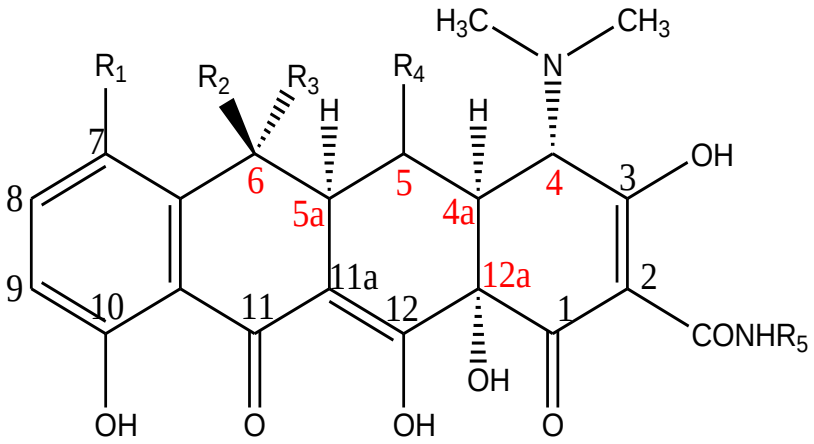
TETRACYCLINES

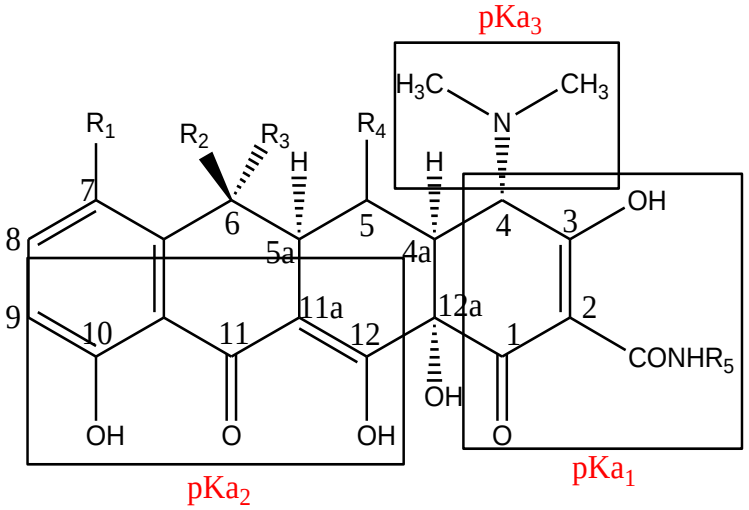
CHEMISTRY AND STRUCTURE



- Carbon atoms 4, 4a, 5, 5a, 6 and 12a are potentially chiral, depending on substitutions.(Oxytetracycline and Doxycycline, each with a 5α-hydroxyl substituent, have six asymmetric centers and others lacking chirality at C-5)
- Conjugated system exist in the structure from C-10 through C-12 and from C-1 through C-3.

CHEMISTRY AND STRUCTURE

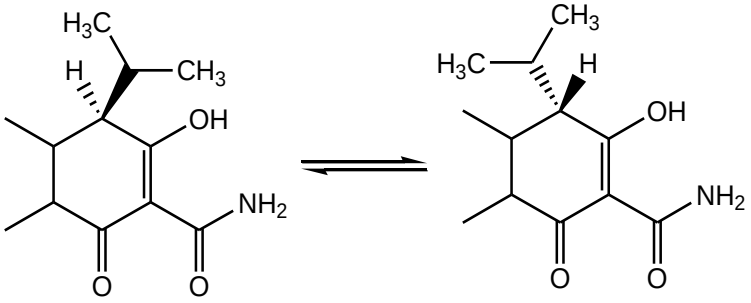
- The structural groupings in the tetracyclines produce three acidity constants in aqueous solution of the acid salts.



Sr. No.	Name	pKa_1	pKa_2	pKa_3
1	Tetracycline	3.3	7.7	9.5
2	Chlortetracycline	3.3	7.4	9.3
3	Demeclocycline	3.3	7.2	9.3
4	Oxytetracycline	3.3	7.3	9.1
5	Doxycycline	3.4	7.7	9.7
6	Minocycline	2.8	7.8	9.3

CHEMISTRY AND STRUCTURE

- Tetracyclines undergo epimerization at C-4 in solutions of intermediate pH range. Epitetracyclines exhibit less activity than natural isomers.



