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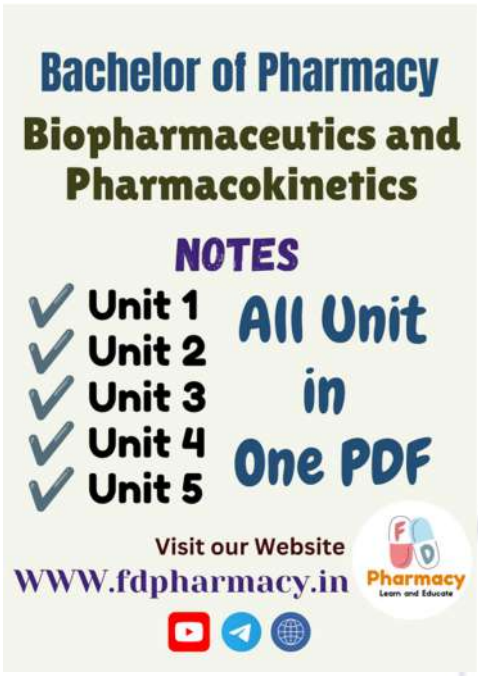
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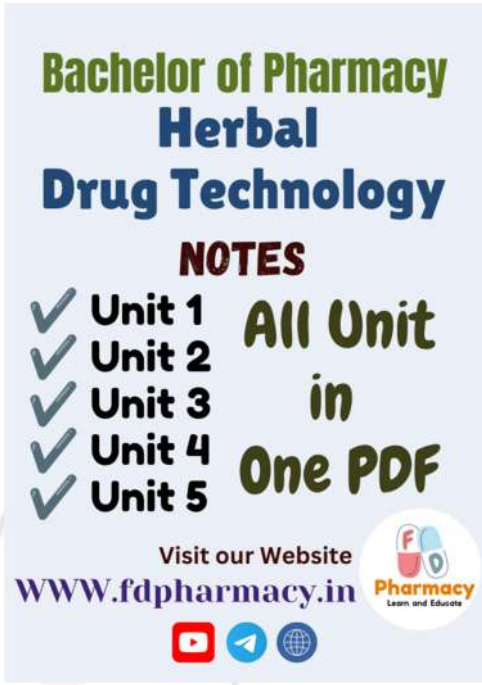
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MEDICINAL CHEMISTRY - III

UNIT 3

TOPIC :

- **Urinary tract anti-infective agents**

  Quinolones : SAR of quinolones, Nalidixic Acid,Norfloxacin, Enoxacin, Ciprofloxacin, *Ofloxacin, Lomefloxacin, Sparfloxacin, Moxifloxacin*

Urinary Tract Anti-Infective Agents (UTAs)

→ Urinary tract infections (UTIs) are caused by bacterial infections affecting the kidneys, ureters, bladder, or urethra.
→ Urinary tract anti-infective agents are drugs used to treat bacterial infections of the urinary tract.
→ These drugs may act locally in the urinary tract or systemically after absorption.

Classification

A. Urinary Tract-Specific Anti-Infectives

- Act primarily in urine or urinary tract
- Useful for lower UTIs (cystitis)
- Limited systemic effect
- Examples:
  - Nitrofurantoin
  - Methenamine
  - Fosfomycin

B. Systemic Anti-Infectives Used for UTIs

- Broad-spectrum antibiotics that reach therapeutic levels in urine
- Useful for upper and complicated UTIs
- Examples:
  - Trimethoprim
  - Sulfonamides (Sulfamethoxazole)
  - Fluoroquinolones (Ciprofloxacin, Levofloxacin)
  - Beta-lactams (Amoxicillin, Ampicillin, Cephalosporins)

Mechanism of Action

Drug	Mechanism
Nitrofurantoin	Reduced by bacterial flavoproteins → reactive intermediates that damage bacterial DNA and enzymes
Methenamine	Hydrolyzed in acidic urine → formaldehyde, which is bactericidal
Fosfomycin	Inhibits cell wall synthesis by blocking enolpyruvyl transferase
Trimethoprim	Inhibits dihydrofolate reductase, preventing DNA synthesis
Sulfonamides	Inhibit dihydropteroate synthase, interfering with folic acid synthesis
Fluoroquinolones	Inhibit DNA gyrase/topoisomerase II, preventing DNA replication

