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MEDICINAL CHEMISTRY - III

UNIT 4

TOPIC :

- **Anti-protozoal Agents :** Metronidazole, *Tinidazole, Ornidazole, Diloxanide, Iodoquinol, Pentamidine Isethionate, Atovaquone, Eflornithine.*

Anti-Protozoal Agents

- Anti-protozoal agents are drugs used for the prevention and treatment of infections caused by protozoa such as Entamoeba, Plasmodium, Giardia, Leishmania, and Trichomonas.

Classification

A. Anti-amoebic Drugs

1. Luminal Amoebicides

- Diloxanide furoate
- Iodoquinol
- Paromomycin

2. Tissue Amoebicides

- Metronidazole
- Tinidazole
- Emetine
- Dehydroemetine

3. Mixed Amoebicides

- Metronidazole
- Tinidazole

B. Anti-malarial Drugs

- Chloroquine
- Primaquine
- Quinine
- Artemisinin derivatives
- Proguanil

C. Anti-giardial Drugs

- Metronidazole
- Tinidazole
- Albendazole

D. Anti-trichomonal Drugs

- Metronidazole

- Tinidazole

E. Anti-leishmanial Drugs

- Sodium stibogluconate
- Meglumine antimoniate
- Amphotericin-B
- Miltefosine

F. Anti-toxoplasma Drugs

- Pyrimethamine
- Sulfadiazine

Mechanism of Action

Metronidazole / Tinidazole

- Reduced inside protozoa
- Forms toxic free radicals
- Damages DNA, Protozoacidal

Chloroquine

- Inhibits heme polymerization
- Toxic heme kills parasite

Primaquine

- Destroys liver hypnozoites
- Prevents relapse of malaria

Pyrimethamine

- Inhibits dihydrofolate reductase
- Blocks DNA synthesis

Artemisinin

- Produces free radicals
- Rapid parasite killing

Spectrum of Activity

Drug	Effective Against
Metronidazole	Amoebiasis, Giardiasis, Trichomoniasis
Chloroquine	*Plasmodium vivax, falciparum*
Primaquine	Liver stage malaria

Pyrimethamine	Toxoplasmosis
Miltefosine	Leishmaniasis

Therapeutic Uses

- Intestinal and hepatic amoebiasis
- Malaria (treatment & prophylaxis)
- Giardiasis
- Trichomoniasis
- Kala-azar (leishmaniasis)
- Toxoplasmosis

Adverse Effects

Metronidazole

- Metallic taste
- Nausea, vomiting
- Disulfiram-like reaction with alcohol

Chloroquine

- GI upset
- Retinopathy (long-term use)

Primaquine

- Hemolysis in G6PD deficiency

Pyrimethamine

- Bone marrow suppression

Resistance

- Altered drug uptake
- Enzyme mutation
- Reduced activation of drug

Metronidazole

- Metronidazole is a synthetic nitroimidazole antimicrobial agent.
- It is active against anaerobic bacteria and protozoa, including Trichomonas, Giardia, and Entamoeba.
- Metronidazole works by disrupting DNA synthesis in susceptible organisms, leading to cell death.
- It has both systemic and topical applications.

Classification

Based on Chemical Class

- Nitroimidazole derivative

Based on Antimicrobial Action

- Bactericidal – against anaerobic bacteria
- Protozoacidal – against Trichomonas, Giardia, Entamoeba
- Mechanism: DNA strand breakage → inhibition of nucleic acid synthesis

Based on Use

- Systemic therapy – oral tablets, IV infusion
- Topical therapy – gels, creams for vaginal infections and skin ulcers

Structure

→ Nitroimidazole ring with a hydroxyl-ethyl side chain

Molecular formula: $C_6H_9N_3O_3$

Structural Characteristics

- Nitro group → responsible for antimicrobial activity
- Imidazole ring → essential for cell penetration and DNA interaction
- Water-soluble → formulated as oral tablets, injections, or gels

Nomenclature

- Metronidazole → generic name
- Brand names: Flagyl, Metrogyl
- Formulations: tablets, capsules, suspension, IV solution, topical gel

Mechanism of Action

- Metronidazole enters anaerobic cells by passive diffusion.
- In anaerobic conditions, nitro group is reduced by bacterial enzymes to reactive intermediates.
- These reactive compounds bind to DNA, causing strand breakage and inhibition of nucleic acid synthesis.
- Leads to cell death.
- Hence, metronidazole is bactericidal and protozoacidal.

