



# TETRACYCLINES

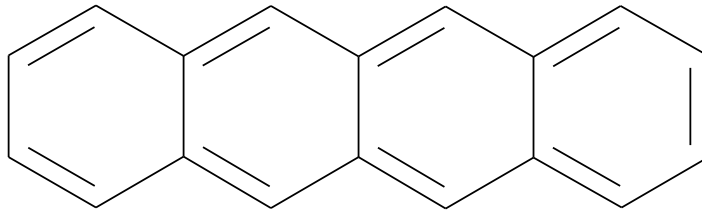
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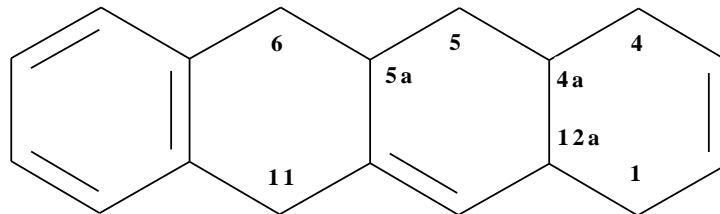
# Tetracyclines

- Are isolated from *Streptomyces* cultures

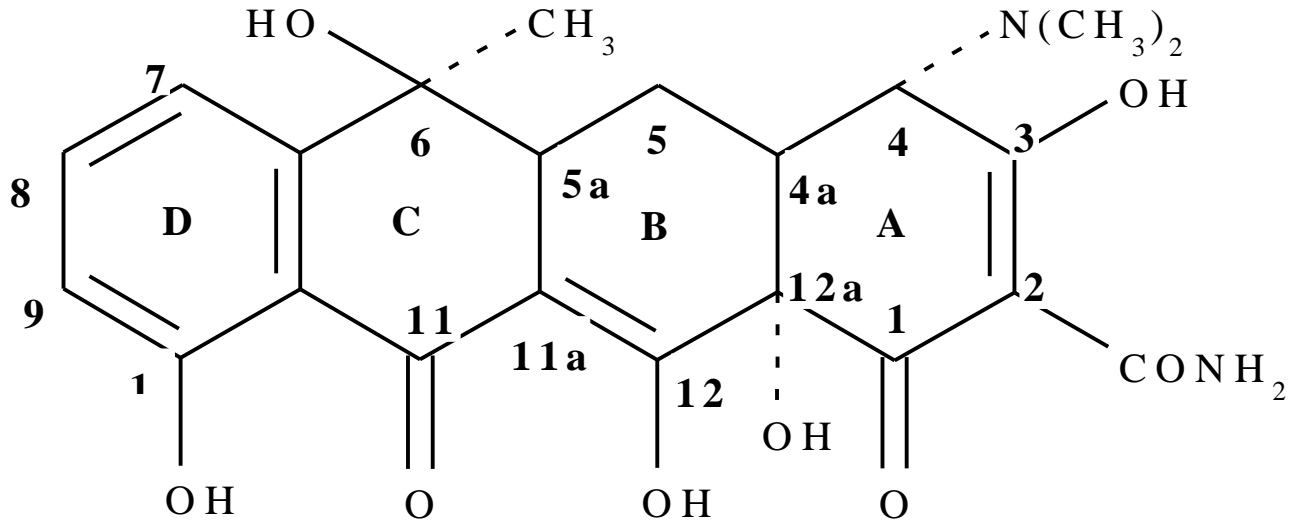
They have a partially saturated naphthacene core (octahydronaphthacene)



**Naftasen**

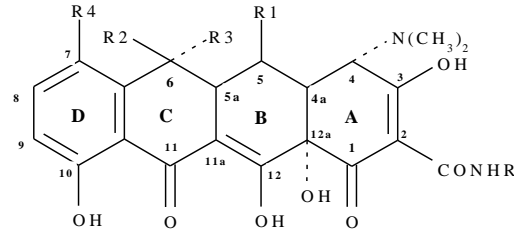


**Oktahidronaftasen**



## Tetracycline

4- (dimethylamino) -1,4,4a, 5,5a, 6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2- naphthacene carboxamide