Indications

→ Acute and chronic cystitis
→ Pyelonephritis
→ Prophylaxis of recurrent UTIs

Pharmacokinetics

- Many urinary anti-infectives are rapidly excreted in urine, providing high urinary concentrations
- Example: Nitrofurantoin is well excreted in urine but has minimal systemic effect

Adverse Effects

Drug	Common Side Effects
Nitrofurantoin	Nausea, pulmonary reactions, hemolytic anemia in G6PD deficiency
Methenamine	Gastrointestinal upset, rare crystalluria
Fosfomycin	Diarrhea, nausea
Trimethoprim	Hyperkalemia, megaloblastic anemia in prolonged use
Sulfonamides	Allergic reactions, crystalluria, photosensitivity
Fluoroquinolones	GI upset, tendonitis, CNS effects

Quinolones

- Quinolones are synthetic broad-spectrum antibacterial agents used to treat urinary tract infections (UTIs).
- They inhibit bacterial DNA replication by targeting DNA gyrase (topoisomerase II) and topoisomerase IV, leading to bacterial death.
- They are bactericidal.

Common Quinolones for UTIs

- Ciprofloxacin – Most widely used
- Ofloxacin
- Levofloxacin – Especially for complicated UTIs
- Norofloxacin – Mild, uncomplicated UTIs
- Pefloxacin – Alternative drug

Mechanism of Action

- Quinolones inhibit DNA gyrase (Gram-negative bacteria)
- In Gram-positive bacteria, they inhibit topoisomerase IV
- Blocks DNA supercoiling and replication
- Prevents transcription → cell death
- Bactericidal effect

Spectrum of Activity

Gram-negative bacteria (mainly)

- *Escherichia coli* (most common in UTIs)
- *Klebsiella*, *Proteus*, *Enterobacter*
- *Pseudomonas aeruginosa* (some quinolones)

Gram-positive bacteria

- *Staphylococcus saprophyticus*
- *Enterococcus* (limited)

Therapeutic Uses

- Uncomplicated UTIs → Ciprofloxacin, Norfloxacin
- Complicated UTIs → Levofloxacin, Ciprofloxacin
- Pyelonephritis → Levofloxacin, Ciprofloxacin
- Prophylaxis in recurrent UTIs → Low-dose quinolones (short-term)

Adverse Effects

Common

- Nausea, vomiting, diarrhea
- Headache, dizziness
- Photosensitivity

Serious

- Tendonitis / tendon rupture
- QT prolongation
- CNS effects – confusion, seizures
- Cartilage toxicity (avoid in children & pregnancy)

Resistance

Resistance occurs due to:

- Mutation in DNA gyrase or topoisomerase IV genes
- Efflux pumps
- Reduced bacterial permeability
- Cross-resistance among quinolones

Nalidixic Acid

→ Nalidixic acid is the first synthetic quinolone antibiotic, primarily used to treat urinary tract infections (UTIs).
→ It is bactericidal and acts by inhibiting bacterial DNA synthesis.
→ Nalidixic acid is active against Gram-negative bacteria, especially
→ *Escherichia coli* and *Proteus* species.
→ It is orally administered and largely confined to the urinary tract, making it suitable for UTIs.

Classification

Based on Chemical Class

- Quinolone antibiotic (1st generation)

Based on Antibacterial Action

- Bactericidal
- Active mainly against Gram-negative organisms

Based on Origin

- Synthetic antibacterial agent

Structure

Nalidixic acid contains:

- 1,8-naphthyridine ring
- Carboxylic acid group at C-3
- Keto group at C-4

Molecular formula: $C_{12}H_{12}N_2O_3$

Structural Characteristics

- Active form: carboxylic acid
- Small, lipophilic molecule → good oral absorption
- Interferes with bacterial DNA replication

Nomenclature

- Nali → derived from naphthyridine nucleus
- Dixic acid → carboxylic acid group
- Available as oral tablets or suspensions

Stereochemistry

- Nalidixic acid is achiral
- No stereochemical requirements for antibacterial activity

Mechanism of Action

- Nalidixic acid inhibits bacterial DNA gyrase (topoisomerase II).
- Prevents supercoiling and relaxation of DNA, necessary for replication and transcription.
- Blocks DNA synthesis, leading to bacterial death.
- Hence, nalidixic acid is a DNA synthesis inhibitor.

Spectrum of Activity

Gram-negative bacteria:

- *Escherichia coli*
- *Proteus* spp.
- *Klebsiella* spp.

