iJRASET
International Journal For Research in Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 13 **Issue:** IX **Month of publication:** September 2025

DOI: https://doi.org/10.22214/ijraset.2025.74036

www.ijraset.com

Call: 08813907089 | E-mail ID: ijraset@gmail.com

International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.538
Volume 13 Issue IX Sep 2025- Available at www.ijraset.com

Gepotidacin: A Novel Therapeutic Agent for Gonorrhoea Treatment

Dr. Garlapati Usha Kiran[1], Guntru Pavan Kumar[2], Gollamudi Nehemiah[3], Kankanala Uma Satya Manikanta[4], Loya Pavan Kumar[5], Maareedu Mahesh[6]

Professor, HOD Department of Pharmacology, NRI College Of Pharmacy, Pothavarappadu, Agiripalli, Eluru district
[2, 3,4 ,5, 6]IV B PHARMACY STUDENT , NRI College Of Pharmacy, Pothavarappadu, Agiripalli, Eluru district

Abstract: ***Gepotidacin is an exciting new oral antibiotic that's currently in Phase III trials, targeting uncomplicated urinary tract infections (UTIs) and urogenital gonorrhoea. 1.It works by blocking two essential topoisomerase enzymes that are vital for bacterial DNA replication. The early results from Phase II trials are looking quite promising, and if it gets approved, it could be the first new oral antibiotic for UTIs in over twenty years! To get a better understanding of how it interacts with other medications, Phase I studies were carried out with healthy volunteers to assess gepotidacin's drug drug interaction (DDI) profile. When taken with the CYP3A4/P-glycoprotein (P-gp) inhibitor itraconazole, there was a modest increase in the area under the curve (AUC) by about 48–50%. On the other hand, rifampicin, a strong CYP3A4 inducer, significantly reduced gepotidacin's plasma AUC by 52%, indicating a moderate DDI. No major interactions were observed with cimetidine, although some biomarkers suggested a partial inhibition of organic cation transporters. Interestingly, gepotidacin didn't act as a DDI perpetrator for P-gp or CYP3A4, but it did slightly elevate the plasma levels of digoxin and showed weak inhibition of CYP3A4 when combined with midazolam. These insights will be crucial for ensuring the safe clinical use of gepotidacin alongside other medications.***

Keywords: ***Gepotidacin,Oralantibiotic,Phase III trials,Urinary tract infections (UTIs), Urogenitalgonorrhoea, Topoisomeraseenzymes, DNAreplication,Phase II trials,Drug–drug interaction (DDI),CYP3A4,P-glycoprotein.***

I. INTRODUCTION

The ongoing emergence and spread of antimicrobial resistance (AMR) among Gram-negative organisms pose a major global public-health challenge. Two of the most frequently encountered Gram-negative infections are urinary tract infections (UTIs) and urogenital gonorrhoea. In 2019[1], the uropathogen*Escherichia coli* was ranked the second leading bacterial cause of death worldwide.

Gonorrhoea is a sexually transmitted infection (STI) produced by the bacterium *Neisseria gonorrhoeae*. The infection can affect the genital tract, oral cavity, or rectum. It is the second most common bacterial STI and incidence is climbing globally. Transmission typically occurs through sexual contact with an infected partner, and it can also be passed from mother to child during delivery. Infected men may report pain or a burning sensation when passing urine, penile discharge, or testicular pain. Women may present with dysuria, abnormal vaginal discharge, intermenstrual bleeding, or pelvic pain. In the United States, the Centers for Disease Control and Prevention (CDC) documented that gonorrhoea rates in 2018 had risen by 82.6% relative to the historic nadir observed in 2009[2].

Approximately 468,500 gonococcal cases were reported in the United States in 2016 an 18.5% rise from 2015 while Europe reported about 66,000 cases in 2014, marking a 25% increase from 2013. If left untreated, gonococcal infection may result in pelvic inflammatory disease (PID), infertility in both sexes, ectopic pregnancy, tubo-ovarian abscess, neonatal conjunctivitis, and disseminated disease.

