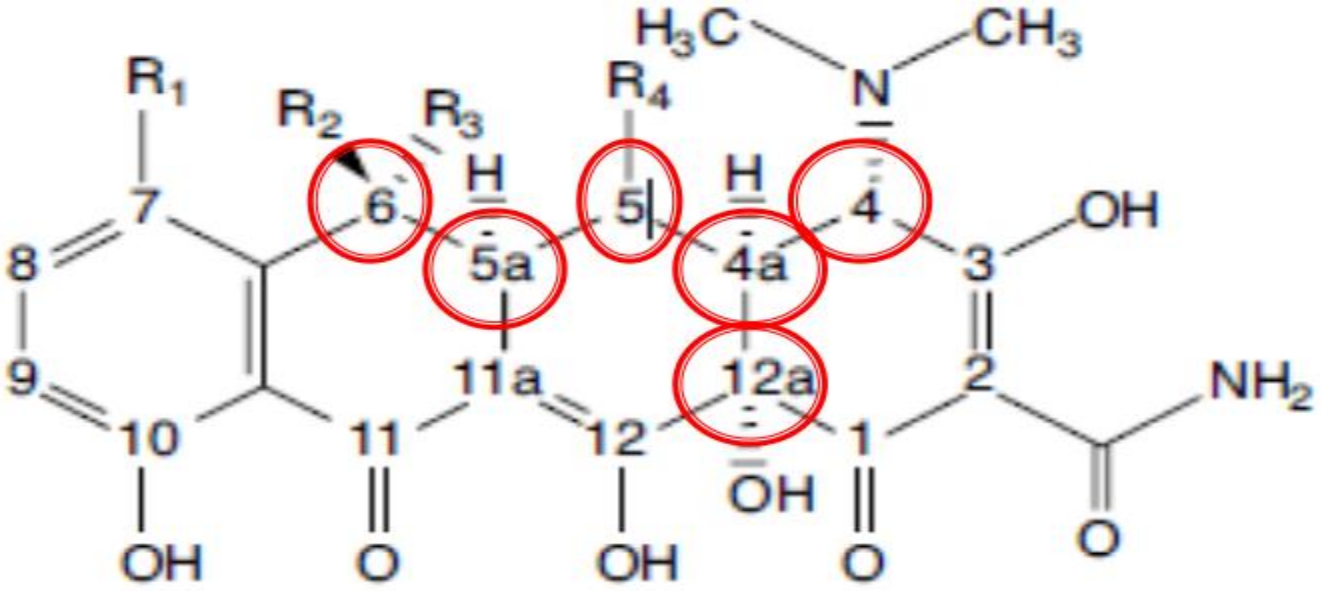
Pharmaceutical chemistry

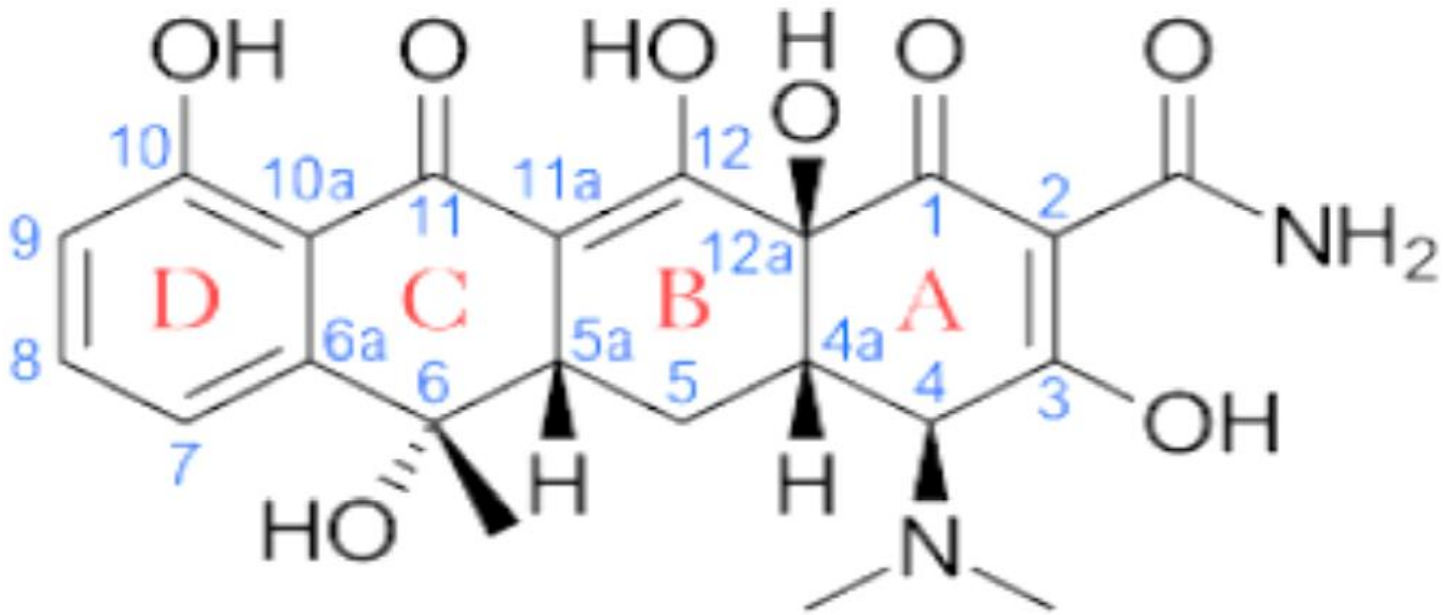
Antibacterial Antibiotics

Tetracyclines

- **Chemistry**
- Among the most important broad-spectrum antibiotics are members of the tetracycline family. Nine such compounds— tetracycline, rolitetracycline, oxytetracycline, chlortetracycline, demeclocycline, meclocycline, methacycline, doxycycline, and minocycline—have been introduced into medical use. Several others possess antibiotic activity. The tetracyclines are obtained by fermentation procedures from Streptomyces spp. or by chemical transformations of the natural products