- Limited activity against Gram-positive bacteria
- Ineffective against anaerobes

Uses

- Urinary tract infections (UTIs) caused by Gram-negative bacilli
- Occasionally used in gastrointestinal infections
- Not used for systemic infections due to rapid renal excretion

Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- Headache, dizziness
- Photosensitivity (rare)
- Hypersensitivity reactions: rash
- Rare: crystalluria (drink plenty of water)

Chemical Degradation

- Sensitive to alkaline conditions
- Stable in acidic conditions
- Light and heat may degrade
- Store in cool, dry place

Structure–Activity Relationship (SAR)

- 1,8-Naphthyridine ring → essential for DNA gyrase inhibition
- Carboxylic acid at C-3 → required for antibacterial activity
- Keto group at C-4 → stabilizes DNA-enzyme complex
- Lipophilicity → facilitates penetration into bacterial cells

Norfloxacin

→ Norfloxacin is a synthetic fluoroquinolone antibiotic used primarily for urinary tract infections (UTIs) and gastrointestinal infections.
→ It is bactericidal and acts by inhibiting bacterial DNA synthesis.
→ Norfloxacin has improved Gram-negative coverage and better pharmacokinetic properties than nalidixic acid, including broader spectrum and longer half-life.
→ It is orally administered and partially excreted unchanged in urine.

Classification

Based on Chemical Class

- Fluoroquinolone antibiotic (2nd generation quinolone)

Based on Antibacterial Action

- Bactericidal
- Active mainly against Gram-negative bacteria, some Gram-positive coverage

Based on Origin

- Synthetic antibacterial agent

Structure

Norfloxacin contains:

- **1,8-naphthyridine nucleus** (quinolone core)
- Fluorine atom at **C-6** → enhances activity
- Piperazinyl group at **C-7** → improves Gram-negative coverage
- Carboxylic acid at **C-3**

Keto group at **C-4**

Molecular formula: $C_{15}H_{14}FN_3O_3$

Structural Characteristics

- Fluorine increases lipophilicity and bacterial penetration
- Piperazinyl group enhances activity against *E. coli*, *Klebsiella*, *Proteus*

Nomenclature

- Nor → distinguishes from nalidixic acid
- Floxacin → fluoroquinolone class
- Available as oral tablets, suspension, and sometimes IV formulations

Stereochemistry

- Norfloxacin is achiral
- Activity does not depend on stereochemistry

Mechanism of Action

- Norfloxacin inhibits bacterial DNA gyrase (topoisomerase II) and, to a lesser extent, topoisomerase IV.
- Prevents supercoiling and relaxation of DNA, necessary for replication and transcription.
- Blocks DNA synthesis, leading to bacterial death.
- Hence, norfloxacin is a DNA synthesis inhibitor.

Spectrum of Activity

Gram-negative bacteria:

- *Escherichia coli, Klebsiella* spp, *Proteus* spp.
- *Pseudomonas aeruginosa* (moderate)

- Limited Gram-positive activity: *Staphylococcus aureus*, *Streptococcus* spp.
- Ineffective against anaerobes

Uses

- Urinary tract infections (UTIs)
- Gastrointestinal infections (traveler's diarrhea, dysentery)
- Prophylaxis in recurrent UTIs (occasionally)

Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- CNS: headache, dizziness, confusion

Chemical Degradation

- Sensitive to alkaline hydrolysis
- Stable in acidic conditions

Structure–Activity Relationship (SAR)

- Fluorine at C-6 → increases lipophilicity and activity
- Piperazinyl group at C-7 → improves Gram-negative coverage
- Carboxylic acid (C-3) and keto (C-4) → essential for DNA gyrase inhibition
- Small molecular size → good oral absorption and renal excretion

Enoxacin

- Enoxacin is a synthetic fluoroquinolone antibiotic used primarily for urinary tract infections (UTIs) and some gastrointestinal infections.
- It is bactericidal and acts by inhibiting bacterial DNA synthesis. Enoxacin has improved Gram-negative coverage compared to first-generation quinolones and is orally active.