The History and Evolution of Gonorrhea: A 300-Word Summary

Back around 2600 BC, gonorrhea was one of the first sexually transmitted illnesses (STIs) ever discovered. For what reason is this? In Chinese medical writings, BC. 1. The symptoms were described by Galen and Hippocrates as "gonorrhea," "strangury," and "flow of seed." The sickness is also described in Roman and medieval documents, with many people connecting it to to immorality and blameblaming women. It is possible that the slang term "The Clap" was coined from the names of symptoms, rough remedies, or Les Clapierres, a French brothel district.

Legislation was passed in England (1161) and France (1256) to control Gonorrhea. Gonadotropin was rapidly disseminated among soldiers in battle, from the Romans to those engaged in the Crimean War. It wasn't until Philippe Ricord's 1838 work that unified the conundrum of syphilis, proving that each of them was a distinct illness. Additional advancements in diagnosis and treatment included the Credé method for preventing neonatal infections and also the NAAT test, which is widely recognized as the gold standard. However.

Antibiotics were created using treatments that utilized mercury and silver.. Resistance to sulfa drugs and penicillin was first identified in the 1940s, after their initial effectiveness. During the 1950s, 1980s (decade), there was an increase in resistance to tetracyclines, ciprofloxacin, and azithromycin. Canadian resistance remains low (less than 0.3%), and ceftriaxone and its cefixime are the most effective current treatments of cephalosporins. Why? A 500 mg increase in the dose of ceftriaxone is necessary to prevent resistance.

Canada has only reported isolated cases of drug-resistant gonorrhea, and it's extremely rare. Surveillance, public health measures, and new therapies will soon be necessary due to the pressing threat posed by evolutionists. The long and complex history of Gonorrhea is a reflection of both scientific progress and changes in attitudes towards sex, disease, and stigma.

SIGNS AND SYMPTOMS:

In women

In women, the major genitourinary manifestations include:

Vaginal discharge typically the most common symptom, arising from endocervicitis and often described as thin, purulent, and mildly malodorous, though many women have minimal signs of cervicitis.

- Dysuria.
- Intermenstrual bleeding.
- Dyspareunia (painful intercourse).
- Mild lower abdominal pain.

If the infection ascends and progresses to PID, clinical features may include:

- Lower abdominal pain (the most consistent symptom of PID).
- Increased vaginal or mucopurulent urethral discharge**.**

Fig;1 sytoms of gonorrhea

- Dysuria, often without urinary urgency or frequency.
- Cervical motion tenderness.
- Bilateral adnexal tenderness or an adnexal mass.
- Intermenstrual bleeding.
- Fever, chills, nausea, and vomiting (less common).

In men

In males, the principal genitourinary features include:

Urethritis classically producing burning on urination and an initial serous discharge that often becomes more profuse and purulent over several days, sometimes tinged with blood.

- Acute epididymitis: usually unilateral and commonly accompanied by urethral exudate.

- Urethral strictures: now less common in the antibiotic era, but when present can cause diminished or abnormal urine flow and may be complicated by prostatitis or cystitis.
- Rectal infection: may produce pain, itching, discharge, or tenesmus

II. PATHOPHYSIOLOGY

1) Initial Adhesion and Colonization :

Infection begins when gonococci contact mucosal surfaces commonly the urethra, cervix, pharynx, or rectum in adults, and the conjunctiva or pharynx in neonates. Colonization depends on the bacterium's ability to adhere firmly to epithelial cells that line these mucosal sites. Adhesion is primarily mediated by pili (fimbriae), fine filamentous structures that protrude from the bacterial surface and play an important role in early attachment. Pili act like grappling structures that can extend and retract, drawing the organism into close contact with host cells and enabling stable colonization.

