

TETRACYCLINES



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Introduction:

- ✘ Tetracyclines are introduced 50 years ago as potent broad spectrum antibiotics.
- ✘ They are biosynthesized from acetic acid and propionic acid units in microorganisms.
- ✘ Tetracyclines possess a wide spectrum of activity i.e. gram+ve and gram-ve bacteria.
- ✘ They are mainly designed for oral route but parenteral and topical forms are available.
- ✘ **Historical background:**
- ✘ In 1945 Chlortetracycline (prototype) of tetracyclines was discovered by Dr. Benjamin, M. Duggar under the guidance of Yellapragada Subba Rao.
- ✘ He was born in a poor Telugu Niyogi Brahmin family in Bhimavaram in West Godavari district, Andhra Pradesh.
- ✘ He was an employee of Lederle Laboratories in U.S.A.
- ✘ Dr. Duggar produced Chlortetracycline (Aureomycin) from golden – colored soil bacterium called *Streptomyces aureofaciens* by fermentation technology.



- ✘ He discovered many life saving drugs.
- ✘ Vitamin B-12 (Cyanocobalamine).
- ✘ Folic acid vitamin : A remedy medicine to cure “sprue”
- ✘ Aureomycine (world’s first Tetracycline and cure cholera, typhoid, plague & dysentry).
- ✘ He was the first to discover Gramicidine (polypeptide antibiotic).
- ✘ Methotrexate (To prevent blood cancer in children).
- ✘ Hetrazin (elephantiasis & isonophelia, filariasis).
- ✘ This **Fisco Subbarao method** got recognition amongst the world famous
- ✘ scientists.
- ✘ Isonicotinic acid Hydrazide (INH) (To cure Tuberculosis).
- ✘ Discovered the role of ATP which are the sources of energy in human body.

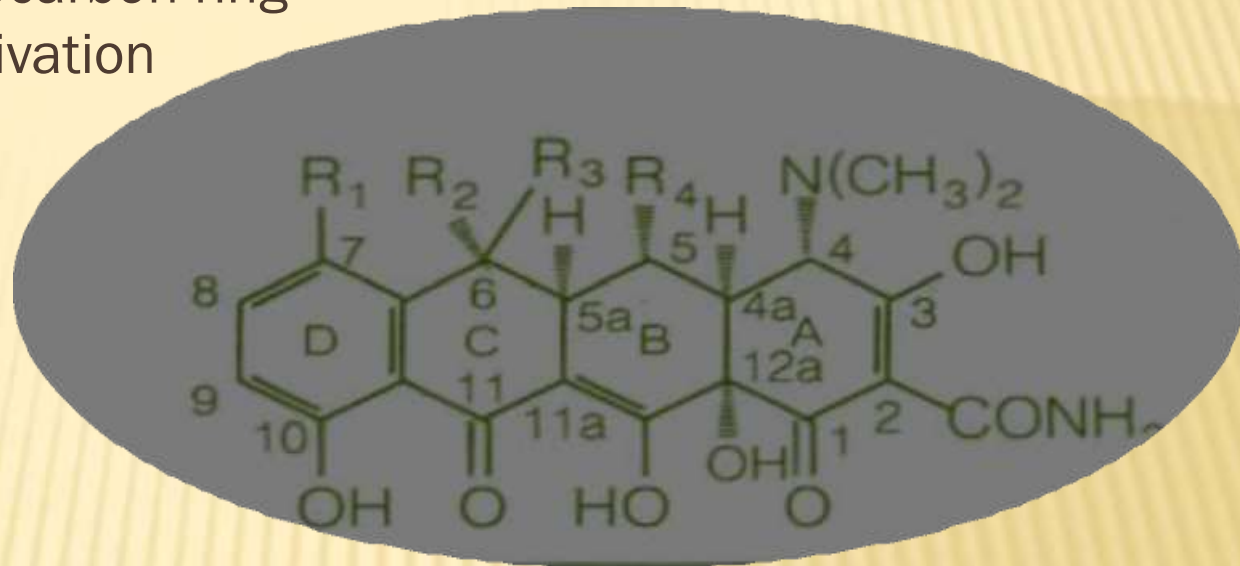
TETRACYCLINES

Tetra means = Four

Cycl means = Hydrocarbon ring

Line means = Derivation

Definition :



General structure

Tetracyclines are octahydro naphthacene derivatives which are bacteriostatic and broad spectrum antibiotics that kills certain infection - causing microorganisms and are used to treat wide variety of infections.

Sources :

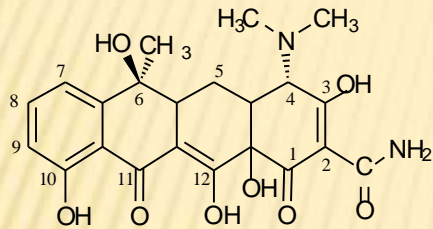
Tetracyclines are obtained from various species of *Streptomyces* bacteria by fermentation technology

- ✘ Chlortetracycline(aureomycin) from *Streptomyces aureofaciens*.
- ✘ Oxytetracycline (Terramycin) from *Streptomyces rimosus*.

Tetracyclines were divided into different categories i.e., based on source, and duration of action .

