

BP601T Medicinal Chemistry III (Theory)

UNIT II



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Unit II 10 Hours

Antibiotics

Historical background, Nomenclature, Stereochemistry, Structure activity relationship
Chemical degradation classification and important products of the following classes

Macrolide: Erythromycin, Clarithromycin, Azithromycin.

Miscellaneous: Chloramphenicol*, Clindamycin.

Prodrugs: Basic concepts and application of prodrug design.

Antimalarials: Etiology of malaria.

Quinolines: SAR, Quinine sulphate, Chloroquine*, Amodiaquine, Primaquine phosphate, Pamaquine*, Quinacrine hydrochloride, Mefloquine.

Biguanides and dihydro triazines: Cycloguanil pamoate, Proguanil.

Miscellaneous: Pyrimethamine, Artesunate, Artemether, Atovaquone.



Macrolide Antibiotics

Introduction

- The macrolides are a class of natural products that consist of a large macrocyclic lactone ring to which one or more deoxy sugars, usually cladinose and desosamine, may be attached.
- The lactone rings are usually 14-, 15-, or 16-membered.
- Macrolides belong to the polyketide class of natural products

History

- The first macrolide discovered was erythromycin, which was first used in 1952.
- Erythromycin was widely used as a substitute to penicillin in cases where patients were allergic to penicillin or had penicillin-resistant illnesses.
- Later macrolides developed, including azithromycin and clarithromycin, stemmed from chemically modifying erythromycin; these compounds were designed to be more easily absorbed and have fewer side-effects (erythromycin caused gastrointestinal side-effects in a significant proportion of users).

Classification

MACROLIDES

- ERYTHROMYCIN
- CLARITHROMYCIN
- AZITHROMYCIN
- ROXITHROMYCIN
- SPIRAMYCIN

KETOLIDES

- TELITHROMYCIN

Mechanism of action

- Macrolides are protein synthesis inhibitors.
- The mechanism of action of macrolides is inhibition of bacterial protein biosynthesis, and they are thought to do this by preventing peptidyltransferase from adding the growing peptide attached to tRNA to the next amino acid (similarly to chloramphenicol as well as inhibiting bacterial ribosomal translation. Another potential mechanism is premature dissociation of the peptidyl-tRNA from the ribosome.
- Macrolide antibiotics do so by binding reversibly to the P site on the 50S subunit of the bacterial ribosome. This action is considered to be bacteriostatic.
- Macrolides are actively concentrated within leukocytes, and thus are transported into the site of infection.

Uses

They are used to treat infections caused by Gram-(+) bacteria (*Streptococcus pneumoniae*) and limited Gram-(-) bacteria (*Bordetella pertussis*, *Haemophilus influenzae*), and some respiratory tract and soft-tissue infections, *Legionella pneumophila*, *Mycoplasma*, *Mycobacteria*, some rickettsia, and chlamydia.

(1) Erythromycin:

It received the widest clinical acceptance amongst the macrolides. Its isolation was reported by McGuire et al in 1952 from *Streptomyces erythreus*. It is treated as a drug of choice for the treatment of variety of upper respiratory and soft - tissue infections due to gram-positive bacteria.

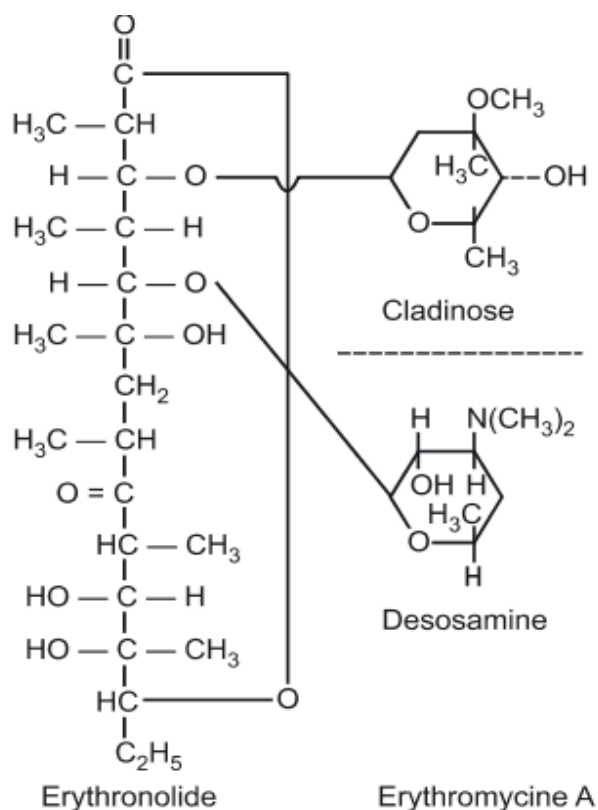
The aminosugar, desosamine is attached to C - 5 while another carbohydrate skeleton i.e. cladinose is linked glycosidically to C - 3. The large lactone structure is known as erythronolide. Two structures closely related to erythromycin have been isolated from *S. erythreus*. They are identified as Erythromycins B and C. The B analog does not possess C-12 hydroxyl group and is more stable but less active than erythromycin A. Erythromycin C lacks cladinose methoxy group and is equipotent with A. The clinical grade erythromycin contains 90% erythromycin A and about 10% erythromycin B with minute quantity of analog C.