2) Role of Surface Proteins in Attachment and Invasion :

In addition to pili, several outer-membrane proteins support adherence and promote invasion. Opacity (Opa) proteins mediate intimate binding to epithelial and immune cells, including neutrophils and macrophages, and contribute to modulation of host responses. Lipo oligosaccharide (LOS), a glycolipid of the outer membrane similar to lipopolysaccharide but lacking extended O-antigen chains, has multiple roles: it facilitates adherence (including interactions with sperm that may aid sexual transmission), contributes to immune evasion, and helps resist complement activity .

3) Invasion of Epithelial Cells:

After firm attachment, *N. gonorrhoeae* triggers host-cell signaling pathways that permit bacterial internalization. A key receptor involved is complement receptor 3 (CR3). Interaction of bacterial pili with CR3 on the
apical surface.

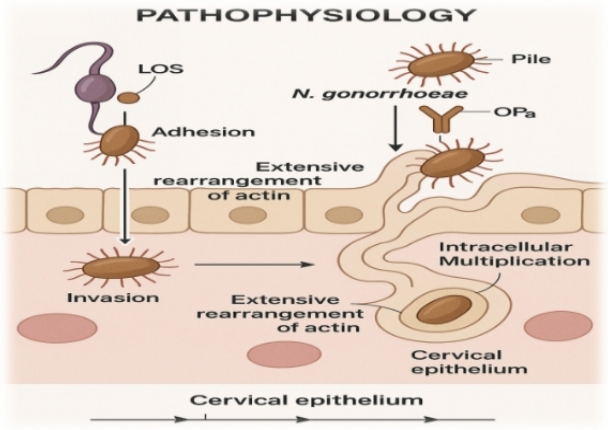


Fig :2pathophysiology oggonorrgea

These ruffles engulf the bacteria and form large intracellular vesicles macropinosomes into which gonococci are internalized. Inside these vesicles the organisms can survive and replicate, partly sheltered from extracellular immune defenses, and later exit to infect neighbouring cells or be shed, promoting transmission .

4) Localized Infection and Tissue Tropism:

Typically, infection remains localized to the site of inoculation commonly the urethra in men and the cervix in women though rectal, pharyngeal, and conjunctival infections may occur depending on exposure. In neonates, vertical transmission can produce ophthalmia neonatorum, a potentially severe eye infection. The symptoms observed at infection sites largely result from the host inflammatory response: components such as LOS provoke neutrophil influx and proinflammatory cytokine release, which lead to pain, swelling, pus formation, and tissue damage.

5) Immune Evasion and Serum Resistance :

Neisseria gonorrhoeae has evolved multiple strategies to escape both innate and adaptive immunity. Antigenic variation allows changes in pili, Opa proteins, and LOS, making it difficult for host antibodies to recognize and clear the organism. Phase variation enables on/off switching of surface proteins like Opa to adapt to changing host environments. Some strains are serum-resistant: they bind host complement-regulatory proteins (for example, factor H or C4b-binding protein), thereby limiting complement activation and preventing bacteriolysis. These combined strategies help gonococci persist despite strong immune responses.

6) Disseminated Gonococcal Infection (DGI) :

Although most gonococcal infections remain localized, certain serum-resistant strains can invade the bloodstream and spread to distant tissues, producing disseminated gonococcal infection (DGI). DGI can manifest as septic arthritis, tenosynovitis, dermatitis, and rarely endocarditis or meningitis. Individuals with complement deficiencies, HIV infection, or women during menstruation are at increased risk for dissemination. Prompt antibiotic therapy is necessary to avert severe complications.

Neisseria gonorrhoeae therefore produces primarily localized disease at mucosal sites of inoculation (urethra, cervix, pharynx, rectum, or neonatal conjunctiva), but certain strains and host factors permit bloodstream spread. The bacterium's capacity to counteract innate and adaptive defenses underlies its persistence and pathogenicity.

III. CLASSIFICATION

A. First-Line Treatment

1) Ceftriaxone: A third-generation cephalosporin commonly used, often in combination with azithromycin.

2) Azithromycin: A macrolide antibiotic used in combination with ceftriaxone in many regimens.

