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CIPROFLOXACIN AND ITS PHARMACOKINETIC PROPERTIES

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ABSTRACT

In current anti-infective therapy, Ciprofloxacin is a very popular fluoroquinolone with broad activity and diverse therapeutic prospects. The reason for its widespread use is the multidrug-resistant pathogen that is only sensitive to Ciprofloxacin. Available clinical data indicate the potential for increased effect of this drug in various treatments community-acquired and nosocomial infections, such as respiratory and urinary tract infections, skin infections, and sexually transmitted infections. Compared to other drugs in this class, the pharmacokinetic profile of Ciprofloxacin shows equal or greater bioavailability, higher plasma concentrations and increased tissue penetration, which is reflected in the larger volume of distribution. Other molecular modifications have been made to further enhance the effectiveness of this drug. Report on Multiple Methods for the Analytical Determination of Ciprofloxacin and Its Metabolites in Biological Fluids Using Different Methods. This article focuses on synthetic development, pharmacotherapeutic and analytical perspectives for the evaluation of Ciprofloxacin. Ciprofloxacin is a second-line antibiotic and a common drug. It is a very common fluoroquinolone that can treat certain bacterial infections. Quinolones are a family or group with activity against Gram-negative and positive bacteria, related to Ciprofloxacin. The primary objective of this review is to provide a complete update of the analytical methods for the determination of Ciprofloxacin and its combinations, for use in binary or triple compound endodontic treatment of primary teeth. Provided using a combination of antibacterial drugs Various techniques have been described, such as UV, TLC, GC Mass, HPLC and RPHPLC methods.

KEYWORDS: Fluoroquinolones; Ciprofloxacin; Antimicrobial; tuberculosis; antibiotics, HPLC, TLC.

2] INTRODUCTION

Ciprofloxacin is a fluoroquinolone antibiotic with broad-spectrum antibacterial activity. Because it penetrates the bone very well, it is used to treat a variety of infections, especially bone and joint infections.[1,2,3] Ciprofloxacin is the most powerful fluoroquinolone and has activity against various bacteria, among which aerobic Gram-negative bacilli are the most vulnerable.[4] Ciprofloxacin was patented by Bayer AG in 1983 and approved by the US Food and Drug Administration (US FDA) in 1987. Introduction, the value of fluoroquinolones for their respective uses has been recognized.[5] Fluoroquinolones are classified according to their spectrum of activity and pharmacokinetic profile. Ciprofloxacin is the most potent fluoroquinolone and is active against a comprehensive range of bacteria.[4] Ciprofloxacin, a fluoroquinol antibiotic, is no longer used as an advanced treatment for gonorrhoea.[6] Ciprofloxacin is the most commonly prescribed fluoroquinolone for UTIs because it can be administered both orally and intravenously[7] Ciprofloxacin, a widely used broad-spectrum antibiotic, has attracted considerable interest in the scientific community due to its antiproliferative and apoptotic activity in several cancer cell lines. It has been observed May induce time- and dose-dependent growth inhibition and apoptosist growth inhibition and apoptosis in various cell lines carcinoma, osteosarcoma and leukemia.

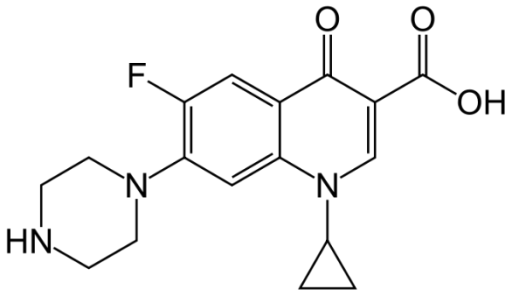


Figure: Structure of Ciprofloxacin.