Classification

Based on Chemical Class

- Fluoroquinolone antibiotic (2nd generation quinolone)

Based on Antibacterial Action

Bactericidal

- Active mainly against Gram-negative bacteria, some Gram-positive coverage

Based on Origin

- Synthetic antibacterial agent

Structure

Enoxacin contains:

- **1,8-naphthyridine nucleus** (quinolone core)
- Fluorine atom at **C-6** → enhances activity
- Piperazinyl group at **C-7** → improves Gram-negative coverage
- Carboxylic acid at **C-3**
- Keto group at **C-4**

Molecular formula: $C_{15}H_{14}FN_3O_3$

Structural Characteristics

- Fluorine increases lipophilicity and bacterial penetration
- Piperazinyl group enhances activity against *E. coli*, *Proteus*, *Klebsiella*
- Small, orally absorbable molecule

Nomenclature

- Eno → derived from chemical naming
- Xacin → fluoroquinolone class
- Available as oral tablets

Stereochemistry

- Enoxacin is achiral
- No stereochemical requirement for antibacterial activity

Mechanism of Action

- Enoxacin inhibits bacterial DNA gyrase (topoisomerase II) and topoisomerase IV.
- Prevents supercoiling and relaxation of DNA, necessary for replication and transcription.
- Blocks DNA synthesis, leading to bacterial death.
- Hence, enoxacin is a DNA synthesis inhibitor.

Spectrum of Activity

Gram-negative bacteria:

- *Escherichia coli, Proteus* spp.
- *Klebsiella* spp., *Pseudomonas aeruginosa* (moderate)

- Limited Gram-positive coverage: *Staphylococcus aureus*
- Ineffective against anaerobes

Uses

- Urinary tract infections (UTIs)
- Prostatitis

Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- CNS: headache, dizziness
- Photosensitivity

Chemical Degradation

- Sensitive to alkaline hydrolysis
- Stable in acidic conditions
- Light and heat may degrade

Structure–Activity Relationship (SAR)

- Fluorine at C-6 → increases lipophilicity and activity
- Piperazinyl group at C-7 → improves Gram-negative coverage
- Carboxylic acid (C-3) and keto (C-4) → essential for DNA gyrase inhibition
- Small molecular size → good oral absorption and renal excretion

Ciprofloxacin

- Ciprofloxacin is a second-generation fluoroquinolone antibiotic with broad-spectrum activity.
- It is bactericidal and acts by inhibiting bacterial DNA synthesis.
- Ciprofloxacin has enhanced Gram-negative activity, moderate Gram-positive coverage, and is effective against some intracellular bacteria.
- It is orally active, well absorbed, and widely distributed in body tissues.

Classification

Based on Chemical Class

- Fluoroquinolone antibiotic (2nd generation)

Based on Antibacterial Action

- Bactericidal
- Active against Gram-negative, some Gram-positive, and atypical bacteria

Based on Origin

- Synthetic antibacterial agent

Structure

Ciprofloxacin contains:

- 1,8-naphthyridine nucleus (quinolone core)
- Fluorine atom at C-6 → enhances activity
- Piperazinyl group at C-7 → improves Gram-negative coverage and tissue penetration
- Carboxylic acid at C-3
- Keto group at C-4

Molecular formula: $C_{17}H_{18}FN_3O_3$

Structural Characteristics

- Fluorine increases lipophilicity and intracellular penetration
- Piperazinyl group enhances activity against *E. coli*, *Klebsiella*, and *Pseudomonas*
- Small, orally absorbable molecule

Nomenclature

- Cipro → distinguishing name from earlier quinolones
- Floxacin → fluoroquinolone class
- Available as oral tablets, suspension, and IV formulations

Stereochemistry

- Ciprofloxacin is achiral
- Activity does not depend on stereochemistry

Mechanism of Action

- Ciprofloxacin inhibits bacterial DNA gyrase (topoisomerase II) and topoisomerase IV.
- Prevents supercoiling and relaxation of DNA, necessary for replication and transcription.
- Blocks DNA synthesis, leading to bacterial death.
- Hence, ciprofloxacin is a DNA synthesis inhibitor.