B. Alternative Treatments

1) Cefixime: A third-generation cephalosporin that may be used when ceftriaxone is unavailable.

2) Gemifloxacin: A fluoroquinolone antibiotic that can serve as an alternative option.

C. Emerging Treatments

Gepotidacin: A novel antimicrobial agent that has demonstrated promise for treating gonorrhea, including resistant strains.

DRUG PROFILE

Generic Name: Gepotidacin

Chemical Formula:

C24H28N6O3

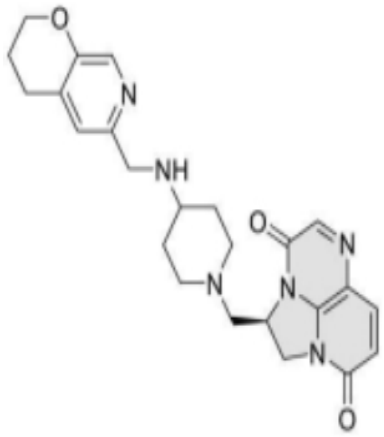


Figure 3:Gepotidacin

Background

Gepotidacin is a first-in-class, bactericidal triazaacenaphthylene antibiotic that disrupts bacterial DNA replication by inhibiting two essential enzymes simultaneously, reducing the likelihood that a single point mutation will confer resistance. The compound's activity is focused on bacterial topoisomerases: it interacts with the GyrA subunit of DNA gyrase and the ParC subunit of topoisomerase IV, with in vitro data showing minimal effect on human topoisomerase IIα. Its mechanism is distinct from other novel agents such as zoliflodacin (a spiropyrimidinetrione that targets GyrB).

Phase III clinical trials are underway or planned to evaluate oral gepotidacin for uncomplicated urinary tract infections (NCT04020341 and NCT04187144) and for urogenital gonorrhea (NCT04010539).

Pharmacokinetics:

Absorption

According to prescribing information for patients with uncomplicated UTI, the steady-state mean Cmax and AUC0–12 are approximately 4.2 µg/mL and 22.8 µg·hr/mL, respectively; oral bioavailability is ~45%.

Volume of distribution

The steady-state Vd in uUTI patients is approximately 172.9 L.

Protein binding

Gepotidacin is ~25–41% protein-bound in plasma.

Metabolism

The drug undergoes primary oxidative metabolism via CYP3A4; M4 is the principal circulating metabolite (~11% of circulating drug-related material).

Route of elimination

Approximately 52% of an administered dose is recovered in feces (about 30% unchanged), and ~31% is recovered in urine (about 20% unchanged). The urinary route predominates for absorbed drug elimination.

Half-life

The terminal half-life at steady state in uUTI patients is about 9.3 hours.

Clearance

Total steady-state clearance is approximately 33.4 L/hr.

Pharmacodynamics

Absorption

- Absolute bioavailability: ~45%.
- Time to peak plasma concentration (Tmax): ~2 hours.
- Peak plasma concentration (Cmax): ~4.2 µg/mL.
- AUC0–12: ~22.8 µg·hr/mL.
- Steady-state achieved by Day 3.

Distribution

- Protein binding: approximately 25–41%.
- Volume of distribution (Vd): ~172.9 L.

Metabolism

- Primary metabolic pathway: oxidative metabolism via CYP3A4.
- Major circulating metabolite: M4 (~11% of circulating drug-related material).

Elimination

- Terminal half-life: ~9.3 hours.
- Total clearance: ~33.4 L/hr.

Excretion

- Feces: ~52% of the dose (≈30% unchanged).
- Urine: ~31% of the dose (≈20% unchanged) the major route for absorbed drug.

.

