MEDICINAL CHEMISTRY -III[rd]

MOST IMPORTANT QUESTIONS

2 MARKS

1. Define & classify Antibiotics
2. Define & Classify β-lactam Antibiotics
3. Write the β-lactamase inhibitors
4. Draw the structure of :—
   - Penicillin
   - Benzyl penicillin
   - Cephalosporins
   - Chlortetracycline
   - Monobactams
   - Sulbactam
5. Draw two chemical structure related with Aminoglycosides.
   - Streptomycin
   - Neomycin

   — structure & uses.
6. MOA of Aminoglycosides (also its uses).
7. Moa of Tetracyclines
8. Write structure (any one) & moa of macrolides..

(9) Write structure & uses of
- Clindamycin
- Chloramphenicol

(10) Define prodrugs and its example. (1,2.. applications..)

(11) Define & classify Antimalarial drugs

(12) Synthesis of chloroquine & its structure
(13) Synthesis of pamaquine & its structure
} Quinolines

(14) Give the example of biguanides & dihydrotriazines with chemical structure

(15) Name the organisms which cause malaria, mention diff-2 steps/mechanism by which malaria can be avoided.

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(16) Define & classify Anti-tubercular agents
first line, second line
antitubercular antibiotics
Define

(17) Structure & MOA of
- Isoniazide
- PAS
- Pyrazinamide
- Rifampicin

also (III)

(18) Define & classify urinary tract anti-infective agents.

(19) Write structure & MOA of Ciprofloxacin.. alternate Ofloxacin

(20) MOA & uses of Nitrofurantoin. (alternate to furazolidine.)

(21) Define & classify Antiviral agents (life cycle of virus in short)

(22) MOA & uses of Saquinavir, Acyclovir, Zidovudine

(23) Define & classify Antifungal agents.

(24) Draw the chemical structure of Amphotericin-B and Nystatin

(25) MOA of antifungal agents (eg. such as Miconazole, ketoconazole, tolnaftate etc.)

(26) Define Anti-protozoal agents with eg.

(27) Define Anthelmintics with eg.

(28) write general synthesis of Sulfonamide. (examples)

(29) Write about folate reductase inhibitors

(30) MOA of trimethoprim. also its synthesis

(31) write about Dapsone

(32) Define drug design (U63 Q)

(33) Define QSAR

(34) Define Partition coefficient & Hammet's electronic parameter, Tafts steric parameter.

(35) Define Pharmacophore modeling

(36) Different technique of docking used in drug design.

(37) Define combinatorial chemistry.

(38) Different b/w structure based drug and ~~ligand~~ ligand based drug design.

1. Define & classify Antibiotics.

- These are those chemical substance which are obtained from various species of microorganism that kill or inhibits the growth of another microorganism in low concentration. (bacteria)
  (eg Penicillin

* Classification.

1. β- lactam antibiotics:- Penicillin, Cephalosporins, Monobactams.
2. Aminoglycosides:- Streptomycin, Neomycin, Kanamycin.
3. Tetracycline:- Oxytetracycline, chlortetracycline, Minocycline, Doxycycline.
4. Macrolids:- Erythromycin, clorithromycin, Azithromycin.
5. Miscellaneous:- Chlormphenical*, clindamycin.

2. Define & classify β- lactam Antibiotics.

- β- lactam is a cyclic amide with four atom (3-C & 1-N). in its ring

named as azetidione.

- β-lactam antibiotic are a class of antibiotics which contain a β-lactam ring and mainly give their action by inhibiting the cell wall synthesis of bacteria. (ig) Penicillin, Cephalosporins.

* Classification.

1. Penicillin :- Penicillin G, Penicillin V, Amoxicillin, Oxacillin, cloxacillin, Methicillin.

2. Cephalosporins :- Cefodroxil, Cephalexin, Cefaclor, Ceftprozil, Cefixime, Cefepime.

3. Monobactams :- Aztreonam.

4. Carbapenems :- Imipenem, Meropenam.

3. Write the β-lactamase inhibitors.

(3) Beta lactamase inhibitors

β-lactamases are a family of enzymes produced by many gram-positive and gram-negative bacteria that inactivates β-lactam antibiotics by opening the β-lactam rings. (↓antibacterial activities).

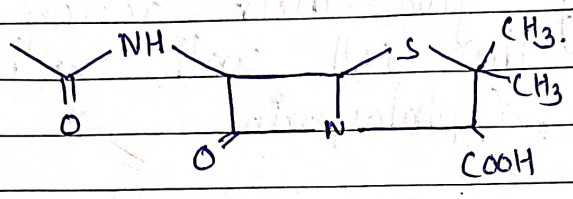
To overcome this, β-lactamase inhibitors drug discovered in 1980s which basically inactivate these beta lactamase enzyme and increases the antibacterial activity of β-lactam antibiotics

They are not used alone, they used in combination with β-lactam antibiotics.

eg.
- Clavulanic acid
- Sulbactam
- Tazobactam

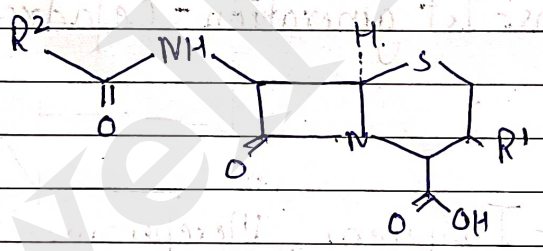
4. Draw the structures of :-

- Penicillin :-



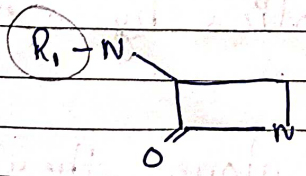
- Uses :- It is used to treat a wide variety of bacterial infections. (Pneumonia, syphilis, R. tract infection.)

- Cephalosporins -



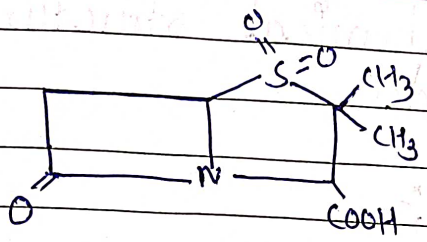
Uses :- These are used to treat bacterial infection such as respiratory tract infection and urinary tract infection.

- Monobactams :-



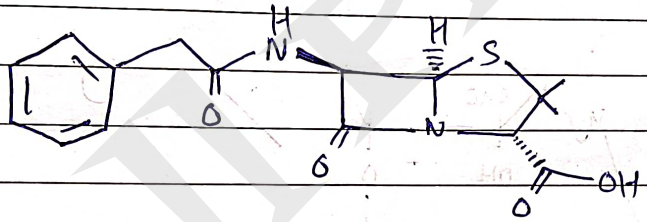
Uses :- Used in various bacterial infection treatment.

