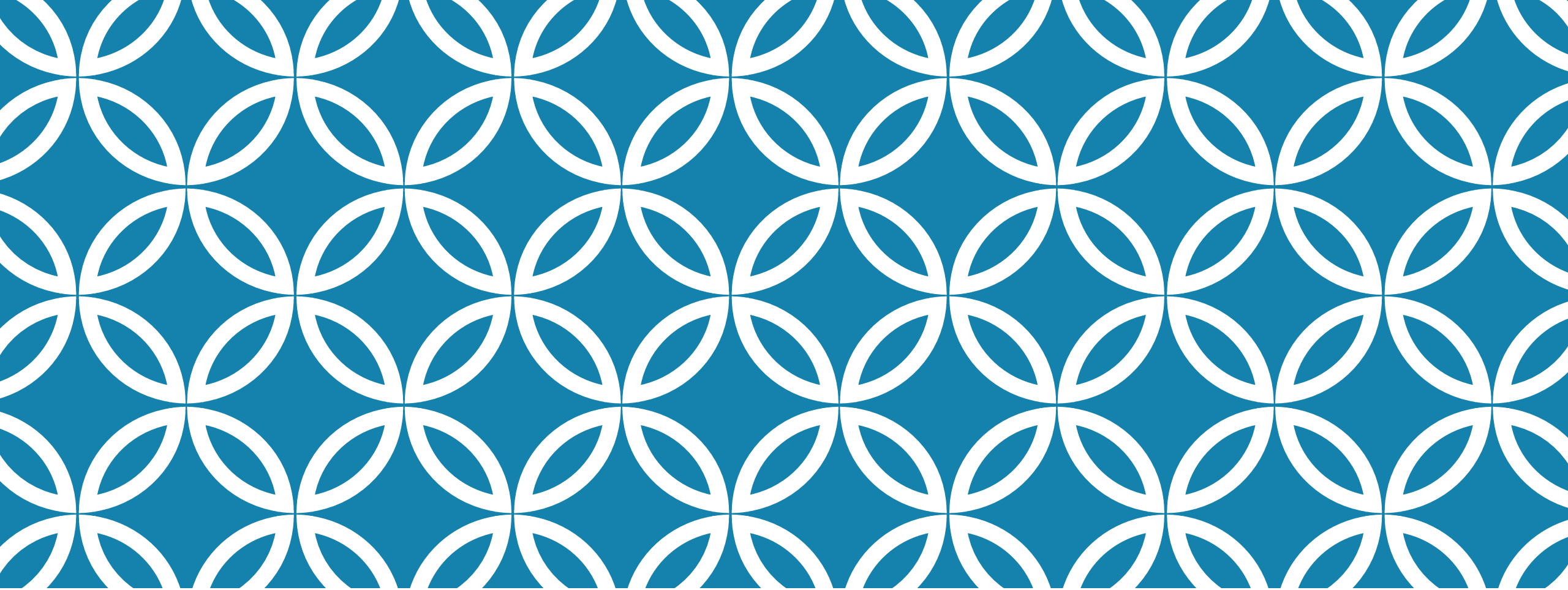
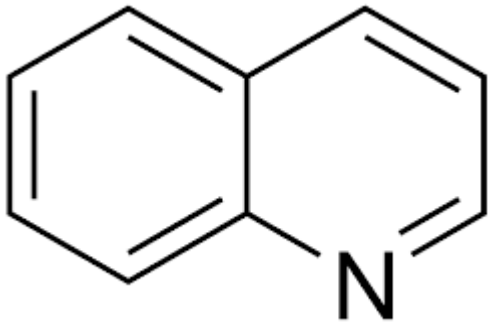