IV. MECHANISM OF ACTION

Gepotidacin's bactericidal effect stems from selective disruption of bacterial DNA maintenance enzymes DNA gyrase (topoisomerase II) and topoisomerase IV[5] both critical for replication, transcription, recombination, and cell division. Unlike fluoroquinolones, gepotidacin binds to a distinct site on these enzymes. Structural studies indicate that it interacts with the catalytic subunits (GyrA and ParC) in a pocket formed at the protein DNA interface, positioning between the two scissile DNA bonds where cleavage normally occurs[6]. By stabilizing the cleaved complex and preventing re-ligation of DNA strands, gepotidacin causes accumulation of DNA breaks that lead to bacterial cell death. Because its binding site differs from fluoroquinolones and other classes, gepotidacin has reduced cross-resistance and retains activity against many strains resistant to existing antibiotics, making it a promising therapeutic for multidrug-resistant pathogens including *E. coli*, *N. gonorrhoeae*, and *Staphylococcus saprophyticus[7]*.

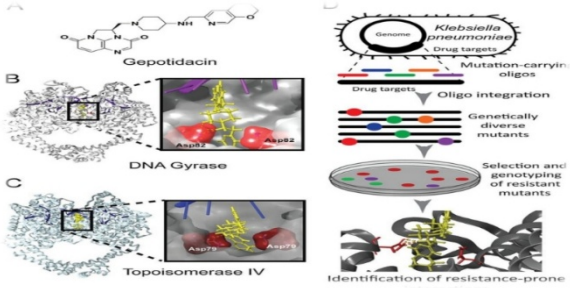


Figure 4: Gepotidacin mechanism of action

V. CONCLUSION

Gepotidacin represents a promising new approach to the treatment of gonorrhea, especially in the face of growing antimicrobial resistance. As a novel antibiotic targeting bacterial DNA gyrase and topoisomerase IV, it demonstrates efficacy against Neisseria gonorrhoeae, including strains resistant to current first-line therapies. Clinical trials have shown that gepotidacin offers an effective oral alternative with a favorable safety profile, making it a potential breakthrough in gonorrhea treatment.

The rise of drug-resistant gonococcal infections poses a significant challenge to public health, and gepotidacin's unique mechanism of action provides hope for overcoming this issue. Although further studies are needed to fully assess long-term safety, resistance development, and its role in combination therapies, gepotidacin holds the potential to significantly improve gonorrhea treatment and reduce the burden of resistance in the future.

Ultimately, gepotidacin's ability to address the urgent need for effective treatment options makes it a promising candidate in the ongoing fight against gonorrhea and antibiotic resistance.

BIBLIOGRAPHY

[1] GBD 2019 Antimicrobial Resistance Collaborators. Global mortality associated with 33 bacterial pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2022; 400: 2221–48.

[2] Centers for Disease Control and Prevention. Sexually transmitted disease surveillance. Availableat: https://www.cdc.gov/std/stats18/STDSurveillance2018-full-report.pdf. Accessed May 2023.9