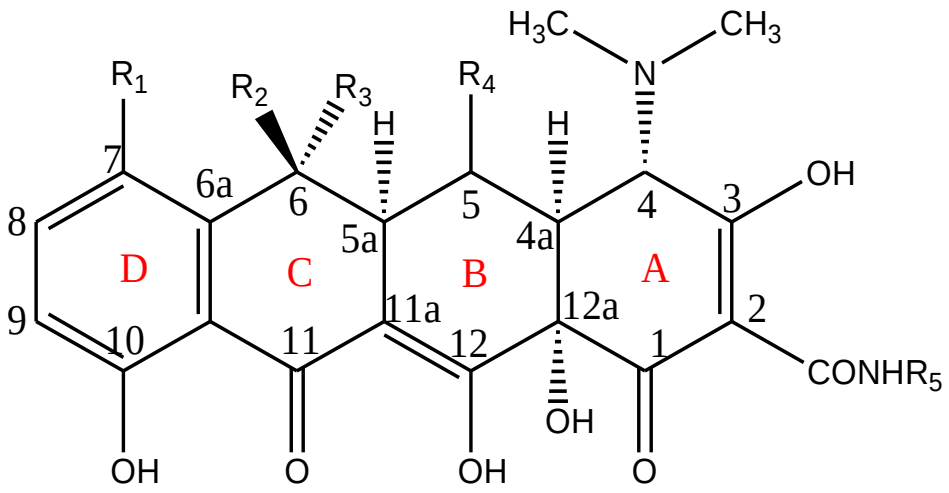
Epi Natural

- Strong acids and bases attack to causes dehydration at 6-OH group and 5α-H and forms double bond.
- Bases promote the reaction between the 6-OH group and 11-ketone group causing the bond between 11 and 11a atom to cleave and forms the lactone ring.

TETRACYCLINES IN PREGNANCY

- Tetracyclines chelates many metals like calcium, magnesium, aluminium and iron.
- The tetracycline-calcium-o-phosphate complex formed is characterized by a yellow fluorescence on teeth which may develop into brown discolouration over a period of time.
- Tetracyclines are distributed into the milk of lactating mothers and will cross the placental barrier into the fetus.
- Their untoward effects on calcium present in newly forming teeth and bone contraindicated their use in pregnancy or children under 8 years of age.

STRUCTURE ACTIVITY RELATIONSHIP



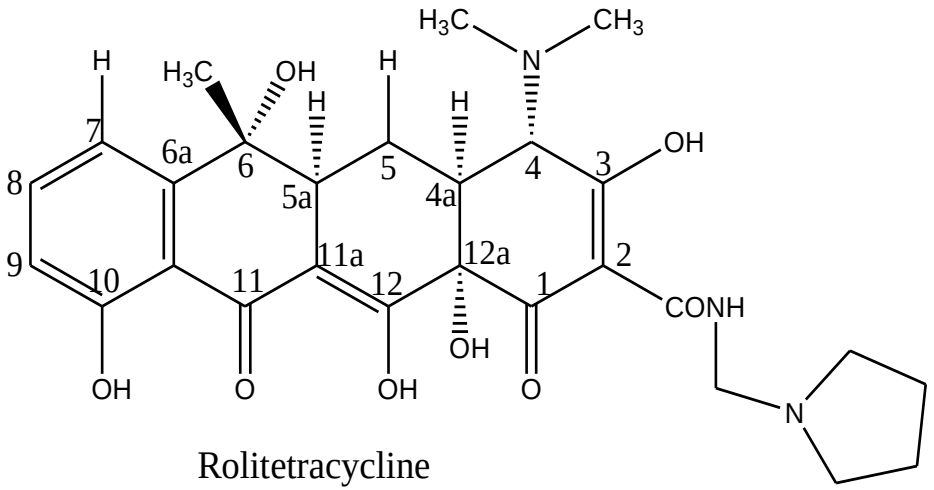
- The basic nucleus common to all tetracyclines is a polycyclic napthacene carboxamide which is comprised of four fused six membered rings A, B, C and D. The group name tetracycline thus describes the pattern of backbone skeleton.