- Sulbactam :-



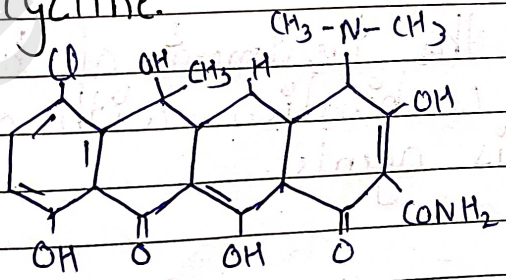
Uses :- It is used to treat severe bacterial infections most commonly pneumonia, bacteremia.

- Benzyl penicillin :-



Uses :- It is used to treat bacterial infection.

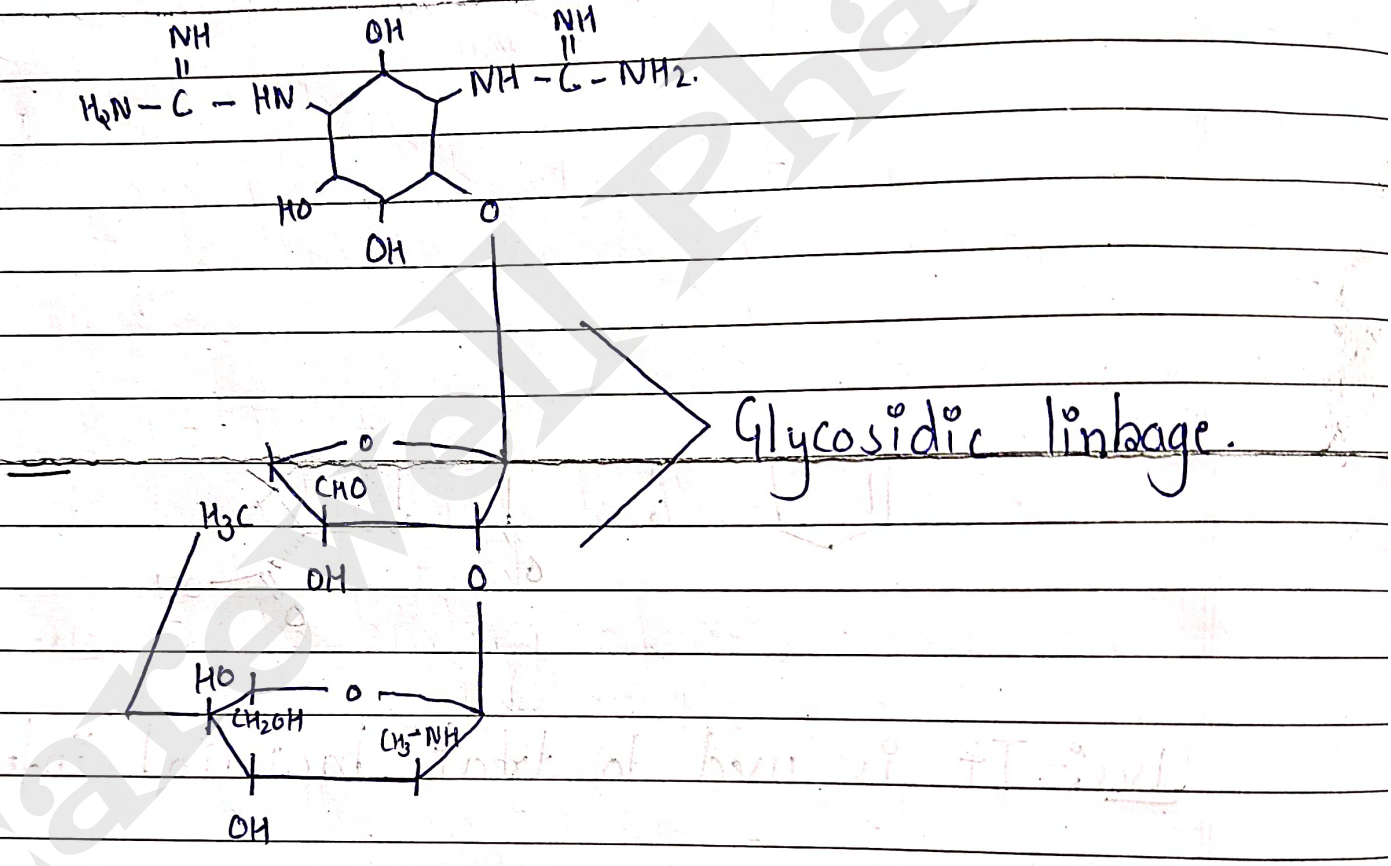
- Chlortracycline.



Uses :- Used in the treatment of infection of respiratory tract, sinuses, middle ear, intestines & Eye infection.

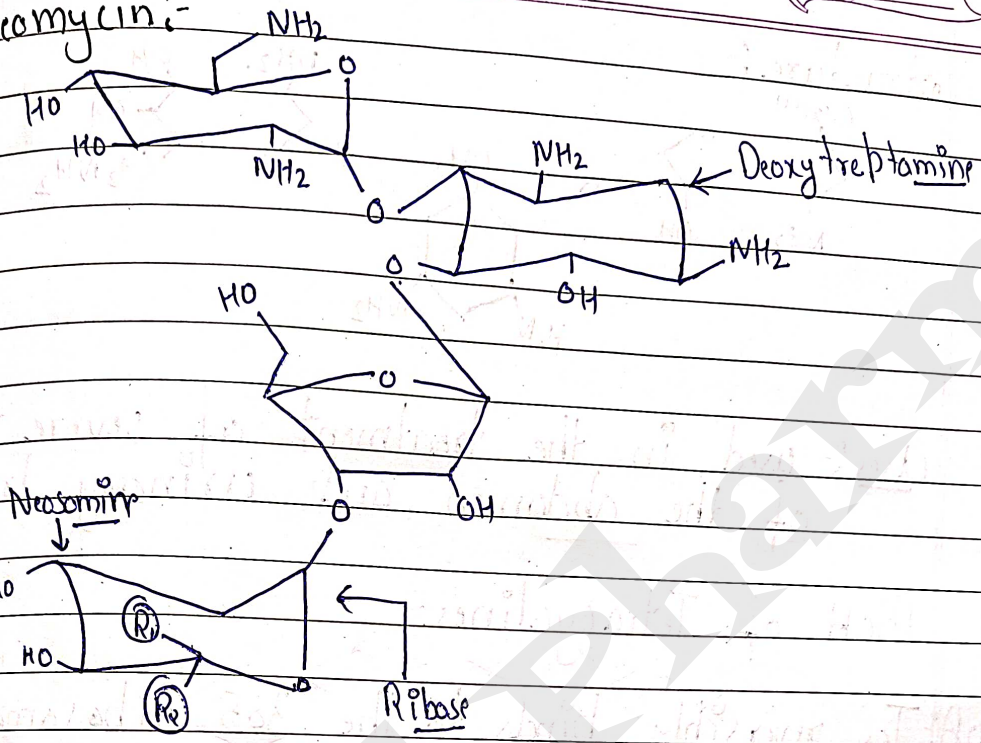
5. Draw two chemical structure related with Aminoglycosides.