Erythromycin is active against - *Neisseria*, *H. influenzae* and *Legionella pneumophila* but not against the Enterobacteriaceae; its activity shows pH dependence, increasing with pH upto about 8.5.

A number of derivatives are designed to improve:

1. either its water or lipid solubility necessary to develop more acceptable dosage form,
2. its acid stability to increase oral absorption, and
3. the acceptance by masking its bitter taste.

The basic nature of the dimethylamino group of the desosamine moiety was utilized to prepare its acid salts, like the lactobionate, glucoheptonate and the stearate, and esters of the 2' - hydroxyl group of the desosamine, including the ethyl carbonate, ethyl succinate and the estolate e.g. Erythromycin estolate being more acid stable, promotes high oral absorption. Due to good water solubility, lactobionate and glucoheptonate forms are used in parenterals. The 2'-esters as such do not possess antibiotic activity and hence efficacy of particular ester depends upon the *in-vivo* rate of ester hydrolysis to release the free - base.





(2) **Spiramycin and Josamycin:**

They are well established clinically in Europe and Japan and now are clinical newcomers in United States. They are mainly indicated for the gram-positive bacterial infections. Both have similar range of activity as erythromycin but are less active. Resistance develops very gradually. However cross - resistance among above four discussed members is reported.

To overcome the drawbacks of erythromycin, a number of semisynthetic macrolides have been produced of which Roxithromycin, Clarithromycin, Azithromycin are some of the examples.

(a) Roxithromycin: It is a semisynthetic long acting acid stable macrolide whose antimicrobial spectrum resembles closely with erythromycin.

(b) Azithromycin: This new azalide congener of erythromycin has an expanded spectrum, improved pharmacokinetics, better tolerability and drug interaction profiles. It is more active than other macrolides against *H. influenzae* but less active against gram positive cocci.

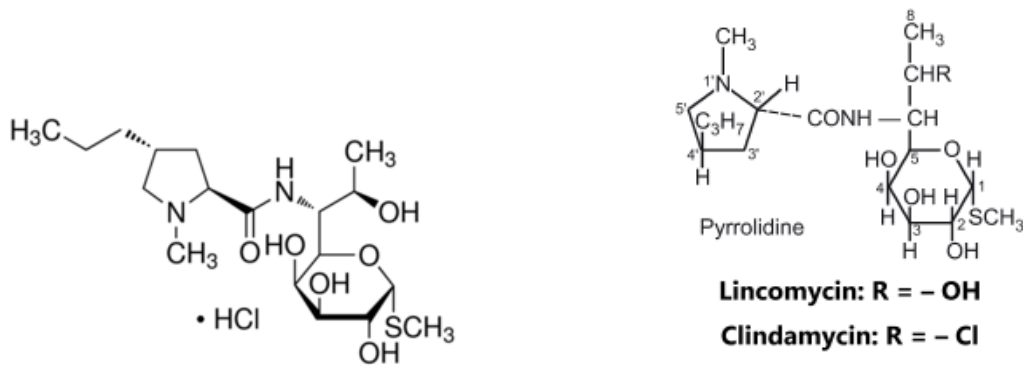
The improved pharmacokinetic properties are acid stability, rapid oral absorption, marked tissue distribution, and intracellular penetration. Due to higher efficacy, better gastric tolerance, it is now preferred over erythromycin in many infections like pneumonia, trachomatis, tonsillitis, sinusitis and pharyngitis.

(c) Clarithromycin: It is a semisynthetic macrolide antibiotic derived from erythromycin. It exerts bactericidal effect by inhibiting bacterial protein synthesis. It is used to treat throat infection, pneumonia, skin infections and *H. pylori* infection. It can also be used in combination with anti-ulcer medications to treat certain types of stomach ulcers. It should not be used to treat viruses such as common cold. Side effects include nausea, vomiting, diarrhea and stomach pain.

Lincosamycins

- Lincomycin is a lincosamide antibiotic that comes from the actinomycete *Streptomyces lincolnensis*.
- A related compound, clindamycin, is derived from lincomycin by using thionyl chloride to replace the 7-hydroxy group with a chlorine atom with inversion of chirality

Structure



Mechanism of Action

- The lincosamides inhibit protein synthesis in susceptible bacteria by binding to the 50s subunits of bacterial ribosomes.
- Thus, inhibiting peptidyltransferases, interference with the incorporation of amino acids into peptides occurs thereby.

SAR

Variation of the substituents on pyrrolidine portion and C-5 side-chain affects the activity. e.g.

- (1) N-demethylation imparts activity against gram-negative bacteria.
- (2) Increase in chain length of the propyl substituent at 4 position in pyrrolidine moiety upto n-hexyl increases in-vivo activity about 1.5 times than parent compound.
- (3) The thiomethyl ether of a-thiolincosamide moiety is essential for activity
- (4) Structural modifications at C-7, like introduction of 7S chloro or 7R- OCH₃; changes the physicochemical parameters of the drug (i.e., partition coefficient) and thus alters activity spectrum and pharmacokinetic properties. The ability of lincomycin to penetrate into bone, adds to its qualities and it gets promoted in chemotherapy of bone and joint infections by penicillin resistant strains of *Staphylococcus aureus*.