STRUCTURE ACTIVITY RELATIONSHIP

- A tetracyclic backbone skeleton is essential for activity.
- The keto-enol system present at carbons 1 to 3 and 11 to 12 must be intact for antibacterial activity. Keto-enol system is vital for magnesium cation binding and subsequent tetracycline uptake by the bacterial cell.

STRUCTURE ACTIVITY RELATIONSHIP

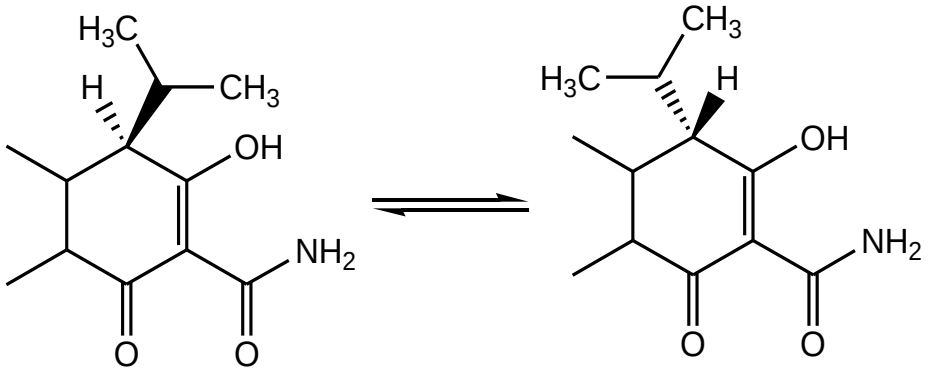
- The amide function at C-2 is essential for the activity. The amide is best left unsubstituted, mono-substitution is acceptable.



Rolitetracycline

STRUCTURE ACTIVITY RELATIONSHIP

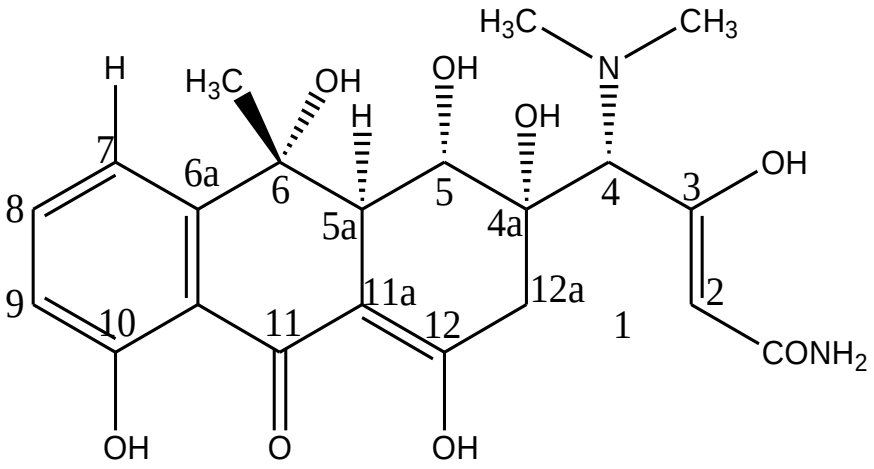
- Epitetracyclines (C-4) are very much less active than natural isomers. Replacement of dimethylamino group with a hydrazone, oxime, or hydroxyl group leads to a pronounced loss of activity, probably due to the increase in heteroatom basicity.



Epi Natural

STRUCTURE ACTIVITY RELATIONSHIP

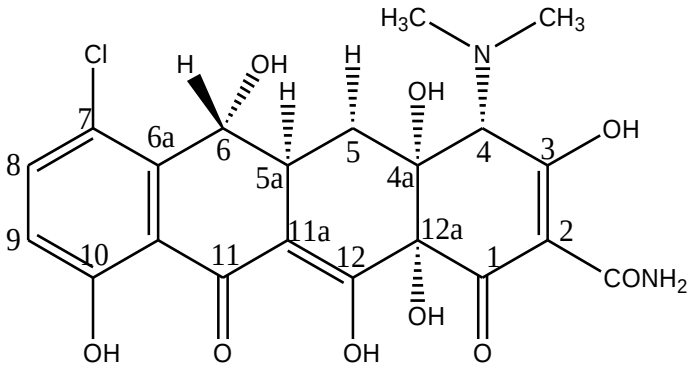
- The α-hydrogen at C-4a position is necessary for activity.
- Unsubstituted methylene moiety at C-5 position is essential for activity. Alkylation of the C-5 hydroxyl group results in loss of activity. (Exception- Oxytetracycline, contains C-5 α-hydroxyl group)