(i) Streptomycin :-



Uses :- Used in the treatment of tuberculosis in the combination with other anti tuberculosis agents.

(iii) Neomycin :-

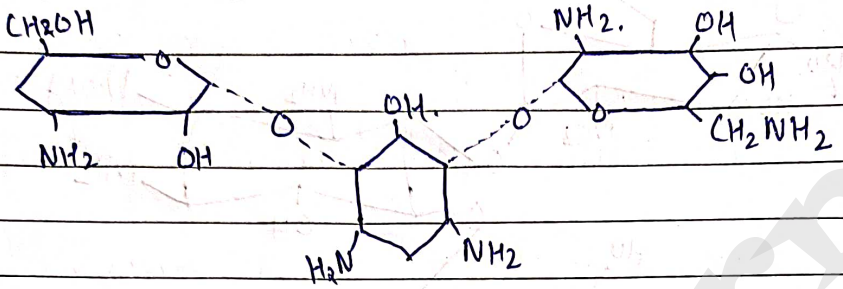


Used :- Used in the treatment of gastrointestinal infection dermatological infection.

(6) MoA of Aminoglycosides —

Penetrate into bacterial cell wall
↓
Cytoplasma through active transport proton pump.
↓
Binds to the 30S ribosomal subunit to form complex
↓
Cannot initiate proper amino acid polymerization
↓
no protein synthesis
↓
No cell wall formation.

Structure :-

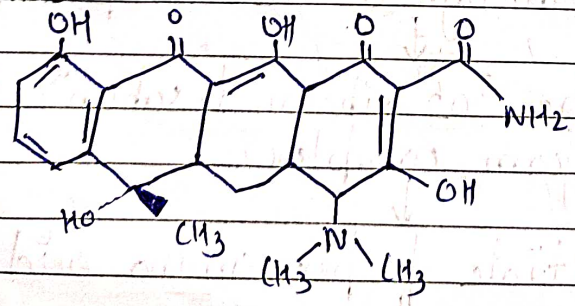


Uses :- used in the treatment of severe infection of the abdomen and urinary tract.

⑦ MoA of Tetracyclines.

MoA :- Tcs reversibly binds to the 30S ribosomal subunit
↓
prevent the binding of aminoacyl and form a ribosomal complex
↓
inhibit the initiating of protein synthesis.
↓
formation of cell coall ↓

Structure :-



Uses :- Used in treatment of infection caused by gram (+ve) and gram (-ive) bacteria.

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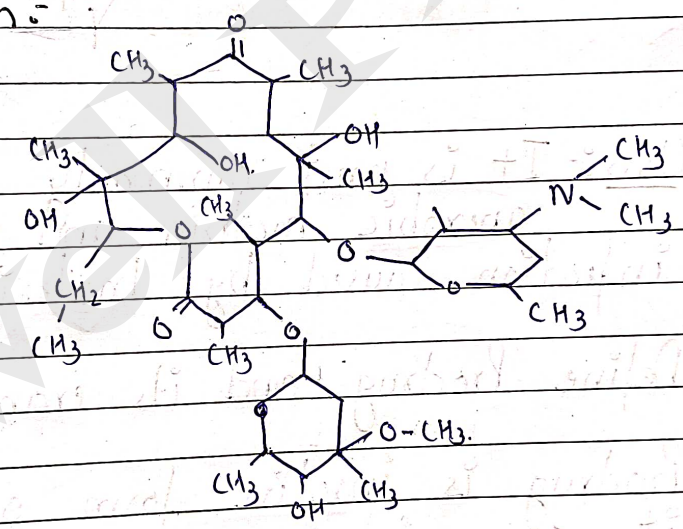
(8) Write structure & MoA of macrolids.

- MoA

Macrolides binds reversibly to the 'P' site
↓
which inhibit the translocation
↓
inhibit binding of new amino acid from tRNA
↓
Resulting in inhibit the growth of bacteria.

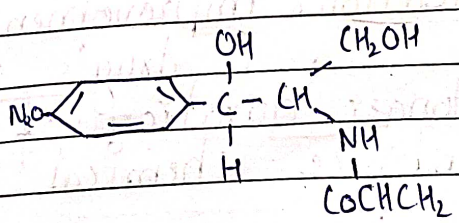
(i) Erythromycin:-



Uses:- used in treatment of Respiratory tract infection.
- used to treat gonorrhea & syphilis.

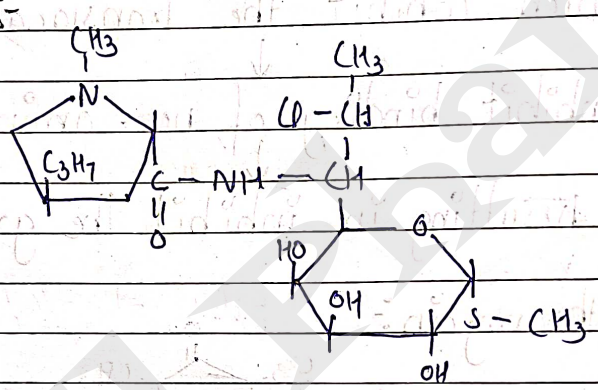
(9) Write structure & used of

- Chloramphenicol-



Uses:- used in treatment of menigitis and also in urinary tract infection.
- It is effective against Richetsia and also against H. pylori for peptic ulcer.

(iii) Clindamycin:-



Uses:- It is most commonly used in anerobic bacteria and treat serious infection caused by bacteria.

(10) Define Prodrug and its example?

Prodrug is inactive form of drug when it goes into our biological system and after biological and chemical change it is converted into active form and shows biological action.
(eg) Aspirin → Salicylic acid.

Application:- improvement of bioavailability & drug's solubility.
- for longer duration of action.
- to inhance chemical stability.

(11) Define & classify Antimalarial drugs.

- Antimalarial drug :- These are those agent / drug which are basically used in the treatment of malaria.
- Malaria :- It is one of the most wide spread disease caused by a plasmodium parasite.
- The parasite is transmitted to humans through the bites of female anopheles mosquitoes or infected mosquitos.

