



**Shree H. N. Shukla Institute of
Pharmaceutical Education and Research,
Rajkot**

**B. Pharm
Semester-VI**

Subject Name: Medicinal Chemistry

Subject Code: BP601TP

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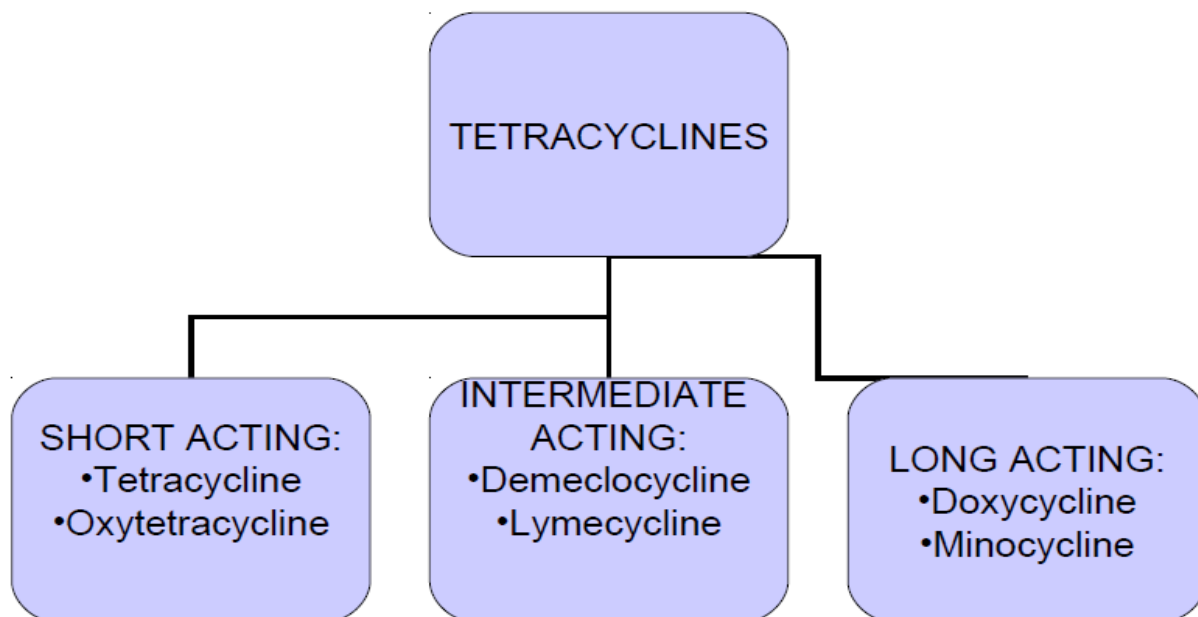
Tetracycline

Tetracyclines is a group of antibiotic that include tetracycline.

Tetracyclines are obtained by fermentation from *Streptomyces* spp. Or by chemical transformation of natural products.

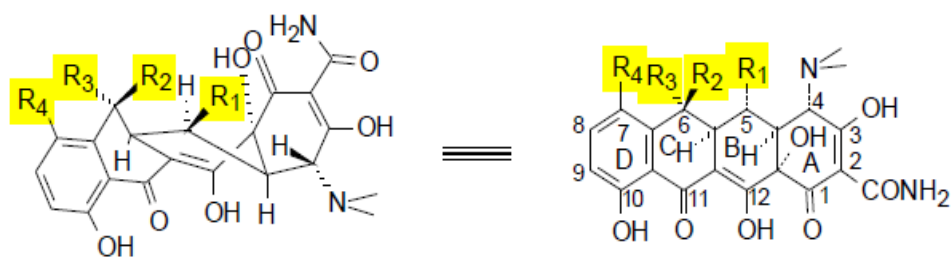
They are derivatives of an octahydro- naphthacene, a hydrocarbon system that comprises four annulated six member rings.

CLASSIFICATION



Structure of Tetracycline

- The stereochemistry of the tetracycline is very complex. carbon atom 4,4a,5,5a,6 and 12a, are potentially chiral depending on substitution.
- Oxytetracycline and Doxycycline possess 5 α -hydroxy substituent have six chiral carbon and others have five chiral carbon.
- These are amphoteric compounds, forming salts with either acids or bases.
- It exists mainly as zwitter ions in neutral solutions .
- They are yellow in colour , The HCL salts are used for oral administration and usually given in the form of capsule to mask the bitter taste.



