Because streptomycin is not absorbed when given orally or destroyed significantly in the GI tract, at one time it was used rather widely in the treatment of infections of the intestinal tract.

For systemic action, streptomycin usually is given by intramuscular injection.

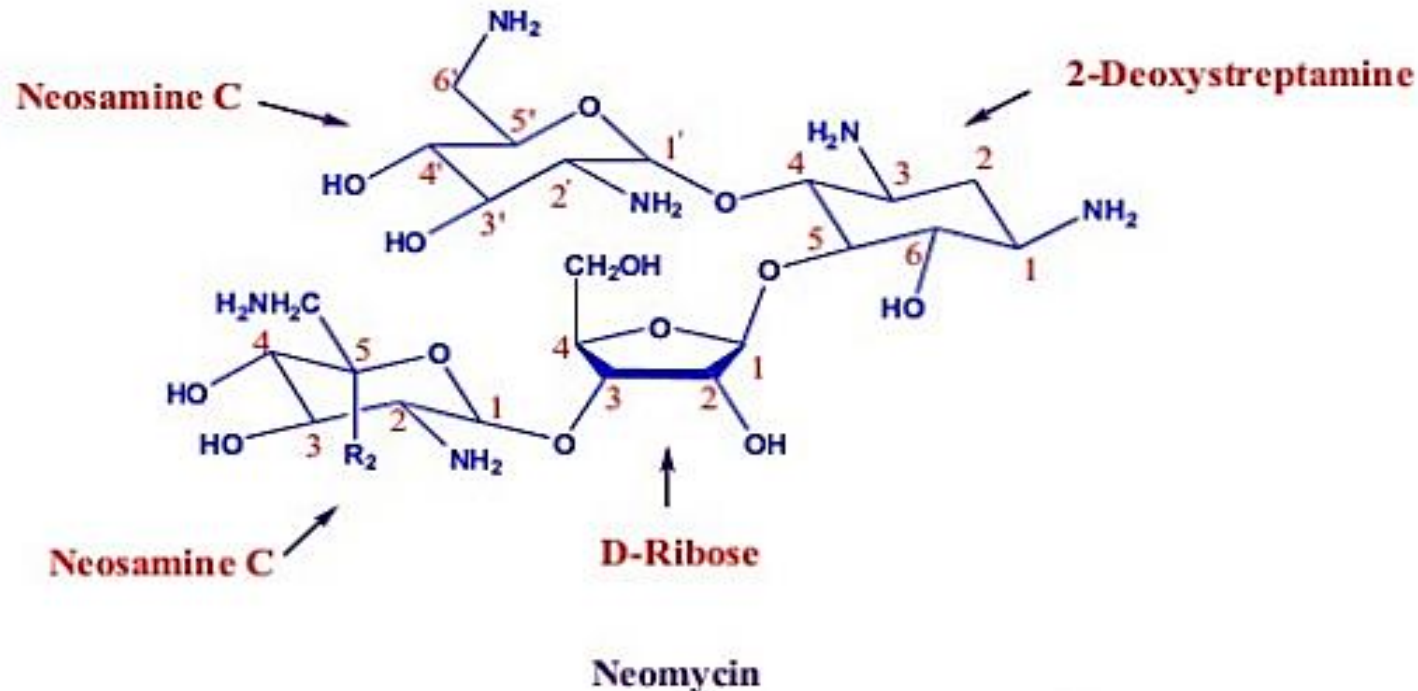
Hydroxystreptomycin differs from streptomycin in having a

**hydroxyl group** in place of one of the hydrogen atoms of the **streptose methyl group**. Mannisidostreptomycin has a mannose residue attached in glycosidic linkage through the hydroxyl group at C-4 of the N-methyl-L-glucosamine moiety.

