ART HAART

Highly Active Anti-Retroviral Therapy

- Inspite of so much advancement, treatment of AIDS is still unsolved problem
- It is mainly due to development of drug resistant virus.
- The other factors like toxicity of drugs, incomplete medication adherence, opportunistic infection, drug-drug interaction etc also contribute to this pandemic
- Hence the above mentioned drugs are used in combination & is known as highly active anti-retroviral therapy (HAART)
- It is done to delay the development of resistance, reduce the dose requirement etc

The preferred initial regimens are either:
- efavirenz + lamivudine or emtricitabine + zidovudine or tenofovir
- lopinavir boosted c ritonavir + zidovudine + lamivudine or emtricitabine

In countries c high rate of baseline resistance, resistance testing is recommended prior to starting treatment or if the initiation of treatment is urgent, then a "best guess" treatment regimen should be started & is then modified on basis of resistance testing.

HAART is effective combination of drug therapy used to treat HIV.

Goals:
- To reduce HIV related problem
- To restore or preserve immune function.
- To improve quality of life
- Prevents transmission to others
- Prevents drug resistance

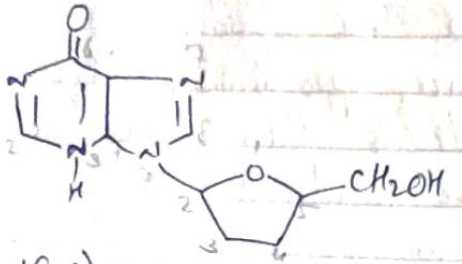
Drugs used for HAART:

1. **Nucleoside reverse transcriptase inhibitors**

Drugs binds competitively to reverse transcriptase enzyme & cause premature DNA chain termination.

Eg: Didanosine, Lamivudine, Zidovudine

Didanosine



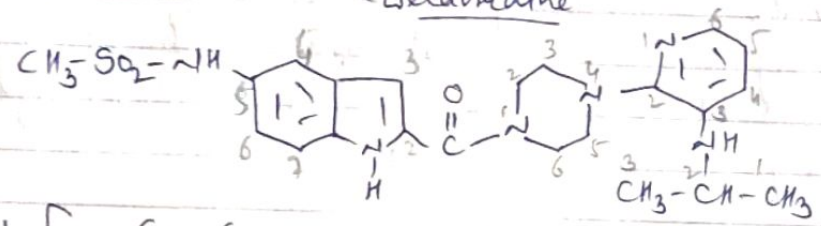
9-(5-(hydroxy methyl) tetrahydro furan-2-yl) 3H-purin-6-(9H) one

2. **Non-nucleoside reverse transcriptase inhibitor**

It binds to HIV reverse transcriptase at an allosteric site. By changing in reverse transcriptase enzyme, results in inhibition of DNA polymerase enzyme

Eg: Delavirdine

Delavirdine



N-[2-(4-(3-propan-2-yl amino) pyridin-2-yl) piperazin-1-yl carbonyl] 1H-indol-5-yl methane

3. **Protease inhibitor (PI's)**

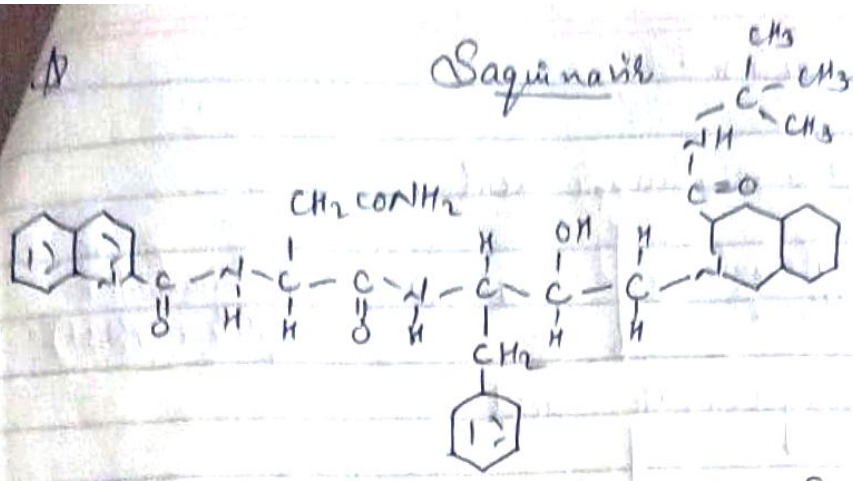
PI's competitively inhibit proteolytic cleavage of polyproteins in HIV infected cells. These results in immature non-infection.