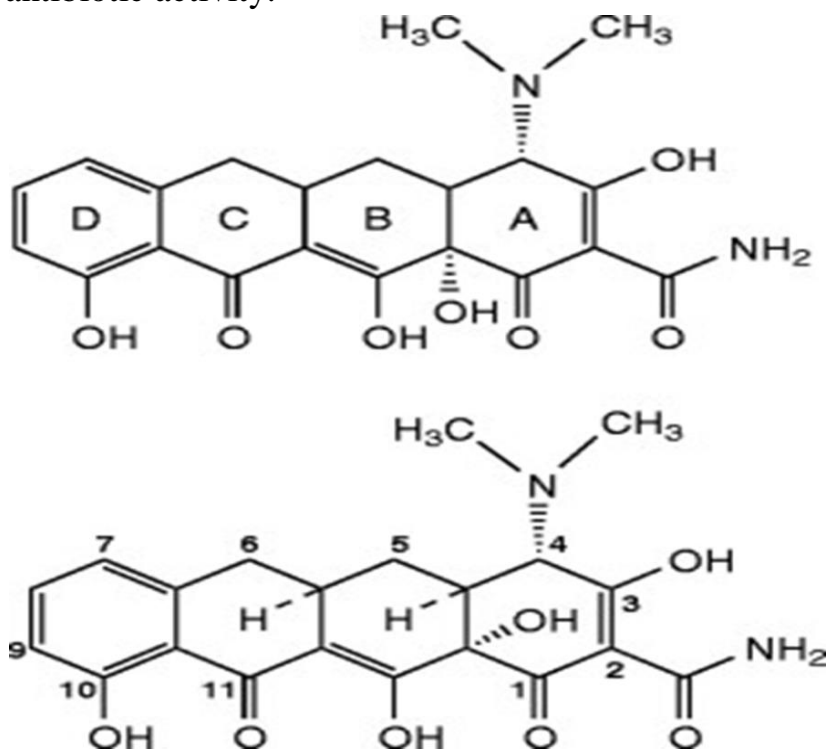
••Oxytetracycline© $R_1 = -OH$ $R_2 = -OH$ $R_3 = -CH_3$ $R_4 = -H$

••Chlotetracycline© $R_1 = -H$ $R_2 = -OH$ $R_3 = -CH_3$ $R_4 = -Cl$

••Tetracycline© $R_1 = -H$ $R_2 = -OH$ $R_3 = -CH_3$ $R_4 = -H$

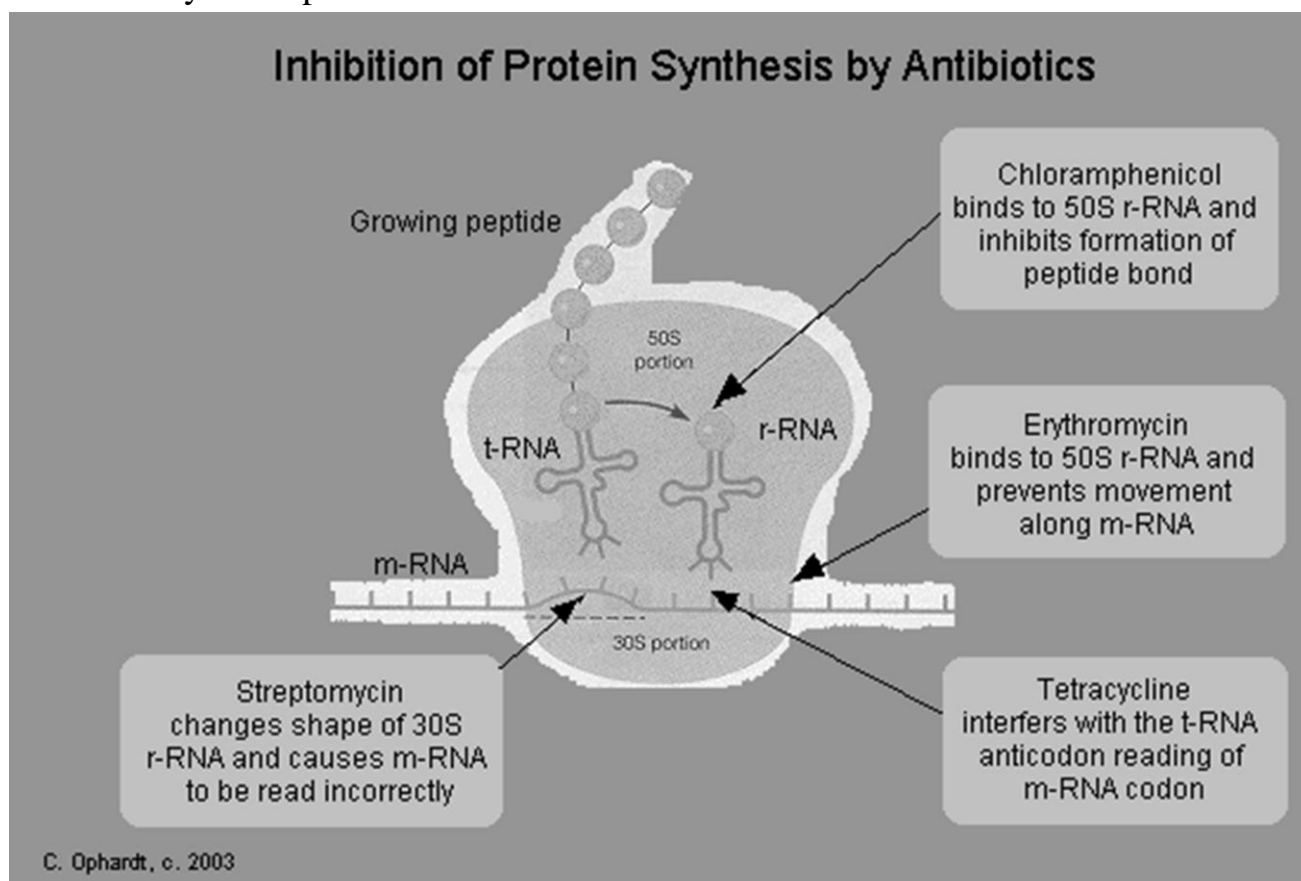
Tetracycline pharmacophore and numbering