Molecular Weight: 367.82 g/mol

Molecular Formula: C17H18FN3O3

Ciprofloxacin is one of the most widely used and most successful compounds in this class.[8] It was patented by Bayer A. Grass in 1983 and granted in the United States in 1987. Ciprofloxacin may interact with several other drugs, the same herbal and natural supplements, and some thyroid drugs.[9]

Table 1: Ciprofloxacin major brands in some countries.[10,11]

Country	Brand Name
Australia	C-Flox, Ciloxan, Ciprol, Ciproxin, Profloxin, Proquin
Ireland	Biofloxcin, Cifloxager, Ciproxin, Profloxin, Truoxin
United Kingdom	Ciloxan, Ciproxin
United States	Ciloxan, Cipro
South Africa	Adco-Ciprin, Biocip, Cifloc, Cifran, Ciloxan, Ciploxx, Ciprobay, Ciprogen, Dynafloc, Orpic, Spec-Topistin
Canada	Ciloxan, Cipro

They also demonstrated inhibition of human prostate cancer cell growth by Ciprofloxacin, which is associated with cell cycle arrest and apoptosis. This fluoroquinolone exhibited antiproliferative and apoptosis-inducing activity against prostate cancer cells at doses normally required for the treatment of antibacterial infections. Ciprofloxacin was also found to have no effect on non-neoplastic epithelial cells of the prostate. The greatest advantage of this antibiotic is that it is relatively non-toxic compared to modern chemotherapy, which is not very effective for the treatment of advanced hormone-resistant prostate cancer.[12] Oral Ciprofloxacin is a safe and effective treatment for many serious infections in cancer patients.[13] Various modifications have been made to enhance the antimicrobial activity of drug molecules. However, the development has mainly focused on the following aspects:[8,14,15]

- Activity against resistant strains of microorganisms, anaerobes and atypical organisms.[16]
- Reducing the rate of resistance development.[17]
- Improving pharmacokinetics and pharmacodynamics profile.[15]

3] Method

Fluoroquinolone creates a negative supercoil by inhibiting DNA gyrase, a bacterial enzyme that breaks down double-stranded DNA, then closes the broken ends. This is to prevent excessive benign supercoiling of the strand when the strand is split to allow for replication and transcription.[15,16] Ciprofloxacin Inhibits the activity of DNA gyrate, a necessary adenosine triphosphate that is enzymatically hydrolyzed by isomerase II, or prevents its dissociation from DNA. Topoisomerase exhibits bactericidal activity by interacting with DNA.[17] During replication and transcription, an enzyme called helicase is responsible for unwinding the DNA double helix. The unwinding process creates tension by over-folding the remaining DNA double helix. You must release this tension to continue the process. The enzyme topoisomerase II allows the relaxation of superhelical DNA by breaking, crossing, and finally reclosing the two strands of DNA.[18]

In recent years, research and development of quinolones has progressed rapidly, resulting in the production of clinically important fluoroquinolones, which have been subjected to various assays or analytical methods Ciprofloxacin was determined in pharmaceutical dosage forms and biological fluids using various physicochemical properties and analytical methods. Physical properties of Ciprofloxacin.

Physical Properties

Ciprofloxacin is a white powder with a bitter taste. It should be stored at 4 °C in the dark to minimize photolysis-induced degradation. Melts at 313-315 ° Ciprofloxacin is readily soluble in acetic acid and sparingly soluble in methanol, ethanol or acetone. Partition coefficient octanol/water partition coefficient of Ciprofloxacin has been reported to be less than 1.[19] The pH solubility profile indicates that the dissociation and isoelectric constants for Ciprofloxacin include pKa1 = 6.09, pKa2 = 8.62 and pI = 7.14 (isoelectric points obtained by calculating the mean of pKa1 and pKa2). This shows that Ciprofloxacin has two ionizable functional groups, a 6-carboxyl group and an N4 piperazine substituent. Since carboxylic acids are generally stronger acids than ammonium groups, the first ionization constant pKa1 (6.09) corresponds the dissociation of a proton from the carboxyl group, whereas pKa2 (8.62) corresponds to the dissociation of a proton from N4 to piperazinyl. Group.[20,21]