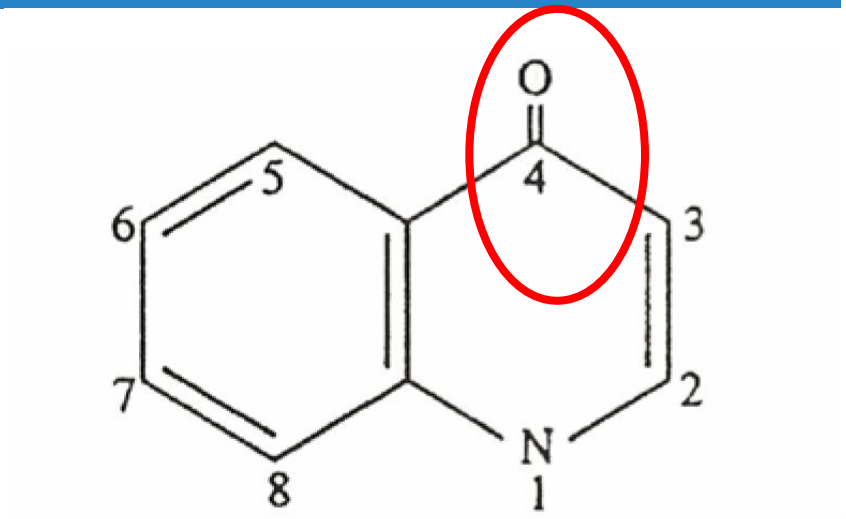
PHARMACOLOGY – II

Dr Shariq Syed
Associate Professor
AIKTC, SoP

QUINOLONES

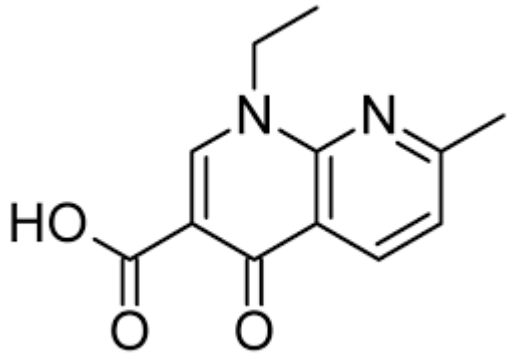


Quinoline



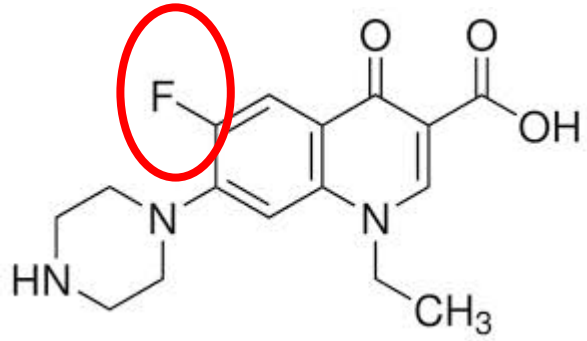
Quinolone

QUINOLONES

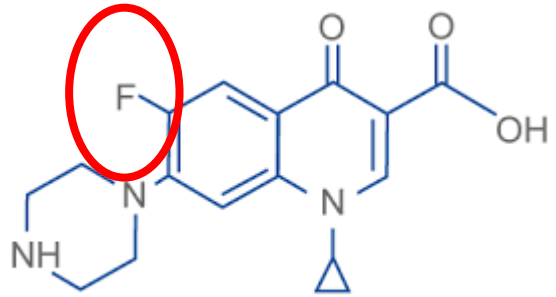


