Aminoglycoside Antibiotics

Zeynep Ates-Alagoz, Ph.D

Ankara University, Faculty of Pharmacy

Department of Pharmaceutical Chemistry

Aminoglycosides

- First member Streptomycin discovered by Waksman in 1944
- Natural and semi-synthetic antibiotics
- Produced from Actinomycetes
  - Those obtained from Streptomyces – Have suffix mycin (eg. Streptomycin)
  - Those obtained from Micromonospora – Have suffix micin (eg. Gentamicin,)
- Semisynthetic derivatives also end up with suffix micin.

Members

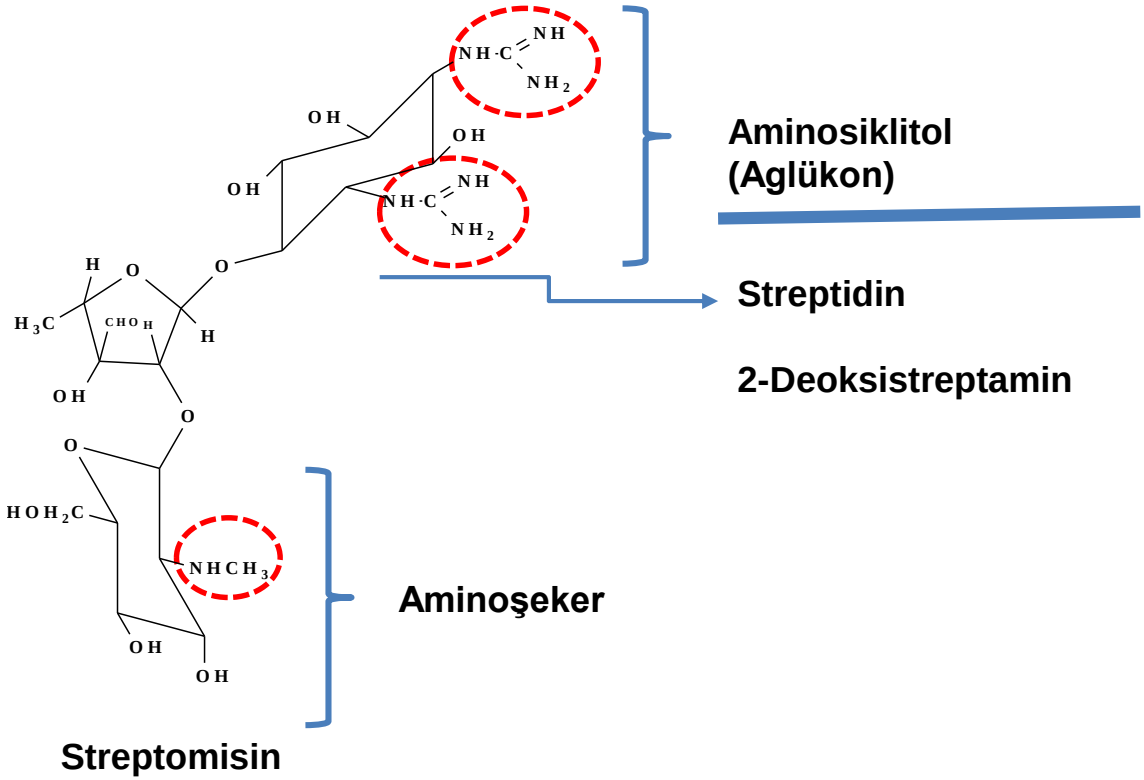
- *Streptomycin*
- *Neomycin*
- *Gentamicin*
- *Tobramycin*
- *Kanamycin*
- *Bekanamicin*
- *Amikacin*
- *Paromomycin*
- Dibekacin
- Arbekacin
- Ribostamycin
- *Astromicin*
- Sisomicin
- Netilmicin
- Ispepamycin
- Verdamicin
- Spektinomicin
- Lividomycin
- Streptozocin

Structure characterized by

- ➢At least one aminosugar joined to
- ➢One aminocyclitol moiety by
- ➢Glycosidic (-O-) bond

In most of members aminoacyclitol moiety is 2-Deoxystreptamine .

In streptomycin the aminocyclitol is Streptidine.