Analytical Methodology

In the following text, several important analytical procedures for the determination of Ciprofloxacin in pharmaceutical formulations and biological fluids are presented and discussed. Samples were analysed by isocratic reversed-phase chromatography on a C18 column (5 x 100 mm). The mobile phase consisted of acetonitrile and 100 mM sodium dihydrogen phosphate (20:80 v/v) and the pH was adjusted to 3.9 with phosphoric acid. Elution of the sample was monitored with a fluorescence detector using an excitation wavelength of 280 nm and a long pass emission filter of 418 nm.[22] A simple and sensitive HPLC method has been developed to measure enrofloxacin and Ciprofloxacin in dog serum and prostate tissue. Sample preparation consisted of mixing dog serum with a 1:1 dilution of acetonitrile and 0.1 M sodium hydroxide followed by ultrafiltration through a 10,000 molecular weight cutoff filter. Prostate tissue was sonicated using the same solution prior to ultrafiltration. Separation of these two quinolones in the ultrafiltrate was performed by ion-pair liquid chromatography using a reversed-phase analytical column eluting with an acetonitrile-methanol-water solution. Enrofloxacin and Ciprofloxacin were detected with a

photometric ultraviolet (UV) visible light detector set at 278.6 nm and confirmed with a photodiode array detector operating in the 230-360 nm range. The detection limits of enrofloxacin and Ciprofloxacin were 4 ng/ml and 2 ng/ml, respectively.[23]

Another method for Ciprofloxacin analysis was to use an HPLC method consisting of a pump (model LC600), UV-Visible spectrophotometer detector and recorder programmed by the system controller. Separation was performed using a 15 cm long pH stable column Spherisorb C18 (phase separation). The mobile phase consisted of citrate buffer, acetonitrile and methanol (85:10:5 v/v/v) to the next adjusted apparent pH. 2.4 sec using perchloric acid. Flow rate was maintained at 1.5 ml/min and the effluent from column was monitored at 280 nm .Phenacetin has been recognized as an internal standard. The relative standard deviations for daily and daily accuracy were within 5%.[24] Thin Layer Chromatography (TLC)-densitometry Designed to identify and quantify of Ciprofloxacin and ethylenediamine compounds, desfluoro compounds and fluoroquinolonic acids, the products of which Ciprofloxacin degrades into pharmaceuticals. The individual components were separated and UV densitometric analysis was performed using a high-performance TLC plate with chloroform-methanol-25% ammonia (43:43:14 v/v/v) as the mobile phase and silica gel 60 as the stationary phase. At 330 nm for fluoroquinolonic acid and at 277 nm to other compound.

This method produces well-developed peaks for easy qualitative and quantitative analysis. Dimethyl sulfoxide (DMSO)-methanol (1:1) was used for drug component extraction. This method showed high sensitivity (detection limit of 10 to 44 ng), wide linearity (3 to 20 µg/ml), good accuracy (2.32 to 6.46% relative standard deviation) and accuracy (98.62 to 101.52% recovery). For individual components,[25]

Analytical procedures using chemiluminescence (CL) technology with flow injection have several advantages, such as sensitivity, speed, ease of use, and simple instrumentation. A chemiluminescent flow injection method for the determination of noscapine, propranolol and ethamsylate in pharmaceutical formulations has been described. A method for the determination of Ciprofloxacin based on the enhancement of weak CL from hydroperoxide by this compound is described. The CL reaction of fluoroquinolone with tris (2, 2'-bipyridyl) ruthenium (II) [Ru (bipy) 32+] and Ce (IV) was studied in sulfuric acid medium. This methohas been used for the determination of Ciprofloxacin hydrochloride in formulations and biological fluids.[26]

4] Pharmacokinetic properties of Ciprofloxacin

The pharmacokinetic properties of Ciprofloxacin such as absorption, distribution, metabolism and excretion are described below.