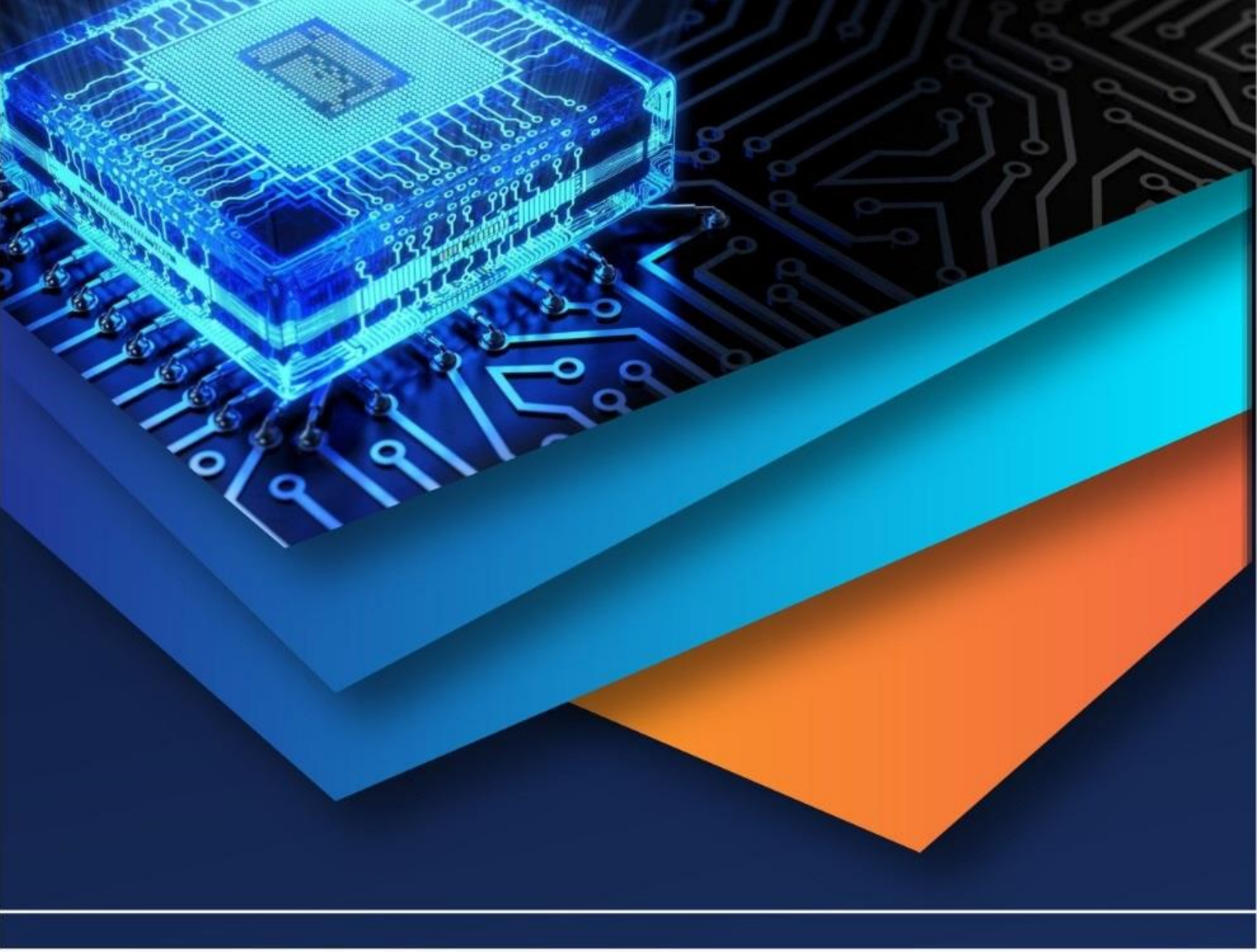
[3] Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2019.

[4] Unemo M, Shafer WM. Antimicrobial resistance in Neisseria gonorrhoeae in the 21st century: past, evolution, and future. Clin Microbiol Rev. 2014 Jul;27(3):587-613. [PMC free article] [PubMed]

[5] Ross JE, Scangarella-Oman NE, Flamm RK, Jones RN: Determination of disk diffusion and MIC quality control guidelines for GSK2140944, a novel bacterial type II topoisomerase inhibitor antimicrobial agent. J Clin Microbiol. 2014 Jul;52(7):2629-32. doi: 10.1128/JCM.00656-14. Epub 2014 Apr 23. [Article]

[6] Collins JA, Osheroff N: Gyrase and Topoisomerase IV: Recycling Old Targets for New Antibacterials to Combat Fluoroquinolone Resistance. ACS Infect Dis. 2024 Apr 12;10(4):1097-1115. doi: 10.1021/acsinfecdis.4c00128. Epub 2024 Apr 2. [Article]

[7] Gibson EG, Bax B, Chan PF, Osheroff N: Mechanistic and Structural Basis for the Actions of the Antibacterial Gepotidacin against Staphylococcus aureus Gyrase. ACS Infect Dis. 2019 Apr 12;5(4):570-581. doi:10.1021/acsinfecdis.8b00315. Epub 2019 Feb 28.



10.22214/IJRASET

45.98

IMPACT FACTOR: 7.129

IMPACT FACTOR: 7.429

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY