SHEET NO.

# PHARMACOLOGY

## DOCTOR 2019 | MEDICINE | JU


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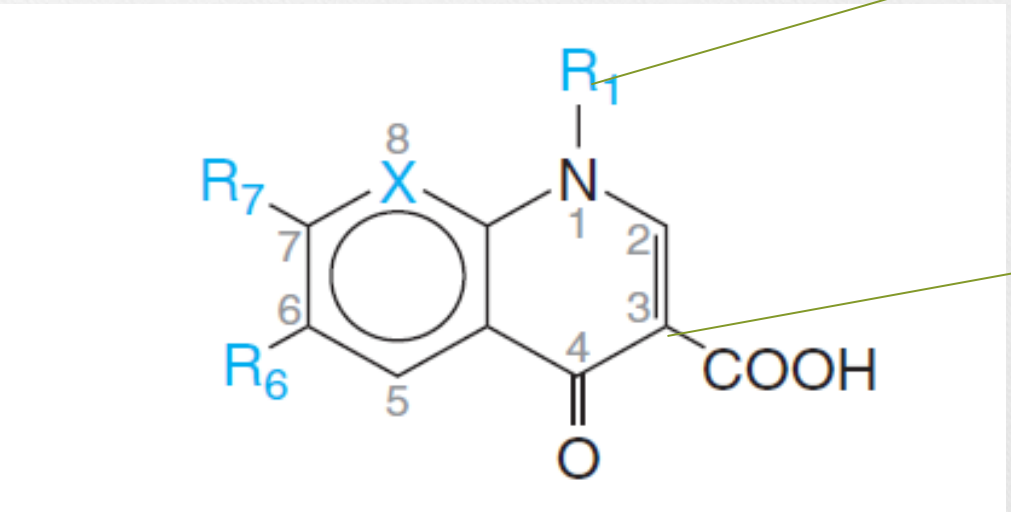
SCIENTIFIC CORRECTION :

GRAMMATICAL CORRECTION :

DOCTOR : Manar alzrikat

# Quinolones( as a second group of antibiotics) available for use are containing a carboxylic acid moiety at position 3 of the primary ring structure

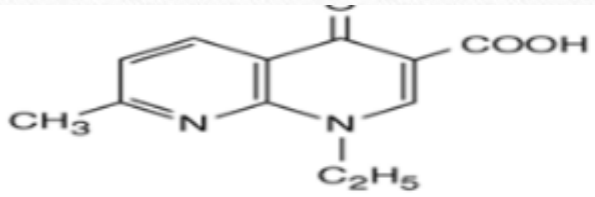
**In all compound related to quinolones there is a carboxylic group at c3 which must to be present in the structure of chromophore which presents in all quinolones all the time)**



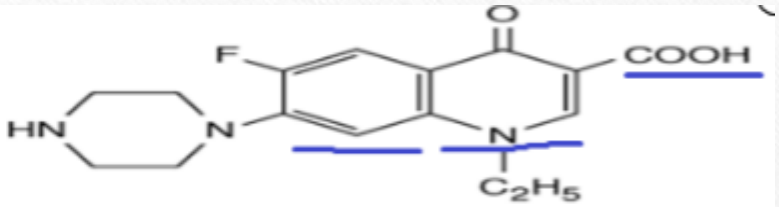

R groups differ from one compound to another depending on the structure

what is in the **blackish color** here usually repeated in these compound

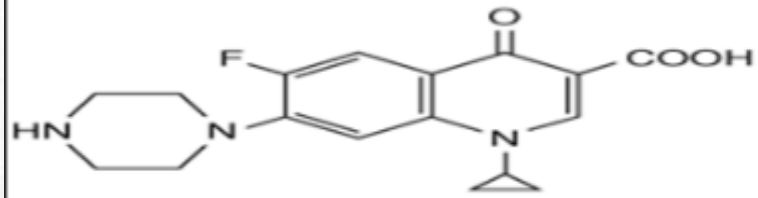
# Quinolones.



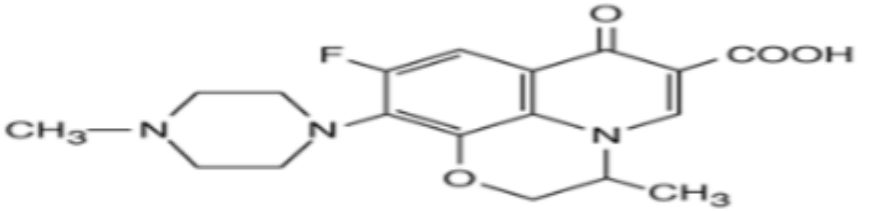

**Nalidixic acid**



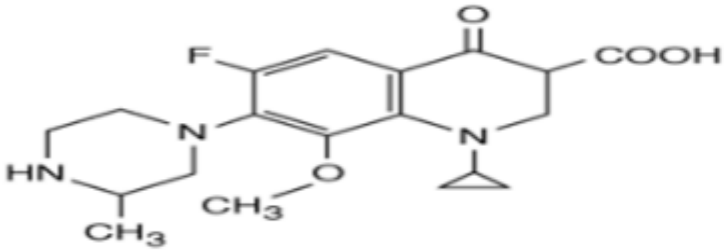

**Norfloxacin**



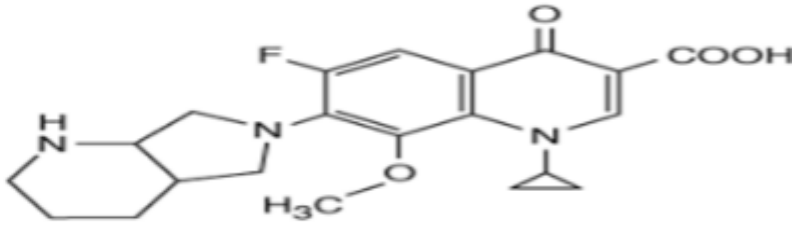

**Ciprofloxacin**



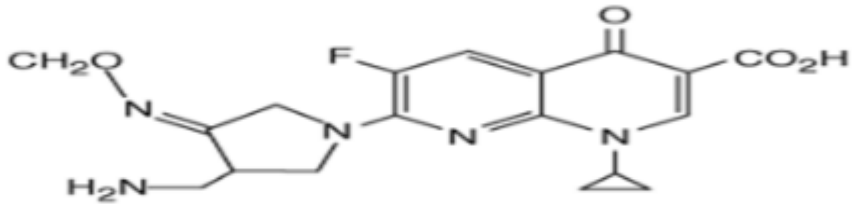

**Levofloxacin**




**Gatifloxacin**

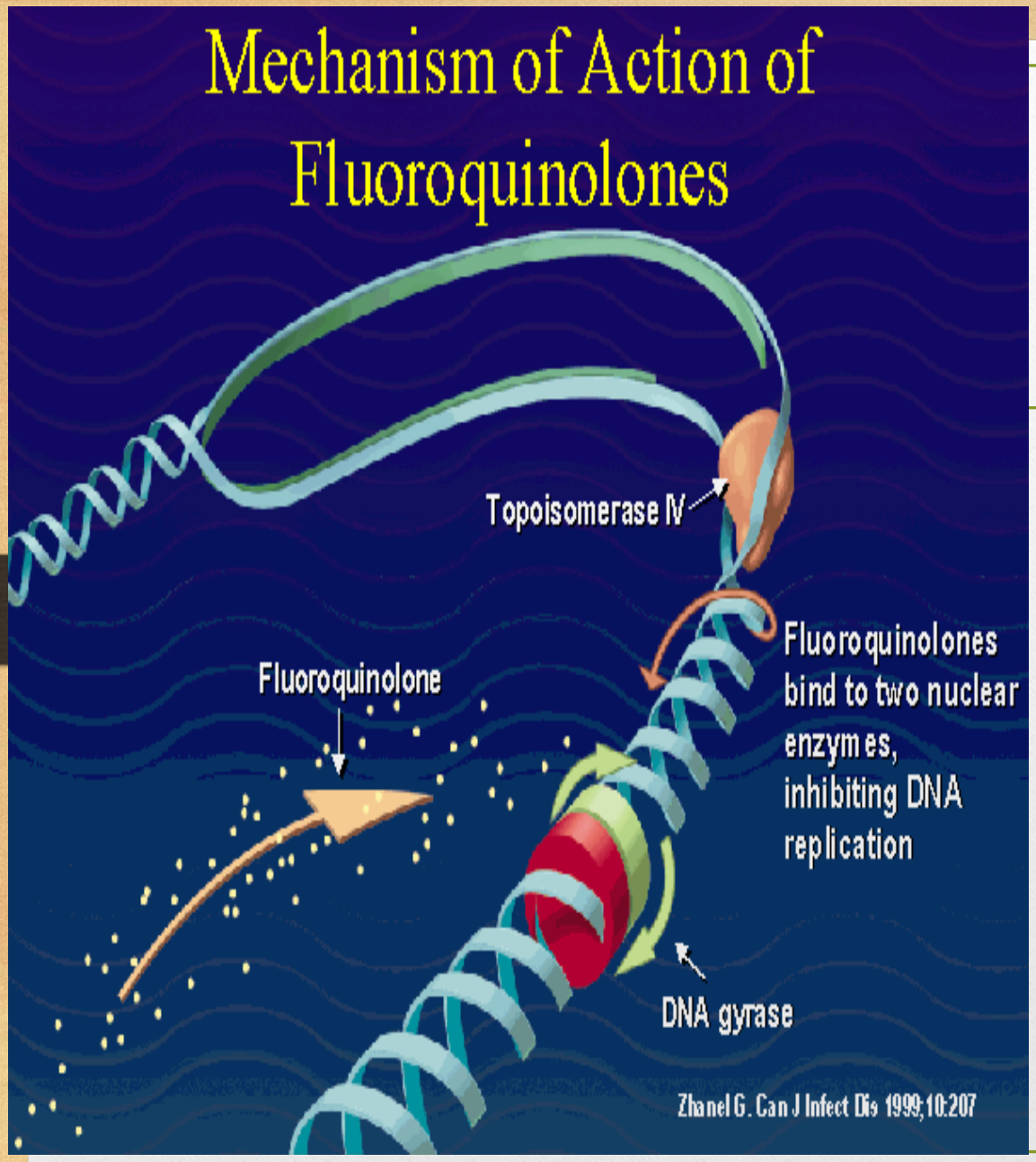



**Moxifloxacin**




**Gemifloxacin**

Just check what we talked about the structure in the previous slide (don't memorize them )




**the mechanism of action of Fluoroquinolone depends directly on inhibiting two major enzymes involved in the replication of bacterial DNA which are Topoisomerase 4 & DNA gyrase**

**( يعني احنا عطلنا اهم انزيمين لعملية انقسام البكتيريا )**

## The quinolone antibiotics target bacterial DNA gyrase and Topoisomeras which is responsible for the continuous introduction of negative supercoils into DNA

حسب كلام الدكتورة :فتخيلوا سلك معكم حاولتوا تثنوه بعدين بلشتوا تبرموا فيه او تلفوا فيه بشكل مستمر لحد ما وصل لنقطة مش قادر يتحمل ضغط اكتر من هيك

حتى نستطيع الاستمرار بعملية لف السلك لا بد انه نخفف الضغط عليه من الجهة الاخرى كإنه بندخل **Negative supercoils**