Adı	R1	R2	R3	R4	2.konum
Tetrasiklin	H	OH	CH <sub>3</sub>	H	H
7-Klorotetrasiklin	H	OH	CH <sub>3</sub>	Cl	H
5-Oksitetrasiklin	OH	OH	CH <sub>3</sub>	H	H
6-Demetil-7-klorotetrasiklin (Demeklosiklin)	H	OH	H	Cl	H
6-Demetil-6-deoksi-5-hidroksi-6-metilen tetrasiklin (Metasiklin)	OH	H	=CH <sub>2</sub>	H	H
6-Deoksi-5-hidroksi tetrasiklin 6-Deoksi-oksitetrasiklin (Doksisiklin)	OH	H	CH <sub>3</sub>	H	H
Rolitetrasiklin	H	OH	CH <sub>3</sub>	H	
Minosiklin	H	H	H	N(CH <sub>3</sub> ) <sub>3</sub>	
Glomosiklin	H	OH	CH <sub>3</sub>	CH <sub>3</sub>	-CH <sub>2</sub> OH
Limesiklin	H	OH	CH <sub>3</sub>	H	-CH <sub>2</sub> NH-CH(COOH)-(CH <sub>2</sub> ) <sub>4</sub> -NH <sub>2</sub>



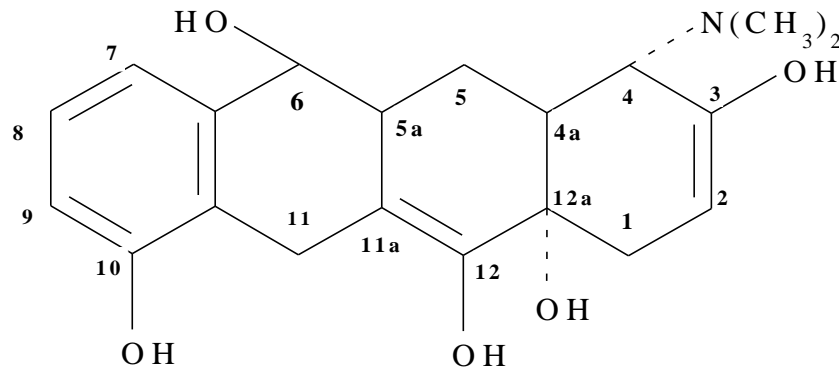
Tetracycline, Clortetracycline, Oxytetracycline,  
Demethylcyortracycline  $\Rightarrow$  natural tetracycline derivatives

Metacycline, Doxycycline, Rolitetracycline, Minocycline,  
Glomocycline, Limesiklin  $\Rightarrow$  Semi-synthetic tetracycline  
derivatives



# General Properties

- Amphoteric compounds. They form salts with acids and bases.

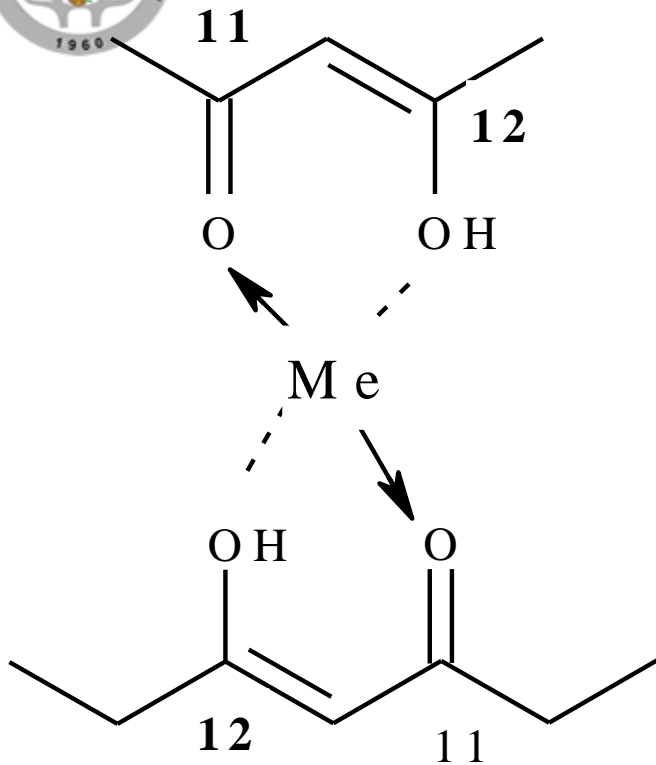


-Enolic hydroxyls in positions 3 and 12  $\Rightarrow$  acid,  
dimethylamine  $\Rightarrow$  basic

- Amine group  $\Rightarrow$  HCl salt  $\Rightarrow$  water soluble

- Enolic hydroxyl  $\Rightarrow$  NaOH and KOH salts  $\Rightarrow$  water soluble, not stable

- They can not be stored in solution for long periods. A solution prepared in neutral will quickly lose 90% activity.