PI's are generally used in patients who failed their HAART regimen & should be administered ± boosting agent.

Eg: Saquinavir
Ritonavir
Indinavir

N

Saquinavir

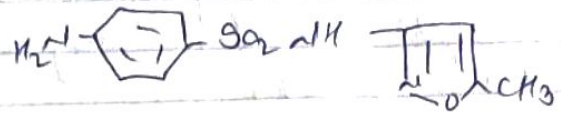


N-(4-(3-tert butyl carbamoyl)-octahydro[1H]isoquinolin-2-yl)-3-hydroxy-1-phenylbutan-2-yl)2-(quinolin-2-carbonylamino) butane diamide

Folate Reductase inhibitors

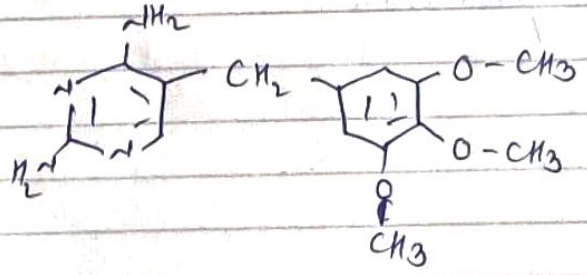
Combination of trimethoprim & sulfamethoxazole is co-trimoxazole

Sulfamethoxazole



3-(4-amino benzene sulphamide)-5-methyl isoxazole

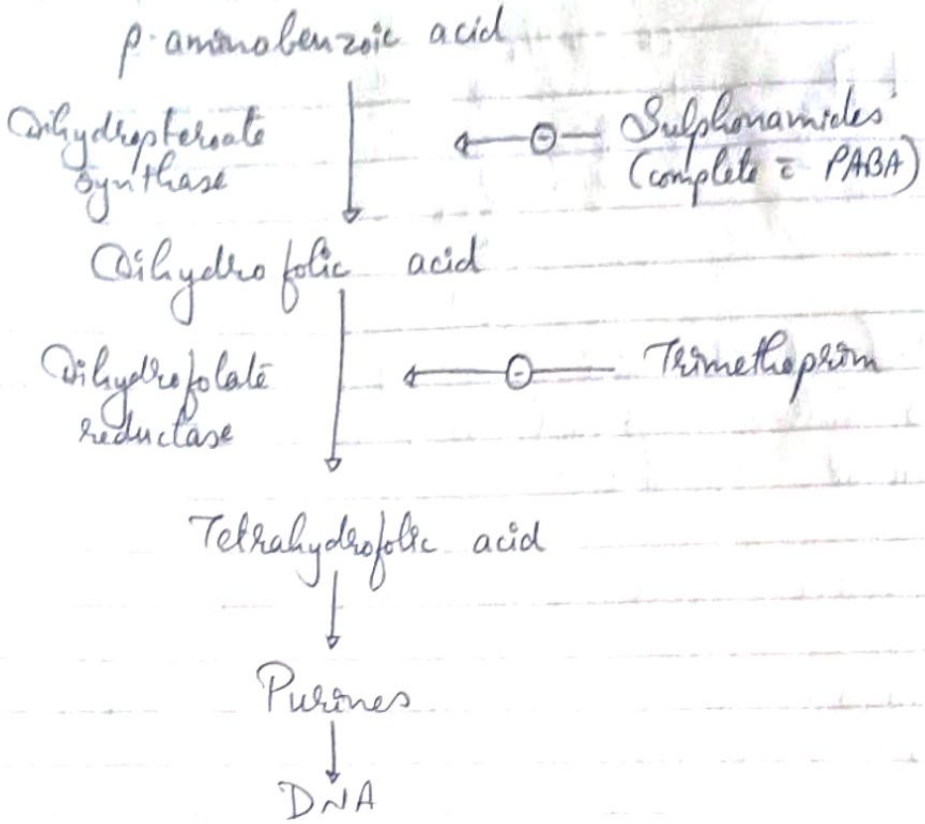
Trimethoprim



5-(3,4,5-trimethoxybenzyl) pyrimidin-2,4-diamine

Trimethoprim is selective inhibitor of bacterial DHFR Individually they both are bacteriostatic but the combination is bactericidal