A. Streptomycin



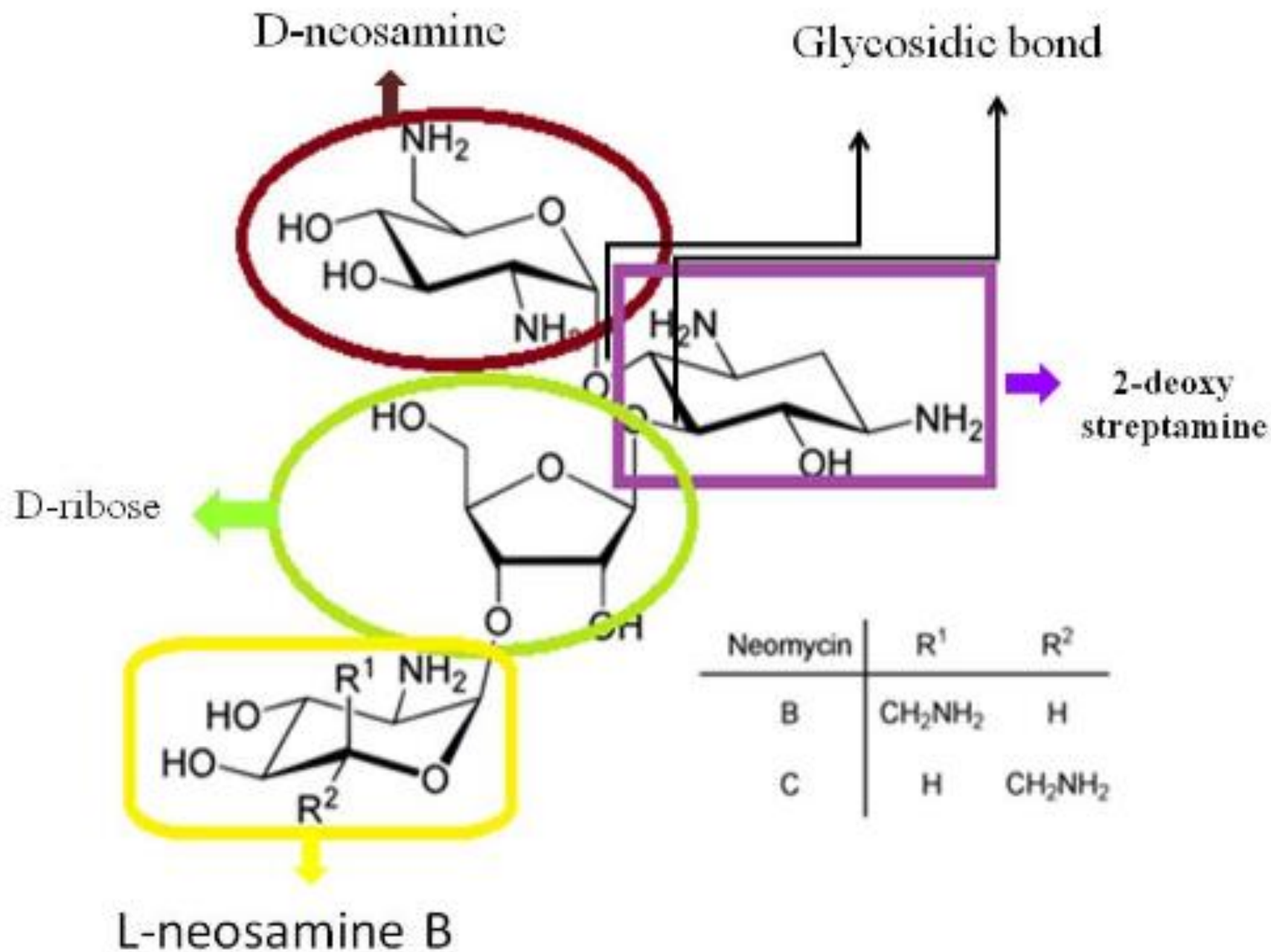
# Neomycin Sulfate



It is considered one of the most useful antibiotics for the treatment of GI infections, It has broad-spectrum activity against various organisms and shows a low incidence of toxic and hypersensitivity reactions.