Classification

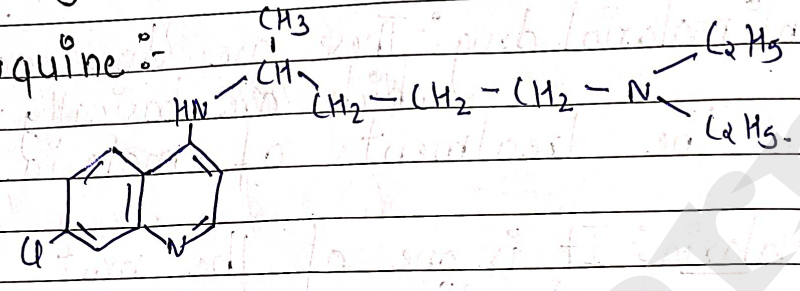
1. Quinolines :-
   - Cinchona alkaloids - Quinine sulphate
   - 4 aminoquinoline - Chlorquine, Amadiaquine
   - 8-aminoquinoline - Primaquine, Pamaquine.
   - 9-aminoacridine - Quinacrine HCl.

2. Biguanides & dihydrotriazines.
   - Cycloguanil pamoate.
   - Proguanil.

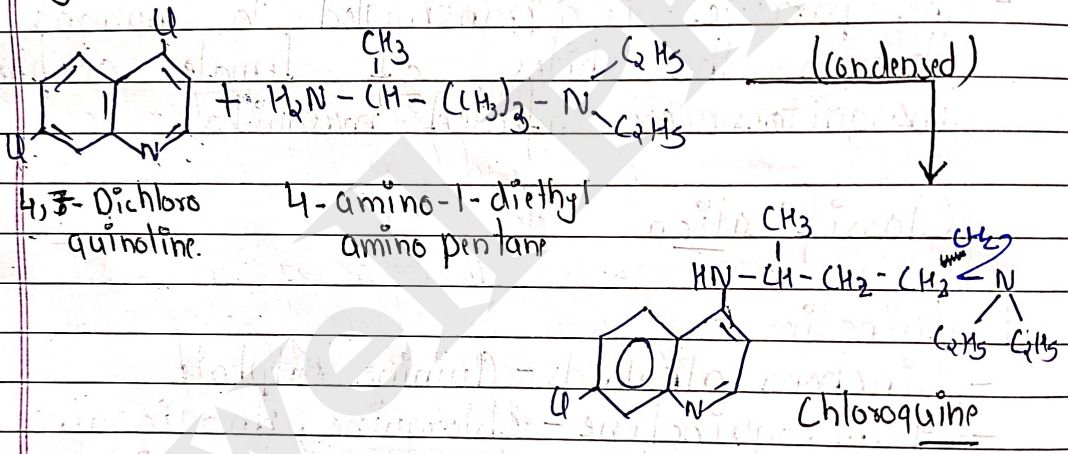
3. Miscellaneous.
   - Pyrimethamine
   - Artesunate
   - Artemether
   - Atovaquone.

(12) Write synthesis of chloroquine & its structure.

- Chloroquine :-

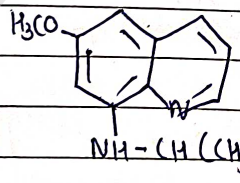


Synthesis :-



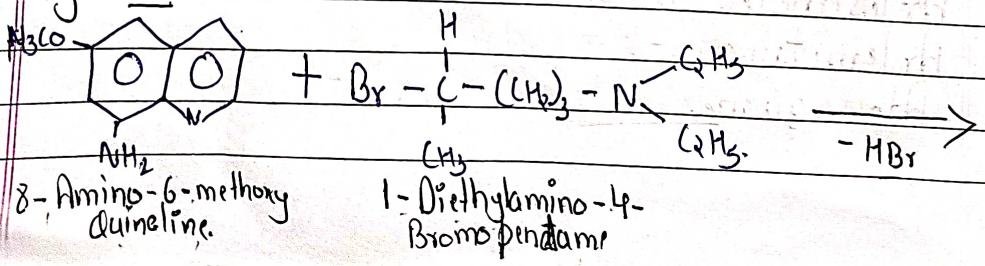
(13) Write synthesis of pamaquine & its structure.

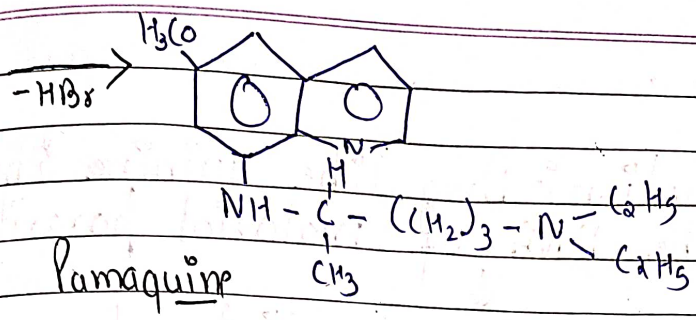
- Pamaquine -



$NH-CH(CH_3)-(CH_2)_3-N(C_2H_5)_2$

Synthesis :-



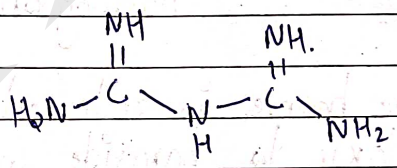


Pamaquine

(14) Give the example of biguamides & dihydrotriazine with chemical structure.

Biguamides :- Biguamide are the derivatives of Guamidine

eg :-



Biguanide

Uses :- It is used for suppression of malaria.

(15) Name the organisms which cause malaria, mention diff-2 steps / mechanism by which malaria can be avoided.

- Malaria is mainly caused by the bite of female anopheles mosquitos or infected mosquitos.

(16) Define & classify Anti-tubercular agents.

- Anti-tubercular agents - These are those drugs which are basically used in the treatment of tuberculosis (TB)

Tuberculosis :- It is a infectious disease usually caused by Mycobacterium tuberculosis bacteria. which attack on lungs. They also damage other parts of body such as brain, kidney etc....

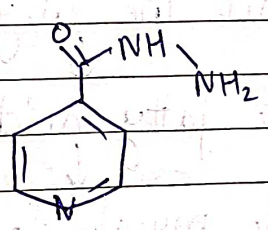
Classification :-

1. First line drugs :- Isoniazide, Rifampicin, Pyrazinamide, Ethambutol.

2. Second line drugs :- Para-aminosalicyclic acid (PAS), Ethionamides, Kanamycin. Cycloserine, Rifabutin.

(7) Write structure & MoA of.

- Isoniazide :-
-also known as Isonicotinic acid hydrazide (INH).