Uses

- Although similar in antibacterial spectrum and mechanism of action to macrolides, lincomycin is also effective against other organisms including actinomycetes and some species of *Mycoplasma* and *Plasmodium*.

- However, because of its adverse effects and toxicity, it is rarely used today and reserved for patients allergic to penicillin or where bacteria have developed resistance.
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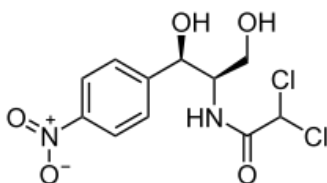
Chloramphenicol

- Chloramphenicol is an antibiotic useful for the treatment of a number of bacterial infections.
- This includes use as an eye ointment to treat conjunctivitis.
- By mouth or by injection into a vein, it is used to treat meningitis, plague, cholera, and typhoid fever.

History

- Chloramphenicol was first isolated from *Streptomyces venezuelae* in 1947 and in 1949 a team of scientists at Parke-Davis including Mildred Rebstock published their identification of the chemical structure and their synthesis, making it the first antibiotic to be made instead of extracted from a microorganism.
- In 2007, the accumulation of reports associating aplastic anemia and blood dyscrasia with chloramphenicol eye drops lead to the classification of “probable human carcinogen” according to World Health Organization criteria, based on the known published case reports and the spontaneous reports submitted to the National Registry of Drug-Induced Ocular Side Effects.

Structure



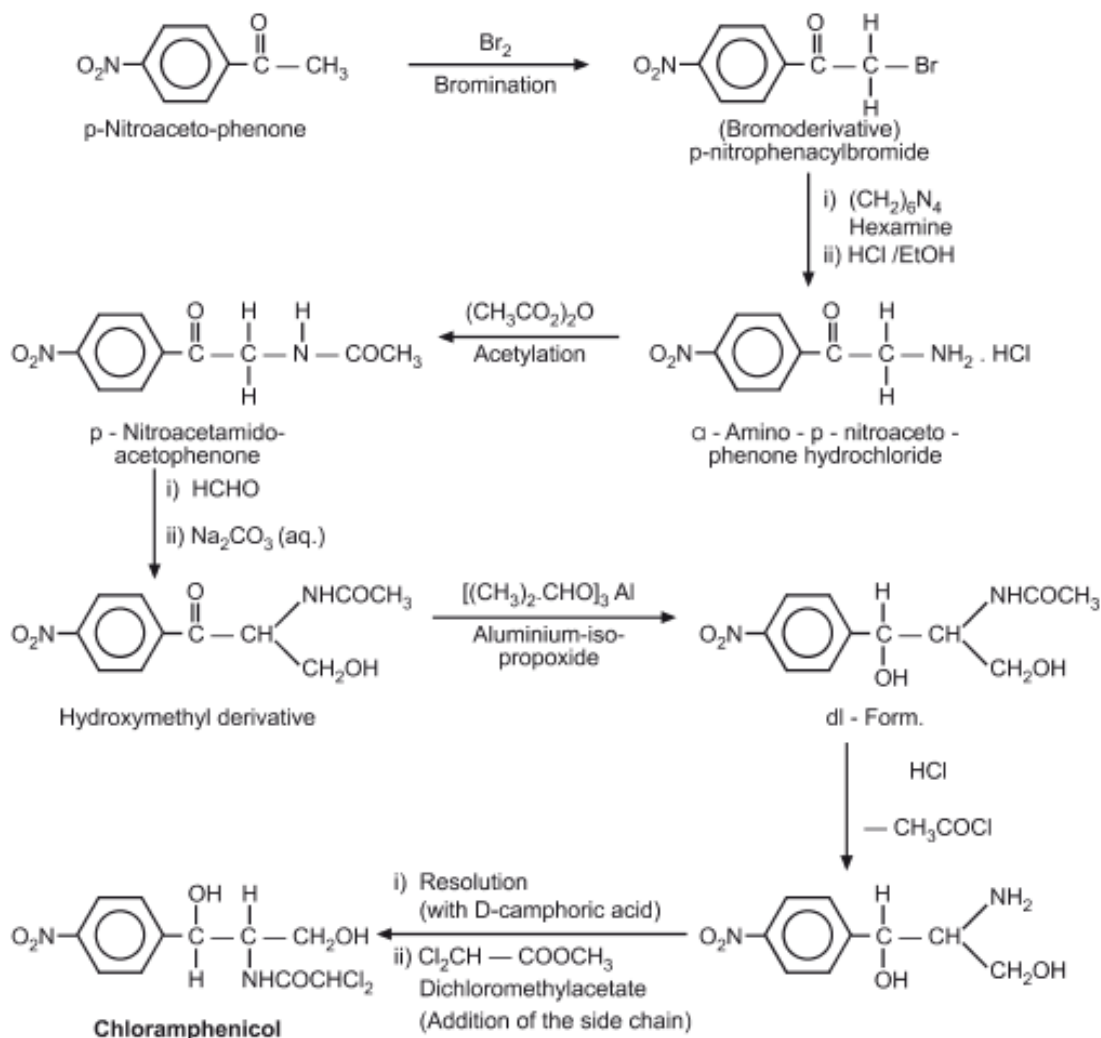
Mechanism of Action

- Chloramphenicol is a bacteriostatic by inhibiting protein synthesis.
- It prevents protein chain elongation by inhibiting the peptidyl transferase activity of the bacterial ribosome.
- It specifically binds to A2451 and A2452 residues in the 23s rRNA of the 50s ribosomal subunit, preventing peptide bond formation.
- Chloramphenicol directly interferes with substrate binding in the ribosome, as compared to macrolides, which sterically block the progression of the growing peptide.