Spectrum of Activity

- Anaerobic bacteria – Bacteroides, Clostridium spp.
- Protozoa – Trichomonas vaginalis, Giardia lamblia, Entamoeba histolytica
- Helicobacter pylori – used in combination therapy for ulcers
- Limited activity against aerobic bacteria

Uses

- Trichomoniasis – genital infection
- Amebiasis – intestinal and hepatic
- Giardiasis – intestinal infection

Adverse Effects

- Gastrointestinal: nausea, vomiting, metallic taste
- Neurological: headache, dizziness, peripheral neuropathy (long-term use)
- Hypersensitivity reactions: rash, urticaria

Chemical Degradation

- Sensitive to light and strong oxidizing agents
- Stable at room temperature in dry conditions
- Store in cool, dry place, protected from light

Structure–Activity Relationship (SAR)

- Nitro group → essential for reduction and DNA damage
- Imidazole ring → cell penetration and interaction with DNA
- Hydroxy-ethyl side chain → improves water solubility and tissue distribution
- Activity is specific to anaerobic environments

Tinidazole

- Tinidazole is a synthetic nitroimidazole antimicrobial similar to metronidazole.
- It is active against anaerobic bacteria and protozoa, including Trichomonas, Giardia, and Entamoeba.
- Tinidazole is more lipid-soluble than metronidazole, resulting in longer half-life and single-dose therapy for certain infections.
- It works by disrupting DNA synthesis, leading to cell death in susceptible organisms.

Classification

Based on Chemical Class

- Nitroimidazole derivative

Based on Antimicrobial Action

- Bactericidal – against anaerobic bacteria
- Protozoacidal – against Trichomonas, Giardia, Entamoeba
- Mechanism: DNA strand breakage → inhibition of nucleic acid synthesis

Based on Use

- Systemic therapy – oral tablets

Structure

- Nitroimidazole ring with a methyl-ethyl side chain

Molecular formula: $C_6H_9N_3O_3$

Structural Characteristics

- Nitro group → responsible for antimicrobial activity
- Imidazole ring → essential for cell penetration and DNA interaction
- Lipophilic → better tissue penetration than metronidazole

Nomenclature

- Tinidazole → generic name
- Brand names: Fasigyn, Tindamax
- Formulations: oral tablets

Mechanism of Action

- Tinidazole enters anaerobic cells by passive diffusion.
- In anaerobic conditions, the nitro group is reduced by microbial enzymes to reactive intermediates.
- These intermediates bind to DNA, causing strand breakage and inhibition of nucleic acid synthesis.
- Leads to cell death.
- Hence, tinidazole is bactericidal and protozoacidal.

Spectrum of Activity

- Protozoa – Trichomonas vaginalis, Giardia lamblia, Entamoeba histolytica
- Anaerobic bacteria – Bacteroides, Clostridium spp.
- Limited activity against aerobic bacteria

Uses

- Trichomoniasis – genital infection
- Amebiasis – intestinal and hepatic
- Giardiasis – intestinal infection
- Bacterial vaginosis – vaginal infection

Adverse Effects

- Gastrointestinal: nausea, vomiting, metallic taste
- Headache, dizziness
- Rare: peripheral neuropathy, hypersensitivity reactions
- Disulfiram-like reaction with alcohol (flushing, vomiting)
- Generally better tolerated than metronidazole

Chemical Degradation

- Sensitive to light and strong oxidizing agents
- Stable at room temperature in dry conditions
- Store in cool, dry place, protected from light

Structure–Activity Relationship (SAR)

- Nitro group → essential for reduction and DNA damage
- Imidazole ring → cell penetration and DNA interaction
- Lipophilic side chain → increases tissue penetration and half-life

- Activity is specific to anaerobic environments

Ornidazole

→ Ornidazole is a synthetic nitroimidazole antimicrobial.
→ It is active against anaerobic bacteria and protozoa, including Trichomonas vaginalis, Giardia lamblia, and Entamoeba histolytica.
→ Ornidazole has high lipid solubility, a longer half-life than metronidazole, and is well-tolerated, allowing single or short-course dosing.
→ Mechanism of action involves DNA strand breakage, leading to cell death in susceptible microorganisms.