Nalidixic Acid

Addition of **Fluorine**



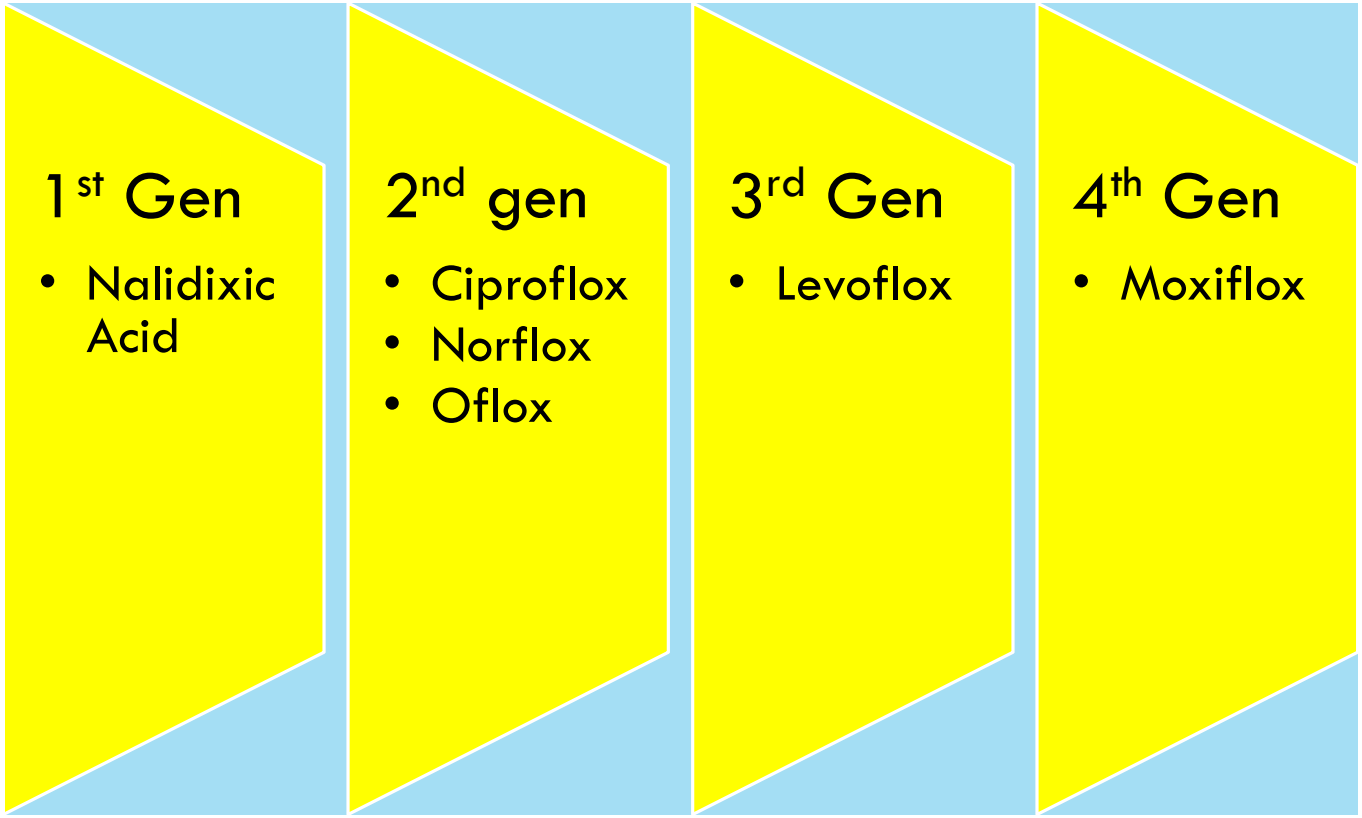
Norfloxacin



Ciprofloxacin

Starting Compound to all fluoroquinolones

QUINOLONES

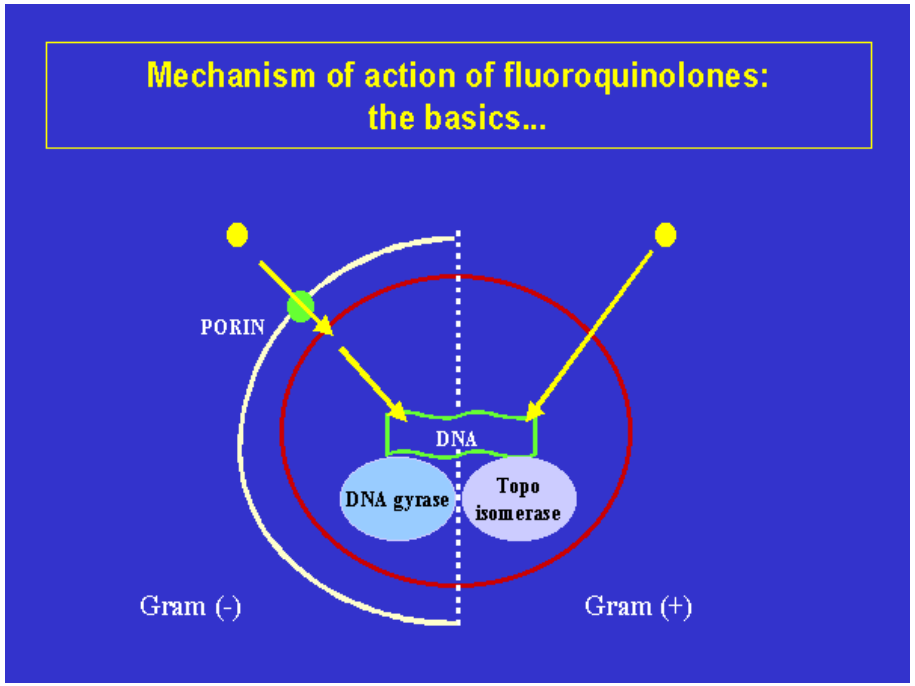


Classification based on spectrum of activity