Uses

- Chloramphenicol is an antibiotic.
- It's mainly used to treat eye infections (such as conjunctivitis) and sometimes ear infections.
- Chloramphenicol comes as eye drops or eye ointment.

Chloramphenicol



Antimalarials

Etiology

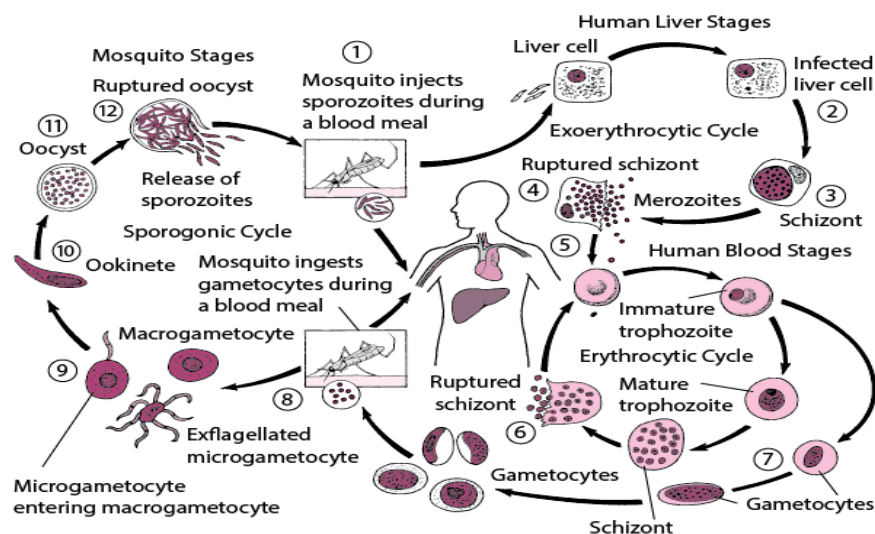
- Malaria is a mosquito born infectious disease of human and other animals caused by eukaryotic protists of the genus plasmodium.
- The disease results from the multiplication of plasmodium parasites within RBC
- Main species plasmodium falciparum (severe disease), plasmodium vivax, plasmodium ovale.

Life cycle of malaria

- Incubation period of the parasite species Incubation period (Liver cycle) P. falciparum 7-14 days P. vivax 12-17 days (with relapse up to 3 years) P. ovale 9-18 days (with relapse up to 20 years) P. malaria 13-40 days.
- The time between the fever episodes can be characteristics of the infecting plasmodium species.
- Duration of fever (erythrocytic cycle)-
 - a. P. falciparum 36-48 h, Malignant tertian malaria.
 - b. P. vivax 48h, Benign tertian malaria.
 - c. P. ovale 48h, Ovale tertian malaria.
 - d. P. malaria 72h, Quartan malaria.

Pathophysiology of malaria-

- Showers of new merozoites are released from the RBCs at intervals of approximately 48h for P.vivax, P.ovale and P.falciparum and 72h for P.malaria.
- The episodic shaking, chills, and fever coincide with this release.
- The parasites destroy large numbers of infected RBC, thereby causing a hemolytic anemia.
- A characteristic brown malaria pigment derived from hemoglobin, called hematin is released from ruptured RBCs and produces discoloration of the spleen, liver, lymph nodes and bone marrow.
- Activation of defense mechanisms in the host leads to a marked hyperplasia of mononuclear phagocytes, producing massive splenomegaly and occasional hepatomegaly.

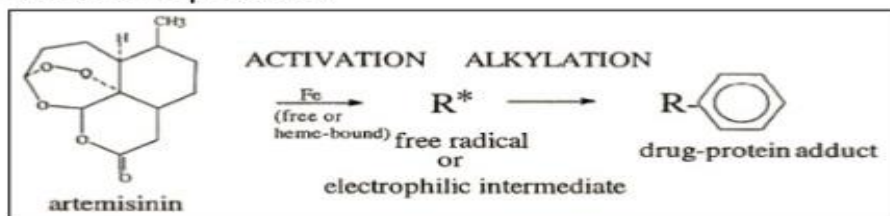


Classification

1. **4-Aminoquinolines** : Chloroquine, Amodiaquine, Piperaquine.
2. **Quinoline-methanol** : Mefloquine.
3. **Cinchona alkaloid** : Quinine, Quinidine.
4. **Biguanide** : Proguanil (Chloroguanide), Chlorproguanil.
5. **Diaminopyrimidine** : Pyrimethamine.
6. **8-Aminoquinolines** : Primaquine, Bulaquine.
7. **Sulfonamides and sulfone-**
Sulfadoxine, Sulfamethopyrazine, Dapsone.
8. **Tetracyclines** : Tetracycline, Doxycycline.
9. **Sesquiterpene lactones** : Artesunate, Artemether, Arteether.
10. **Amino alcohols** : Halofantrine, Lumefantrine.
11. **Mannich base** : Pyronaridine
12. **Naphthoquinone** : Atovaquone.

Mechanism of Action

- These compounds have presence of endoperoxide bridge
- Endoperoxide bridge interacts with heme in parasite
- Heme iron cleaves this endoperoxide bridge
- There is generation of highly reactive free radicals which damage parasite membrane by covalently binding to membrane proteins





Quinolines

Artemisinin

- **SAR Of Artemisinin**
 - a. Artemisinin serve as a lead compound for the development of new antimalarials with improved properties
 - b. The lactone group can be reduced & form dihydroartemisinin which is used to prepare semi synthetic prodrug that are more water & oil soluble
 - c. The hydroxyl group can be alkylated to give oil soluble ether derivatives such as artemether & arteether
 - d. Esterification of the hydroxyl with succinic acid gives the water soluble derivative, artesunate
 - e. 19. SAR Of Artemisinin
 - f. Studies of artemisinin analogues such as deoxyartemisinin which do not contain the endoperoxide bridge, showed vastly reduced biological activity.
 - g. Moreover, derivatisation at the carbonyl lactone demonstrated that it is a possible region of modification that can be manipulated in order to improve pharmacokinetic properties.
 - h. This was demonstrated by the semisynthetic prodrugs.
 - i. Compared to artemisinin itself, artemether, artesunate and dihydroartemisinin are more active.

Quinine & Related Compounds

- **Quinine**
 - a. The bark of the cinchona tree contains antimalarial compounds, most notably the highly fluorescent compound, quinine.
 - b. The bark of the cinchona tree, if made into an aqueous solution was able to treat most cases of malaria.
 - c. The active principle quinine was first isolated from the bark during the early 19th century.
 - d. Quinine is the compound that contributes to the bitter taste of tonic water.
- **4-aminoquinolines**
 - a. Increasing concern about cinchona supplies and the desire to find quinine alternatives with reduced side effects led to a massive search for novel antimalarials.
 - b. Chloroquine was one of the drugs successfully developed.
 - c. The drug was first used during the 1950s.
 - d. Chloroquine is effective against erythrocytic forms of the Plasmodium parasite. Like chloroquine, the drugs amodiaquine and hydroxychloroquine belong to a class of quinine analogues called 4-aminoquinolines.
 - e. Drug designed of Chloroquine as prototype drug
 - f. It consists of 4- aminoquinoline pharmacophore.
 - g. The structural analogues of chloroquine have been designed in such a way that it will show more drug likeness score than the prototype molecule but having the same pharmacophore essential for the antimalarial activity.



SAR of Quinolines

- The side chain present at 4 position of chloroquine have been modified with alteration of halogen atom in some cases at position 8 to get increased drug likeness score.
- In case of designed molecules the chlorine molecule at position 8 have been replaced by –F atom to increase the drug likeness score than the prototype molecule chloroquine.
- The position of R1 and R2 in the 4- aminoquinolone ring are modified in these designed molecules to get increased drug likeness score
- **8-aminoquinolines-**
 - a. Drugs in this group have amino group at position 8 of quinoline ring
 - b. Such drugs have OCH₃ group at position 6
 - c. Pamaquine, primaquine, and tafenoquine are antimalarial drugs that belong to a family named 8-aminoquinolines.
 - d. Pamaquine is closely related to primaquine.
 - e. Compared to primaquine, pamaquine is more toxic and less efficacious.
 - f. Tafenoquine is currently in late clinical trials.
- When side chain is introduced at amino group antimalarial activity is intensified. It causes hemolysis of RBCs Diethyl amino pentyl side chain Pamaquine
- It contains tertiary amino group and when it is converted into primary amino group the compound is called primaquine, which is – Less toxic – Well tolerated It is the most commonly used agent in this group in the treatment of malaria Primaquine
- -OCH₃ is not necessary for antimalarial activity but when replaced by OC₂H₅ the compound became – less active – Toxic in nature
- -OCH₃ when replaced by CH₃ the compound become inactive
- Introduction of halogens increases toxicity
- Presence of quinoline ring is necessary for antimalarial activity. When pyridine ring is converted to piperidine (saturated) the compound became inactive
- Pentyl side chain gives maximum activity, increase or decrease of chain result is reduction of activity.
- The branched side chain when converted into straight chain pentaquine is obtained
- It has less antimalarial activity as compared to both pamaquine and primaquine

Other Quinine Analogues

- Mefloquine is an orally administered 4- methanolquinoline drug used to prevent and treat malaria.
- Like the other drugs, the halo substituents deter Phase I metabolism (hydroxylation) of the rings and also contribute to enhanced lipophilicity.
- Halofantrine contains a phenanthrene ring. The absorption of halofantrine is enhanced when taken with fatty food.
- Lumefantrine is usually taken in combination with the artemisinin based drug, artemether.



Piperaquine-

- Resistance to chloroquine is a major problem which continues to drive the need for new antimalarials structurally similar to chloroquine.
- Resistance to the drug was first documented during the 1950s. The compound has two of the bicyclic 4-aminoquinoline group.
- Piperaquine showed excellent activity against resistant parasites. However, the use of piperaquine declined during the 1980s as a result of the emergence of resistant strains of *P. falciparum*.

Isoquine-

- One disadvantage of amodiaquine is the formation of toxic amodiaquine quinone imine (AQQI) metabolites. Isoquine as a less toxic variant of amodiaquine.
- In fact isoquine is an isomer of amodiaquine, differing only in the positions of the hydroxyl and the diethylamine. Isoquine's hydroxyl group is located in the meta position rather than the para position.
- When OH is in the meta-position, AQQI does not form.
- Isoquine has been described as a new lead compound for less toxic 4-aminoquinolines.

Fluoroamodiaquine (FAQ)-

- Fluorine is commonly used in drug design.
- Substitution with fluorine also contributes to increased lipophilicity.
- In terms of metabolism, fluorine is used to block parts of the drug that are susceptible to metabolism such as the para-position of benzene rings.
- Due to the formation of the toxic amodiaquine metabolite, a series of fluoro-substituted variants of amodiaquine designed and found the desired metabolic stability.

Medicinal Chemistry of Other Antimalarial Drugs

Pyronaridine

- Pyronaridine is an antimalarial compound exhibits high potency towards *P. falciparum* and some chloroquine-resistant strains.
- When used in combination with other antimalarials such as artesunate, the emergence of resistance appears to be slowed down considerably.
- Pyronaridine is an ideal candidate for combination therapy with artemisinins.
- Pyronaridine's core structure is similar to mepacrine (quinacrine). The drug is typically administered orally as pyronaridine tetraphosphate which appears yellowish and has a bitter taste.
- The drug can also be administered via the intramuscular or intravenous route.

Pyrimethamine

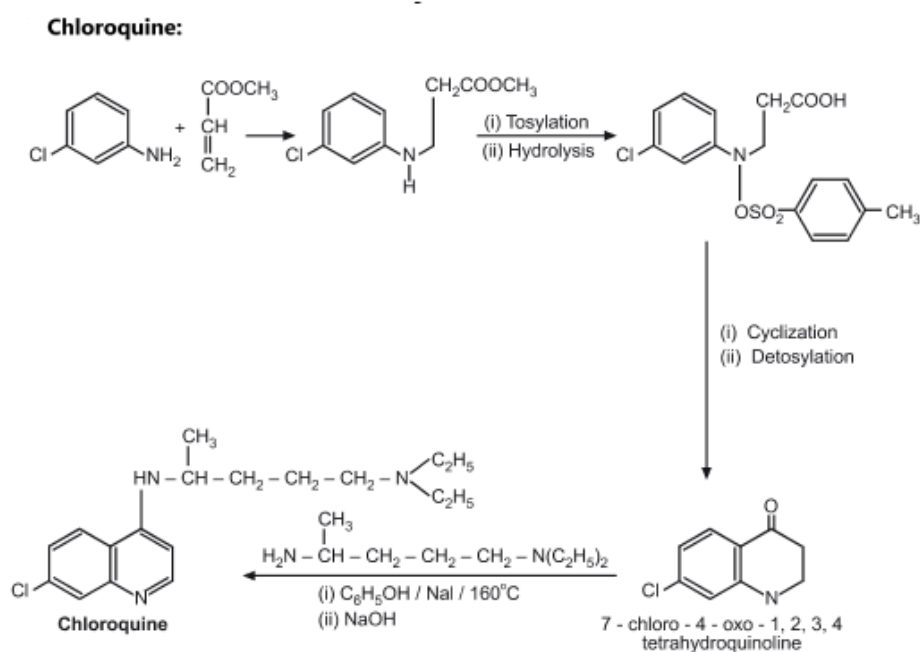
- Often used in combination with other sulfonamide antimalarial drugs, pyrimethamine is also an antifolate drug. Pyrimethamine acts on the dihydrofolate reductase enzyme.
- Pyrimethamine is administered through the oral route and is well-absorbed.

- This drug is also used in the treatment of *Toxoplasma gondii* infections in immunocompromised patients.
- Pyrimethamine is also currently being investigated as a treatment for Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's disease.