Mechanism of action:



- Sequential Blocking of purine Synthesis (Synergism)
- Trimethoprim inhibits dihydrofolate reductase enzyme so inhibits tetrahydrofolic ā Synthesis.

Therapeutic uses:

- Acute or complicated or recurrent UTI especially in females
- Upper respiratory tract infections.
- Pneumocystis jiroveci pneumonia
- Toxoplasmosis
- Shigellosis
- Nocardiosis
- Typhoid fever
- Salmonella infections
- Prostatitis
- Community acquired bacterial pneumonia

Side effects:

- Megaloblastic anemia, leukopenia & granulocytopenia
- All side effects of sulfonamides

TETRACYCLINES

Tetracyclines are octahydronaphthacene derivatives & are bacteriostatic and broad spectrum antibiotics that kills certain infection causing microorganisms and are used to treat wide variety of infections.

Tetracyclines are introduced 50 yrs 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 & -ve bacteria

They are mainly designed for oral route but parenteral & topical forms are available

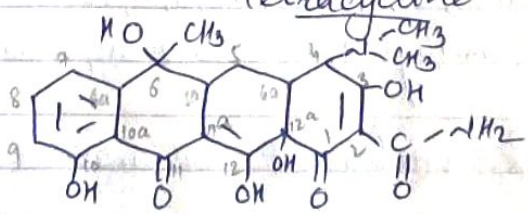
In 1945, Chlortetracyclone (prototype) of tetracyclone was discovered by Dr. Benjamin, M. Duggar under the guidance of Yellapragada Subba Rao.

Classification:

I According to duration of action

a) Short-acting (6-8 hrs half-life)
Eg: Tetracyclone ☆
Chlortetracyclone
Oxytetracyclone

☆ Tetracyclone



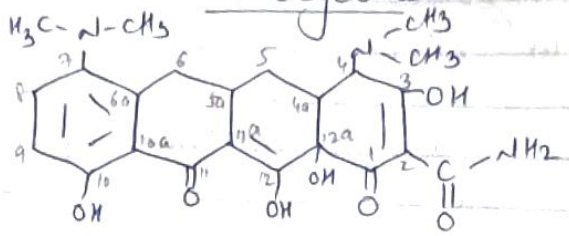
4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacene carboxamide

b) Intermediate acting (upto 12 hrs half life)
Eg: Methacycline
Demeclocycline

c) Long acting (more than 16 hrs half life)
Eg: Monocycline ☆
Doxycycline
Tigecycline

☆

Monocycline



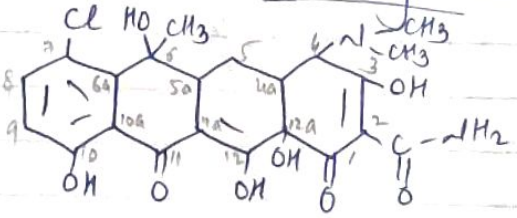
4,7-bis (dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide

II Based on Source

a) Natural tetracyclines
Eg: Chlortetracycline ☆
Tetracycline
Oxytetracycline

☆

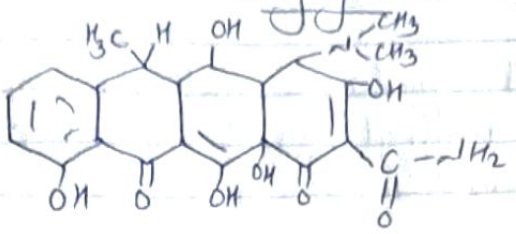
Chlortetracycline



7-chloro-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

b) Semisynthetic with unchanged carboxamide
Eg: Doxycycline ☆
Monocycline
Methacycline