Classification

Based on Chemical Class

⇨ Nitroimidazole derivative

Based on Antimicrobial Action

⇨ Bactericidal – against anaerobic bacteria
⇨ Protozoacidal – against Trichomonas, Giardia, Entamoeba
⇨ Mechanism: DNA strand breakage → inhibition of nucleic acid synthesis

Based on Use

⇨ Systemic therapy – oral tablets, IV injection

Structure

➢ Nitroimidazole ring with ethyl and hydroxyl side chains

Molecular formula: $C_6H_9N_3O_3$

Structural Characteristics

- Nitro group → responsible for antimicrobial activity
- Imidazole ring → essential for cell penetration and DNA interaction
- Lipophilic → allows good tissue distribution

Nomenclature

- Ornidazole → generic name
- Brand names: Ornid, Tiberal
- Formulations: oral tablets, IV injection

Mechanism of Action

- Ornidazole enters anaerobic cells by passive diffusion.
- In anaerobic conditions, the nitro group is reduced by microbial enzymes to reactive intermediates.
- These intermediates bind to DNA, causing strand breakage and inhibition of nucleic acid synthesis.
- Leads to cell death.
- Hence, ornidazole is bactericidal and protozoacidal.

Spectrum of Activity

- Protozoa – Trichomonas vaginalis, Giardia lamblia, Entamoeba histolytica
- Anaerobic bacteria – Bacteroides, Clostridium spp.
- Limited activity against aerobic bacteria

Uses

- Trichomoniasis – genital infection
- Amebiasis – intestinal and hepatic
- Giardiasis – intestinal infection
- Anaerobic infections – intra-abdominal infections, abscesses

Adverse Effects

- Gastrointestinal: nausea, vomiting, metallic taste
- Headache, dizziness
- Rare: peripheral neuropathy, hypersensitivity reactions
- Disulfiram-like reaction with alcohol (flushing, vomiting)
- Generally better tolerated than metronidazole

Chemical Degradation

- Sensitive to light and strong oxidizing agents
- Stable at room temperature in dry conditions
- Store in cool, dry place, protected from light

Structure–Activity Relationship (SAR)

- Nitro group → essential for reduction and DNA damage
- Imidazole ring → cell penetration and DNA interaction
- Lipophilic side chain → increases tissue penetration and half-life
- Activity is specific to anaerobic environments

Diloxanide Furate

→ Diloxanide furate is a synthetic luminal amoebicide.
→ It is used to treat asymptomatic intestinal amoebiasis, specifically Entamoeba histolytica cyst carriers.
→ Diloxanide works by interfering with amoebic metabolism, leading to destruction of trophozoites in the intestinal lumen.
→ It is effective only in the intestinal lumen and has minimal systemic absorption.

Classification

Based on Chemical Class

- Aromatic diamidine derivative
- Synthetic luminal amoebicide

Based on Antimicrobial Action

- Amoebicidal – kills trophozoites in the intestinal lumen
- No systemic effect – does not act on liver abscesses

Based on Use

- Oral therapy – tablets or suspension

Structure

→ Aromatic diamidine with furan ring and substituted amide groups

Molecular formula: $C_{14}H_{20}N_2O_4$

Structural Characteristics

→ Poorly absorbed → acts locally in the intestinal lumen
→ Furan ring → enhances amoebicidal activity
→ Formulated as oral tablets or suspensions

Nomenclature

- Diloxanide furate → generic name
- Brand names: Furamide, Dioxidil
- Formulations: oral tablets, suspension

Mechanism of Action

- Diloxanide furate is converted in the intestinal lumen to its active metabolite, diloxanide.
- Interferes with amoebic metabolic enzymes.
- Disrupts energy metabolism and nucleic acid synthesis in trophozoites.
- Leads to death of amoebic trophozoites.
- Hence, diloxanide is luminal amoebicidal.