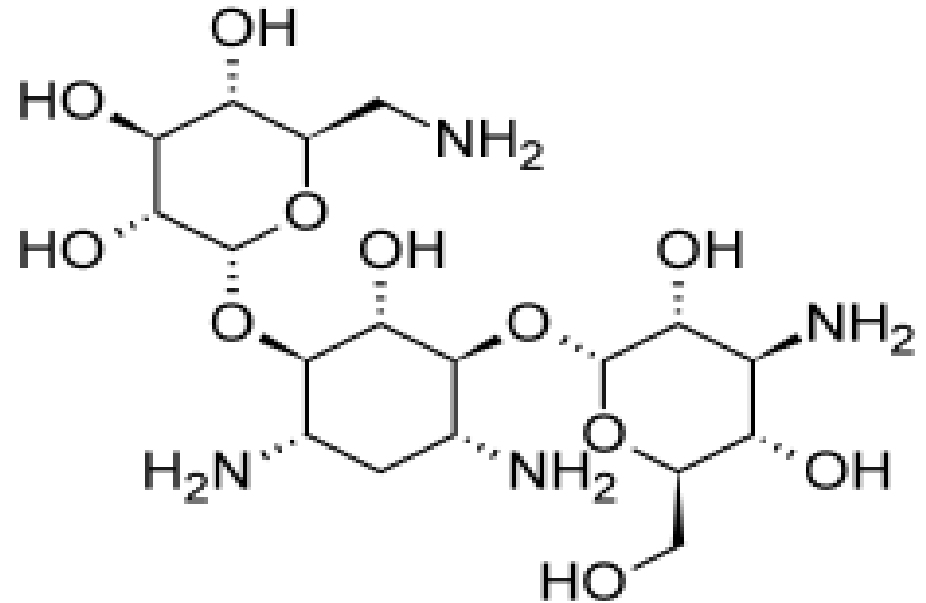
It is absorbed very slightly from the digestive tract, so its oral use ordinarily does not produce any systemic effect.

Neomycin B differs from neomycin C by the nature of the sugar attached terminally to D-ribose. That sugar, called neosamine B, differs from neosamine C in its stereochemistry.





# Kanamycin Sulfate



Chromatography showed that *S. kanamyceticus* elaborates three closely related structures: **kanamycins A, B, and C.**

**Commercially available kanamycin is almost pure kanamycin A,** the least toxic of the three forms.

The kanamycins differ only in the sugar moieties attached to the glycosidic oxygen on the 4- position of the central deoxystreptamine

The kanamycins do not have the **D-ribose** molecule that is present in neomycins and paromomycins. Perhaps this structural difference is related to the lower toxicity observed with kanamycins.

**Kanamycin A** contains 6-amino-6-deoxy-**D-glucose**

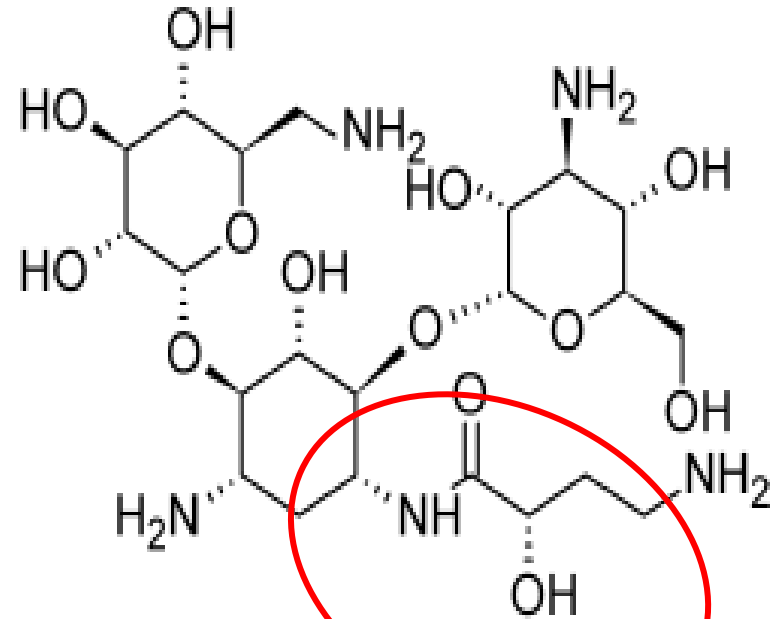
**Kanamycin B** contains 2,6-diamino- 2,6-dideoxy-**D-glucose**