Absorption

Ciprofloxacin is readily absorbed but is generally not completely absorbed after oral administration. When taken orally, the absolute bioavailability of Ciprofloxacin ranges from 70 to 80% without significant loss during the first pass of metabolism.[27] The area under the serum concentration-time curve (AUC) when Ciprofloxacin 400 mg was administered intravenously every 12 hours for 60 minutes was equivalent to the area obtained by oral administration of 500 mg every 12 hours13. Concentrations of Ciprofloxacin in brain tissue. 1 was 0.87 ± 0.08 mg/kg at a single dose of mg 200 mg. (intravenously), doses of 200 mg or more are recommended intravenously. Necessary to provide therapeutic concentrations to brain tissue. 3Several studies have described the pharmacokinetics of Ciprofloxacin in cerebrospinal fluid (CSF) Permeation of was superior to its corresponding serum concentrations, but absolute CSF concentrations were sometimes considered sub-therapeutic.[28] The relative constancy of CSF levels suggests a slow flow of Ciprofloxacin across the blood-brain barrier.[29] Drug interactions with food can affect the area under the concentration-time curve by prolonging the time required to reach maximum plasma concentration (tmax), but this does not significantly alter the bioavailability of the drug.[30] The pharmacokinetic profile of Ciprofloxacin is briefly described in table 2.

Table 2: Pharmacokinetic Properties of Ciprofloxacin.

Pharmacokinetic	Parameter Value
Elimination half – Life (h)	4.16
Oral bioavailability	70-80 %
Maximum Drug Concentration in Plasma (mg/L)	0.56
Area under the curve	2.56
Primary route of Excretion	Renal
Time to peak (h)	1.1
Plasma protein Binding (%)	20-40%
Renal clearance (L/h)	21.4
Disposition (% of dose)	_
Renal	40-60
Fecal / Biliary	15
Metabolized	10-15

Distribution

The distribution of Ciprofloxacin in tissues is superior to that of many other drugs in this class because of its low binding to plasma proteins. After oral administration, it penetrates well into various body fluids and body tissues except for the central nervous system (CNS). Significant drug levels are achieved in the kidneys, prostate, liver and lungs. Penetration into the cerebrospinal fluid is difficult, except in cases of meningeal inflammation. The drug concentration in urine because it is above the minimum inhibitory concentration, it is primarily used to treat urinary tract infections.[31] Small amounts of Ciprofloxacin are passed from the mother. Compartment to the fetal compartment, but this fraction is quite small, indicating that there is a barrier to transport of fluoroquinolones across the human placenta.[32] The availability of Ciprofloxacin at epilepsy target sites is considered an important factor in determining the effectiveness of antibiotic therapy and the clinical outcome of infection. In one study, interstitial fluid spatial concentrations and AUCs at target sites were significantly lower than corresponding plasma concentrations for the 400 and 500 mg doses.[36]

Metabolism and Excretion

Ciprofloxacin is highly metabolized and eliminated in hepatic or renal excretion. Metabolism is inactivated and mainly occurs due to conjugation of glucuronideat the 3-carboxyl group. The piperazine ring is readily metabolized, resulting in reduced antimicrobial activity.[37] Excretion occurs in both renal and nonrenal routes, but the main route of excretion is the kidney by glomerular filtration and tubular secretion.[34] Therefore, dose adjustment is necessary in patients with renal impairment and the elderly. The secondary route of excretion is the liver.[33] Ciprofloxacin is poorly excreted by peritoneal dialysis and hemodialysis. Although diarrhea or skin infections in humans do not affect oral absorption of Ciprofloxacin, some changes in pharmacokinetics are observed in pathological conditions. In the case of bacteremia, serum concentrations are sufficient to effectively treat gram-negative infections, but differences between analogs may be observed. Metabolism of Ciprofloxacin to oxocyprofloxacin is reduced in cirrhosis.[38,39]