General characters of Aminoglycosides group

- Formulations are Sulfate or hydrochloric salts
- Formulations are water soluble and stable
- Highly polar basic drugs

} ***(Not absorbed from GIT)***

- Distribution inside the cells is minimal
- Penetration through BBB is minimal
- Least metabolized by hepatic enzymes
- Excretion is mainly renal (unchanged form, through glomerular filtration)

Mechanism of Action

- Mechanism of Action is by interfering with protein synthesis
- Attach with 30S ribosomal subunit
- Bactericidal (Gram Negative, No action on Anaerobes)
- Concentration dependent
- Mainly gram negative (plus tuberculosis by streptomycin, Kanamycin, Amikacin)
- Cross resistance is partial
- Therapeutic index is narrow
- They also exert a long & concentration dependent post antibiotic effect that is, residual bactericidal activity persisting after the serum concentration has fallen below the minimum inhibitory concentration

Resistance development (Conjugation and transfer of plasmid)

*Development and synthesis of plasmid mediated bacterial transferase enzyme (Acetyltransferase, Phosphotransferase, Adenylyltransferase), which inactivates Aminoglycosides.

*Impermeability of porins, Impaired active transport

*Phosphorylated / Adenylated / Acetylated conjugates of Aminoglycoside can not bind at target ribosomal subunit and site.

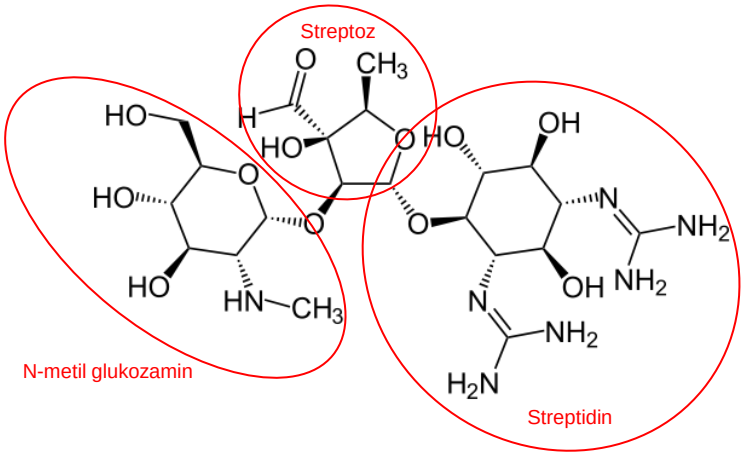
*Decreased affinity of ribosomal proteins for binding with Aminoglycosides

Side effects and Toxicity

Nephrotoxicity and Ototoxicity

- **Streptomycin is least nephrotoxic.**
- **Larger the number of NH2 more nephrotoxicity. KAN (Kanamycin, Amikacin, Neomycin) mainly damage cochlea rest vestibular damage**
- **All are teratogenic**
- **Neomycin and Framycetin have extreme systemic toxicity (only topically used)**
- **Avoid concurrent use of other Ototoxic drugs (Frusemide, Ethacrinic acid, Minocycline)**
- **Avoid concurrent use of other nephrotoxic drugs (Amphotericin B, Vancomycin, Cephalothin, Cephradrine, Cyclosporin, Cisplatin)**

Streptomycin



2-[3-(diaminometiliden amino)-4-[3-[-4,5-dihidroksi-6-(hidroksimetil)-3-(metilamino)oksan-2-il]oksi-4-formil-4-hidroksi-5-metiloksolan-2-il]oksi-2,5,6-trihidroksisiklohekzil] guanidin