Spectrum of Activity

- Gram-negative bacteria: *Escherichia coli, Klebsiella spp., Proteus spp., Pseudomonas aeruginosa*
- Gram-positive bacteria: *Staphylococcus aureus, Streptococcus spp.* (moderate)
- Atypical bacteria: *Chlamydia, Mycoplasma*
- Ineffective against anaerobes

Uses

- Urinary tract infections (UTIs)
- Gastrointestinal infections (e.g., dysentery, traveler's diarrhea)
- Respiratory tract infections (e.g., bronchitis, pneumonia)
- Bone and joint infections
- Prophylaxis for anthrax exposure

Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- CNS: headache, dizziness, confusion
- Photosensitivity
- Tendonitis and risk of tendon rupture
- Hypersensitivity reactions: rash
- Rare: hepatotoxicity, crystalluria (drink plenty of water)
- Caution in renal impairment

Chemical Degradation

- Sensitive to alkaline hydrolysis
- Stable in acidic conditions
- Light and heat may degrade
- Store in cool, dry place

Structure–Activity Relationship (SAR)

- Fluorine at C-6 → increases lipophilicity and potency
- Piperazinyl group at C-7 → improves Gram-negative coverage and tissue penetration
- Carboxylic acid (C-3) and keto (C-4) → essential for DNA gyrase inhibition
- Small, polar molecule → good oral absorption and renal excretion

Ofloxacin

- Ofloxacin is a second-generation fluoroquinolone antibiotic with broad-spectrum activity.
- It is bactericidal and acts by inhibiting bacterial DNA synthesis.
- Ofloxacin has enhanced Gram-negative coverage, moderate Gram-positive activity, and is effective against some atypical and intracellular bacteria.
- It is orally active, well absorbed, and also available as ophthalmic and otic formulations.

Classification

Based on Chemical Class

- Fluoroquinolone antibiotic (2nd generation)

Based on Antibacterial Action

- Bactericidal
- Active against Gram-negative, some Gram-positive, and atypical bacteria

Based on Origin

- Synthetic antibacterial agent

Structure

Ofloxacin contains:

- 1,8-naphthyridine nucleus (quinolone core)
- Fluorine atom at C-6 → enhances activity
- Piperazinyl group at C-7 → improves Gram-negative coverage and tissue penetration
- Carboxylic acid at C-3
- Keto group at C-4

Molecular formula: $C_{18}H_{20}FN_3O_4$

Structural Characteristics

- Fluorine increases lipophilicity and intracellular penetration
- Piperazinyl group enhances activity against *E. coli*, *Klebsiella*, and *Pseudomonas*
- Orally absorbable molecule with good bioavailability

Nomenclature

- Oflo → distinguishing name
- Xacin → fluoroquinolone class
- Available as oral tablets, suspension, IV, and eye/ear drops

Stereochemistry

- Ofloxacin is chiral
- Administered as racemic mixture
- Levofloxacin is the active L-isomer of ofloxacin

Mechanism of Action

- Ofloxacin inhibits bacterial DNA gyrase (topoisomerase II) and topoisomerase IV.
- Prevents supercoiling and relaxation of DNA, necessary for replication and transcription.
- Blocks DNA synthesis, leading to bacterial death.
- Hence, ofloxacin is a DNA synthesis inhibitor.

Spectrum of Activity

- Gram-negative bacteria: *Escherichia coli, Klebsiella spp., Proteus spp., Pseudomonas aeruginosa*
- Gram-positive bacteria: *Staphylococcus aureus*, *Streptococcus spp.* (moderate)
- Atypical bacteria: *Chlamydia, Mycoplasma, Legionella*
- Limited anaerobic activity

Uses

- Urinary tract infections (UTIs)
- Respiratory tract infections (bronchitis, pneumonia)
- Gastrointestinal infections
- Skin and soft tissue infections
- Ophthalmic infections (eye drops)
- Prostatitis

Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- CNS: headache, dizziness
- Photosensitivity
- Tendonitis and risk of tendon rupture
- Hypersensitivity reactions: rash
- Rare: hepatotoxicity, crystalluria (drink plenty of water)
- Caution in renal impairment

Chemical Degradation

- Sensitive to alkaline hydrolysis
- Stable in acidic conditions
- Light and heat may degrade
- Store in cool, dry place

Structure–Activity Relationship (SAR)

- Fluorine at C-6 → increases lipophilicity and potency
- Piperazinyl group at C-7 → improves Gram-negative coverage and tissue penetration
- Carboxylic acid (C-3) and keto (C-4) → essential for DNA gyrase inhibition
- Racemic mixture → L-isomer (levofloxacin) is active

Lomefloxacin

- Lomefloxacin is a synthetic fluoroquinolone antibiotic used primarily for urinary tract infections (UTIs), respiratory tract infections, and skin infections.
- It is bactericidal and acts by inhibiting bacterial DNA synthesis.
- Lomefloxacin is a second-generation fluoroquinolone, orally active, and widely distributed in body tissues.