Positions at the “bottom” of the molecule (10, 11, 1) and most of ring A (positions 2, 3, and 4) represent the invariant pharmacophore region of the molecule, where modifications are not tolerated without loss of antibiotic activity.

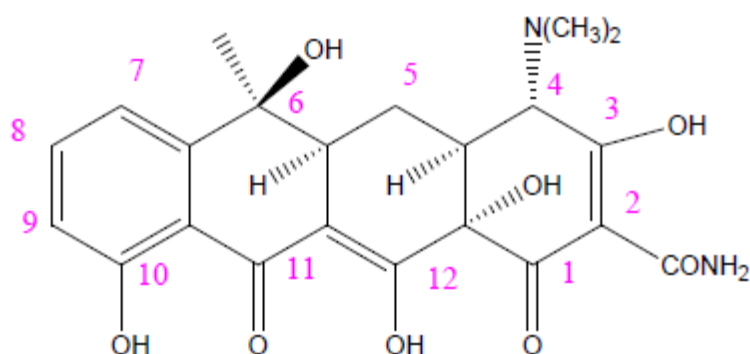


Mechanism of Action

- Tetracyclines are specific inhibitors of bacterial protein synthesis. They bind to the 30S ribosomal subunit and thereby prevent the binding of aminoacyl tRNA to the mRNA ribosome complex.
- Tetracyclines also inhibit protein synthesis in the host, but are less likely to reach the concentration required because eukaryotic cells do not have a tetracycline uptake mechanism.