*** Narrow spectrum (Gram negative + M. tuberculosis)**

Uses

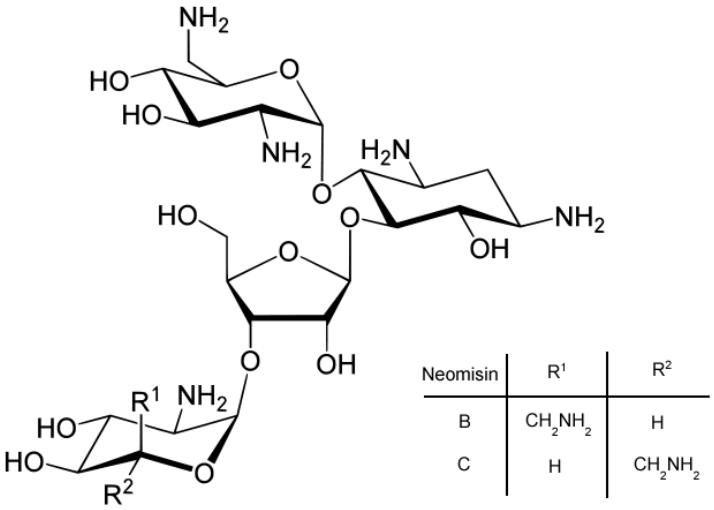
- **Tuberculosis (First drug to show antitubercular activity)**

***Acts against extracellular bacilli (due to poor penetration in the cell)**

***Also active against Atypical Mycobacterium (M. kansasii and M. avium intracellulare.)**

***Resistance develops fast (Never use streptomycin alone as antitubercular)**

Neomycin



Neomisin	R^1	R^2
B	CH_2NH_2	H
C	H	CH_2NH_2

5-amino-2-(aminometil)-6-[(4,6-diamino-2-[4-[(3-amino-6-(aminometil)-4,5-dihidroksioksan-2-il]oksi-3-hidroksi-5-(hidroksimetil)oksolan-2-il]oksi-3-hidroksisiklohekzil]oksioksan-3,4-diol

***Wide spectrum**

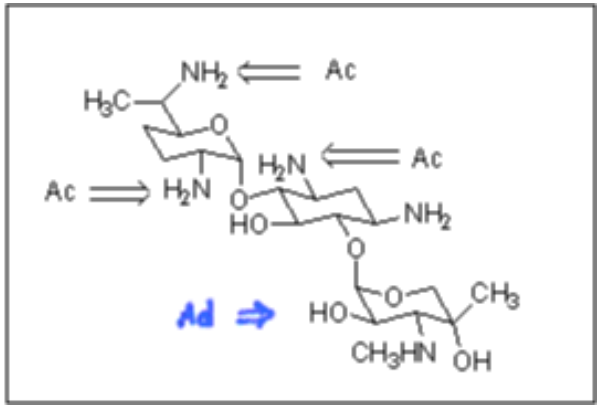
***Highly toxic**

***Most common use is topical, ointment, eye and ear drops**

***Because it is not absorbed by the intestine mucosa, it is used orally for intestinal infections.**

Gentamicin Sulphate

Gentamicin C-2



2-[4,6-diamino-3-[3-amino-6-(aminometil)oksan-2-il]oksi-2-hidroksisiklohekzil]oksi-5-etil-4-(metilamino)oksan-3,5-diol

***It was isolated from Micromonospora griseus.**

***broad spectrum and high antibacterial activity.**

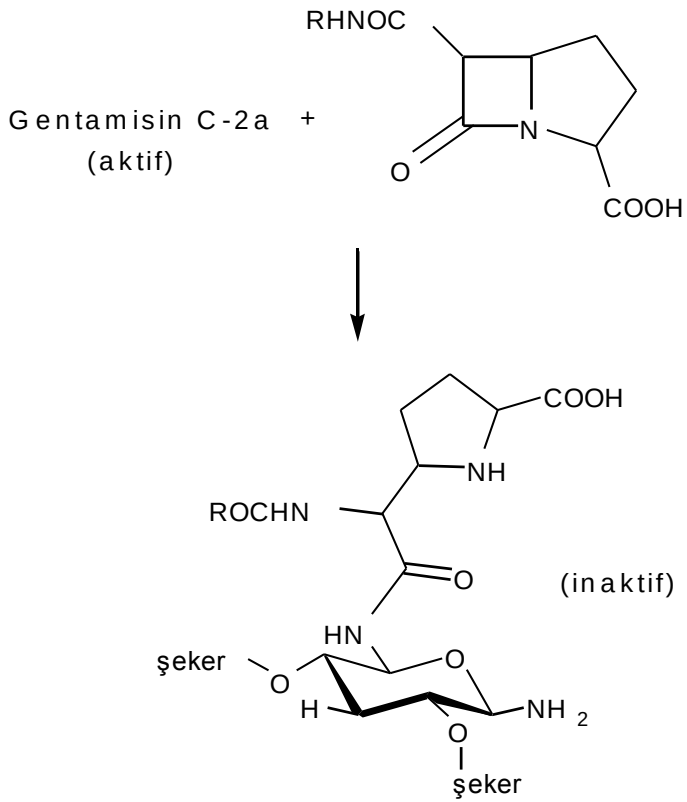
***It is also effective in Gram (-) aeorobs, such as Pseudomonas and proteases.**