MECHANISM OF ACTION

Drugs act on <u>TWO enzymes</u>

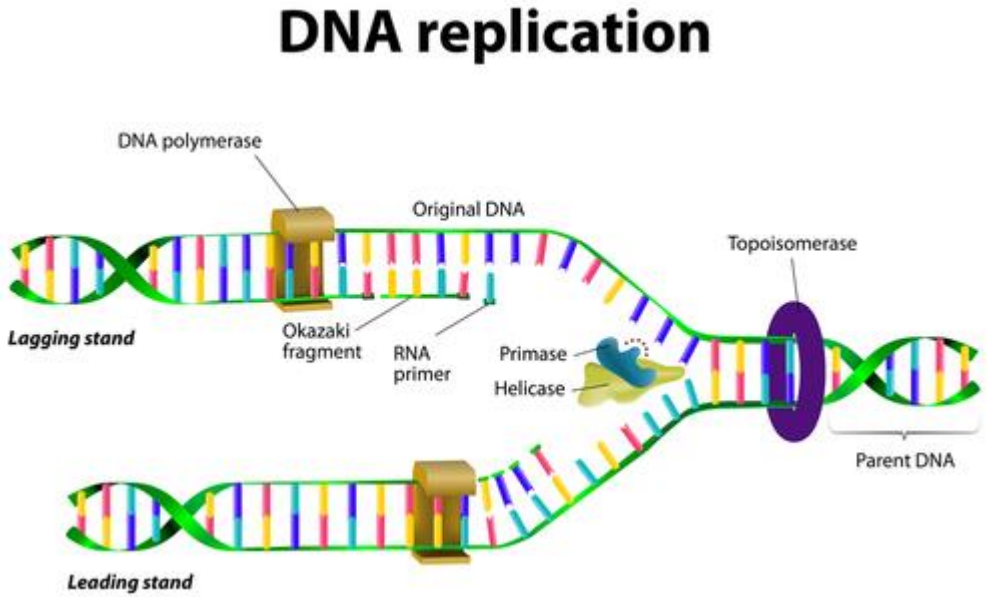
1. Enter bacterium by passive diffusion
2. Entry is through water filled pores (Porin)
3. Once inside- drugs act on these two enzymes preventing DNA replication