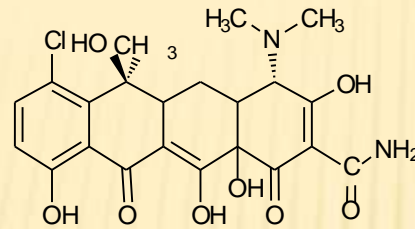
According to source:

1. Naturally occurring compounds:



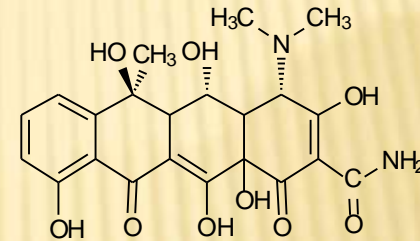
TETRACYCLINE

Achrommycin, Sumycin,
Panmycin, Teracap, Tetracycl, Tetralan



CHLORTETRACYCLINE

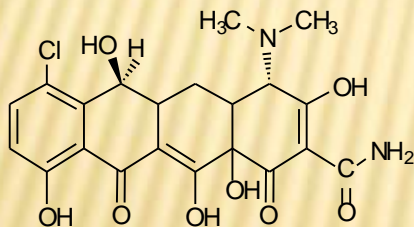
Aureomycin



OXYTETRACYCLINE

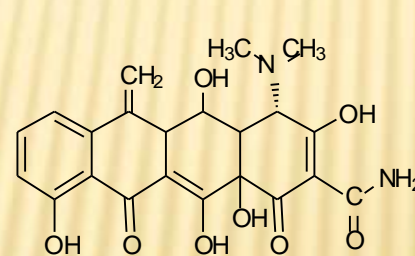
Terramycin, (Urobiotic)

2. Semi-synthetic compounds:



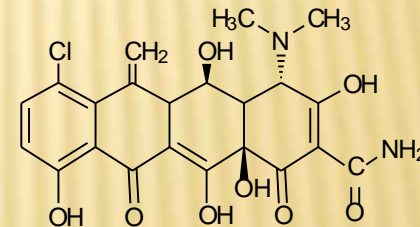
DEMECLOTETRACYCLINE

Declomycin



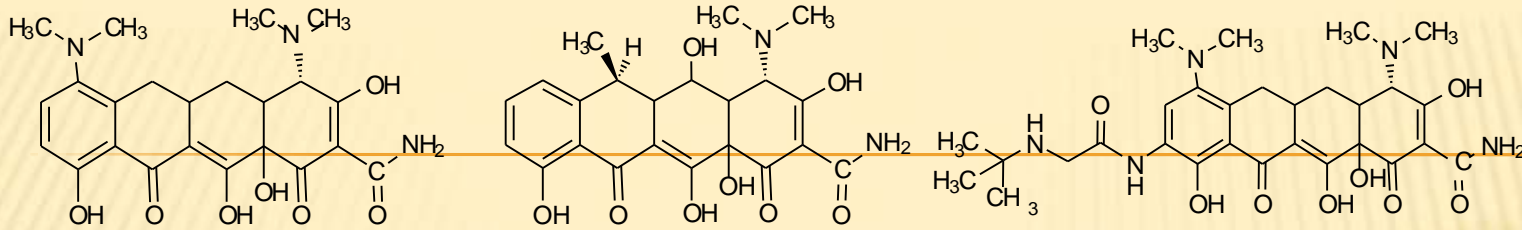
METHACYCLINE

[Rondomycin]



MECLOCYCLINE

Meclan



MINOCYCLINE
Arestin, Dynacin,
Vectrin, Minocin

DOXYCYCLINE
Vibramycin, Vibra-Tabs
Doryx, Doxy

TIGECYCLINE
Tygacil™

Classification:

According to duration of action:

1. Short-acting (Half-life is 6-8 hrs)

Tetracycline Chlortetracycline Oxytetracycline

2. Intermediate-acting (Half-life is ~12 hrs)

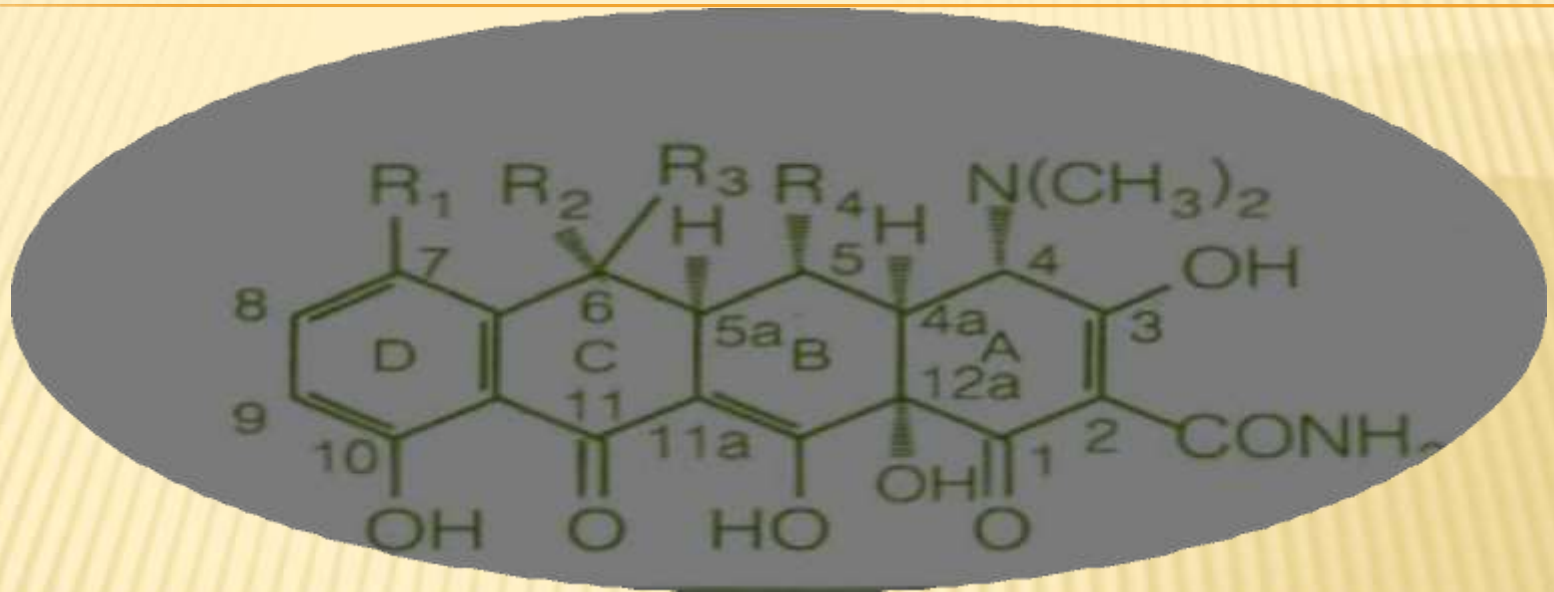
Demeclocycline Methacycline

3. Long-acting (Half-life is 16 hrs or more)

Doxycycline Minocycline Tigecycline

Stereochemistry of tetracyclines:

It is very complex



4,4a,5,5a,6,12a

Methacycline, Oxytetracycline, Meclocycline, Doxycycline possess 5-hydroxy Substituent have 6 chiral carbon atoms.

Others have only 5 chiral carbon atoms.

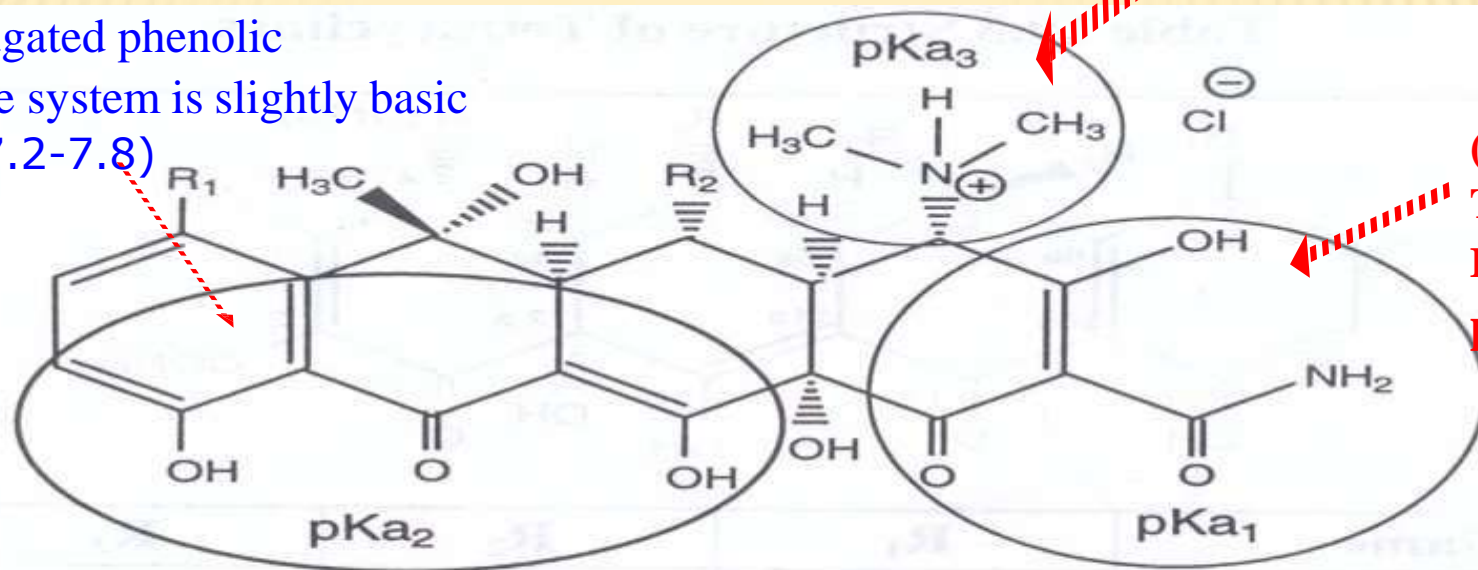
✘ Important structural units and the three acidity constants in the tetracycline molecule.

(Conjugated phenolic

Enone system is slightly basic

Pka (7.2-7.8)

Strong alkaline Pka3 (9.1-9.7)



pKa values of Tetracyclines Hydrochlorides in Aqueous Solution at 25°C

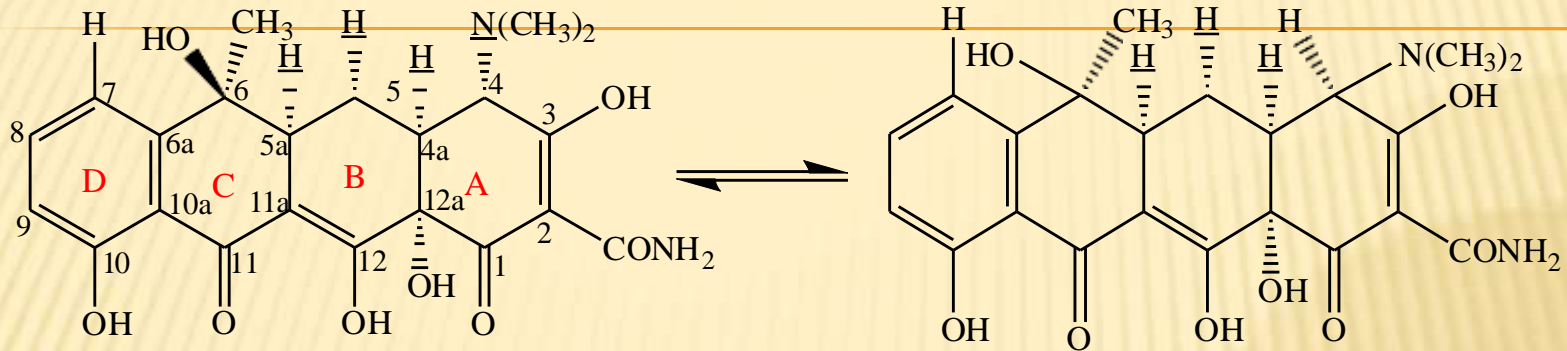
S.No	Name	Pka ₁	pKa ₂	pKa ₃
1.	Tetracycline	3.3	7.7	9.5
2.	Chlortetracycline	3.3	7.4	9.3
3.	Demeclocycline	3.3	7.2	9.3
4.	Oxytetracycline	3.3	7.3	9.1
5.	Doxycycline	3.4	7.7	9.7
6.	Minocycline	2.8	7.8	9.3

Nature of tetracyclines (Amphoteric):

- Tetracyclines are amphoteric compounds.
- **Amphoteric = form salts with both strong acids and bases.**
- ✘ Three structural units of tetracyclines representing 3 pKa values.
- **Pka1--- Conjugated trione system extending from C₁ to C₃**
of ring A is acidic nature of **Pka 2.8-3.4.**
- **Pka2--- Conjugated phenolic enone system from C₁₀-C₁₂ is**
 - ✘ associated with weak basic Pka values ranging from **7.2-7.8.**
- **Pka3-- C₄ atom and its substituents exhibits Pka3 ranging from**
 - ✘ **9.1 to 9.7.** which represents strong alkaline nature.

Because of the amphoteric nature tetracyclines forms water soluble salts with strong acids such as HCl and strong bases such NaOH, KOH.

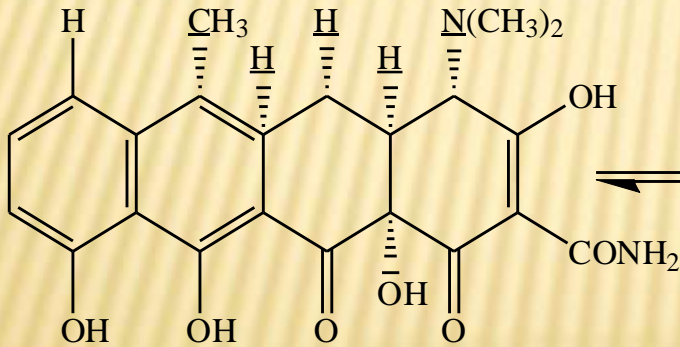
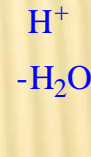
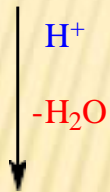
Epimerization:



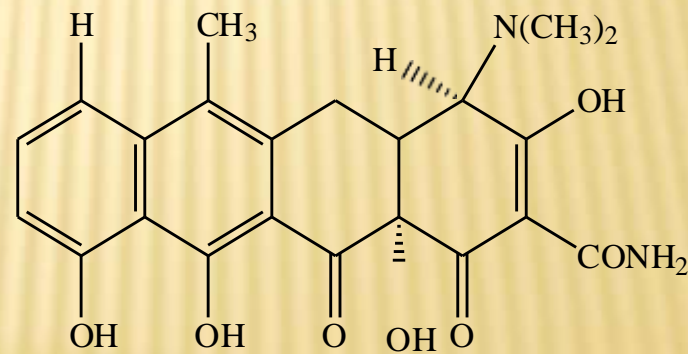
Tetracycline
(Active)

**Strong acids and bases
Attack those tetracyclines
Which possess an -OH group at
C-6 and form inactive
anhydrotetracyclines**

4-Epi tetracycline
(Inactive)