With a few exceptions, the side effects of Ciprofloxacin are not overly severe for their beneficial properties. Toxicity at therapeutic doses is negligible and is usually limited to gastrointestinal disturbances such as nausea, vomiting and diarrhea.[40] Although pneumococcal resistance to this class of antibiotics is rare, some reports suggest that

resistance to Ciprofloxacin is increasing.[41,43] Recently, Ciprofloxacin has been reported as an effective treatment for anthrax[43,44], but a high dose is required... Because of the blood-brain barrier (BBB), intensive use of Ciprofloxacin has the potential to cause aseptic meningitis[45] ad arthritis damage[46], so it is necessary to increase the absorption rate of Brain[47] - Antibiotic prophylaxis in prostate biopsies is still effective, but infection complications and resistance are increasing.[48] Treatment-reported skin photosensitivity reactions.[49] The biggest concern with the use of Ciprofloxacin in children is possible. Damage to bones and joints.[50] Central nervous system exposure is the second most common type of adverse reaction associated with Ciprofloxacin therapy. Dizziness, insomnia, and mood swings were common during treatment. Convulsions or hallucinations have also been described.[51] The use of Ciprofloxacin for the treatment of multidrug-resistant tuberculosis in Childhood tuberculosis has resulted in cases of invasive pneumococcal disease.[52] It is shown in Table 3.

Table 3: Frequency of adverse reactions when taking Ciprofloxacin.[53]

Rate of adverse events	Rate of occurrence
Nausea	5.2
Diarrhea	2.3
Taste change	0.02
Headache	1.2

5] Drug Interactions

Oral absorption of Ciprofloxacin is reduced by the presence of antacids containing magnesium, aluminum and other agents such as sucralfate.[40] Ciprofloxacin also interacts with products that contain polyvalent cations. In exceptional cases, ranitidine does not affect oral absorption of Ciprofloxacin.[50] These interactions with Ciprofloxacin and antacids can be dangerous while treating serious infections.[54] A more confusing interaction occurs between Ciprofloxacin and other methylxanthines such as theophylline or caffeine. This interaction, involving isoenzyme 1A2 of the cytochrome P450 pathway, appears to be most prominent, and the occurrence of May significantly increase serum opilin concentrations. The clinical implications of this interaction require dose reduction and monitoring of serum xanthine concentrations of xanthine.[55] Increased serum concentrations of cyclosporine have been reported when co-administered with Ciprofloxacin. The interaction between and Ciprofloxacin reduces the concentration of anticancer drugs in the serum.[50] A significant decrease in clearance is observed with an increase in serum Ciprofloxacin concentrations when interacting with Azlocillin, Imetidine and probenecid. Drugs that cause an alkaline

urinary tract reaction, such as sodium bicarbonate, carbonic anhydrase inhibitors, and citrate, may decrease the solubility of Ciprofloxacin and increase the likelihood of crystalluria.[50,54,56]