MoA :- Drugs like isoniazides activated and bind with some enzyme (enoyl-acyl carrier protein reductase)

↓

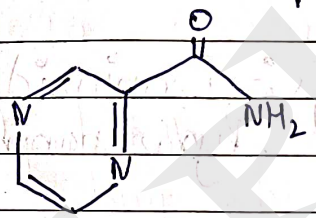
↓ mycolic acid synthesis.

↓

↓ Cell wall synthesis.

Uses:- commonly used in the treatment of tuberculosis.
- used to treat both latent & active tuberculosis infection.

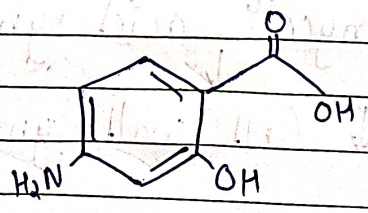
(ii) Pyrazinamide:- It is synthetic amide derivatives with bactericidal property.



MoA:- Pyrazinamide drug activated by enzyme Pyrazinamidase and convert into Pyrazinoic acid
↓
inhibit the enzyme fatty acid synthase-I
↓
↓ fatty acid & mycolic acid synthesis
↓
↓ mycobacterial growth.

Uses:- Used to treat tuberculosis along with isoniazide & rifampicin.

(iii) Paraminosalicylic acid:- It is an aminobenzoic acid.
PAS



MoA:- Pteridine + PABA (PAS)
↓ synthase
Dihydropteroic acid
↓ dihydrofolate synthase
dihydrofolic acid
↓
Tetrahydrofolic acid
↓ folic acid synthesis
DNA & RNA synthesis.
↓
↓ bacteria growth & reproduction.

Uses:- Used in the treatment of TB
- also used in the treatment of Inflammatory bowel disease.

(iv) Rifampicin:- These drugs are antibiotics.

MoA:- It binds to DNA dependent RNA polymerase
↓
↓ RNA synthesis
↓
Cell death

Uses:- used as antibacterial
- used in treatment of TB in combination.

(18) Define & classify urinary tract anti-infective agents.

- UTIs :- It is an infection that affects the urinary tract and its parts i.e kidney, bladder and urethra., ureters.
- It is mainly caused by Escherichia coli and most common in women than men (8:1).

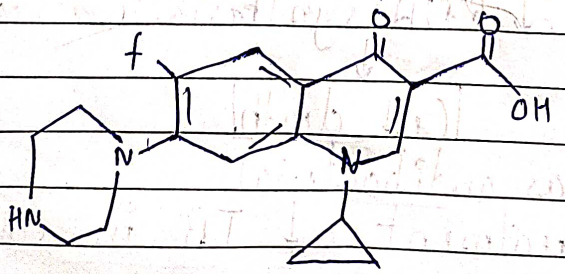
Anti infective Agents :- These are those agents or drug which are used in the treatment of urinary-tract infection (UTIs).

* Classification :-

1. Quinolones :- Nalidixic acid, Enoxacin, Ciprofloxacin, ~~of~~ ofloxacin, Lomefloxach, Sparfloxacin, Gatifloxacin, Moxifloxacin.
2. Miscellaneous :- furazolidine, Nitrofurantoin, Methanamine.

(19) Write structure & MOA of Ciprofloxacin.

- Ciprofloxacin :- It is a broad spectrum antibiotics of the flouroquinolone class.

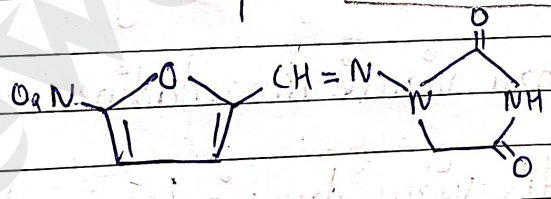


MoA :- Drug bind with DNA gyrase (Topoisomerase - II)
↓
inhibit synthesis of protein by inhibiting formation of single strands DNA & mRNA.
↓
Bactericidal (cell death).

Uses :- used to treat mild to moderate urinary and respiratory tract infection.
- Effective against E. coli.

(20) MoA & uses of Nitrofurantoin.

- Nitrofurantoin :- It is synthetic derivatives of imidazolidinedione.



MoA :- Nitrofurantoin inhibits the bacterial DNA, RNA, protein and cell wall synthesis.
↓
inhibition of bacterial growth / cell death.

Uses :- Used in treatment of UTI caused by E-coli, enterococci, staphylococcus etc

(21) Define & classify Antiviral agents.

- Anti-viral agents:- These are those agents / drugs which are used in the treatment of viral infection.

Virus:- Viruses are the obligates parasites which are multiply only inside host cells.
- Only visible in ultra microscope or electron microscope.

Classification:-

1. Anti-herpes virus drugs:- Idoxuridine, Acyclovir, Gancyclovir.
2. Anti-influenza virus:- Amantadine, Rimantadine.
3. Anti-hepatitis virus drugs:- Lamivudine, Ribavirin
4. Nucleoside Reverse Transcriptase inhibitor (NRTIs):- Zidovudine, Didanasine, Lamivudine
5. Non-nucleoside Reverse Transcriptase inhibitor (NNRTIs):- Delavirdine
6. Protease inhibitor (PI,):- Rifanavir

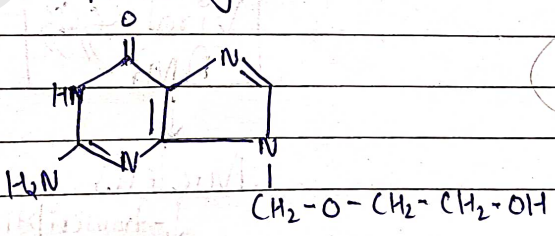
(22) MoA & uses of Saquinavir, Acyclovir, Zidovudine.

- Saquinavir :- It acts as an analog of an HIV protease cleavage site.

MoA :- It inhibit the HIV viral protease enzyme
↓
prevent cleavage of gag-pol polyprotein.
↓
Results in non-infection.

Uses :- It is used along with antiretroviral nucleoside analogues in the treatment of HIV.

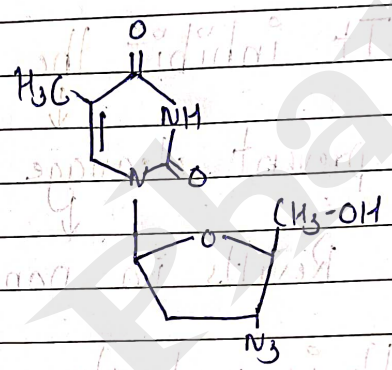
- Acyclovir :- It is prodrug.



MoA :-
Acyclovir drug bind with enzyme & activated the Acyclovir Monophosphate
↓
with the help of enzyme convert into Acyclovir triphosphate
↓
inhibit viral DNA polymerase.
↓
↓ Replication & grow of virus.