***Topical, IM and IV.**

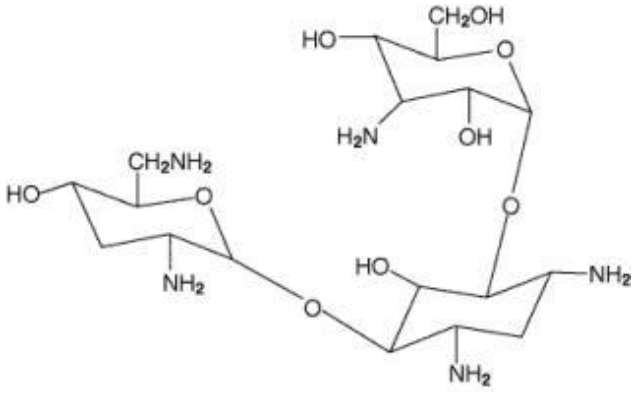
***Beta-lactam antibiotics should be used separately because they are incompetent.**

***Nephrotoxic and ototoxic**

Gentamicin-beta-lactam incompatibility



Tobramycin



4-amino-2-[4,6-diamino-3-[3-amino-6-(aminometil)-5-hidroksioksan-2-il]oksi-2-hidroksisiklohekzil] oksi-6-(hidroksimetil)oksan-3,5-diol

***It was isolated from Streptomyces tenebrarius.**

***Effective against many Gr (+) and Gr (-).**

***Especially effective against Pseudomonas aeruginosa.**

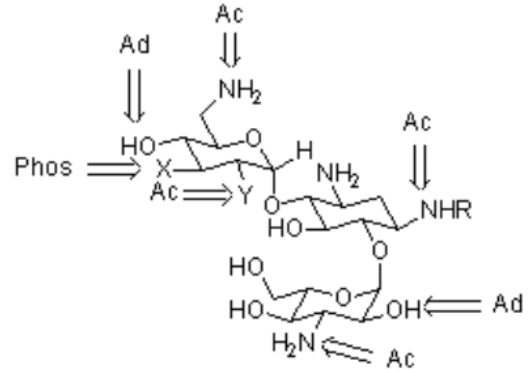
***used as in Sulfate salt form.**

***ophthalmic, inhalation, IM and IV.**

***ototoxic**

***It is not Substrate for APH (3 ') - I or -II due to the inability of C-3'-OH so it has broad spectrum.**

Kanamycin



KANAMİSİN B	, X=OH, Y = NH_2, R =H
TOBRAMİSİN	X=H, Y= NH_2, R =H
AMİKASİN	X=OH, Y=OH, R=CO CHOHCH$_2$CH$_2$NH$_2$

2-(aminometil)-6-[4,6-diamino-3-[4-amino-3,5-dihidroksi-6-(hidroksimetil)oksan-2-il]oksi-2-hidroksisiklohekzil]oksioksan-3,4,5-triol

***It was isolated from Streptomyces kanamyceticus.**

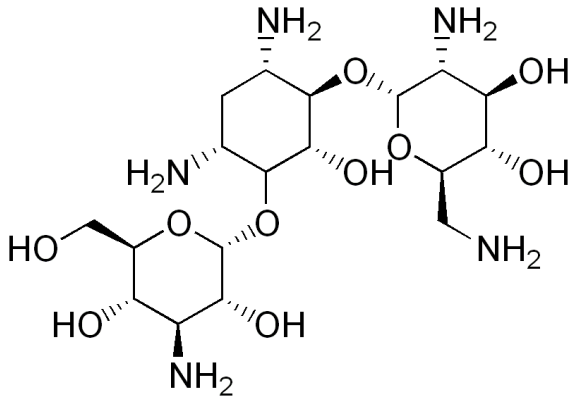
***Used in infections caused by Shigella, Klebsiella, E. coli, Enterobacter.**