- The stereochemistry of the tetracyclines is very complex. Carbon atoms 4, 4a, 5, 5a, 6, and 12a are potentially chiral, depending on substitution. Oxytetracycline and doxycycline, each with a 5αhydroxyl substituent, have six asymmetric centers; the others, lacking chirality at C-5, have only five.




OH
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NH2
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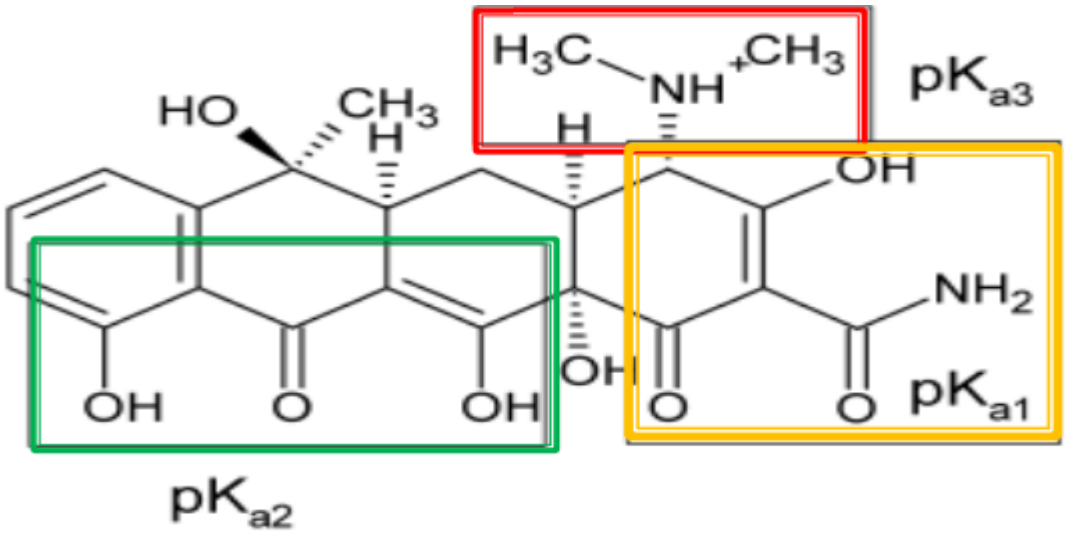
Structures of Tetracyclines