MECHANISM OF ACTION

Drugs act on <u>TWO enzymes</u>

1. DNA Gyrase (Topoisomerase –II)



MECHANISM OF ACTION

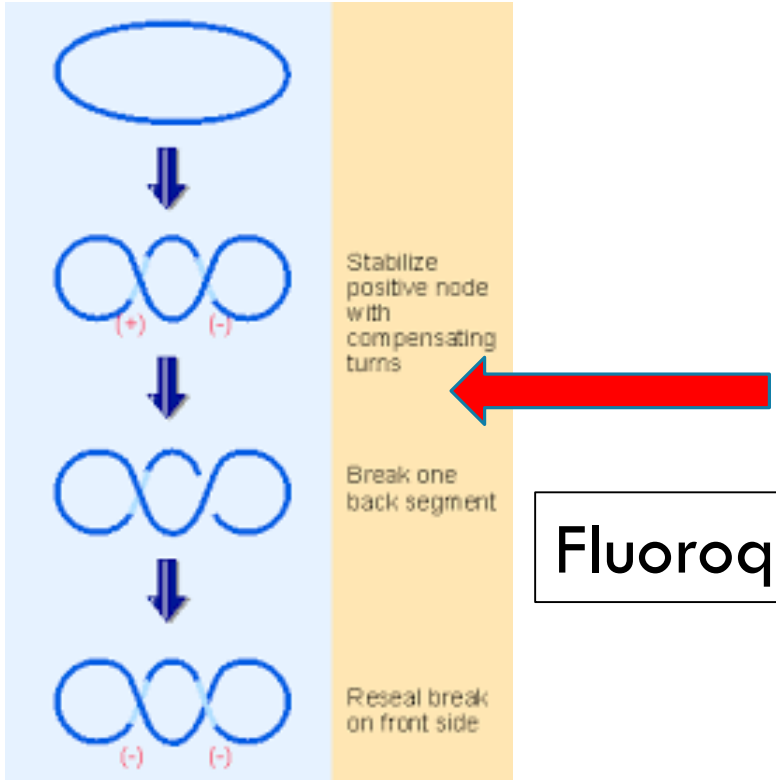
Drugs act on <u>TWO enzymes</u>

1. DNA Gyrase (Topoisomerase –II)

Binding to DNA and enzyme forms a complex that prevents resealing step

Cause cell death by cleavage of DNA

Mostly Gram –ve organism



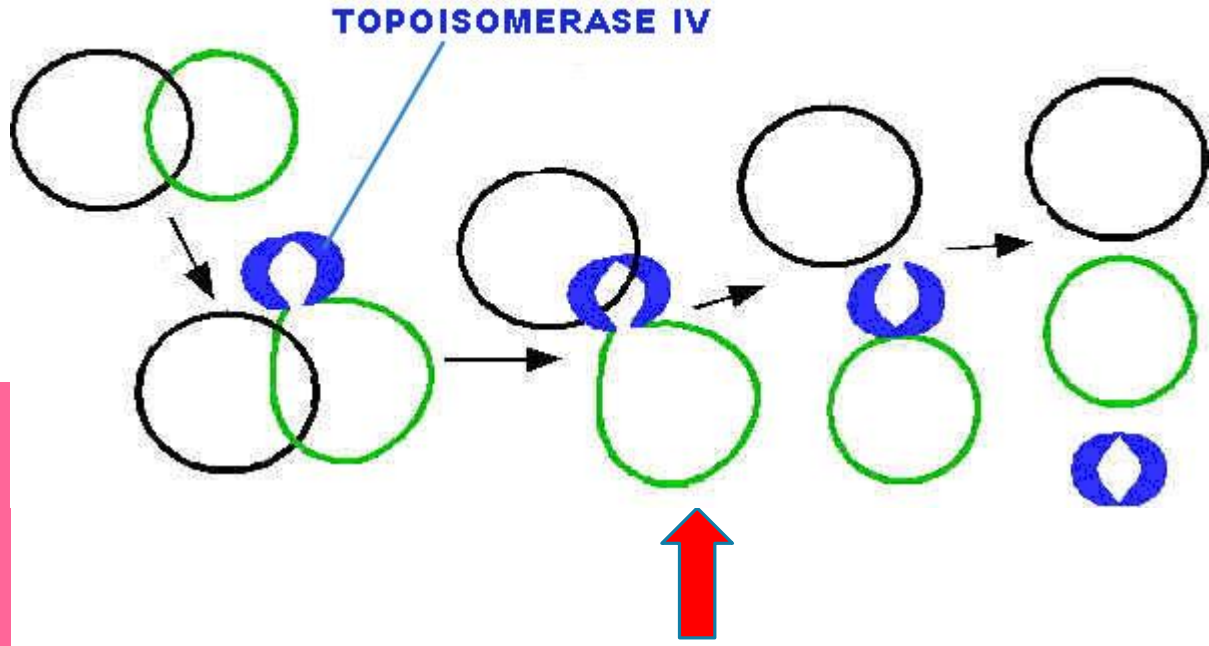
Fluoroquinolones

MECHANISM OF ACTION

Drugs act on <u>TWO enzymes</u>

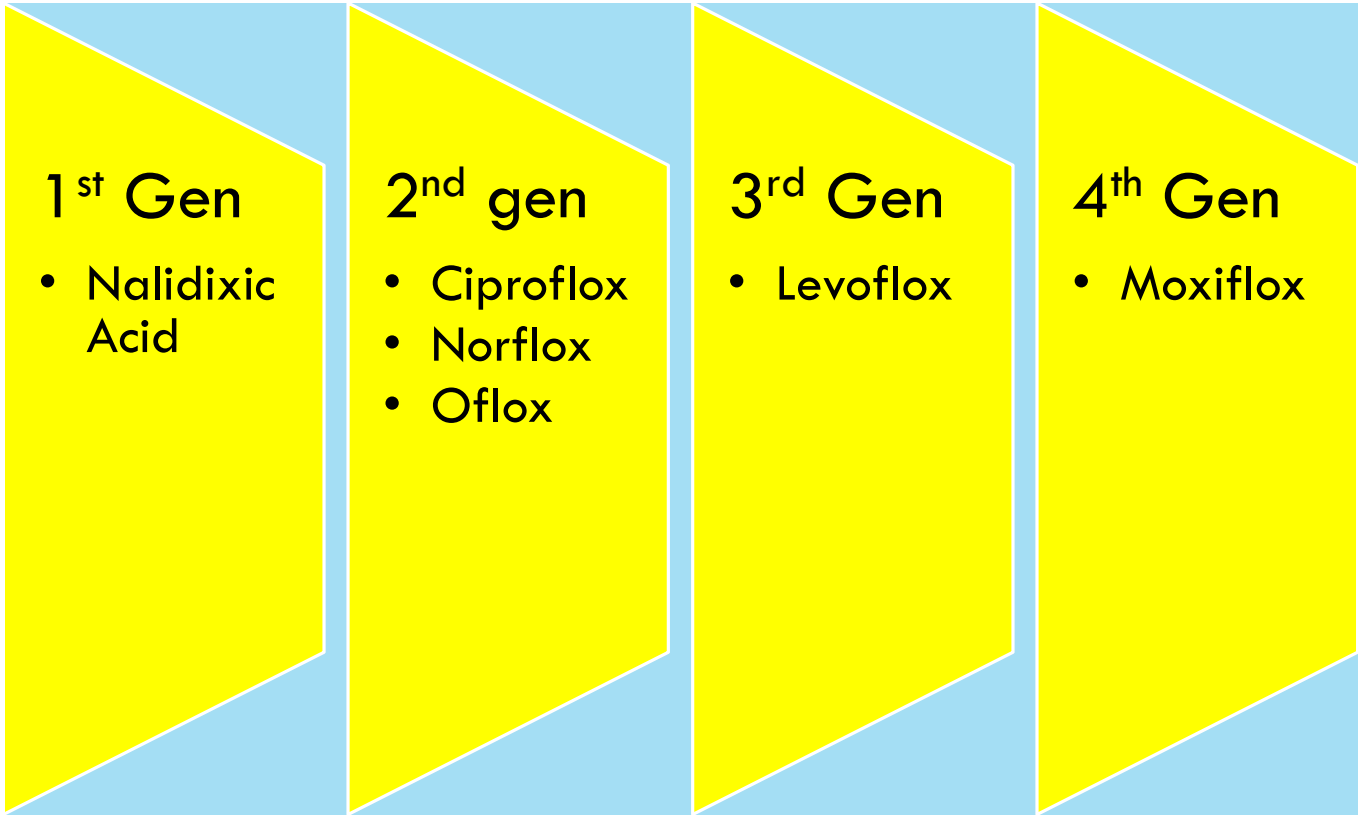
1. Topoisomerase –IV

- Topoisomerase-IV involved in segregating newly formed DNA
- FQ Inhibits this enzyme
- G+ve organism are MORE sensitive to this inhibition



Fluoroquinolones

QUINOLONES



Classification based on spectrum of activity

ANTIMICROBIAL SPECTRUM

FIRST GENERATION

- Gram –ve
- Moderate G-ve activity
- Minimal concentration achieved
- Restricted to minor UTI

SECOND GENERATION

- G+/G-
- Atypical bacteria (Mycoplasma, Chlamydia)

THIRD GENERATION

- Expanded activity against G+/G-
- Improved activity against Atypical organism

FOURTH GENERATION

- Improved G+
- Maintained G-
- Anaerobic coverage as well

Gram negative

- Enterobacteria
- Pseudomonas species
- H.Influenzae

Gram Positive

- Streptococcus
- Staphyococcus

ADME

❖ Absorption:

1. **Good Oral absorption** (85-95 %) except Norflox
2. IV prep of Cipro, Levoflox available