Uses :- active against herps simplex viruses.
- used in the treatment of varicella-zoster infection.

- Zidovudine :- It is also known as Azidothymidine.



MoA :-

Viral RNA SS ← Zidovudine.

Reverse transcriptase ⊖

↓

Viral DNA

↓

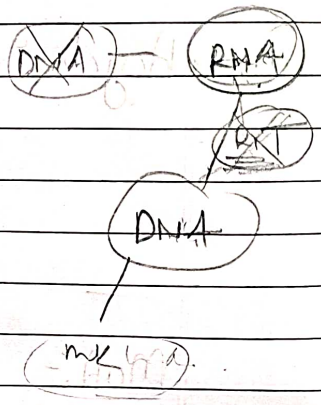
Nucleus

↓ - transcription.

RNA (mRNA)

↓

protein.



Uses :-
- Used in HIV treatment & AIDs.
- also used as anti-infective agents, antimetabolites, antineoplastic...

(23)

→ **Antifungal agents →**

These are those agents which are used in the treatment of fungal infection (mycoses) that may be superficial or may cause deep infection.

- fungal infection may be caused due to yeasts, molds, rusts and mushrooms.. eg. Candida albicans

(eg. Amphotericin B, Ketoconazole, fluconazole etc –

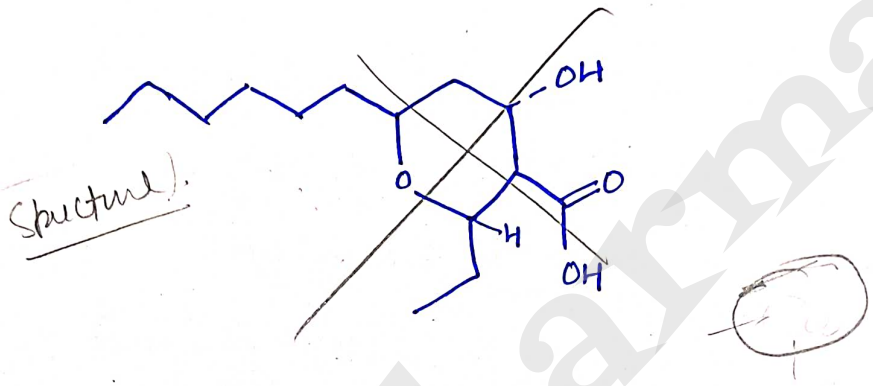
classification →

Antifungal antibiotics	Synthetic Antifungal agents		
• Amphotericin-B	• Cotrimazole	• Tioconazole	• Tolnaftate*
• Nystatin	• Econazole	• Miconazole*	
• Natamycin	• Butoconazole	• Ketoconazole	
• Griseofulvin (inhibit mitosis)	• Oxiconazole	• fluconazole	

(24)

→ **Amphotericin-B →** It is a polyene antifungal antibiotics isolated in 1956 and purified from the fermentation beer of a soil culture

of the actinomycetes



Structure

- MOA → It act by binding to ergosterol, an essential components of fungal cell membrane, thereby causing depolarisation of the membrane and altering cell membrane permeability.

This leads to leakage of important intracellular, cell rupture and eventually cell death.

Nystatin →

Same structure

- Uses → It is used for the treatment of local and gastrointestinal infection caused by Candida albicans and other candida species.

(25)

→ MOA of Antifungal agents →

- fungal cell wall synthesis - Caspofungin
- Bind to fungal cell membrane
  ergosterol → Amphotericin-B, Nystatin
- Inhibition of ergosterol synthesis →
  Azoles (ketoconazole, fluconazole, miconazole)
- Inhibition of mitosis → griseofulvin..

(26)

→ Antiprotozoal agents →

These are those agents which are used to infectious disease which is caused due to protozoa.

- disease such as amebiasis, malaria, Leishmaniasis, Giardiasis etc..
- infection caused by anaerobic protozoa ~~that~~ Entamoeba histolytica..

- **Classification** →
  - Anti-amoebic drug - Tissue amoebicides, luminal amoebicides..

- Drugs for amebiasis → Metronidazole, Diloxanide, Emetine, chloroquine
- Drugs for giardiasis → Metronidazole, Nitazoxanide, furazolidine

(27)

→ Anthelmintic drug →

Anthelmintic or Antinelmintics are a group of antiparasitic drugs that expel parasitic worms (~~kistosmes~~) (helmintics) and other internal parasites from the body by either stunning or killing them and without causing damage to the host.

(large macroparasite infect GIT)

eg. Albendazole, Mebendazole etc.

(28)

→ Sulphonamide →

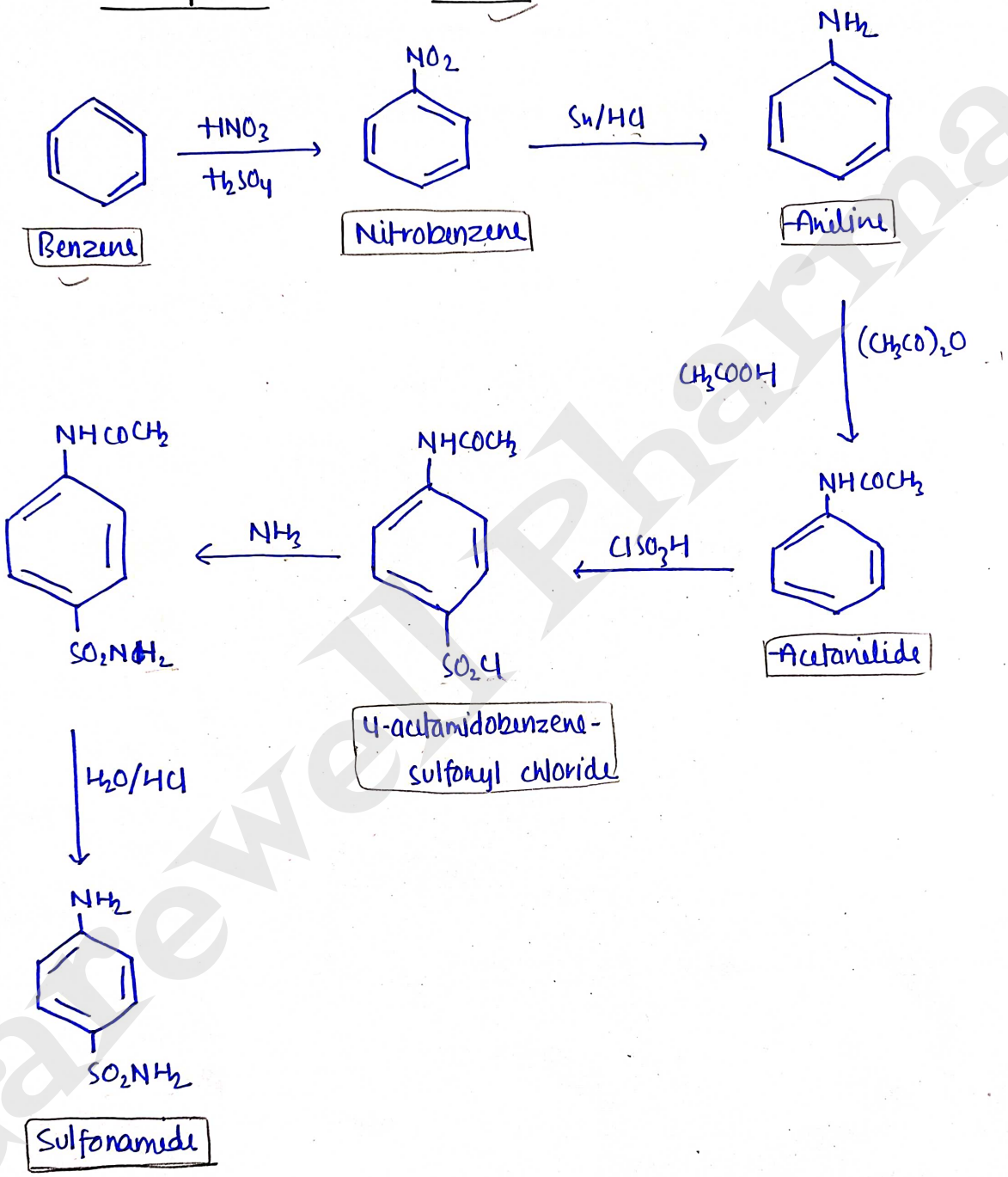
It is first antimicrobial agents which is effective against pyrogenic bacterial infection.