***Oral, IM and IV.**

***It is used orally for intestinal infections.**

***Nephrotoxic**

Bekanamisin

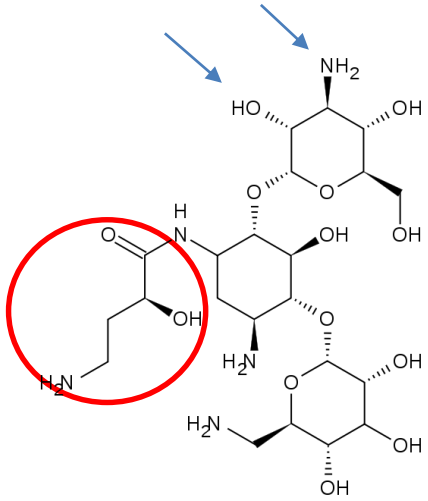


5-amino-2-(aminometil)-6-[4,
6-diamino-3-[4-amino-3,5-dihidroksi-6-
(hidroksimetil)oksan-2-il]oksi-2-
hidroksisiklohekzil]oksioksan-3,4-diol

***It has been obtained from kanamycin by semi-synthetic method.**

***It is used as Sulfate salt form.**

Amikacin



4-amino-N-[5-amino-2-[4-amino-3,5-dihidroksi-6-(hidroksimetil)oksan-2-il]oksi-4-[-6-(aminometil)-3,4,5-trihidroksioksan-2-il]oksi-3-hidroksisiklohekzil]-2-hidroksibütanamid

***It was obtained from kanamycin A by semi-synthetic method.**

***Adenylation and phosphorylation of C-2 'and C-3 is prevented by the presence of the hydroxbutyrylamino, this lead to broad spectrum.**

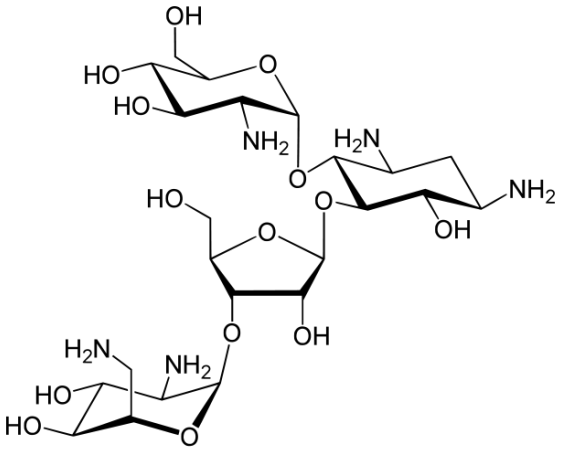
***It is the broadest spectrum aminoglycoside**

***It is effective against Pseudomonas, Escherichia coli, Proteus, Providencia, Klebsiella, Enterobacter, Serratia, Acinetobacter and Citrobacter.**

***IM and IV.**

***Nephrotoxic and ototoxic**

Paromomycin



5-amino-6-[4,6-diamino-2-[4-[3-amino-6-(aminometil)-4,5-dihidroksioksan-2-il]oksi-3-hidroksi-5-(hidroksimetil)oksolan-2-il]oksi-3-hidroksisiklohekzil] oksi-2-(hidroksimetil)oksan-3,4-diol

***It was isolated from Streptomyces kresomuceticus.**

***It is available in the form of sulfate salts.**

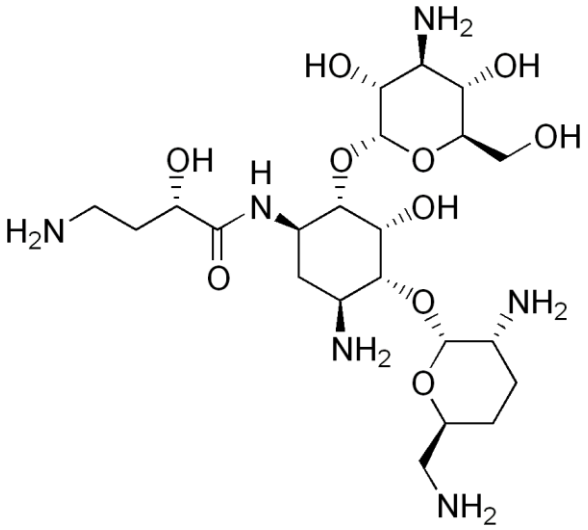
***It is used in intestinal infections caused by Salmonella, Shigella and E. coli.**