Doxycycline



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

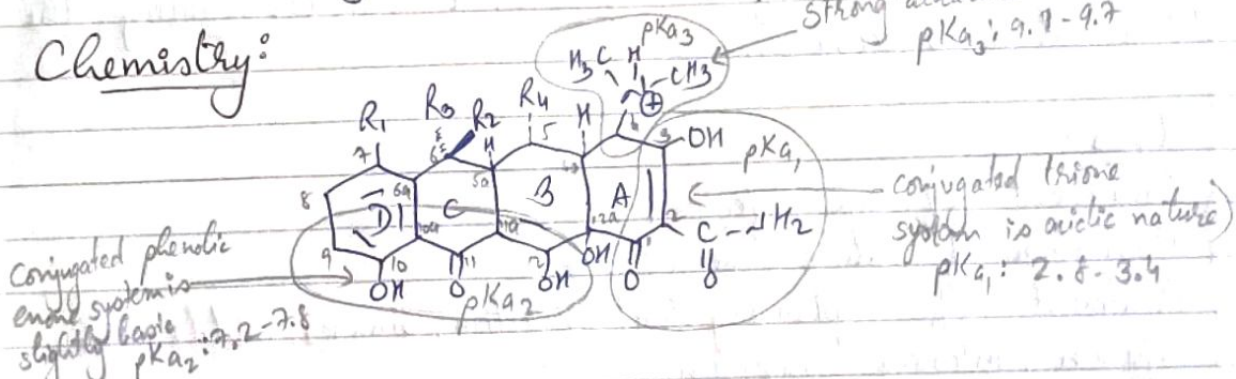
c) Latent form - Latentiation by various ways

(i) by a Manich reaction at amide functions - Apicycline, Clomycline
Eg: Rolitetracycline

(ii) by formation of salt
Eg: Tetracycline lactate, tetracycline phosphate, Tetracycline Lauryl Sulphate

(iii) by molecular association
Eg: Etamocycline
Penimocycline

Chemistry:



	pKa1	pKa2	pKa3
Tetracycline	3.3	7.7	9.5
Chlortetracycline	3.3	7.4	9.3
Oxytetracycline	3.3	7.3	9.1
Minocycline	2.8	7.8	9.3
Doxycycline	3.4	7.7	9.7

Mechanism of action:

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

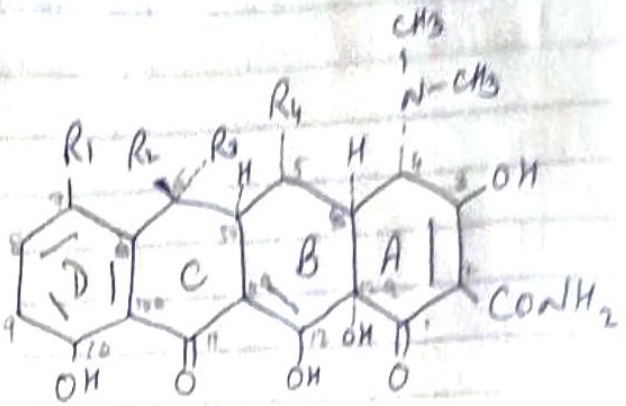
Uses:

- Treatment of eye infections
- Prevention of cancer recurrence
- Treatment of respiratory tract infection, sinuses, middle ear infection, intestine infection
- Gonorrhoea

Side effects:

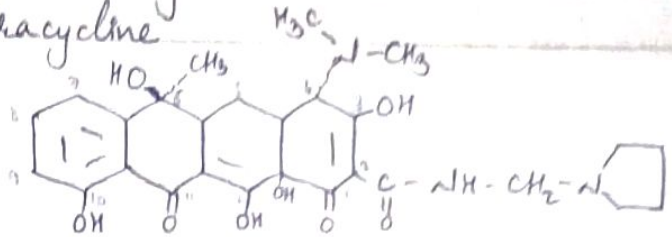
- Mild nausea, vomiting, diarrhoea
- White patches or sore inside mouth or lips
- Swollen tongue, trouble swallowing
- Vaginal itching or discharge
- Loss of apetite, jaundice

SAR OF TETRACYCLINES



- At 1st position
  Any modification at C_1 results in no bacterial activity.