3. Heavy metals known to chelate & lower absorption
4. Food known to lower bioavailability

❖

ADME

❖ Distribution & Elimination:

1. Protein bound 10 – 30 %
2. Well distribution across tissues, concentrated in Kidney
3. Concentrated in **Macrophages** & **Neutrophils**
4. Therapeutic levels in lungs and bones
5. **Poor distribution in CNS** except Ofloxacin
6. Substantial **excretion and re-absorption in colon**

ADME

❖ Elimination:

1. Metabolism of Fluoroquinolones varies considerable
2. Some cleared by **Kidney** while some by **Liver,** while some by **Both**
3. **Dose reductions** in case of **poor Renal or Liver function**
4. **Potent inhibitors of liver enzymes,** can affect PK of other drugs

MAJOR CLINICAL USES

- Complicated UTI (P. Aeruginosa)
- Anthrax (Prophylaxis and Treatment)
- Gastro-intestinal Tract Infections (Diarrhea due to enteric pathogens)
- Resistant Respiratory Tract infections (Acute Pneumonia, Bronchitis)
- Atypical bacterial infections
- Multi Drug Resistance TB

CLINICAL USES OF IMPORTANT DRUGS

❖ Ciprofloxacin

1. Systemic levels effective against many systemic infective agents
2. Effective against G-ve such as Enterobacteria (E.coli), Pseudomonas.A
3. Good alternative to more toxic aminoglycosides
4. Commonly used against typhoid fever
5. Role in resistant TB in Combination with beta-lactam antibiotics
6. Drug of choice in Anthrax