Spectrum of Activity

- Entamoeba histolytica – intestinal trophozoites and cysts
- Ineffective against hepatic amoebiasis
- Does not act on other protozoa or bacteria

Uses

- Asymptomatic intestinal amoebiasis – cyst carriers
- Adjunct therapy with systemic amoebicides (like metronidazole) for liver abscess
- Prevention of amoebic spread in endemic areas

Adverse Effects

- Gastrointestinal: mild diarrhea, nausea, abdominal discomfort
- Rare: rash, urticaria
- Minimal systemic toxicity due to poor absorption

Chemical Degradation

- Stable under normal storage conditions
- Store in cool, dry place, protected from light
- Avoid moisture to maintain tablet stability

Structure–Activity Relationship (SAR)

→ Furan ring → essential for amoebicidal activity
→ Diamidine moiety → interacts with amoebic enzymes
→ Poor absorption → acts locally in lumen
→ Activity is limited to intestinal trophozoites and cysts

Iodoquinol

→ Iodoquinol is a synthetic luminal amoebicide.
→ It is primarily used for the treatment and eradication of asymptomatic intestinal amoebiasis, especially Entamoeba histolytica cyst carriers.
→ It works by interfering with protozoal metabolic processes, leading to death of trophozoites in the intestinal lumen.
→ Iodoquinol has minimal systemic absorption, acting mainly locally in the gut.

Classification

Based on Chemical Class

- 8-Hydroxyquinoline derivative
- Synthetic luminal amoebicide

Based on Antimicrobial Action

- Amoebicidal – kills trophozoites and cysts in the intestinal lumen
- No systemic effect – ineffective for hepatic amoebiasis

Based on Use

- Oral therapy – tablets or suspension

Structure

- Hydroxyquinoline ring with iodine substitution

Molecular formula: C_9H_5INO

- Lipophilic, poorly absorbed → acts locally in the intestine

Nomenclature

◈ Iodoquinol → generic name
◈ Brand names: Yodoxin, Diodin
◈ Formulations: oral tablets, suspension

Mechanism of Action

- Iodoquinol acts in the intestinal lumen.
- Interferes with protozoal enzymes, especially those involved in energy metabolism.
- Disrupts nucleic acid synthesis and enzymatic activity.
- Leads to death of Entamoeba trophozoites and cysts.
- Hence, iodoquinol is luminal amoebicidal.

Spectrum of Activity

- Entamoeba histolytica – trophozoites and cysts in the gut
- Ineffective for hepatic amoebiasis
- Limited action against other protozoa or bacteria

Uses

- ⮝ Asymptomatic intestinal amoebiasis – cyst carriers
- ⮝ Adjunct therapy with systemic amoebicides (like metronidazole) for liver abscess
- ⮝ Prevention of amoebic spread in endemic areas

Adverse Effects

- ⇨ Gastrointestinal: mild nausea, diarrhea, abdominal discomfort
- ⇨ Rare: rash, urticaria, headache
- ⇨ Minimal systemic toxicity due to poor absorption
- ⇨ Long-term use may cause peripheral neuropathy

Chemical Degradation

- ○ Sensitive to light and moisture
- ○ Stable under cool, dry conditions
- ○ Store in airtight containers, protected from light

Structure–Activity Relationship (SAR)

- ❖ Hydroxyquinoline ring → essential for amoebicidal activity
- ❖ Iodine substitution → enhances potency and activity against cysts
- ❖ Poor absorption → acts locally in intestinal lumen
- ❖ Activity is limited to intestinal trophozoites and cysts

Pentamidine Isethionate

→ Pentamidine isethionate is a synthetic aromatic diamidine antimicrobial.
→ It is used primarily for the treatment and prophylaxis of protozoal infections, particularly African trypanosomiasis (sleeping sickness) and leishmaniasis.
→ Pentamidine interferes with protozoal DNA, RNA, and protein synthesis, leading to cell death.