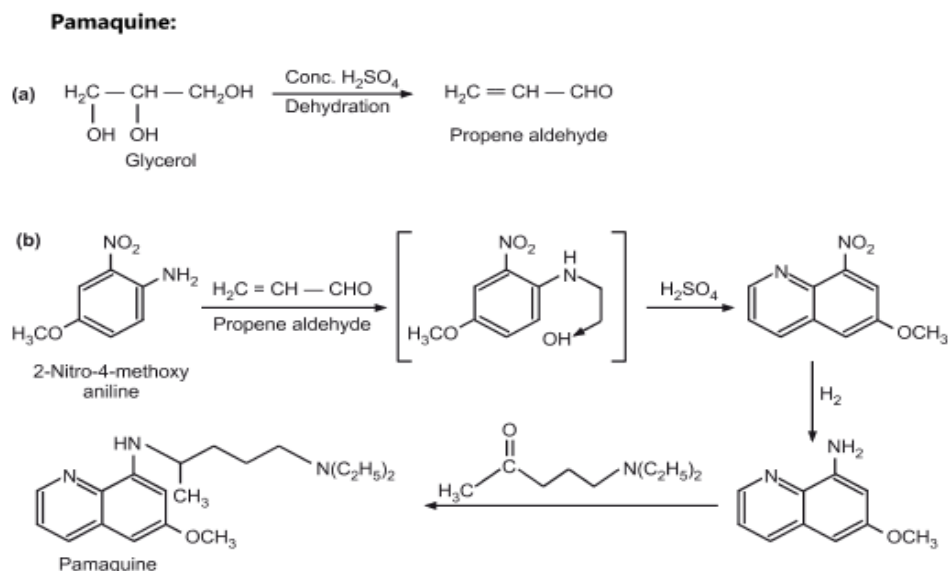
Sulfadoxine or sulphadoxine

- It is a sulfonamide drug that was used in combination with pyrimethamine to treat or prevent malaria.
- Due to the emergence of resistance, its use has been reduced.
- Sulfadoxine acts by competitively inhibiting plasmodial dihydropteroate synthase, an enzyme not biosynthesised by most eukaryotes including humans.

Synthesis of Chloroquine



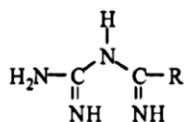
Synthesis of Pamaquine




Biguanides

- Biguanides are a class of medications used to treat type 2 diabetes and other conditions.
- They work by reducing the production of glucose that occurs during digestion.
- Metformin is the only biguanide currently available in most countries for treating diabetes

Structure

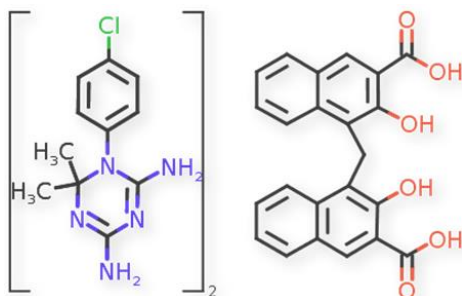


	R
Metformin	—N—(CH ₃) ₂
Phenformin	—NH—(CH ₂) ₂ — 

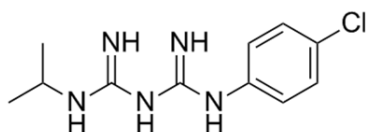
Mechanism of Action

- Activate AMP activated protein kinase (AMPA-PK)
- Reduce hepatic glucose production Lower blood glucose level
- Impairment of renal gluconeogenesis
- Slowing of glucose absorption from the gastrointestinal tract
- Increased glucose to lactate conversion by enterocytes
- Direct stimulation of glycolysis in tissues
- Increased glucose removal from blood
- Reduction of plasma glucagon levels

Cycloguanil Pamoate



Proguanil





Prodrugs

- A prodrug is a medication or compound that, after administration, is metabolized (i.e., converted within the body) into a pharmacologically active drug.
- Instead of administering a drug directly, a corresponding prodrug can be used to improve how the drug is absorbed, distributed, metabolized, and excreted (ADME).
- Prodrugs are often designed to improve bioavailability when a drug itself is poorly absorbed from the gastrointestinal tract.
- A prodrug may be used to improve how selectively the drug interacts with cells or processes that are not its intended target. This reduces adverse or unintended effects of a drug, especially important in treatments like chemotherapy, which can have severe unintended and undesirable side effects.

Classification

- Prodrugs can be classified into two major types, based on how the body converts the prodrug into the final active drug form:
- Type I prodrugs are bioactivated inside the cells (intracellularly).
Examples of these are anti-viral nucleoside analogs that must be phosphorylated and the lipid-lowering statins.
- Type II prodrugs are bioactivated outside cells (extracellularly), especially in digestive fluids or in the body's circulatory system, particularly in the blood.
Examples of Type II prodrugs are salicin (described above) and certain antibody-, gene- or virus-directed enzyme prodrugs used in chemotherapy or immunotherapy.
- Both major types can be further categorized into subtypes, based on factors such as (Type I) whether the intracellular bioactivation location is also the site of therapeutic action, or (Type 2) whether or not bioactivation occurs in the gastrointestinal fluids or in the circulation system.

Type	Bioactivation site	Subtype	Tissue location of bioactivation	Examples
Type I	Intracellular	Type IA	Therapeutic target tissues/cells	Aciclovir, fluorouracil, cyclophosphamide, diethylstilbestrol diphosphate, L-DOPA, mercaptopurine, mitomycin, zidovudine
		Type IB	Metabolic tissues (liver, GI mucosal cell, lung etc.)	Carbamazepine, captopril, carisoprodol, heroin, molsidomine, leflunomide, paliperidone, phenacetin, primidone, psilocybin, sulindac, fursultiamine, codeine
Type II	Extracellular	Type IIA	GI fluids	Loperamide oxide, oxyphenisatin, sulfasalazine
		Type IIB	Systemic circulation and other extracellular fluid compartments	Acetylsalicylate, bacampicillin, bambuterol, chloramphenicol succinate, dipivefrin, fosphenytoin, lisdexamfetamine, pralidoxime
		Type IIC	Therapeutic target tissues/cells	ADEPTs, GDEPTs, VDEPTs

Applications of Prodrug design

1. Taste or Odour

- Undesirable taste arises due to adequate solubility and interaction of drug with taste receptors. It can be solved by lowering the solubility of drug or prodrug in saliva. Eg: chloramphenicol palmitate is the sparingly soluble of prodrug of chloramphenicol, which is practically tasteless due to its low aqueous solubility, as



well as it is hydrolysed to active chloramphenicol by the action of pancreatic lipase. Eg: Ethyl mercaptan has a boiling point of 25°C and a strong disagreeable odour. But diethyl dithio isophthalate, prodrug of ethyl mercaptan has a higher boiling point and is relatively odourless.