Classification

Based on Chemical Class

- Fluoroquinolone antibiotic (2nd generation)

Based on Antibacterial Action

- Bactericidal
- Active against Gram-negative, some Gram-positive, and atypical bacteria

Based on Origin

- Synthetic antibacterial agent

Structure

Lomefloxacin contains:

- 1,8-naphthyridine nucleus (quinolone core)
- Fluorine atom at C-6 → enhances activity
- Piperazinyl group at C-7 → improves Gram-negative coverage
- Methoxy substitution at C-8 → reduces phototoxicity
- Carboxylic acid at C-3
- Keto group at C-4

Molecular formula: $C_{17}H_{18}FN_3O_4$

Structural Characteristics

- Fluorine increases lipophilicity and intracellular penetration
- Piperazinyl group enhances activity against *E. coli*, *Klebsiella*, and *Proteus*
- Methoxy group reduces phototoxicity compared to earlier fluoroquinolones

Nomenclature

- Lome → distinguishing chemical name
- Floxacin → fluoroquinolone class
- Available as oral tablets

Stereochemistry

- Lomefloxacin is achiral
- Activity does not depend on stereochemistry

Mechanism of Action

- Lomefloxacin inhibits bacterial DNA gyrase (topoisomerase II) and topoisomerase IV.
- Prevents supercoiling and relaxation of DNA, necessary for replication and transcription.
- Blocks DNA synthesis, leading to bacterial death.
- Hence, lomefloxacin is a DNA synthesis inhibitor.

Spectrum of Activity

- Gram-negative bacteria: *Escherichia coli, Klebsiella spp., Proteus spp., Pseudomonas aeruginosa*
- Gram-positive bacteria: *Staphylococcus aureus*, *Streptococcus spp.* (moderate)
- Atypical bacteria: *Chlamydia, Mycoplasma*
- Limited anaerobic activity

Uses

- Urinary tract infections (UTIs)
- Respiratory tract infections (bronchitis, pneumonia)
- Skin and soft tissue infections
- Occasionally used for prostatitis

Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- CNS: headache, dizziness
- Photosensitivity (less than older fluoroquinolones due to C-8 methoxy)
- Tendonitis and risk of tendon rupture
- Hypersensitivity reactions: rash
- Rare: crystalluria (drink plenty of water)
- Caution in renal impairment

Chemical Degradation

- Sensitive to alkaline hydrolysis
- Stable in acidic conditions
- Light and heat may degrade
- Store in cool, dry place

Structure–Activity Relationship (SAR)

- Fluorine at C-6 → increases lipophilicity and potency
- Piperazinyl group at C-7 → improves Gram-negative coverage
- Methoxy group at C-8 → reduces phototoxicity
- Carboxylic acid (C-3) and keto (C-4) → essential for DNA gyrase inhibition
- Small molecular size → good oral absorption and renal excretion

Sparfloxacin

- Sparfloxacin is a third-generation fluoroquinolone antibiotic with broad-spectrum activity.
- It is bactericidal and acts by inhibiting bacterial DNA synthesis.
- Sparfloxacin has enhanced activity against Gram-positive bacteria, in addition to Gram-negative coverage, and is orally active with good tissue penetration.

Classification

Based on Chemical Class

- Fluoroquinolone antibiotic (3rd generation)

Based on Antibacterial Action

- Bactericidal
- Active against Gram-negative, Gram-positive, and atypical bacteria

Based on Origin

- Synthetic antibacterial agent

Structure

Sparfloxacin contains:

- 1,8-naphthyridine nucleus (quinolone core)
- Fluorine atom at C-6 → enhances activity
- Cyclopropyl group at N-1 → improves potency
- Methoxy group at C-8 → reduces phototoxicity
- Piperazinyl or modified heterocyclic group at C-7 → improves Gram-negative coverage
- Carboxylic acid at C-3
- Keto group at C-4

Molecular formula: $C_{17}H_{16}FN_3O_3$

Structural Characteristics

- Methoxy group at C-8 → reduced phototoxicity
- Cyclopropyl group → enhances Gram-positive and atypical activity
- Good oral absorption and tissue distribution

Nomenclature

- Spar → distinguishing name
- Floxacin → fluoroquinolone class
- Available as oral tablets

Stereochemistry

- Sparfloxacin is achiral
- Activity does not depend on stereochemistry

Mechanism of Action

- Sparfloxacin inhibits bacterial DNA gyrase (topoisomerase II) and topoisomerase IV.
- Prevents supercoiling and relaxation of DNA, essential for replication and transcription.
- Blocks DNA synthesis, leading to bacterial death.
- Hence, sparfloxacin is a DNA synthesis inhibitor.