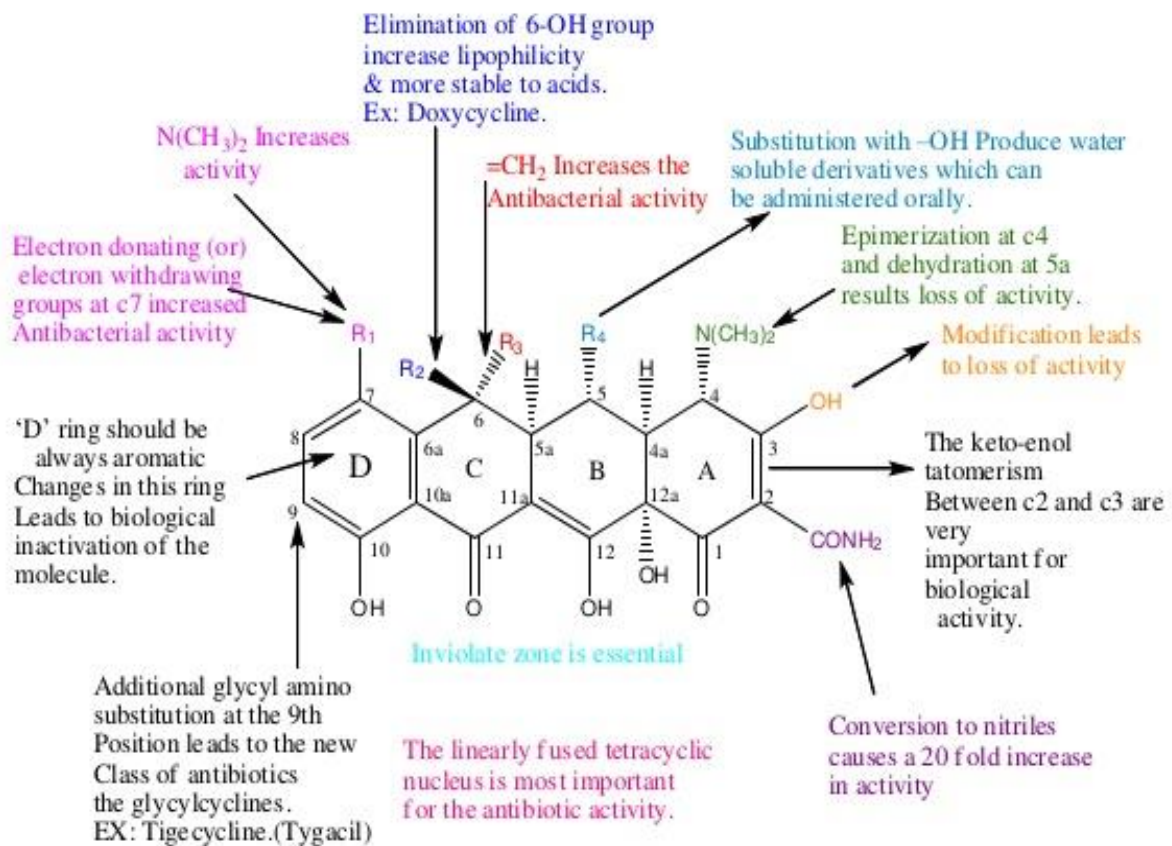


SAR of tetracyclines



6-methyl-4-(dimethylamino)-3,6,10,12,12a-pentahydroxy-1,4,4a,5,5a,6,11,12a-octahydro-2-naphthacenicarboxamide.

Structural Activity Relationship:



SAR OF TETRACYCLINES

Electron donating (or) electron withdrawing groups at c7 increased Antibacterial activity

Replacement of $-NO_2$ group Gives

more potent but carcinogenic compounds. $(=CH_2$ at c_6 increases the Antibacterial activity Ex: Methacycline).

Presence Of $-N(CH_3)_2$ group at C_4 Tetracyclines exists Zwitter ion Which can be possible to distribute in The body. Removal of this group loss of activity.

Substitution with $-OH$ Produce water soluble derivatives which can be administered orally.

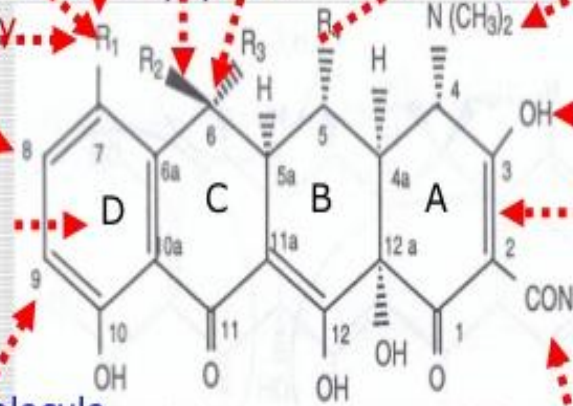
Substitution of $-N(CH_3)_2$ at 7 increase the activity.

Elimination of $6-OH$ group Causes increase lipophilicity And more stable to acids Ex: Doxycycline.

Epimerization at c_4 and dehydration at 5a results loss of activity. (any modification at C_3 loss of activity.)

Ex: Minocycline. Little information available.

'D' ring should be always aromatic Changes in this ring Leads to biological inactivation of the molecule.



The keto-enol tautomerism Between c_2 and c_3 are very important for biological activity.

Inviolable zone is essential

Conversion of corboxamide group to nitriles cause a 20 fold loss of activity.

Additional glycy amino substitution at the 9th Position leads to the new Class of antibiotics the glycyclines. EX: Tigecycline.(Tygacil)

The linearly fused tetracyclic nucleus is most important for the antibiotic activity.