Classification

Based on Chemical Class

- Aromatic diamidine derivative
- Synthetic antiprotozoal

Based on Antimicrobial Action

- Trypanocidal and leishmanicidal – kills protozoa
- Mechanism: binds to DNA and inhibits replication and transcription

Based on Use

- Parenteral therapy – intravenous or intramuscular injection

Structure

- Aromatic diamidine with ether and amidine groups

Molecular formula: $C_{22}H_{24}N_4 \cdot C_2H_6O_4S$

- Highly polar → administered parenterally

Nomenclature

- Pentamidine isethionate → generic name
- Brand names: Pentam, Nebupent
- Formulations: injectable solution (IM/IV)

Mechanism of Action

- Pentamidine binds to protozoal DNA, especially AT-rich regions in the minor groove.
- Inhibits DNA replication and transcription.
- Interferes with RNA and protein synthesis.
- Leads to protozoal cell death.
- Hence, pentamidine is trypanocidal and leishmanicidal.

Spectrum of Activity

- ❖ Trypanosoma brucei gambiense and T. b. rhodesiense – early stage sleeping sickness
- ❖ Leishmania donovani – visceral leishmaniasis
- ❖ Limited activity against other protozoa

Uses

- ⅄ African trypanosomiasis (sleeping sickness) – early hemolymphatic stage
- ⅄ Visceral leishmaniasis – second-line therapy
- ⅄ Prophylaxis – in endemic areas for susceptible populations

Adverse Effects

- ▪ Parenteral administration can cause pain at injection site
- ▪ Hypotension, tachycardia, arrhythmias
- ▪ Pancreatitis, hyperglycemia or hypoglycemia
- ▪ Renal and hepatic toxicity
- ▪ Rare: hematological toxicity (leukopenia, anemia)

Chemical Degradation

- Stable in aqueous solution at recommended storage conditions
- Store in cool, dry place, protected from light
- Avoid freezing

Structure–Activity Relationship (SAR)

- ❖ Aromatic diamidine moiety → essential for DNA binding and protozoal activity
- ❖ Ether linkage → enhances solubility and tissue distribution
- ❖ Administered parenterally due to poor oral absorption
- ❖ Activity is specific to trypanosomes and leishmania

Atovaquone

→ Atovaquone is a synthetic hydroxynaphthoquinone antiprotozoal.
→ It is used primarily for malaria (Plasmodium falciparum) treatment and prophylaxis and for Pneumocystis jirovecii pneumonia (PCP) in immunocompromised patients.
→ Atovaquone acts by inhibiting mitochondrial electron transport in protozoa, leading to loss of ATP production and parasite death.

Classification

Based on Chemical Class

- Hydroxynaphthoquinone derivative
- Synthetic antiprotozoal

Based on Antimicrobial Action

- Protozoacidal – kills Plasmodium and Pneumocystis
- Mechanism: inhibits mitochondrial electron transport and oxidative phosphorylation

Based on Use

- Oral therapy – tablets or suspension

Structure

- Hydroxynaphthoquinone nucleus with substituted alkyl side chain

Molecular formula: $C_{22}H_{19}ClO_3$

Structural Characteristics

- Highly lipophilic → poor aqueous solubility
- Lipid solubility aids oral absorption and tissue distribution
- Usually formulated with fat-containing meals to improve bioavailability

Nomenclature

- Atovaquone → generic name
- Brand names: Mepron, Malanil
- Formulations: oral suspension, tablets

Mechanism of Action

- ◈ Atovaquone selectively inhibits cytochrome bc1 complex in protozoal mitochondria.
- ◈ Blocks electron transport, preventing oxidative phosphorylation.
- ◈ Leads to loss of mitochondrial membrane potential and ATP depletion.
- ◈ Results in death of malaria parasites and Pneumocystis jirovecii.
- ◈ Hence, atovaquone is protozoacidal.