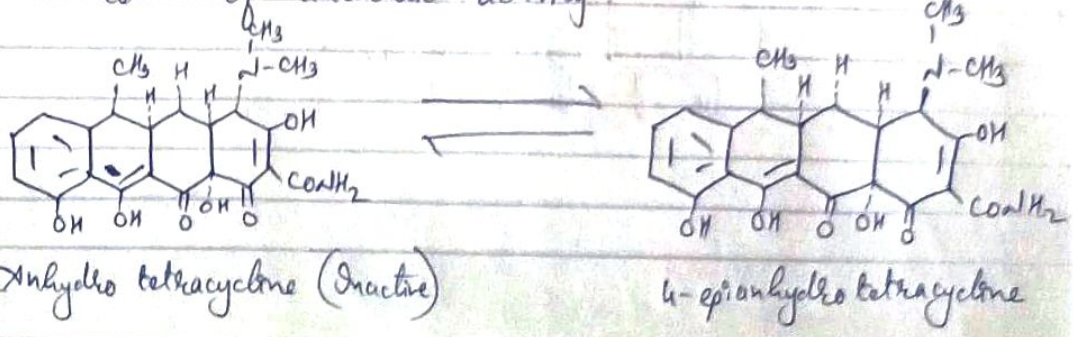
- At 2nd position
  Amide conversion to nitriles causes a 20 fold increase in activity.
  Eg: Rolitetracycline



- The keto-enol tautomerism b/w C_2 & C_3 are very important for biological activity.

- At 3rd position
  Any modification at C_3 position leads to loss of activity.

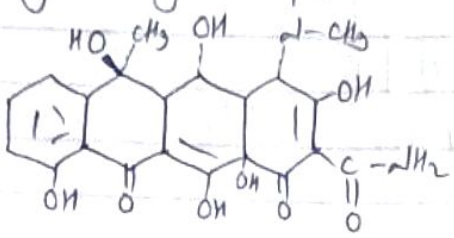
- At 4th position
  Epimerisation at C_4 and dehydration at 5a results into loss of antibiotic activity.



Anhydro tetracycline (Inactive)

4-epianhydro tetracycline

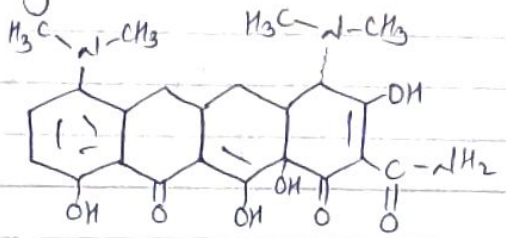
- At 5th position
Substitution with hydroxy group at R_4 produce water soluble derivatives which can be easily administered orally
Eg. Oxytetracycline



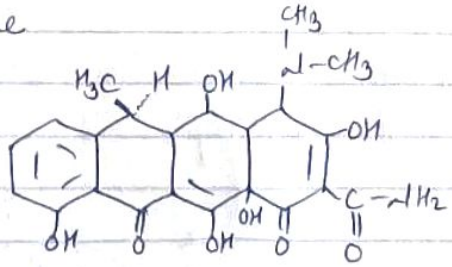
- At Loss of H from 5a leads to inactive degradation product.

- At 6th position
At R_3, ($=CH_2$) methylene group increases the antibacterial activity
Eg. Methacycline

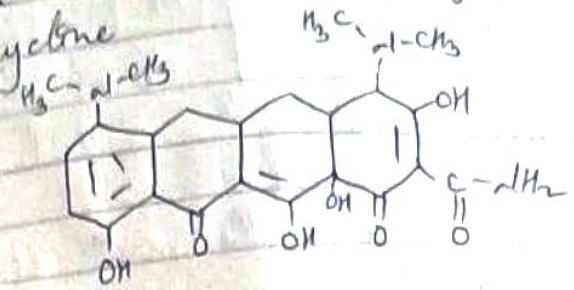
Removal of OH, CH_3 or both give more stable compound and increases lipophilicity.
Eg. Minocycline