Spectrum of Activity

- Gram-negative bacteria: *Escherichia coli, Klebsiella spp., Proteus spp.*
- Gram-positive bacteria: *Staphylococcus aureus, Streptococcus pneumoniae* (enhanced compared to 2nd generation)
- Atypical bacteria: *Chlamydia, Mycoplasma, Legionella*
- Limited anaerobic activity

Uses

- Respiratory tract infections (pneumonia, bronchitis)
- Urinary tract infections (UTIs)
- Skin and soft tissue infections
- Atypical bacterial infections

Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- CNS: headache, dizziness
- Photosensitivity (less due to C-8 methoxy)
- Tendonitis and risk of tendon rupture
- Hypersensitivity reactions: rash
- Rare: hepatotoxicity
- Caution in renal impairment

Chemical Degradation

- Sensitive to alkaline hydrolysis
- Stable in acidic conditions
- Light and heat may degrade
- Store in cool, dry place

Structure–Activity Relationship (SAR)

- Fluorine at C-6 → increases lipophilicity and potency
- Cyclopropyl group at N-1 → enhances Gram-positive and atypical activity
- Methoxy at C-8 → reduces phototoxicity
- Carboxylic acid (C-3) and keto (C-4) → essential for DNA gyrase inhibition
- C-7 heterocyclic/piperazinyl group → improves Gram-negative coverage
- Small, orally active molecule → good absorption and tissue penetration

Gatifloxacin

- Gatifloxacin is a fourth-generation fluoroquinolone antibiotic with broad-spectrum activity.
- It is bactericidal and acts by inhibiting bacterial DNA synthesis.
- Gatifloxacin has enhanced activity against Gram-positive bacteria (including *Streptococcus pneumoniae*), Gram-negative bacteria, and some atypical organisms.
- It is orally active and also available as ophthalmic drops.

Classification

Based on Chemical Class

- Fluoroquinolone antibiotic (4th generation)

Based on Antibacterial Action

- Bactericidal
- Active against Gram-negative, Gram-positive, and atypical bacteria

Based on Origin

- Synthetic antibacterial agent

Structure

Gatifloxacin contains:

- 1,8-naphthyridine nucleus (quinolone core)
- Fluorine atom at C-6 → enhances activity
- Methoxy group at C-8 → reduces phototoxicity
- Piperazinyl group at C-7 → improves Gram-negative coverage
- Carboxylic acid at C-3
- Keto group at C-4

Molecular formula: $C_{19}H_{22}FN_3O_4$

Structural Characteristics

- Methoxy at C-8 → reduces phototoxicity
- Fluorine at C-6 → increases lipophilicity and activity
- Piperazinyl group at C-7 → improves Gram-negative and tissue penetration

Nomenclature

- Gati → distinguishing name
- Floxacin → fluoroquinolone class
- Available as oral tablets, IV infusion, and ophthalmic drops

Stereochemistry

- Gatifloxacin is chiral
- Administered as a racemic mixture
- The active isomer contributes mainly to antibacterial activity

Mechanism of Action

- Gatifloxacin inhibits bacterial DNA gyrase (topoisomerase II) and topoisomerase IV.
- Prevents supercoiling and relaxation of DNA, essential for replication and transcription.
- Blocks DNA synthesis, leading to bacterial death.
- Hence, gatifloxacin is a DNA synthesis inhibitor.