CLINICAL USES OF IMPORTANT DRUGS

❖ Norfloxacin

1. Effective against G-ve (P.Aeruginosa) & G+ve in treating UTI's, Prostatitis
2. Drug not effective in treating systemic infections due to poor bioavailability

❖ Levofloxacin

1. Isomer of Oflox, replaced Oflox clinically
2. Treatment of prostatitis (E.Coli), STD
3. Used in wide range of infections (Respiratory infections) due to broad spectrum

CLINICAL USE SUMMARY

Name	Oral BA %	Half Life (hours)	Clearing Organ	Dose	Indications
Norflox	30-40	3-4	Kidney/Liver	400mg BID	UTI, Prostatitis
Lomeflox	~90	6-8	Kidney	400mg OD	
Cipro	60-70	3-5	Kidney/Liver	250mg OD, 250-750mg BID	UTI, Skin, Soft tissue, Bone , joint infections esp G+ve
Oflox	95	5-7	Kidney	200-400 mg OD	
Peflox		8-13	Liver	400mg BID, IV	
Sparflox	➢ 90	21	Kidney	500mg OD	Similar to above, preferred in acquired pneumonia
Levoflox		6-8	Kidney/Liver	400mg OD	
Moxiflox		12	Liver	300mg OD	

ADVERSE REACTIONS

❖ Overall well tolerated

1. GI Tox: Most common (nausea, Vomiting, Diarrhea)
2. CNS Issues: headache, dizziness
3. Phototoxicity
4. Connective Tissue problems: Tissue erosion, contraindicated in Nursing mothers, Kids (Black Box Warning Added)
5. Cardiac events: Moxiflox & others prolong QTc Interval, care advised for cardiac patients (prone to Arrhythmia)
6. DDI: Cipro, Oflox are CYP Inhibitors, potential for DDI (Increase conc of CYP substrates)

MOXIFLOXACIN QT PROLONGATION

Cardiol J. 2008;15(1):71-3.

Moxifloxacin-induced torsades de pointes.

Sherazi S[1], DiSalle M, Daubert JP, Shah AH.

⊕ Author information

Abstract

Torsade de pointes (TdP) is increasingly recognized as a complication of drug therapy. The most common cause of drug-induced QT prolongation is inhibition of the rapidly activating component of the delayed potassium current (I(Kr)). Moxifloxacin, a widely used fluoroquinolone, is a weak I(Kr) inhibitor and has been associated with QT prolongation. We report a case of marked QT prolongation (618 ms) and TdP associated with moxifloxacin use. Although it is difficult to predict which patients are at risk from TdP, careful assessment of the risk/benefit ratio is important before prescribing drugs known to cause QT prolongation.

J Biopharm Stat. 2010 May;20(3):497-507. doi: 10.1080/10543400903581945.

Statistical characteristics of moxifloxacin-induced QTc effect.

Yan LK[1], Zhang J, Ng MJ, Dang Q.

⊕ Author information

Abstract

Moxifloxacin has been the most commonly used positive control in "thorough" QTc (TQT) studies. In a TQT study, the assay sensitivity is often considered to be established if the baseline corrected mean difference in QTc between moxifloxacin and placebo is greater than 5 ms in common practice at one or more prespecified time points and the observed moxifloxacin induced QTc effect over time follows the proper pharmacokinetics profile. To better understand the statistical characteristics of moxifloxacin-induced QTc prolongation and to provide guidance for future studies, 20 TQT studies that involved moxifloxacin have been evaluated. We study the QTc profile of the baseline adjusted mean difference in QTc between moxifloxacin and placebo over time. Zhang (2008) proposed that the moxifloxacin induced QTc effect can be evaluated between 1 and 4 h after a

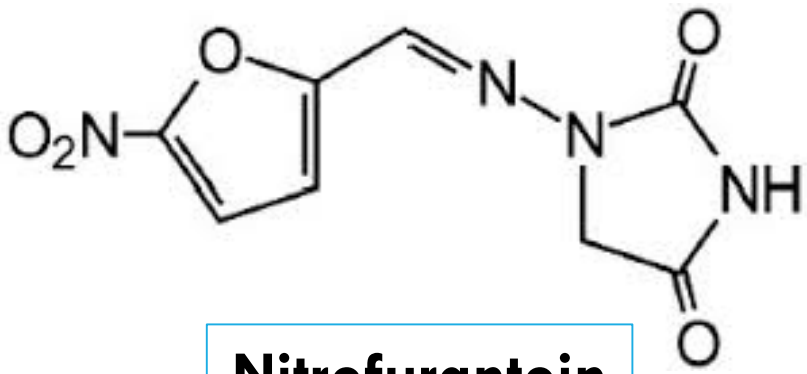
DRUG RESISTANCE

- Optimism of NO resistance initially
- Resistance due to chromosomal mutations
- Biochemical mechanism of resistance