-Chelate complexes with two or three valent metals.

-The resulting chelates can not be absorbed from the GIT.

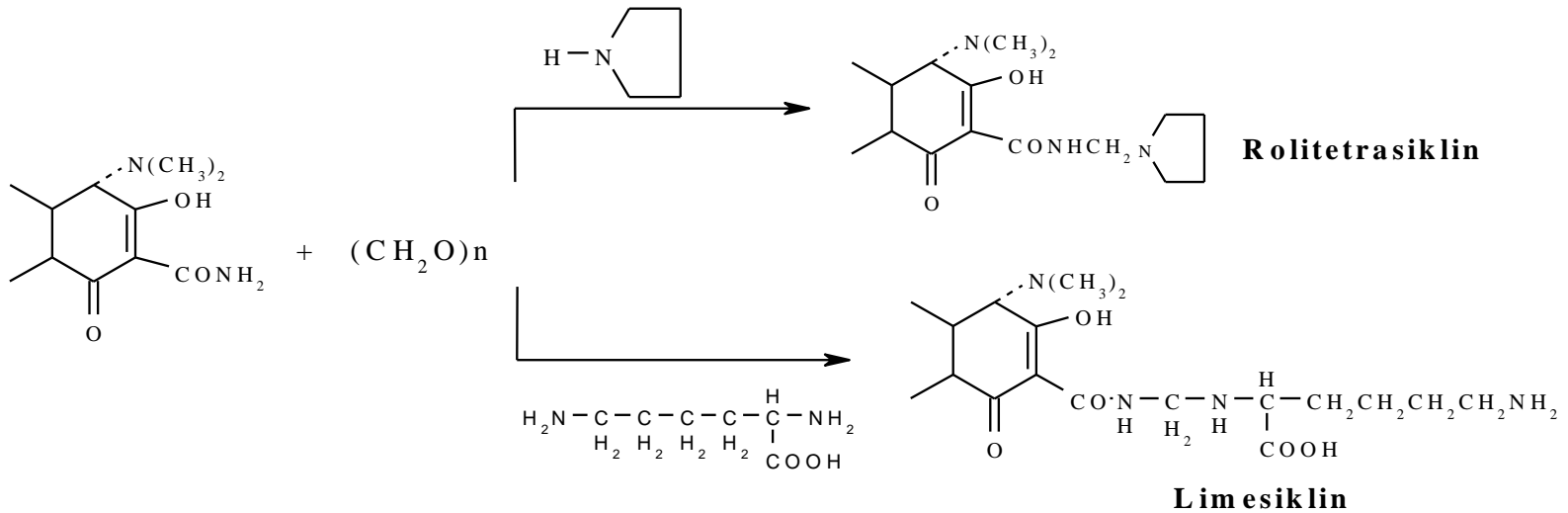
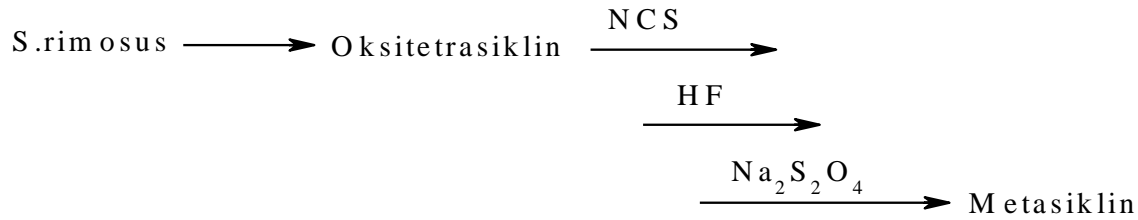
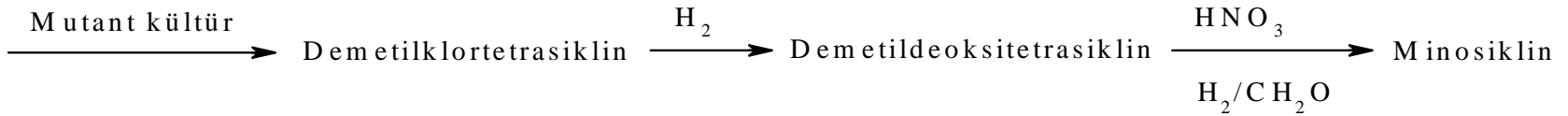
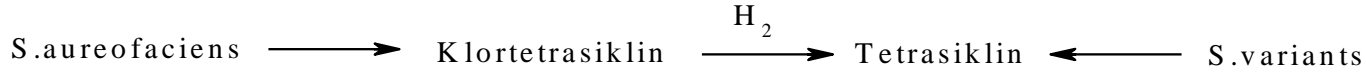
-Therefore, tetracyclines should not be taken with medicines (antacids) and foods (calcium-rich foods such as milk and products) that carry these metals.