(producing fever)

It is primarily bacteriostatic against many gram (+) & gram (-) bacteria.

eg. Sulfamethoxazole, Sulfadiazine, etc.

- General synthesis of Sulfonamides



29

→ ~~These~~ folate Reductase Inhibitors →

These are those drugs which basically

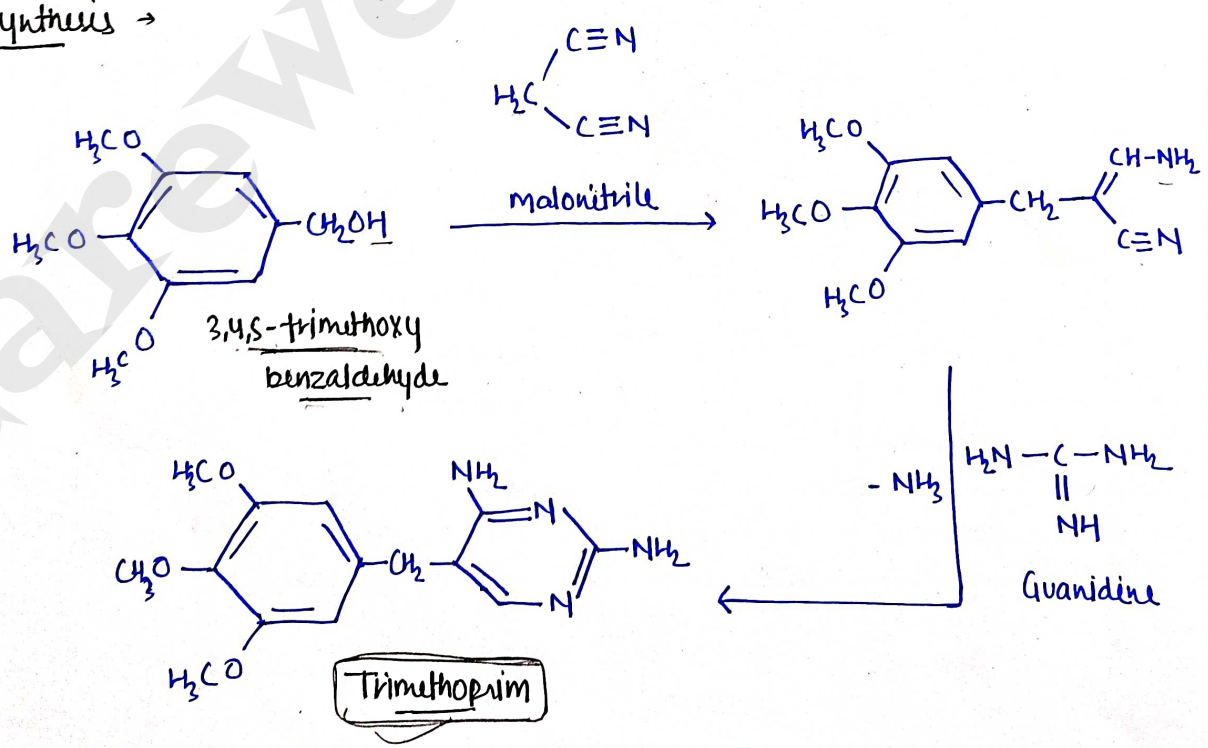
inhibit the folate synthase enzyme which is responsible for the synthesis of folic acid which further used in synthesis of DNA & RNA... (eg.) ~~Sulfonamide~~ — photo attached. trimethoprim

(30)

→ Trimethoprim →

It is an antimalarial drug which inhibits bacterial dihydrofolate reductase (DHFRase). Individually, It is bacteriostatic but in combination with sulfonamide it form cotrimoxazole which act as bactericidal.

Synthesis →



(31)