***The antiamibiotic effect is stronger than the other aminoglycosides.**

***There are oral and IM use.**

***Nephrotoxic.**

Arbekacin



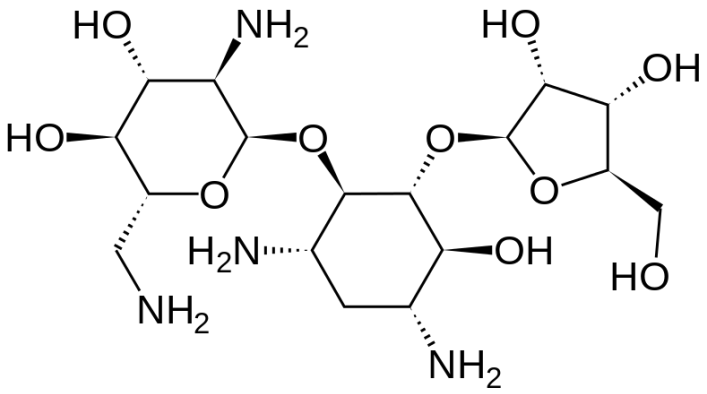
4-amino-N-[5-amino-4-[3-amino-6-(aminometil)oksan-2-il]oksi-2-[4-amino-3,5-dihidroksi-6-(hidroksimetil)oksan-2-il]oksi-3-hidroksisiklohekzil]-2-hidroksibütanamid

***It was obtained from dibeacin by semi-synthetic method.**

***It is especially used against methicillin-resistant staphylococcus aureus (MRSA).**

***IM and IV.**

Ribostamycin

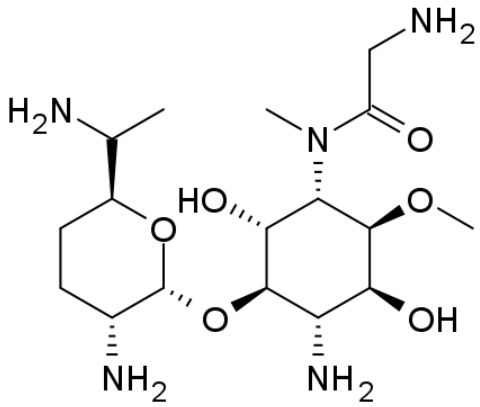


5-amino-2-(aminometil)-6-[4,6-diamino-2-[3,4-dihidroksi-5-(hidroksimetil)oksolan-2-il]oksi-3-hidroksisiklohekzil] oksioksan-3,4-diol

***It was isolated from Streptomyces ribosidificus.**

***Ophthalmic is used because of its good penetration into the ocular tissue.**

Astromicin



2-amino-N-[(4-amino-3-[3-amino-6-[1-aminoetil]oksan-2-il]oksi-2,5-dihidroksi-6-metoksisiklohekzil]-N-metilasetamid

***It was isolated from Micromonospora olivasterospora.**

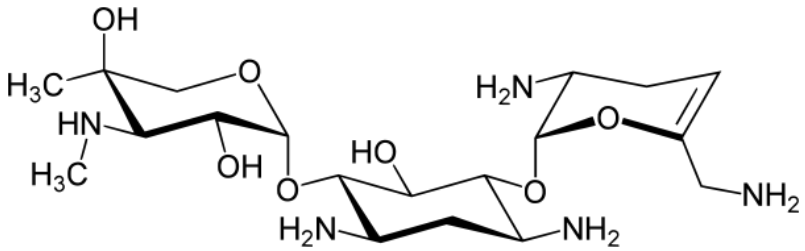
***It is used in gonorrhea treatment.**

***Used as IM.**

***bacteriostatic.**

***not ototoxic**

Sisomicin



2-[4,6-diamino-3-[[3-amino-6-(aminometil)-3,4-dihidro-2H-piran-2-il]oksi]-2-hidroksisiklohekzil]oksi-5-metil-4-(metilamino)oksan-3,5-diol