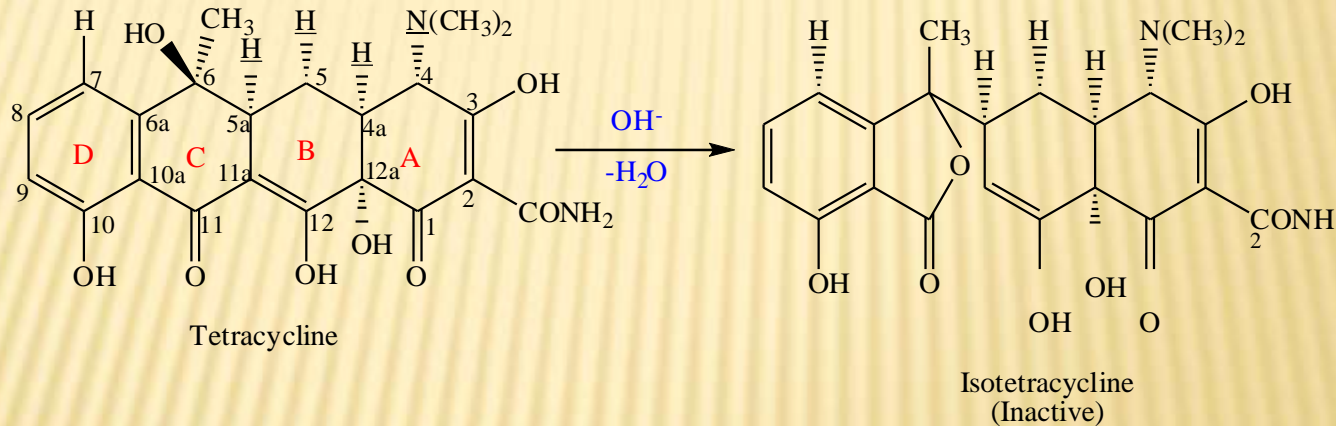
Anhydrous Tetracycline
(Inactive)



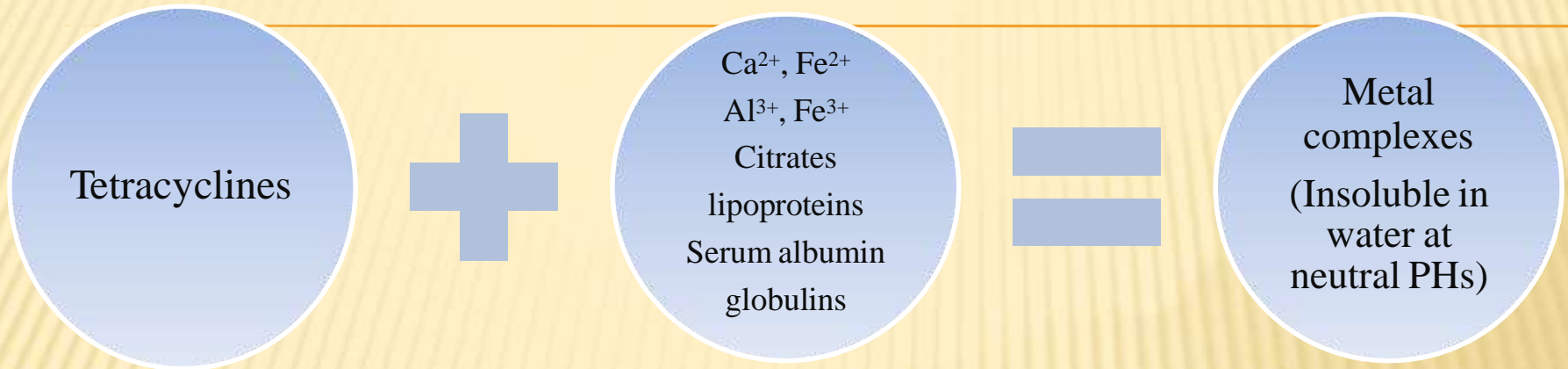
4-Epi anhydro tetracycline
(Inactive)

Base-catalyzed instability of tetracyclines:

Under **alkaline** condition, **OH at C₆** change into oxygen anion and then attacks the C-11 (ketone group) lead to **intramolecular nuclear reaction, by electron transfer, C ring rupture** to generate inactive isotetracycline lactone.



CHELATION:



- This insolubility is not only inconvenient for the preparation of solutions but also interferes with blood levels on oral administration.
- The tetracycline's are **incompatible** with co-administered, multivalent ion-rich **antacids** and with **hematinics** and concomitant consumption of **daily products rich in calcium** ion also is contraindicated.

SPECTRUM OF ACTIVITY :