**Kanamycin C** contains 2-amino-2-deoxy-**D-glucose**

The use of kanamycin in the United States usually is restricted to infections of the intestinal tract (e.g., bacillary dysentery) and to systemic infections arising from Gram negative bacilli.

# Amikacin

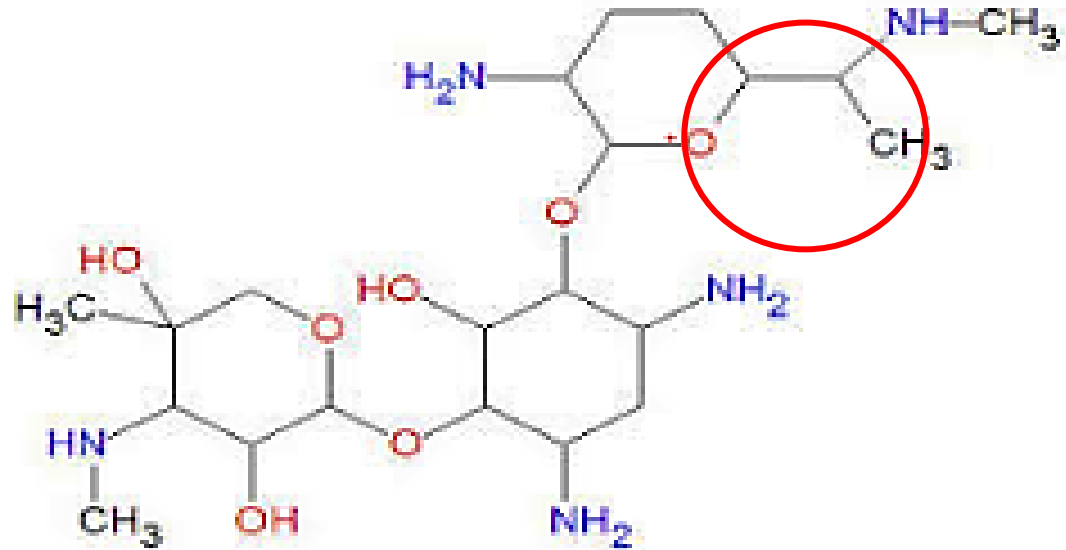
1-N-amino- $\alpha$ -hydroxy butyryl  
kanamycin A (Amikin),  
is a semisynthetic aminoglycoside  
first prepared in Japan.