***isolated from Micromonospora inyoensis.**

***It is effective against Klebsiella, Enterobacter, Escherichia, Salmonella, Citrobacter, Staphylococcus aureus.**

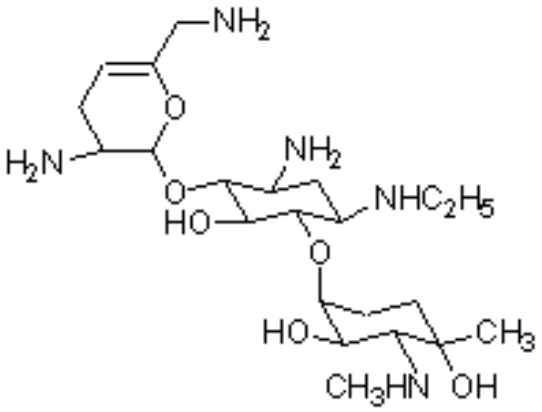
***has similar properties to gentamycin and tobramycin. However, does not cause resistance to these compounds.**

***because it is not absorbed by GI, it is used in GI infections**

***creams, eye drops**

***Topical and oral.**

Netilmicin Sulphate, Netromycin



Netilmicin

2-[4-amino-3-[[3-amino-6-(aminometil)-3, 4-dihidro-2H-piran-2-il]oksi]-6-(etilamino)-2-hidroksisiklohekzil]oksi-5-metil-4-(metilamino)oksan-3,5-diol

***It has been obtained from sisomicin by semisynthesis.**

***It is especially used in those who have resistance to Gentamycin.**

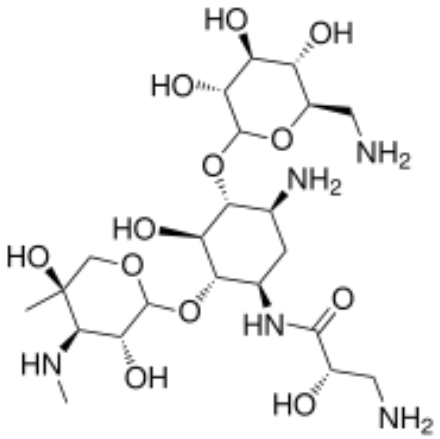
***The antibacterial spectrum is broad.**

***It is used in sulfate salt form.**

***IV and IM**

***Ototoxic and nephrotoxic**

Isepamicin



3-amino-N-[5-amino-4-[6-(aminometil)-3,4,5-trihidroksioksan-2-il]oksi-2-[3,5-dihidroksi-5-metil-4-(metilamino)oksan-2-il]oksi-3-hidroksisiklohekzil]-2-hidroksipropanamide

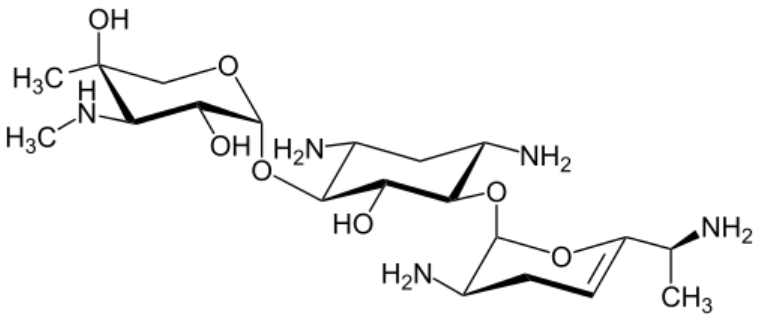
***It has been obtained from sisomicin by semisynthesis.**

***It is particularly good against bacteria which show resistant with acetyltransferase.**

***It is not used for people with hypersensitivity and Myastenia gravis.**

***Neurotoxic and nephrotoxic**

Verdamicin



2-[4,6-diamino-3-[[3-amino-6-(1-aminoetil)-3,4-dihidro-2H-piran-2-il]oksi]-2-hidroksisiklohekzil]oksi-5-metil-4-(metilamino)oksan-3,5-diol