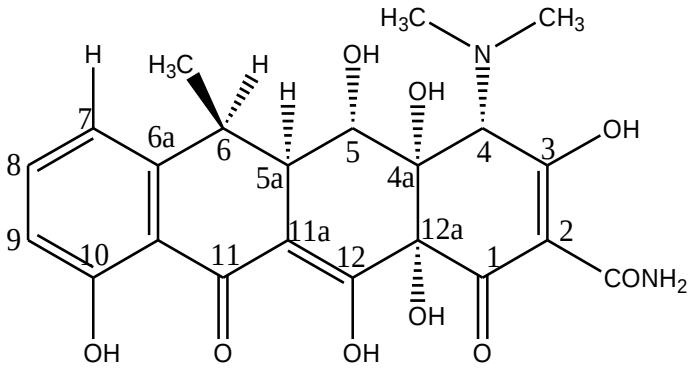
Oxytetracycline

STRUCTURE ACTIVITY RELATIONSHIP

- Hydrogen present at 5-position should have α-configuration; epimerization is detrimental to antibacterial activity.
- The majority of tetracyclines have a α-methyl group and a β-hydroxyl group at C-6 position. (Exceptions: Demeclocycline and Doxycycline)



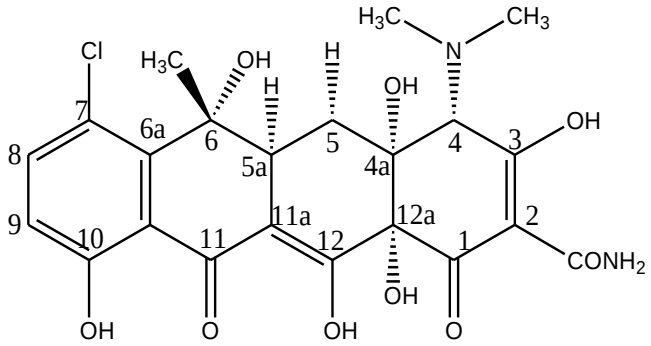
Demeclocycline



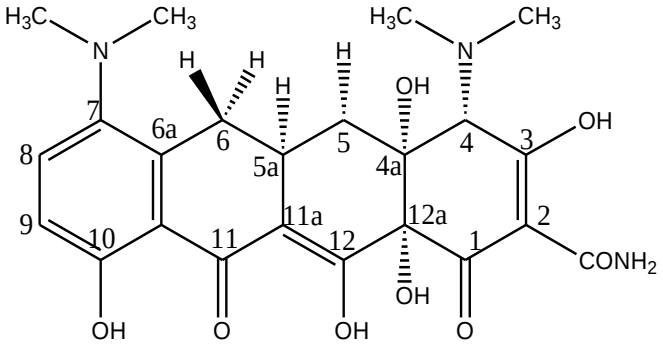
Doxycycline

STRUCTURE ACTIVITY RELATIONSHIP

- 6-Thiatetracyclines contain a sulphur atom at C-6. (Thiacycline is more active than Minocycline)
- C-7 substitution results in increased potency. Electron withdrawing groups and electron donating groups both are equally effective at C-7, e. g. Chlortetracycline and Minocycline



Chlortetracycline



Minocycline

STRUCTURE ACTIVITY RELATIONSHIP

- The C-10 phenolic moiety is absolutely necessary for antibacterial activity.
- C-12a hydroxyl group is needed for antibacterial activity, although this moiety can be esterified (preferably alkyl esters) to provide tetracycline with increases lipophilicity.
- The aromatic D ring and cis type fusion between A/B with an α- hydroxyl group at 12a is necessary for antibacterial activity.

RESISTANCE TO TETRACYCLINES

- Efflux mediated by transmembrane–spanning, active–transport proteins that reduces the intracellular tetracycline concentration (This mechanism of resistance is clinically most significant),
- Ribosomal protection, in which the bacterial protein synthesis apparatus is rendered resistant to the action of tetracyclines by an inducible cytoplasmic protein, and
- Enzymatic oxidation.