Spectrum of Activity

- Plasmodium falciparum – malaria treatment and prophylaxis
- Plasmodium vivax, malariae – adjunct therapy
- Pneumocystis jirovecii – PCP prophylaxis and treatment
- Often combined with proguanil (Malarone) for enhanced efficacy

Uses

- ⇨ Treatment of uncomplicated P. falciparum malaria (alone or with proguanil)
- ⇨ Treatment and prophylaxis of PCP in immunocompromised patients
- ⇨ Often used in patients intolerant to standard antimalarials

Adverse Effects

- ❖ Gastrointestinal: nausea, vomiting, diarrhea, abdominal pain
- ❖ Headache, rash, fever
- ❖ Rare: elevated liver enzymes, hypersensitivity reactions

Chemical Degradation

- Sensitive to light and heat
- Poor aqueous solubility → formulated as suspension with fat
- Store in cool, dry place, protected from light

Structure–Activity Relationship (SAR)

- ➢ Hydroxynaphthoquinone nucleus → essential for inhibition of mitochondrial electron transport
- ➢ Lipophilic side chain → improves oral absorption and tissue penetration
- ➢ Selective for protozoal mitochondria over human mitochondria

➢ Combined with proguanil → synergistic effect and reduced resistance

Eflornithine

→ Eflornithine is a synthetic antiprotozoal drug.
→ It is primarily used for the treatment of African trypanosomiasis (sleeping sickness) caused by Trypanosoma brucei gambiense.
→ Eflornithine is also used topically for reducing unwanted facial hair in women (hirsutism).
→ It works by inhibiting polyamine biosynthesis, which is essential for parasite growth and proliferation.

Classification

Based on Chemical Class

- Ornithine analog
- Synthetic antiprotozoal

Based on Antimicrobial Action

- Trypanocidal – kills Trypanosoma parasites
- Mechanism: irreversible inhibition of ornithine decarboxylase → blocks polyamine synthesis

Based on Use

- Parenteral therapy – intravenous or intramuscular injection
- Topical therapy – cream for facial hirsutism

Structure

- Analog of L-ornithine with difluoromethyl substitution

Molecular formula: $C_6H_{13}F_2N_3O_2$

Structural Characteristics

◈ Hydrophilic → poor oral absorption; administered parenterally
◈ Structural mimicry of ornithine → competitive inhibition of ornithine decarboxylase

Nomenclature

⇨ Eflornithine → generic name
⇨ Brand names: Ornidyl (injectable), Vaniqa (topical cream)
⇨ Formulations: IV/IM injection, topical cream

Mechanism of Action

- Eflornithine irreversibly inhibits ornithine decarboxylase (ODC) in trypanosomes.
- Blocks polyamine synthesis, which is essential for DNA stabilization and cell proliferation.
- Leads to inhibition of parasite growth and death.
- Hence, eflornithine is trypanocidal.

Spectrum of Activity

- Trypanosoma brucei gambiense – early and late-stage sleeping sickness
- Limited activity against T. b. rhodesiense
- No activity against other protozoa or bacteria

Uses

- African trypanosomiasis (sleeping sickness) – particularly T. b. gambiense
- Topical treatment of facial hirsutism in women (Vaniqa cream)
- Used in combination therapy with nifurtimox for enhanced efficacy

Adverse Effects

- Parenteral: nausea, vomiting, diarrhea, headache
- Hematological: leukopenia, anemia (rare)
- Neurological: seizures, dizziness, tremor
- Topical: mild skin irritation, redness

Chemical Degradation

- Stable under normal storage conditions
- Store in cool, dry place, protected from light
- Injectable forms should be reconstituted immediately before use

Structure–Activity Relationship (SAR)

- Difluoromethyl group → enhances irreversible binding to ODC
- Ornithine analog structure → essential for competitive inhibition
- Hydrophilic → requires parenteral administration
- Selective for trypanosomal ODC over human ODC