***It was isolated from Micromonospora grisea.**

***Effective against S. aureus.**

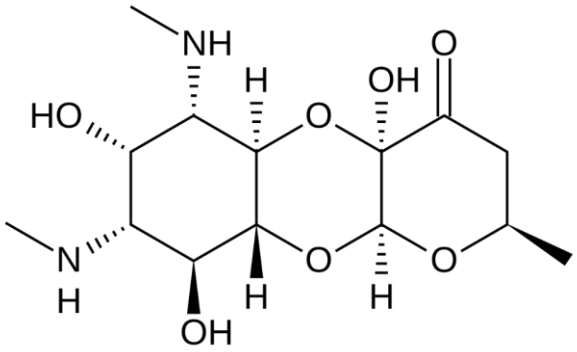
***Less effective against E. coli.**

***used in sulfate salt form.**

***Used as IV.**

***IV toxicity is less than Gentamycin, Tobramycin and Sisomycin.**

Spectinomycin HCl



*It was isolated from Streptomyces spectabilis

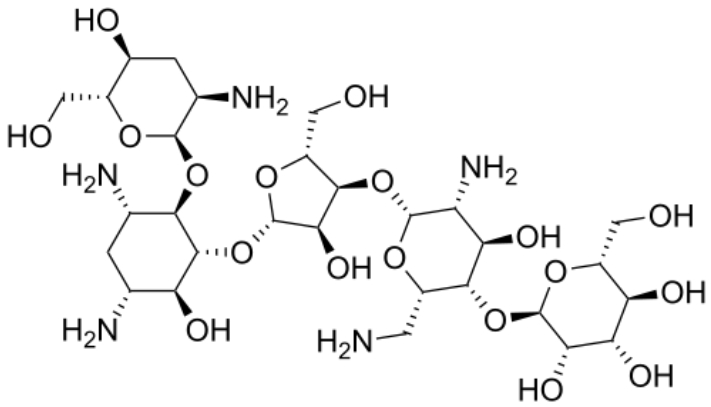
*Especially used against Neisseria gonorrhoeae.

Unlike other aminoglycosides:

Bacteriostatic and less toxic.

Primer use in gonorrhea treatment (single dose, especially for penicillinase producing strains).

Lividomycin



2-[5-amino-2-(aminometil)-6-[5-[3,5-diamino-2-[3-amino-5-hidroksi-6-(hidroksimetil)oksan-2-il]oksi-6-hidroksisiklohekzil]oksi-4-hidroksi-2-(hidroksimetil)oksolan-3-il]oksi-4-hidroksioksan-3-il]oksi-6-(hidroksimetil)oksan-3,4,5-triol

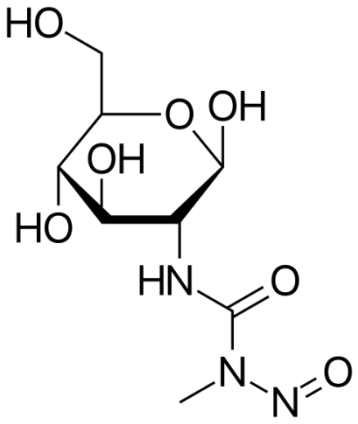
***It was isolated from Streptomyces lividus.**

***used in Sulfate salt form.**

***P. aeruginosa has resistance to lividomycin (phosphotransferase). For this reason it is not used against P. aeruginosa.**

***It acts like paromomycin and neomycin.**

Streptozocin



1-metil-1-nitrozo-3-[2,4,5-trihidroksi-6-(hidroksimetil)oksan-3-il] üre

***Both antibacterial and antineoplastic**

***Mutagen. May lead to deterioration of DNA structure**

***The nephrotoxic effect can be fatal.**

GENTAMYCIN: Aminoglycoside with the most antibiotic power

NETILMISIN: Aminoglycoside with the least ototoxic effect

TOBRAMISIN: The most effective Aminoglycoside to P. aeruginosa

AMIKACIN: Aminoglycoside with the widest spectrum.

SPECTINOMYCIN: Only effective against gonorrhea.