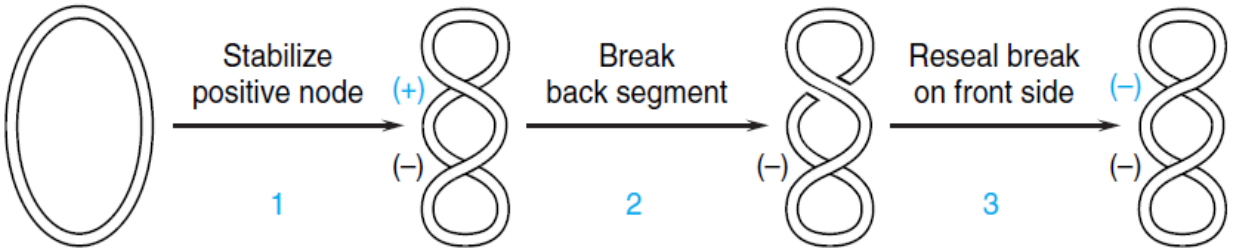
يعني من جهة بنزيد الضغط على السلك و من الجهة الثانية بنفك السلك

و عمل الانزيمات الي ذكرناهم بشبه هذا الكلام همه بقوموا بنوع من الفك خلال عملية النسخ

**So to continue the replication process the strands of double-helical DNA must be separated from one side and replication satarts but the other side will have severe stress, and these enzymes will reduce this stress**

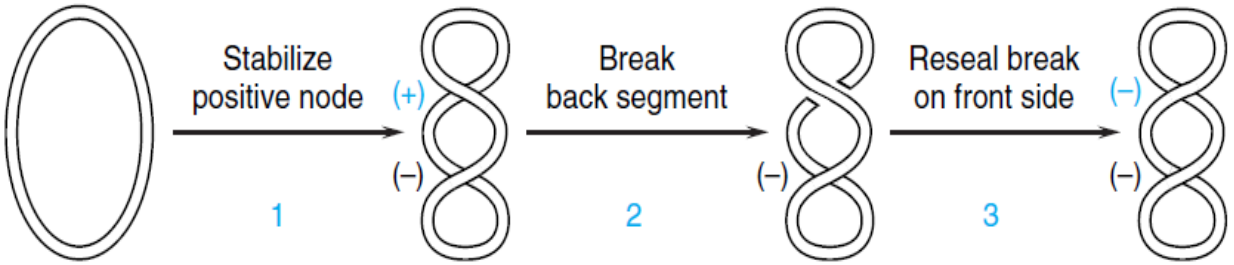
**So When we use quinolone antibiotic, it will target these two enzymes and the replication will not continue**

# More explanation for the same idea




**The individual strands of double-helical DNA must be separated to permit DNA replication or transcription. However, anything that separates the strands results in "overwinding" of the DNA. To combat this mechanical obstacle, the bacterial enzyme DNA gyrase is responsible for the continuous introduction of negative supercoils into DNA**

## How do the two enzymes work?

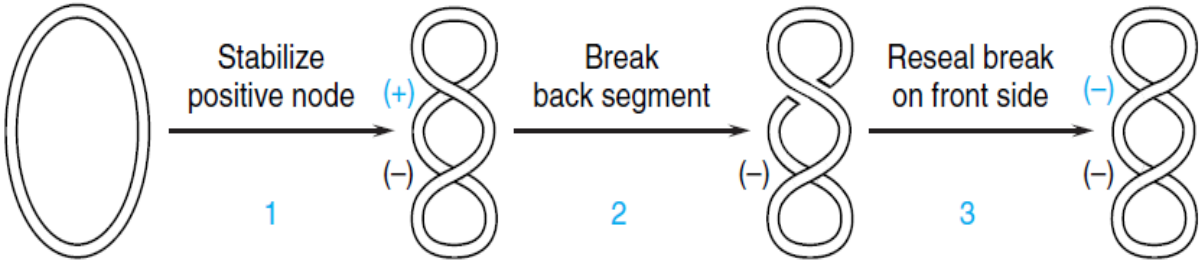



The enzyme binds to two segments of DNA (1), creating a node of positive (+) superhelix. The enzyme then introduces a double-strand break in the DNA and passes the front segment
through the break (2). The break is then resealed (3), creating a negative (–) supercoil.

nicking and closing are the reasons that make the replication continuous .