	R_1	R_2	R_3	R_4
Tetracycline	H	OH	CH_3	H
Chlortetracycline	Cl	OH	CH_3	H
Oxytetracycline	H	OH	CH_3	OH
Demeclocycline	Cl	OH	H	H
Methacycline	H	CH_2		OH
Doxycycline	H	CH_3	H	OH
Minocycline	$N(CH_3)_2$	H	H	H

Structures of Tetracyclines

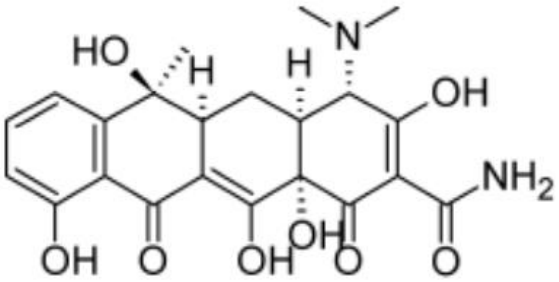
- The tetracyclines are amphoteric compounds, forming salts with either acids or bases. In neutral solutions, these substances exist mainly as zwitterions. The unusual structural groupings in the tetracyclines produce three acidity constants in aqueous solutions of the acid Salts (pKa1 pKa2 pKa)



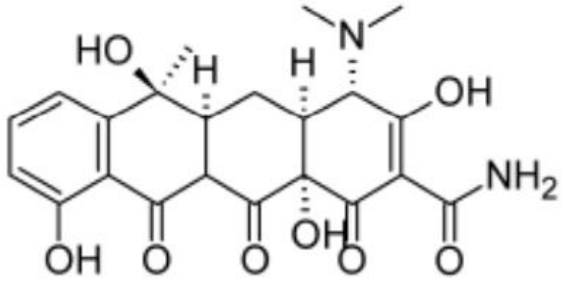
Structures of Tetracyclines

- **Strong acids** and strong bases attack tetracyclines with a hydroxyl group on C-6, causing a loss in activity through modification of the C ring.
- **Strong acids** produce dehydration through a reaction involving the 6-hydroxyl group and the 5a-hydrogen.
- **The double** bond thus formed between positions 5a and 6 induces a shift in the position of the double bond between C-11a and C-12 to a position between C-11 and C-11a, forming the more energetically favored resonant system of the naphthalene group found in the inactive anhydrotetracyclines.

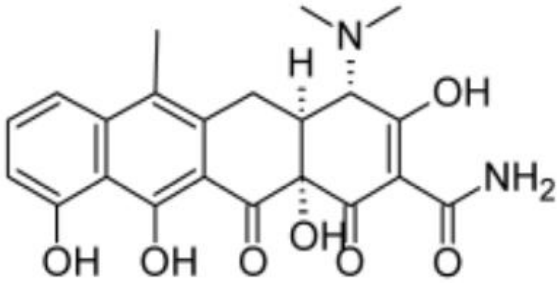
- **Bases** promote a reaction between the 6-hydroxyl group and the ketone group at the 11-position, causing the bond between the 11 and 11a atoms to cleave, forming the lactone ring found in the inactive isotetracycline. These two unfavorable reactions stimulated research that led to the development of the more stable and longer acting compounds 6-deoxytetracycline, methacycline, doxycycline, and minocycline.