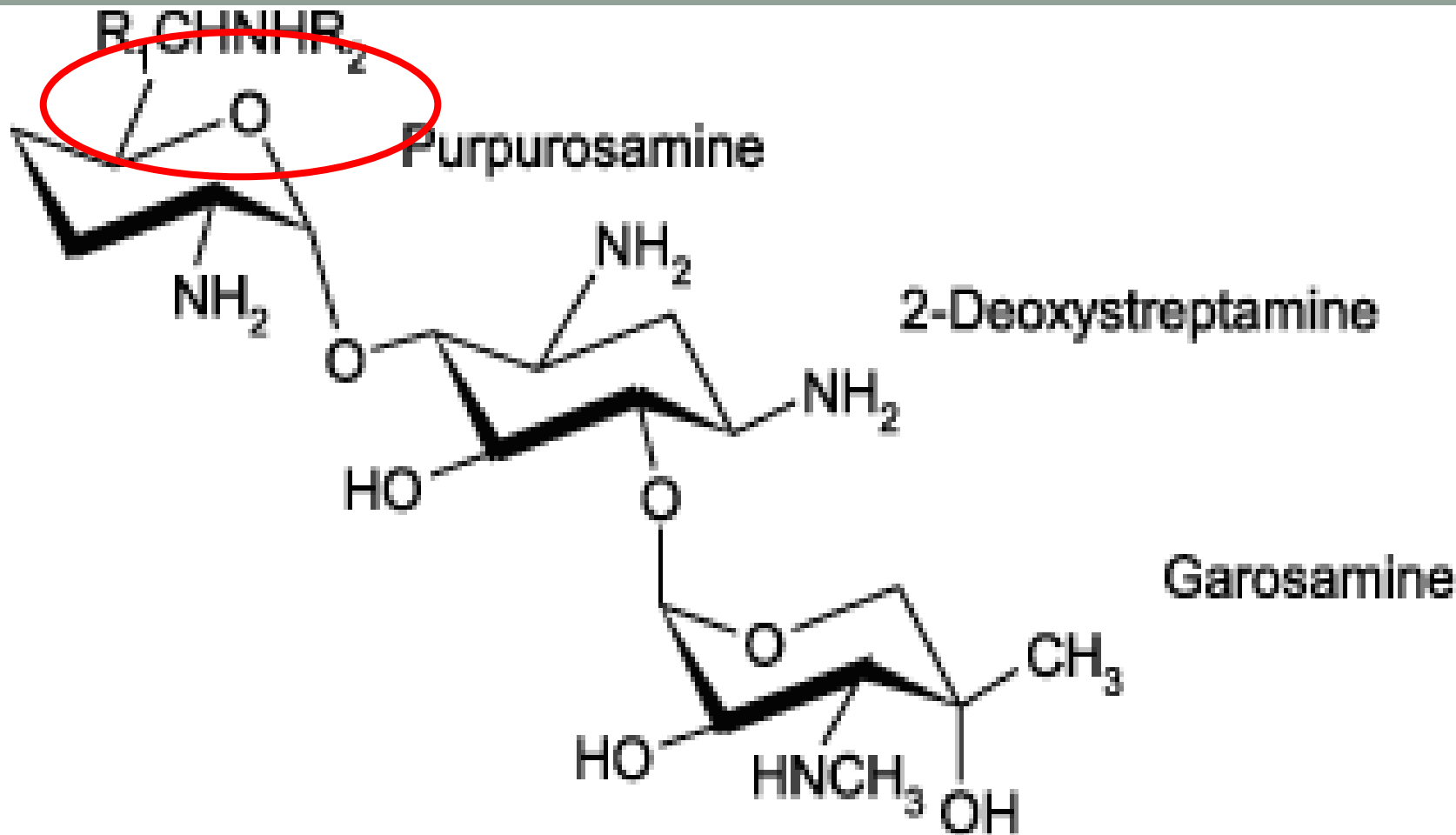
The synthesis formally involves simple acylation of the 1 amino group of the deoxystreptamine ring of kanamycin A.

The remarkable feature of Amikacin is that it resists attack by most bacteria-inactivating enzymes and, therefore, is effective against strains of bacteria that are resistant to other aminoglycosides, including gentamicin and tobramycin.