Quinolones consider efficient to treat many serious diseases and still using because they work on 2 enzymes

**Quinolones inhibit the nicking and closing activity of the gyrase and also block the activity of topoisomerase IV**



# The 3rd group of antibiotics is Nitrofurans (Nitrofurantoin)

## Chemistry and Mechanism of Action

- A number of **5-nitro-2-furaldehyde** derivatives, called nitrofurans,
- are used in the treatment and/or prophylaxis

of microbial infections, primarily in the **urinary tract**

- modify various bacterial

macromolecules that affect a variety of biochemical processes (e.g., **DNA and RNA synthesis, protein synthesis**

## Why the nitrofurans will not affect the human cell ?

It is presumed that the nitrofurans are selectively toxic to microbial cells because in humans, the **slower reduction** by mammalian cells( compared to the bacterial cells) with prevents high serum concentrations

Nitrofurantoin is primarily active against gram-negative bacteria (E. coli, P. mirabilis is variable) and some susceptible gram-positive organisms, such as S. aureus and Enterococcus faecalis

Development
of resistant strains is virtually unknown, and cross resistance
with other antimicrobials has not been reported(because it works on more than one factor or step so it considers a strong antibiotic with resistance)

**Because**

Intermediate metabolites modify various bacterial macromolecules that affect a variety of biochemical processes (e.g., DNA and RNA synthesis, protein synthesis);
this observation may explain the lack of resistance development to these drugs.

## Clinical Use

- The singular indication for nitrofurantoin is the treatment and **long-term prophylaxis** of lower UTIs caused by susceptible bacteria
- it is not used as a bacterial suppressant.
- It is often used **prophylactically** post intercourse in women with chronic UTIs.
- It considers prophylaxis on long term and this means that it can't be used to
- treat onset acute infections (preventive manner rather than a curative manner)
- The bacteriostatic or bactericidal activity of nitrofurantoin

is concentration dependent; a urinary concentration greater than 100 ug/mL ensures bactericidal activity

Nausea and vomiting are the most commonly observed adverse effects.

## Methenamine (an example about Nitrofurans)

- Methenamine (hexamethylenetetramine) is an **aromatic acid**
- hydrolyzed at an acid pH (less than 6) to liberate **ammonia** and the active alkylating agent **formaldehyde**
- **formaldehyde denatures protein and is bactericidal.**
- Methenamine is usually **administered as a salt**
- this salt is either mandelic (Mandelamine) or hippuric (Hiprex, Urex) acid.
- these **acids acidify the urine**, which is necessary to generate formaldehyde.
- also, the resulting low urine pH is by itself bacteriostatic for some organisms
- **So it works on stimulating the Acidity in urinary tract (bacteriostatic) and formaldehyde that's result after Salt dissolution (bactericidal)**

- Methenamine is **administered orally and is well absorbed from the intestinal tract**.

- **10 to 30% decomposes in the stomach unless the tablets are protected by an enteric coating.**
- **So enteric coating increases the efficiency of methenamine by lowering the**
- **decomposition of it in the stomach ( by protecting it from stomach acidic**
- **Secretions)**
- **The inactive form (methenamine) is distributed to virtually every body fluid.**
- **Inactive form means (not efficient (not formaldehyde ) and its mostly ammonia which will Distribute for every part within the body )**
- **Almost all of the methenamine moiety is excreted into the urine by 24 hours**

•Methenamine is primarily used for the long-term prophylactic or suppressive therapy of recurring UTIs for people who suffer from chronic UTIs

•It is not a primary drug for therapy of acute infections its prophylactic agent

• prophylactic agent to avoid any future infection

It should be used to maintain sterile urine after appropriate antimicrobial agents have been employed to eradicate the infection.

long term urine sterilizer ( someone who just recovered from acute
infection ( a stronger antibiotic rather than methenamine was used
in his treatment ) then we give him methenamine to ensure no other infections will
arise and to keep the urine sterile from any bacteria ).