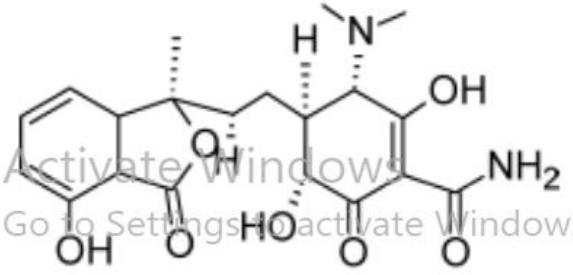


Base



Acid





- **Stable chelate complexes** are formed by the tetracyclines with many metals, including **calcium**, **magnesium,** and **iron**.
- Such chelates are usually very insoluble in water, accounting for the impaired absorption of most (if not all) tetracyclines in the presence of milk; calcium-, magnesium-, and aluminum-containing antacids; and iron salts. Soluble alkalinizers, such as sodium bicarbonate, also decrease the GI absorption of the tetracyclines. The affinity of tetracyclines for calcium causes them to be incorporated into newly forming bones and teeth as tetracycline–calcium orthophosphate complexes

Mechanism of Action and Resistance

- 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. Three biochemically distinct mechanisms of resistance to tetracyclines have been described in bacteria:
- **(a)** efflux mediated by trans membrane-spanning, active transport proteins that reduces the intracellular tetracycline concentration
- **(b)** ribosomal protection, in which the bacterial protein synthesis apparatus is rendered resistant to the action of tetracyclines by an inducible cytoplasmic protein
- **(c)** enzymatic oxidation.

Spectrum of Activity

- The tetracyclines have the broadest spectrum of activity of any known antibacterial agents. They are active against a wide range of Gram-positive and Gram-negative bacteria, spirochetes, mycoplasma, rickettsiae, and chlamydiae.
- Resistance to tetracyclines among both Gram-positive and Gram-negative bacteria is relatively common.

Structure–Activity Relationships

- 1. All derivatives containing fewer than four rings are inactive or nearly inactive.
- 2. The simplest tetracycline derivative that retains the characteristic broad-spectrum activity associated with this antibiotic class is 6-demethyl-6-deoxytetracycline.
  3. The enolized tricarbonylmethane system at C-1 to C3 must be intact for good activity.
- 4. Replacement of the amide at C-2 with other functions (e.g., aldehyde or nitrile) reduces or abolishes activity.
- 5. Mono alkylation of the amide nitrogen reduces activity proportionately to the size of the alkyl group

- 6. The dimethyl amino group at the 4-position must have the α- orientation: 4-epitetracyclines are very much less active than the natural isomers.
- 7. Removal of the 4-dimethylamino group reduces activity even further.
- 8. Activity is largely retained in the primary and Nmethyl secondary amines but rapidly diminishes in the higher alkylamines.
- 9. A cis-A/B-ring fusion with a -hydroxyl group at C12a is apparently also essential.
- 10. Esters of the C-12a hydroxyl group are inactive, with the exception of the formyl ester, which readily hydrolyzes in aqueous solutions.
- 11. Alkylation at C-11 a also leads to inactive compounds

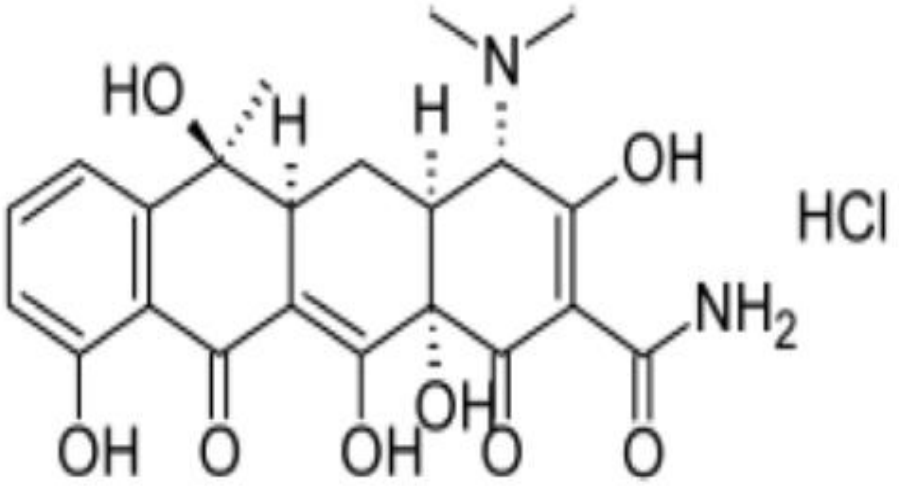
- 12. Dehydrogenation to form a double bond between C-5a and C-11a markedly decreases activity, as does aromatization of ring C to form anhydrotetracyclines. 13. substituents at positions 5, 5a, 6, 7, 8, and 9, representing the largely hydrophobic “northern and western” faces of the molecule, can be modified with varying degrees of success, resulting in retention and, sometimes, improvement of antibiotic activity.
- 14. A 5-hydroxyl group, as in oxytetracycline and doxycycline, may influence pharmacokinetic properties but does not change antimicrobial activity