2. Reduction of gastric irritation

Eg: Aspirin is a prodrug of salicylic acid designed to reduce gastric irritation

Drug Prodrug Salicylic acid, Aspirin Diethyl stilbestrol, Fosfestrol, Kanamycin, Kanamycin pamoate, Phenylbutazone, N-methyl piperazine salt, Nicotinic acid, Nicotinic acid hydrazide, Oleandrin, oleandrin acetate

3. Reduction in Pain at Site of Injection

- Pain caused by intramuscular injection is mainly due to the weakly acidic nature or poor aqueous solubility of drugs. Eg: IM injection of antibiotics like clindamycin and anti convulsant like phenytoin was found to be painful due to poor solubility. So, prodrugs are produced like 2'phosphate ester of clindamycin and hydantoic ester prodrug of phenytoin (fosphenytoin) an aqueous soluble form of phenytoin respectively. Fosphenytoin Phenytoin

4. Enhancement of drug solubility and dissolution rate

- The prodrug approach can be used to increase or decrease the solubility of a drug, depending on its ultimate use. Eg: chloramphenicol succinate and chloramphenicol palmitate, ester prodrugs of chloramphenicol, have enhanced and reduced aqueous solubility respectively.
- On the basis of altered solubility, chloramphenicol sodium succinate prodrug is found suitable for parenteral administration.
- The prodrug approach is also made useful for better gastrointestinal absorption. Eg: sulindac, a prodrug of sulindac sulfide being more water soluble with sufficient lipophilicity, makes this drug suitable for oral administration Testosterone - testosterone phosphate ester Tetracycline - tetralysine ,Diazepam - diazepam L-lysine ester

5. Enhancement of chemical stability

- Chemical stability is an utmost necessary parameter for every therapeutic agent.
- The prodrug approach is based on the modification of the functional group responsible for the instability or by changing the physical properties of the drug resulting in the reduction of contact between the drug and the media in which it is unstable. Eg: Inhibiting the auto aminolysis, which occur due to capability of NH₂ group of side chain to attach β lactam ring of other molecule, in ampicillin molecule in concentrated solution it generates polymeric species of ampicillin. By making hetacillin, a prodrug of ampicillin formed by the reaction of acetone and ampicillin „ties up“ the amine group and thus inhibits auto aminolysis

6. Pharmacokinetic Applications

- Improvement of Bioavailability and Enhancement of Oral Bioavailability



- Various therapeutic agents such as water soluble vitamins, structural analogues of natural purine and pyrimidine nucleoside, dopamine, antibiotics like ampicillin and carbenicillin, phenytoin and cardiac glycoside such as gitoxin suffers with poor gastrointestinal absorption.
- The prime cause of the poor absorption of these agents is their highly polar nature, poor lipophilicity and/or metabolism during the absorption process.
- On contrary gitoxin, a cardiac glycoside has very poor oral bioavailability due to limited aqueous solubility

7. Absorption of water soluble vitamin was enhanced by derivatization of thiolate ion to form lipid soluble prodrugs .

- Dopamine was made useful by making its precursor L-Dopa. Though L- Dopa is highly polar, it is actively transported through specific L–amino acid active transport mechanism and regenerates dopamine by decarboxylation.
- Penta acetyl prodrug of gitoxin has four to five times more aqueous solubility. To increase aqueous solubility esterification with amino acids is done.
- Examples of such prodrugs are valacyclovir and valgancyclovir, which are valine esters of the antiviral drugs acyclovir and gancyclovir, respectively.

8. Prevention of Presystemic metabolism

- Following oral administration, a drug must pass through two metabolizing organs i.e., liver and gastrointestinal mucosa, before reaching the general circulation.
- Phenolic moiety, oxidative N– and O– dealkylation, ester cleavage and peptide degradation are responsible for the pre-systemic metabolism of various drugs.
- Two types of drugs fall into this category. The first are drugs rapidly degraded by the acid condition of the stomach and the Drugs of second category degrade due to enzymes present in the gastrointestinal mucosa and liver.

9. Prodrugs may protect a drug from presystemic metabolism

- Naltrexone (treatment of opioid addiction) and is readily absorbed from GIT and hence undergoes Presystemic metabolism.
- Ester prodrugs such as O- nitrobenzoate and acetylsalicylate increased bioavailability 45 and 28 fold respectively.
- Drug Prodrug Propranolol Propranolol hemisuccinate Dopamine L-DOPA Morphine Heroin

10. Prolongation of duration of action

- Drugs with short half life require frequent dosing with conventional dosage forms to maintain adequate plasma concentration of the particular drug.
- In plasma level time profile and consequently patient compliance is often poor. Prolongation of duration of action of a drug can be accomplished by the prodrug .
- Prodrug can be formed by two approaches- Control the release of the drug from complex Control the conversion of prodrug in to the parent drug.



- Drug Prodrug Testosterone Testosterone propionate Estradiol Estradiol propionate Fluphenazine Fluphenazine deaconate