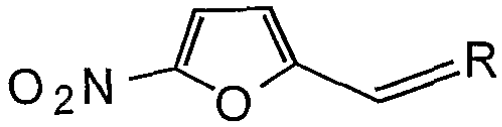
1. Altered target : Changes in Gyrase enzyme
2. Decreased accumulation: Either by less number of porins or efflux pumps

NITROFURANS

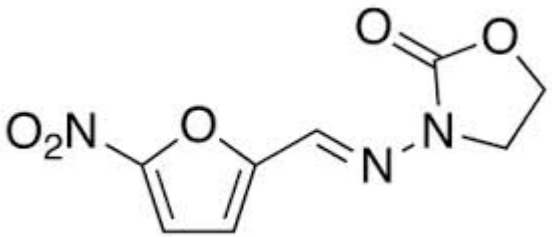
- Originally discovered by Dodd & Stillman in 1944



Nitrofurantoin



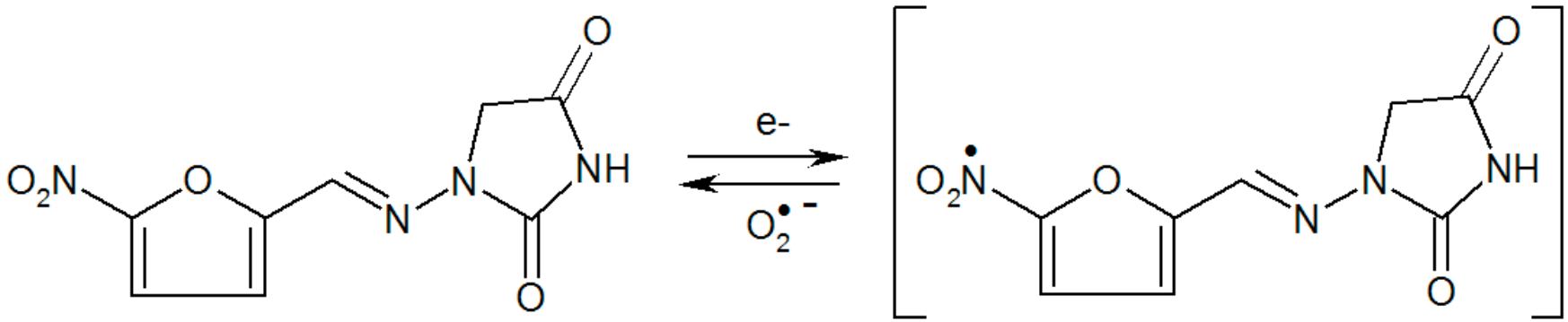
Nitrofurans



Furazolidone

MECHANISM OF ACTION

1. Drug gets reduced by inside bacterial cell by reductase
2. Reduced intermediates active, attack ribosomes & Bacterial DNA
3. Complex leads to Damage bacterial DNA



SPECTRUM OF ACTIVITY

- Class is active against G+ve/G-ve
- Some also have ant-protozoal (Furazolidone) and anti-fungal activity (Nifuroxime)
- Nitrofurantoin is active against common urinary tract pathogens
- Active against E.Coli (Most common, causing 80% UTI)
- Furazolidone used in GI infections (Bacterial dysentery, enteritis)
- Nifuroxime effective against fungus Candida Albicans causing vaginal infections

ADME & DOSING

- Orally administered; Rapidly & completely absorbed by GI tract
- Unfortunately levels are low in plasma as rapidly cleared by Kidney (NOT bacteriostatic, No use in systemic infections)
- Plasma half life is 03 – 1 hr
- Almost 40 % excreted in Urine, Bactericidal conc in Urine
- Used exclusively as Urinary antiseptic, renewed interest due to resistance to other drugs
- Susceptible bacteria rarely develop resistance
- Typical dose of Nitrofurantoin: 100 mg daily for susceptible UTI

NITROFURANTOIN

❖ Adverse Events:

1. GI: Discomfort, nausea, vomiting
2. Polyneuritis in kidney failure patients
3. Rarely can develop hemolytic anemia with G6PD deficiency
4. Avoided in pregnancy and infancy