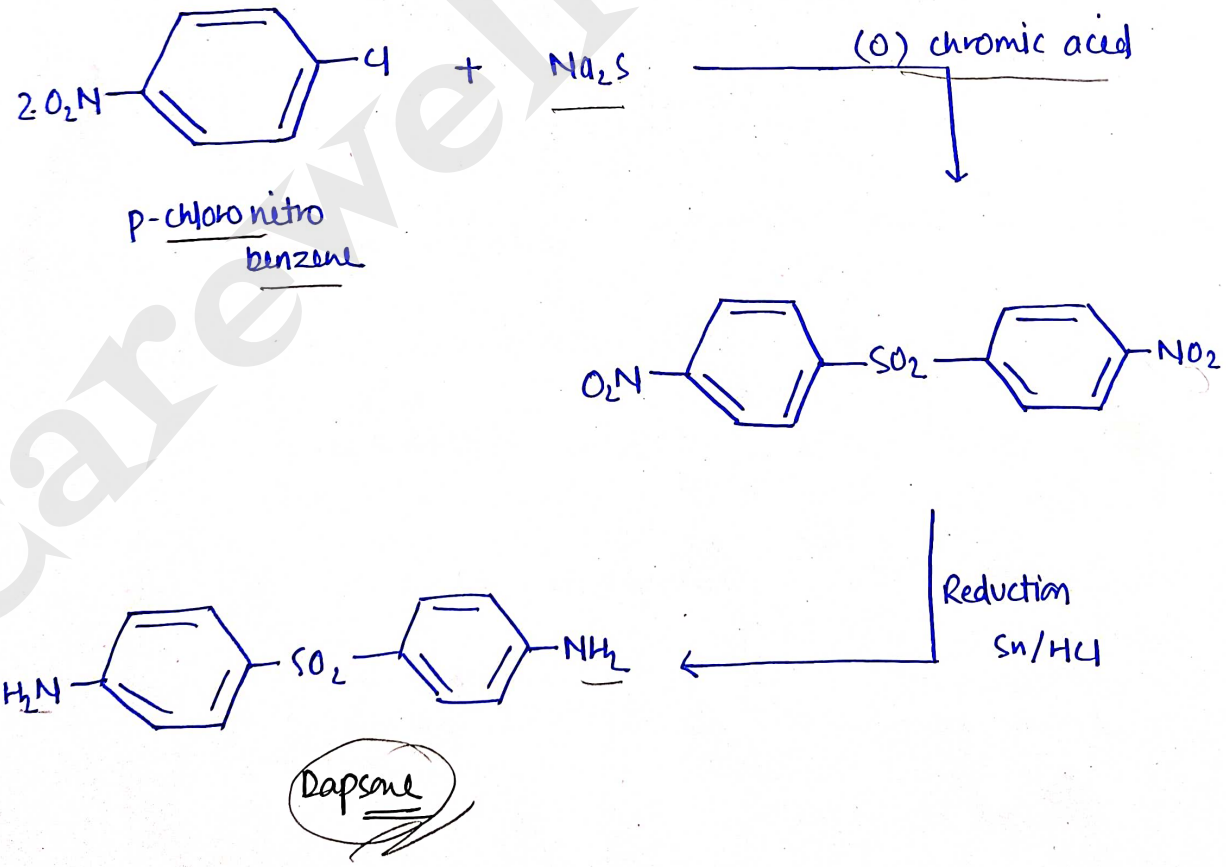
→ Dapsone →

It is a synthetic derivatives of diamino-sulphone with anti-bacterial activity (sulphonamides)

MOA → It is folic acid synthesis inhibitors

Uses → used as anti-leprotic, anti-infective and an anti-inflammatory drug

Synthesis →



(32)

→ Drug design →

It is the inventive process of finding new medicines based on the knowledge of a biological targets.

The main aim to develop a drug with high degree of chemotherapeutic index & specific action.

(33)

→ QSAR →

Quantitative Structure Activity Relationship.

- It is a mathematical relationship b/w a biological activity of a molecular system, its structure and its physiochemical properties..
- Vary in physicochemical properties affects the biological activity.

(34)

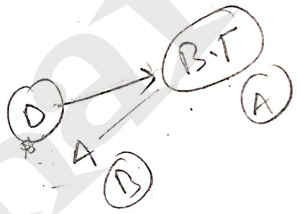
→ Partition coefficient →

$$P = \frac{\text{conc}^n \text{ of drug in n-octanol (organ}}{\text{conc}^n \text{ of drug in aq. sol}^n}$$

If $P > 1$ – hydrophobic drug / lipophilic

$P < 1$ – hydrophilic drug

- Hammet's electronic parameter →



It is an electronic parameter which measure the ionization & polarity of molecules.. (how they change biological activity.)

It used to know how easily drug can pass through the cell membrane or how strongly it can interact with a binding site.

- Used benzoic acid for eqn.
- Hammett substitution constant (σ)

$$\sigma_x = \log (K_x / K)$$

$$\sigma_x = \log K_x - \log K$$

K_x → equilibrium constant of X

K → equilibrium constant for standard Benzoic acid

where, σ_x → Hammet substitution constant for a particular substituent (X).

- Tafts steric paramter →

shape & size of drug molecules
bulky group creat hindrance

It is an steric parameter used to measure the drug-receptor interaction which reflect the change in the onset & duration of biological action.

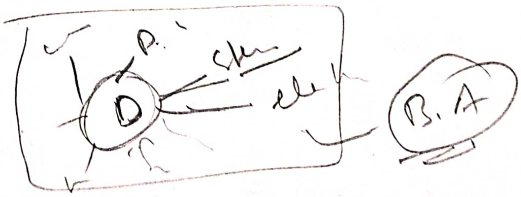
- Tafts steric paramter (E_s) measure by comparing the rate of hydrolysis of substituted aliphatic esters against a standard ester under acidic conditions.

$$E_s = \frac{\log K}{\log K_0}, \quad E_s = \log K - \log K_0$$

where,
K = rate of acid hydrolysis of substituted ester
K_0 = rate of hydrolysis of parent ester

(35)

→ Pharmacophore modeling →



It is a 3D molecular framework that carries the essential features responsible for a drug's biological activity.

" It ensemble (group) of steric & electronic features necessary to ensure the optimal supra-molecular interaction with a specific biological target & to trigger its biological responses."

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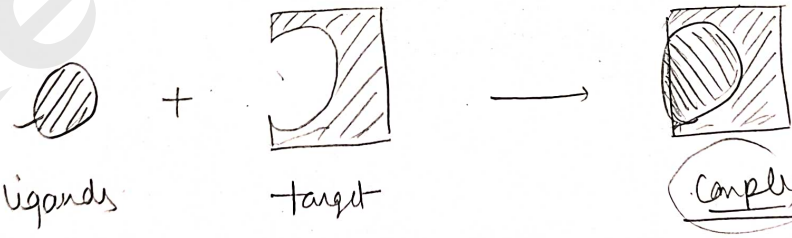
→ Molecular docking → (Docking technique)

Docking is a method which predicts preferred orientation of one ligand when bound to an active site to form a stable complex

- It is a framework to understand drug biomolecular interaction for the rational drug design & discovery



types
- Rigid docking (lock & key)
- flexible docking (Induced fit)

(37)

→ Combinatorial chemistry →

It is a new methodology by which we can simultaneously synthesized a large no. of possible compounds that could be formed from a no. of building blocks

at a same time

Normally,

$A + B \longrightarrow AB$

C·C

A_1 B_1 → A_1B_1 A_1B_2 A_1B_3 - -
A_2 B_2 - - - - - - - -
A_3 B_3 - - - - - - - -
A_4 + B_4 → A_2B_1 A_2B_2 A_2B_3 - -
A_5 B_5 - - - -
A_6 B_6 - - - - - -
⋮ | ($A_{1-n}B_{1-n}$)
A_n B_n