Spectrum of Activity

- Gram-negative bacteria: *Escherichia coli, Klebsiella spp., Proteus spp.*
- Gram-positive bacteria: *Streptococcus pneumoniae, Staphylococcus aureus*
- Atypical bacteria: *Mycoplasma, Chlamydia, Legionella*
- Some anaerobic coverage

Uses

- Respiratory tract infections (community-acquired pneumonia, bronchitis)
- Urinary tract infections (UTIs)
- Ophthalmic infections (eye drops)
- Skin and soft tissue infections

Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- CNS: headache, dizziness
- Photosensitivity
- Tendonitis and tendon rupture risk
- Hypersensitivity reactions: rash
- Rare: QT interval prolongation, hepatotoxicity

Chemical Degradation

- Sensitive to alkaline hydrolysis
- Stable in acidic conditions
- Light and heat may degrade
- Store in cool, dry place

Structure–Activity Relationship (SAR)

- Fluorine at C-6 → increases lipophilicity and potency
- Methoxy at C-8 → reduces phototoxicity
- Piperazinyl at C-7 → improves Gram-negative coverage and tissue penetration
- Carboxylic acid (C-3) and keto (C-4) → essential for DNA gyrase inhibition
- Racemic mixture → active isomer contributes to antibacterial effect
- Enhanced Gram-positive activity compared to 2nd generation fluoroquinolones

Moxifloxacin

- Moxifloxacin is a fourth-generation fluoroquinolone antibiotic with broad-spectrum activity, particularly effective against Gram-positive bacteria, Gram-negative bacteria, and anaerobes.
- It is bactericidal and acts by inhibiting bacterial DNA synthesis.
- Moxifloxacin is orally active, well distributed in tissues, and often used for respiratory infections, skin infections, and tuberculosis (as part of MDR-TB regimens).

Classification

Based on Chemical Class

- Fluoroquinolone antibiotic (4th generation)

Based on Antibacterial Action

- Bactericidal
- Active against Gram-positive, Gram-negative, atypical bacteria, and some anaerobes

Based on Origin

- Synthetic antibacterial agent

Structure

Moxifloxacin contains:

- 1,8-naphthyridine nucleus (quinolone core)
- Fluorine atom at C-6 → enhances activity
- Methoxy group at C-8 → reduces phototoxicity and increases activity against anaerobes
- Piperazinyl or bicyclic group at C-7 → improves Gram-negative coverage
- Carboxylic acid at C-3
- Keto group at C-4

Molecular formula: $C_{21}H_{24}FN_3O_4$

Structural Characteristics

- Methoxy at C-8 → reduces phototoxicity and enhances anaerobic coverage
- Fluorine at C-6 → increases lipophilicity and antibacterial potency
- C-7 substituent → improves tissue penetration and Gram-negative activity

Nomenclature

- Moxi → distinguishing name
- Floxacin → fluoroquinolone class
- Available as oral tablets, IV infusion, and ophthalmic drops

Stereochemistry

- Moxifloxacin is chiral
- Administered as a single active S-isomer
- S-isomer is responsible for the antibacterial activity

Mechanism of Action

- Moxifloxacin inhibits bacterial DNA gyrase (topoisomerase II) and topoisomerase IV.
- Prevents supercoiling and relaxation of DNA, essential for replication and transcription.
- Blocks DNA synthesis, leading to bacterial death.
- Hence, moxifloxacin is a DNA synthesis inhibitor.

Spectrum of Activity

- Gram-positive bacteria: *Streptococcus pneumoniae, Staphylococcus aureus*
- Gram-negative bacteria: *Escherichia coli, Klebsiella spp., Haemophilus influenzae*
- Atypical bacteria: *Mycoplasma, Chlamydia, Legionella*
- Anaerobic bacteria: *Bacteroides spp.*
- More potent than 2nd generation fluoroquinolones against Gram-positive cocci

Uses

- Community-acquired pneumonia
- Respiratory tract infections
- Skin and soft tissue infections
- Intra-abdominal infections
- Ophthalmic infections (eye drops)

Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- CNS: headache, dizziness
- Photosensitivity (less than older fluoroquinolones)
- Tendonitis and tendon rupture risk
- Hypersensitivity reactions: rash
- Rare: QT interval prolongation, hepatotoxicity

Chemical Degradation

- Sensitive to alkaline hydrolysis
- Stable in acidic conditions
- Light and heat may degrade
- Store in cool, dry place

Structure–Activity Relationship (SAR)

- Fluorine at C-6 → enhances lipophilicity and activity
- Methoxy at C-8 → reduces phototoxicity, increases anaerobic coverage
- C-7 substituent (piperazinyl or bicyclic) → improves Gram-negative coverage and tissue penetration
- Carboxylic acid (C-3) and keto (C-4) → essential for DNA gyrase inhibition
- Single S-isomer → responsible for enhanced antibacterial activity
- Broad-spectrum activity including Gram-positive, Gram-negative, atypical, and anaerobes