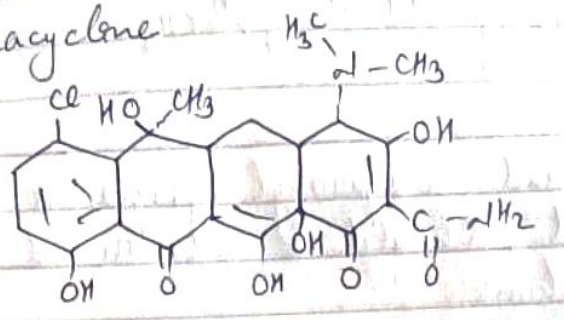
Elimination of 6-hydroxy group of (R_2) increases lipophilicity and more stable to acids
Eg. Doxycycline



At 7th position
Addition of dimethyl amino groups at R_1 position increases the antibiotic activity.
Eg: Mino cycline

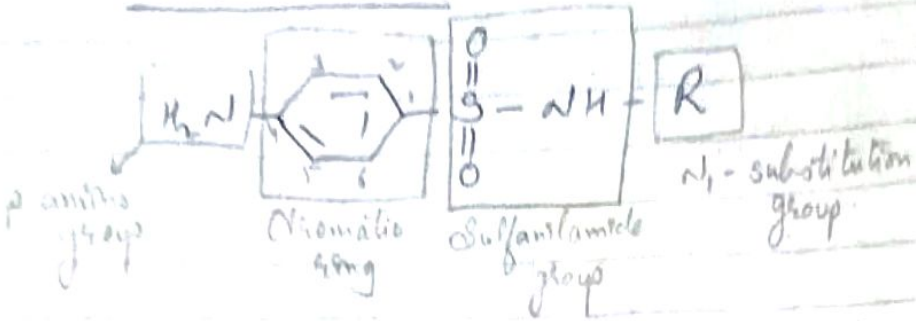


Introduction of electron withdrawing group (Cl, Br, NO_2) at C_7 position increases antibacterial activity
Eg: Chlortetracycline

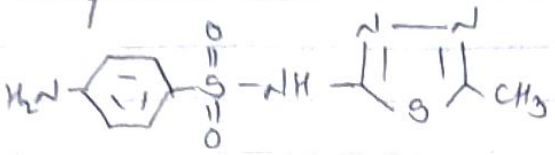


- Ring 'D' should always be aromatic, any changes on this ring leads to biological inactivation of molecule
- At 9th position
Additional glycyl amino substitution at 9th position lead to new class of antibiotics ie glycylcyclines
Addition of Cl & CH_3 leads to decreased activity
Eg: Tigecycline (Tygacil).
- Unisolated zone is essential for antibiotic activity.
- The linearly fused tetracycline nucleus is most important for antibiotic activity.

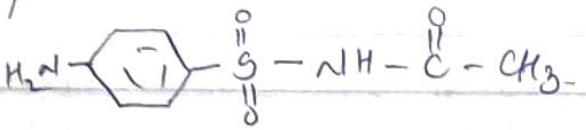
SAR OF SULPHONAMIDE



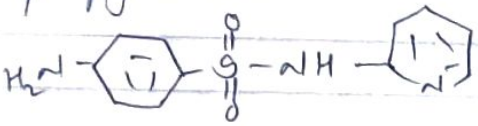
- Sulphanilamide skeleton is the minm structural requirement for antibacterial activity.
  Eg. Sulphamethizole



- The amino and sulphonyl groups on benzene ring are essential and should be in 1 and 4 position.
  Eg Sulphacetamide



- Replacement of aromatic ring by other ring systems or introduction of additional substituents on it decreases or abolish activity.
- Exchange of the $-SO_2NH$ group by $-CO-NH$ reduce the activity.
- Substitution of aromatic heterocyclic nuclei at N1 - yields highly potent compounds.
  Eg Sulphapyridine



- N1-disubstitution in general leads to inactive.
- The free aromatic amino groups should reside para to sulphonamide group. Its replacement at ortho or meta position results in compounds lacking of antibacterial activity.