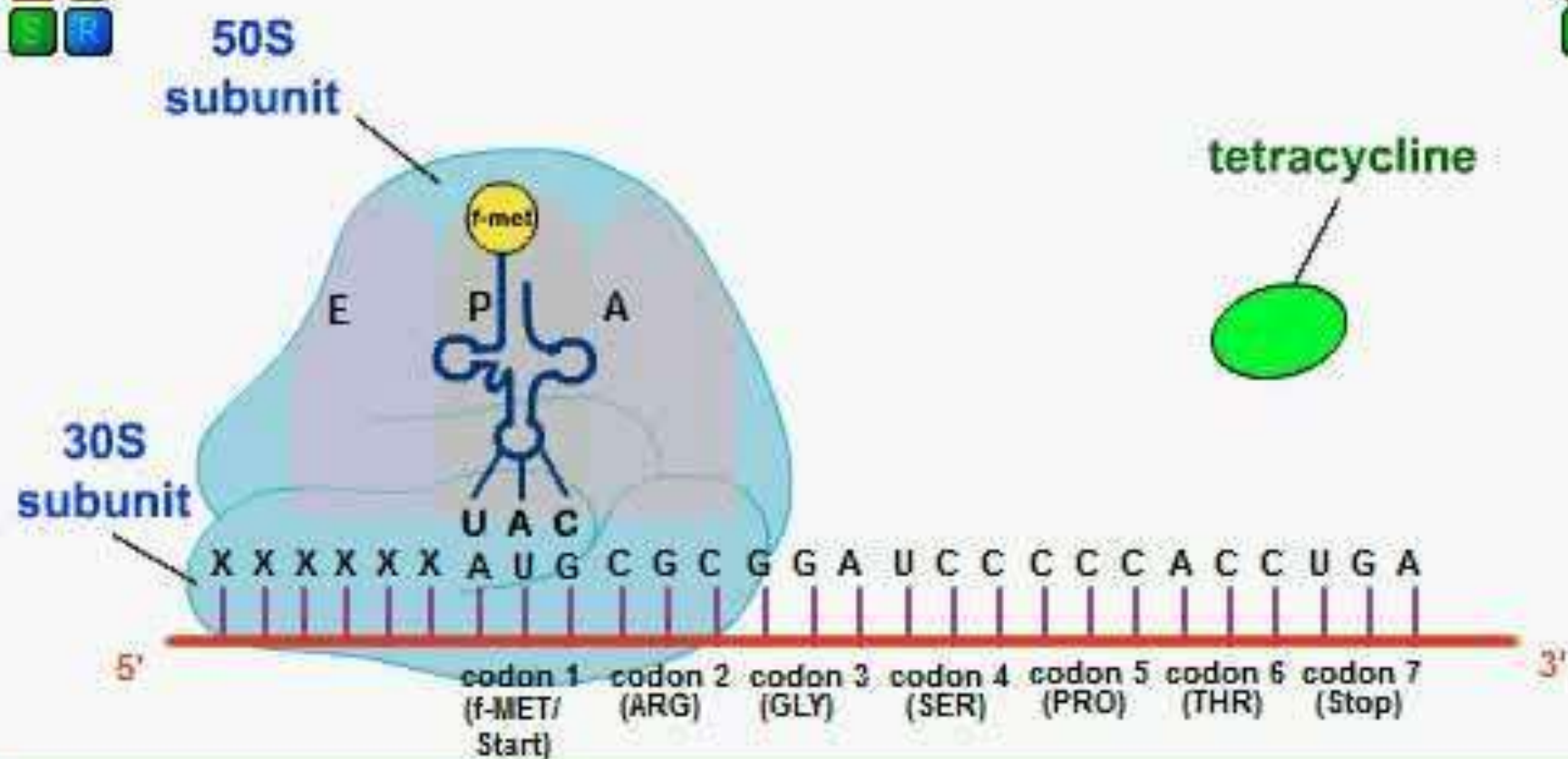
TETRACYCLINES ARE BROAD SPECTRUM ANTIBIOTICS.

THEY ARE ACTIVE AGAINST FOLLOWING MICRO ORGANISMS:

- ✓ Gram +ve & -ve bacteria
- ✓ Spirochetes
- ✓ Mycoplasmas
- ✓ Rickettsiae
- ✓ Candida Albicans
- ✓ Mycoplasma Pneumoniae
- ✓ Chlamydia Trachomatis
- ✓ Borrelia Recurrentis
- ✓ Yersinia Pestis
- ✓ Vibrio Cholerae
- ✓ Campylavacter Fetus
- ✓ Brucella Specie
- ✓ Neisseerie Gonorrhoeae

MECHANISM OF ACTION OF TETRACYCLINES:

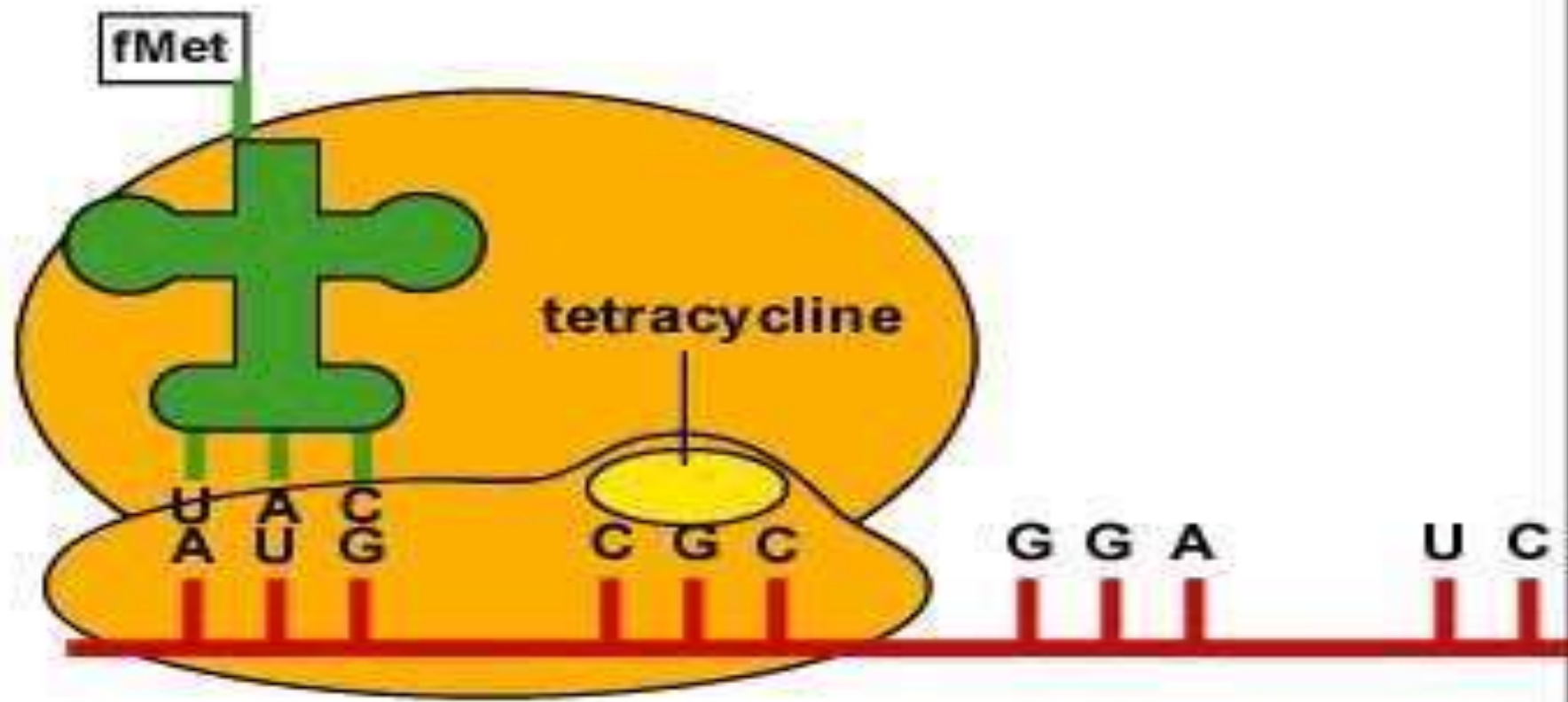
- Tetracyclines **inhibit protein synthesis** by binding to the bacterial ribosome involved in the translation (protein synthesis) process and making them bacteriostatic.
- The bacterial ribosome is a 70s particle **made up of 30s subunit and 50s subunit.**
- The 30s subunit binds mRNA and initiates the protein synthesis.
- The **50s subunit combines with the 30s subunit-mRNA complex to form a ribosome** then binds aminoacyl tRNA and catalyses the building of the protein chain..
- There are **two** main binding sites for the tRNA molecule.
- The peptidyl(**p-site**) binds the tRNA bearing the peptide chain
- The acceptor aminoacyl site (**A-site**)
- ***Tetracyclines reversibly bind to the 30S subunit at the A-site to prevent attachment of the amino acyl tRNA, terminating the translation process..***



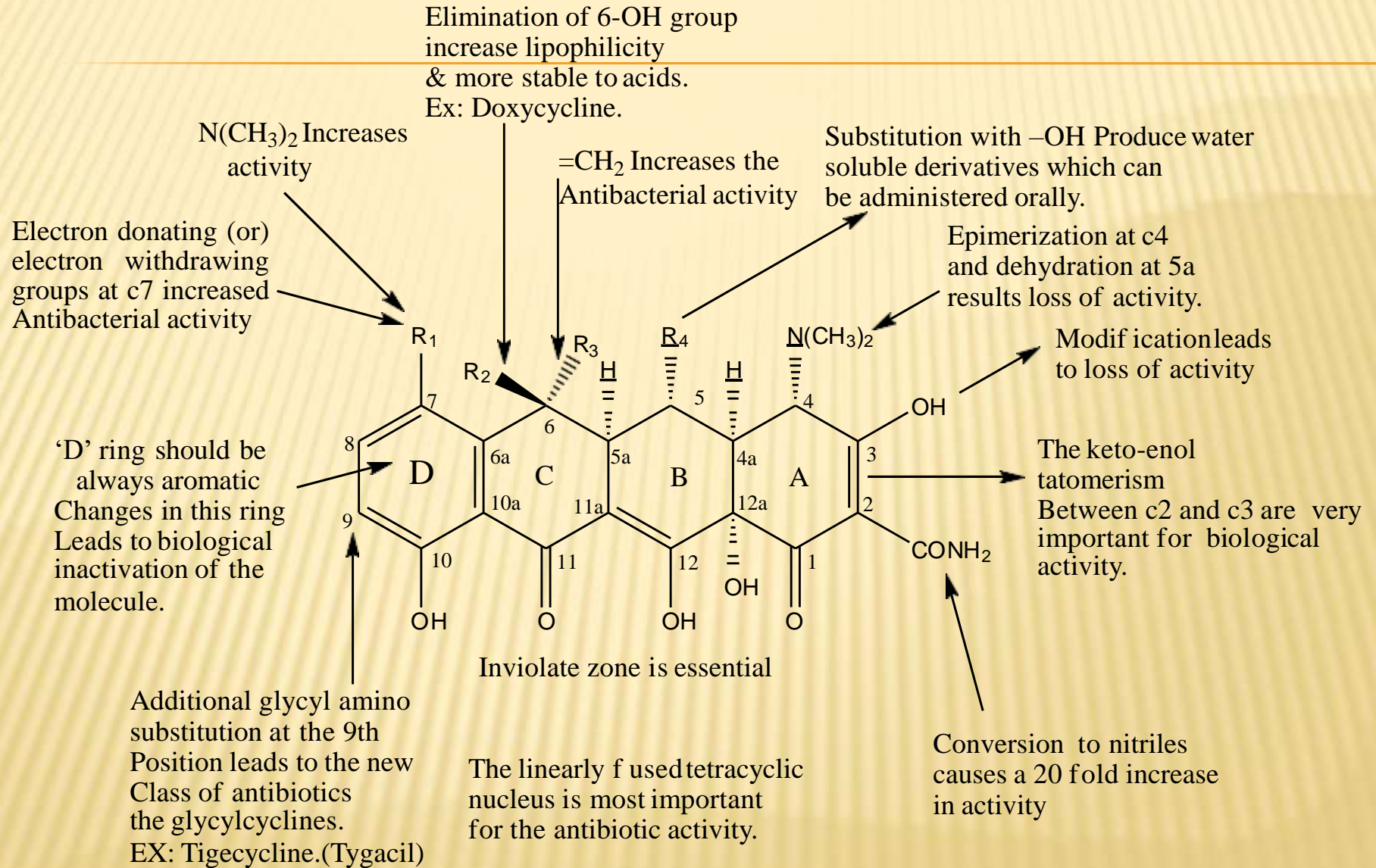
The tetracyclines block bacterial translation by binding reversibly to the 30S ribosomal subunit. This prevents the binding of the aminoacyl tRNAs (charged tRNAs) to the A-site of the ribosome.