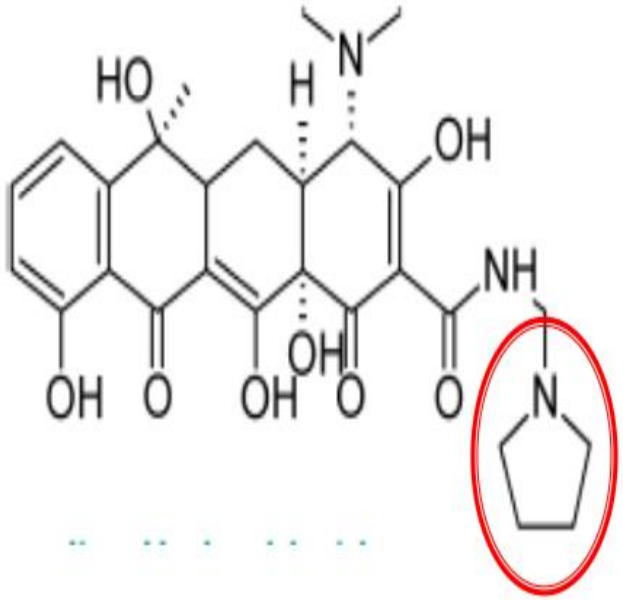
- 15. Acid-stable 6-deoxytetracyclines and 6- demethyl6-deoxytetracyclines have been used to prepare various mono substituted and di substituted derivatives by electrophilic substitution reactions at C-7 and C-9 of the D ring.
- 16. The more useful results have been achieved with the introduction of substituents at C-7.
- 17. Oddly, strongly electron withdrawing groups (e.g., chloro [Chlortetracycline] and nitro) and strongly electron-donating groups (e.g., dimethyl amino [**minocycline**]) enhance activity.

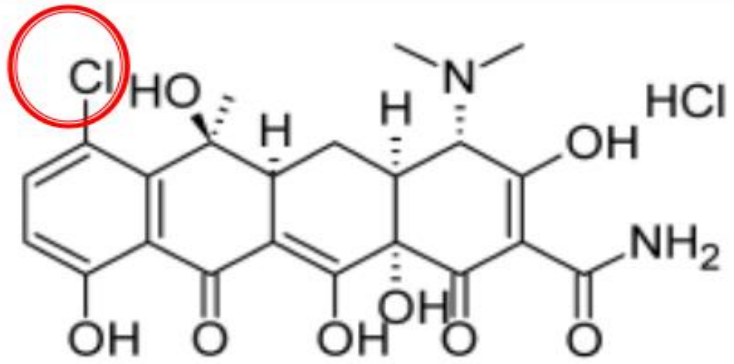
- 18. The most fruitful site for semisynthetic modification of the tetracyclines has been the 6-position. Neither the 6α-methyl nor the 6α-hydroxyl group is essential for antibacterial activity.
- 19. Polar substituents (i.e., hydroxyl groups) at C-5 and C-6 decrease lipid versus water solubility of the tetracyclines. The 6-position is, however, considerably more sensitive than the 5-position to this effect. Nonpolar substituents have the opposite effect