Due to the chelate with calcium, it accumulates in the teeth and forms colored spots.

It should not be used in children until 8 years old and pregnant.

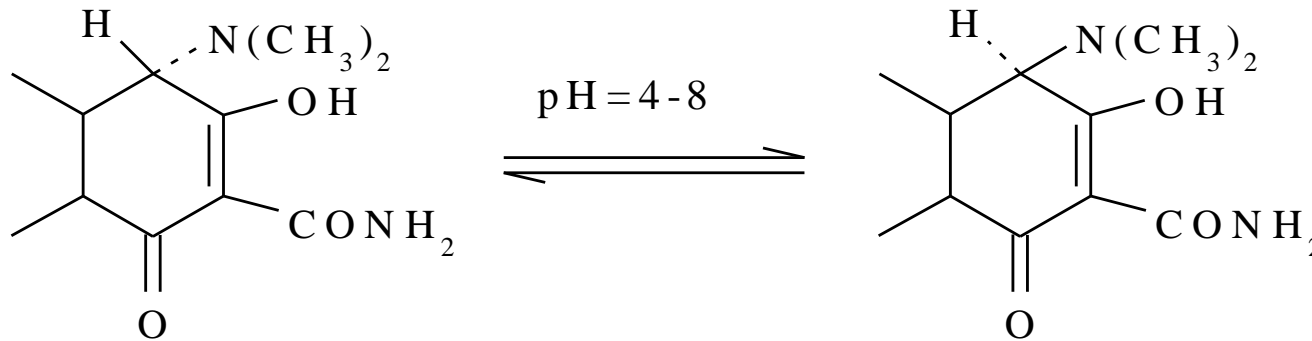


## Genel Elde Edilişleri





# Structure-Activity Relations

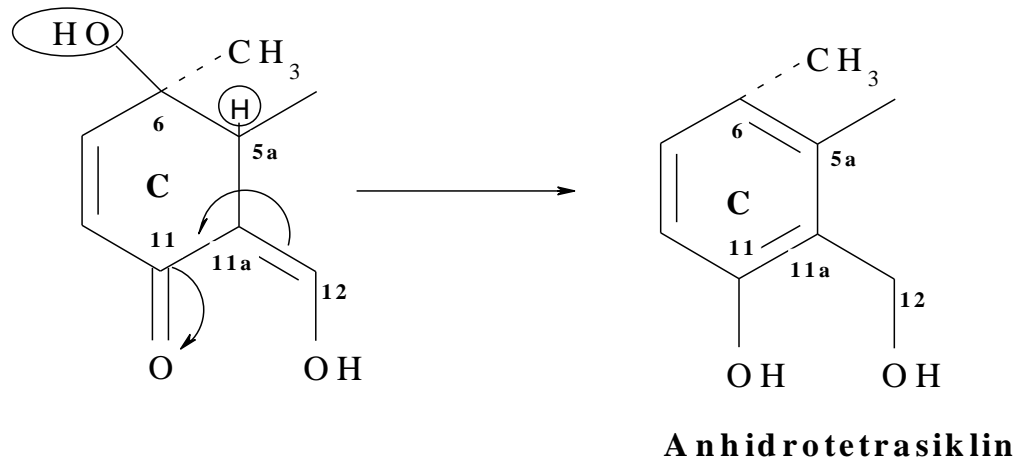


- Dimethylamine group at the 4th position is below the plane.
- The epimerization occurs at pH = 4-8 → **epitetracyclins**
- Epimerization can not be completely prevented.
- The best possible crystallized pure compound is 25% epimer derivative.