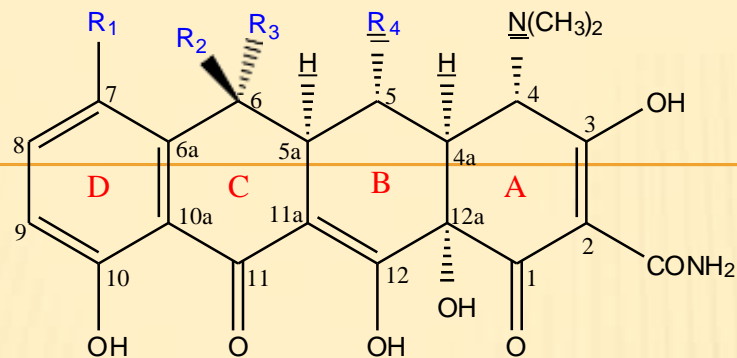


Role of tetracyclines in blocking protein synthesis



Structural Importance: Structural Activity Relationship





General structure of tetracyclines

S.NO	Structural Modifications	Effects
1.	Any modification	No bacterial activity
2.	Acetyl group only	Slightly activity retained
3.	Any modification	No bacterial activity
4.	α dimethylamino group	NHCH_3 retains more activity
5a.	Loss of H	Inactive degradation product
6.	Remove OH, CH_3 or both	More stable compound
7.	Cl, Br, NO_2 , $(\text{CH}_3)_2\text{N}$ -	Activity retained
8.	Little information available	—
9.	Cl and CH_3	Decreased activity
10,11,11a,12.	“Inviolable zone” including C-1	Diminished activity

- Uses of tetracyclines :
-
- Tetracyclines are called "broad-spectrum" antibiotics, because they can be used to treat a **wide variety of infections**.
 - Physicians may prescribe these drugs to treat **eye infections**.
 - Tetracyclines are generally a low-cost alternative among antibiotics.
 - Interestingly, a form of tetracycline has recently been used in prevention of cancer recurrence.
 - Tetracyclines may be used in the treatment of infections of the **respiratory tract, sinuses, middle ear, intestines**.
 - Gonorrhoea

Contraindications of Tetracycline Antibiotics :

- ❖ Can stain developing teeth (even when taken by the mother during pregnancy)
- ❖ Inactivated by Ca^{2+} ion, not to be taken with milk, yogurt, and other dairy products.
- ❖ Skin photosensitivity; exposure to the Sun or intense light is not recommended
- ❖ Drug-induced lupus, and hepatitis
- ❖ Can induce microvesicular fatty liver.
- ❖ May interfere with methotrexate by displacing it from the various protein binding sites

Tetracyclines should therefore be avoided in pregnant or lactating women.



They can cause skin reactions



Tetracycline might cause stains to developing adult teeth, which cannot be easily removed with conventional tooth whitening



Side effects :

- Mild nausea, vomiting, diarrhea.
- White patches or sores inside your mouth or on your lips .
- Swollen tongue, trouble swallowing.
- Vaginal itching or discharge.
- Loss of appetite, jaundice (yellowing of the skin or eyes).

Some of drugs effects tetracyclines:

- Cholesterol-lowering medications such as cholestyramine (Prevalite, Questran) .
- Isotretinoin (Accutane).
- Tretinoin (Renova, Retin-A, Vesanoid) .
- A blood thinner such as warfarin (Coumadin).
- A penicillin antibiotic such as amoxicillin (Amoxil, Trimox, others).
- Penicillin (BeePen-VK, Pen-Vee K, Veetids, others).
- Dicloxacillin (Dynapen)

Some of indications to use tetracyclines:

- Finish the prescription.
- Take on empty stomach.
- Take with plenty of water.
- Shake well.
- Do not take with milk, antacids, or iron
- Avoid exposure to sun.

- Do not use this medication if you are pregnant..
- Tetracycline passes into breast milk and may affect bone and tooth development in a nursing baby.
- Do not give tetracycline to a child younger than 8 years old.
- Avoid exposure to sunlight or artificial UV rays.
- Do not take iron supplements, multivitamins, calcium supplements, antacids.
- Throw away any unused tetracycline when it expires or when it is no longer needed.

Thank you