Products

- **Tetracycline**
- Tetracycline has become the most popular antibiotic of its group, largely because its plasma concentration appears to be higher and more enduring than that of either oxytetracycline or chlortetracycline

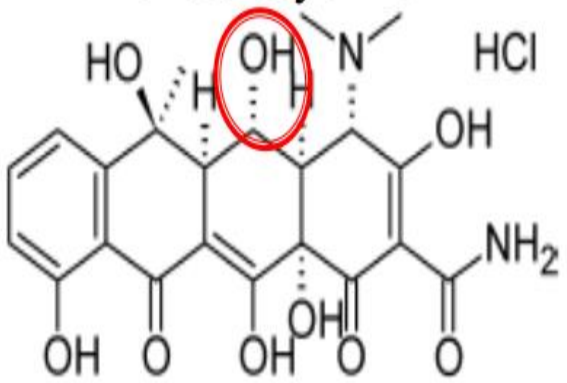


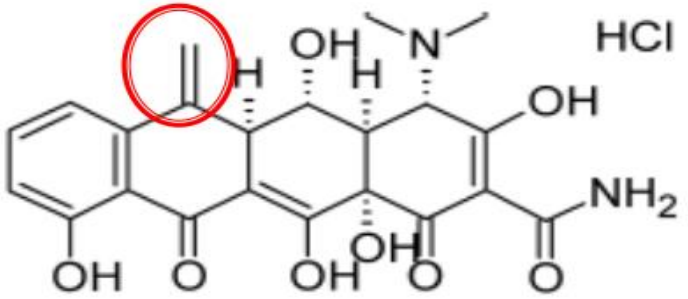




Chlortetracycline Hydrochloride

Rolitetracycline



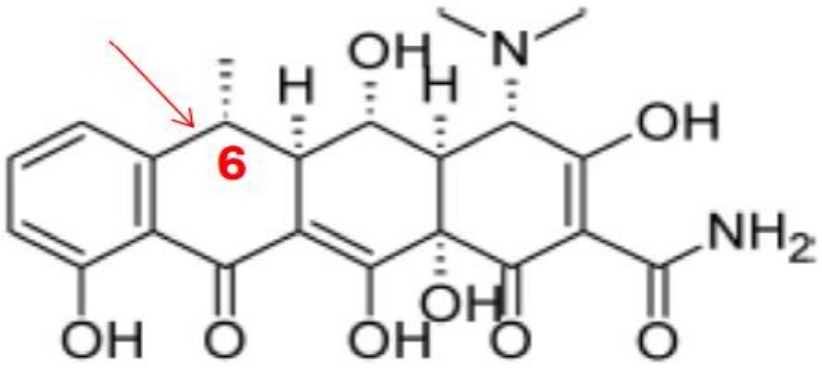


methacycline

- The greater stability of methacycline, both in vivo and in vitro, results from modification at C-6. Removal of the 6- hydroxy group markedly increases the stability of ring C to both acids and bases, preventing the formation of iso tetracyclines by bases

Doxycycline

- A more recent addition to the tetracycline group of antibiotics available for antibacterial therapy is doxycycline, α-6-deoxy-5-oxytetracycline (Vibramycin). The 6α-methyl epimer is more than 3 times as active as its β-epimer. Apparently, the difference in orientation of the methyl groups, which slightly affects the shapes of the molecules, causes a substantial difference in biological effect



- absence of the 6-hydroxyl group produces a compound that is very stable in acids and bases and that has a long biological half-life.
- In addition, it is absorbed very well from the GI tract, thus allowing a smaller dose to be administered

Newer tetracyclines

- Substituted in the aromatic (D) ring in an effort to discover analogs that might be effective against resistant strains. Glycylcyclines, a class of 9- dimethylglycylamino-(DMG)-substituted tetracyclines were discovered. The first of these to be marketed was **Tigecycline**.