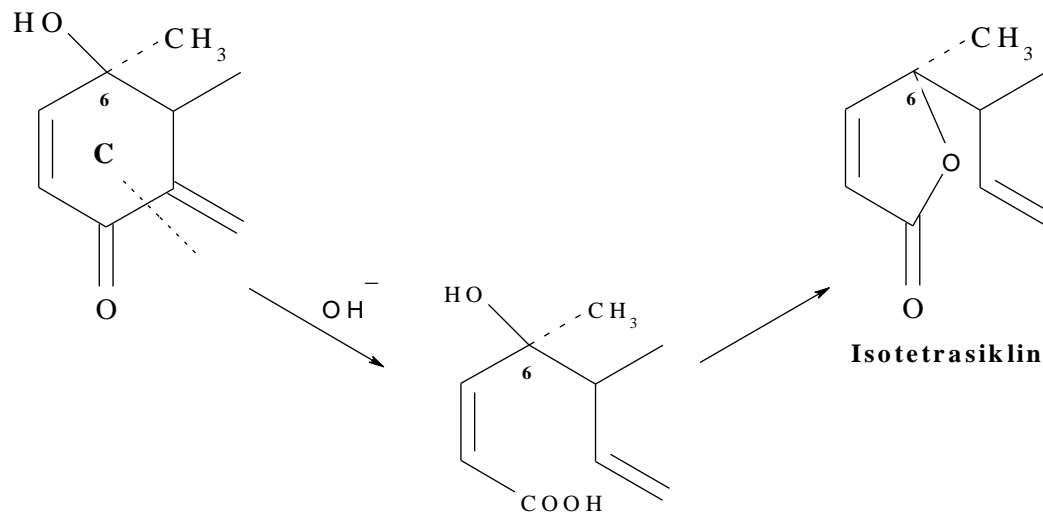
In the acid medium, 1 molecule H<sub>2</sub>O is separated from the -OH at position 6 and H at position 5a → (=) occurs between position 5a and position 6.

(=) between 11a-12 → shifts 11-11a → C ring aromatized → activity is lost .

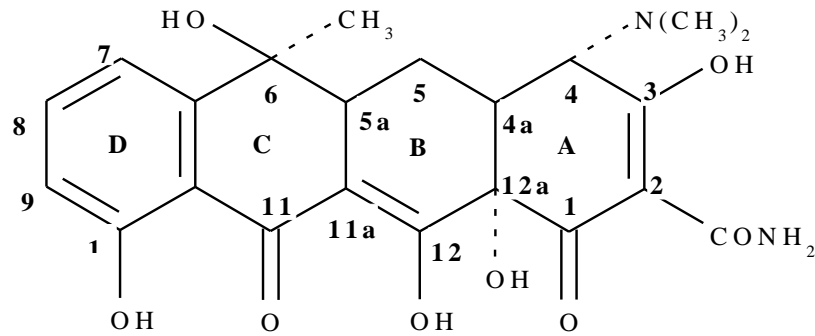


The C ring is opened in strong basic medium

- the -COOH group which is released is esterified with the -OH group at the 6-position → the inactive isotetracycline occurs



-OH at the 6th position interacts with acids and bases → to increase stability; semi-synthetic derivatives (Doxycycline, Minocycline) are prepared which carry no -OH moiety at this position.



-Demethylation at 6th position does not change activity

-CONH<sub>2</sub> at the 2nd position is replaced by -CN, -COCH<sub>3</sub> → activity is decreased.

-"H" in [-CONH<sub>2</sub> replaced with various groups to increase water solubility  
(Rolitetracycline, Limesiklin)]

-If Ring A is aromatized (12a-OH is removed), the activity is reduced.

-Octahidronaphthacene ring is absolutely necessary. Splitting or breaking any of the rings leads to loss of the activity.



- Bacteriostatic effect by inhibiting protein synthesis in bacterial ribosomes.
- Antibacterial spectra are identical (Gr (-) meningococcus and gonococci, Gr (+) Streptomyces pneumoniae, S. pyogenes, S. viridans)
- Absorption ratios, elimination routes, biological half-lives are different.
- Average absorptions are 60-70%.
- The most lipophilic tetracycline derivatives Doxycycline and Minocycline (used in acne treatment) are absorbed 90-95% of the gastrointestinal tract.
- Due to the formation of calcium chelates in the teeth, discolorations are brought to the spots.
  - More frequent in blond people, causing photosensitization (absorbance at 360-370 nm due to strong chromophore groups) causes photodermatosis.