# Gentamicin Sulfate



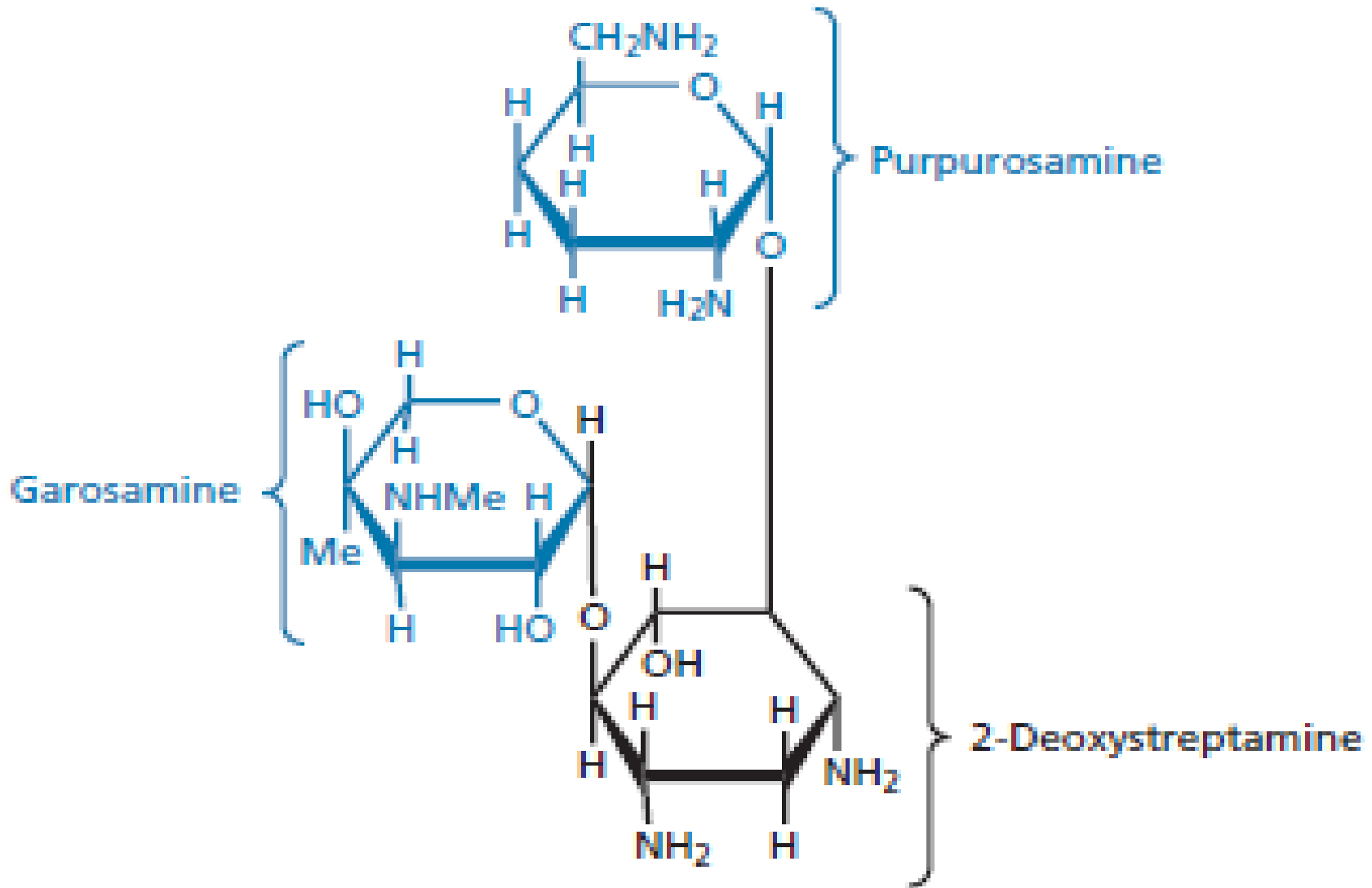
Gentamicin is composed of a number of related gentamicin components and fractions which have varying degrees of antimicrobial potency. The main components of gentamicin include members of the gentamicin C complex: gentamicin C1, gentamicin C1a, and gentamicin C2 which compose approximately 80% of gentamicin and have been found to have the highest antibacterial activity. Gentamicin A, B, X, and a few others make up the remaining 20% of gentamicin and have lower antibiotic activity than the gentamicin C complex



Gentamicin  $C_1$  :  $R_1 = R_2 = CH_3$

$C_2$  :  $R_1 = CH_3$ ;  $R_2 = H$

$C_{1a}$  :  $R_1 = R_2 = H$



Gentamicin C1a