6] Clinical Indications

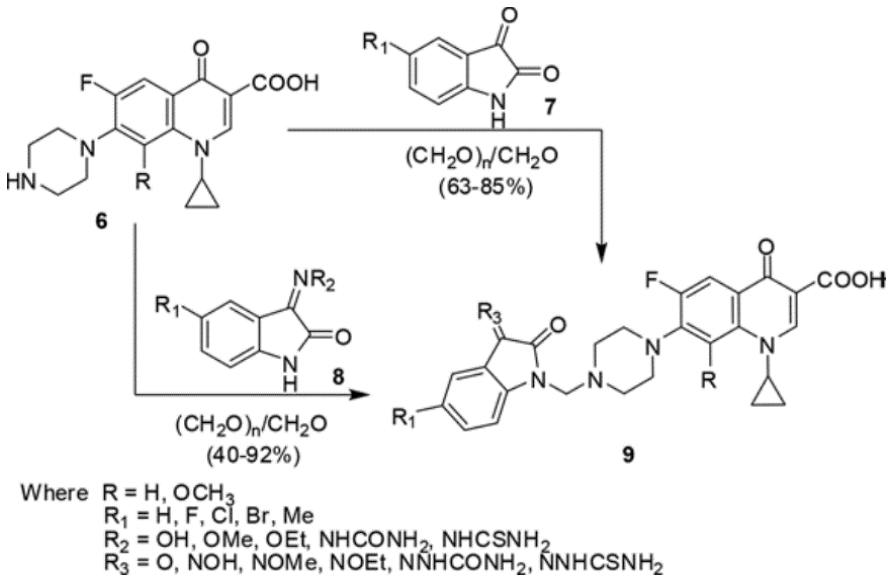
Ciprofloxacin is effective for a wide range of infections, including difficult-to-treat infections. Because of its broad bactericidal activity, oral efficacy, and good tolerability, is widely used for the blinded treatment of infections but should not be used in mild cases or when a gram positive organism is first suspected[50,57,58,59] Ciprofloxacin use Some clinical indications for It is appropriate to mention that, despite efficacy in the clinical trial, Ciprofloxacin is not the drug of first choice in the treatment of suspected or confirmed pneumonia. Secondary for Streptococcus pneumonia.[10,11]

Clinical indication	***Infection-causing organisms***
Urinary tract infections	*E. coli, bacillus pneumococcus, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Providencia rettgeri, Citrobacter morganii, Citrobacter mor Enterococcus faecalis*
Acute uncomplicated cystitis in Women	*Escherichia coli* or *Staphylococcus saprophyticus*
Chronic bacterial prostatitis	E. coli or Proteus mirabilis
Lower respiratory tract infection	*Escherichia coli, Klebsiella pneumoniae, Enterobac. Streptococcus pneumoniae*
Acute sinusitis	*Haemophilus influenzae, Streptococcus pneumoniae,*
Infection of skin and skin structures	E. coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus aureus, Staph locus b
Bone and Joint Infections	*Enterobacter cloacae, Serratia marcescens,* or *Pseudomonas aeruginosa*
Infectious diarrhoea	*Escherichia sallotoxy bacteria 44 enterobacteria, Enterobacteria s gyphi*
Typhoid fever	*Salmonella typhi*
Simple cervical and urethral gonorrhea	Neisseria gonorrhoeae

7] Synthesis of New CP Derivatives by the Mannich Reaction

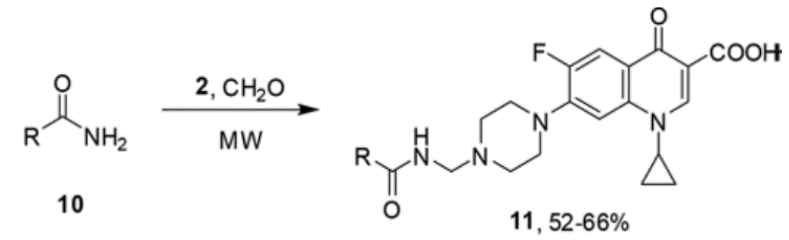
(Severe Respiratory Infection) is caused by Mycobacterium tuberculosis .and kills up to 2 million people each year. At the same time, the number of cases of human immunodeficiency virus (HIV) is increasing. Recently, the number of patients with multidrug-resistant tuberculosis increased by 4,444, which is a serious situation. The research group of Shriram[60] and Feng et al.[61] reported the synthesis of a novel Ciprofloxacin derivative synthesized by Mannich reaction during work on the antifungal evaluation of the novel Ciprofloxacin derivative. In their work, the secondary amino (piperazino) function of Ciprofloxacin 6 was reacted with is at in derivatives 7 or 8 using formaldehyde/formaldehyde p to obtain the desired Mannich base. The replacement plan for 7and 8 had a significant impact on the reaction outcome.

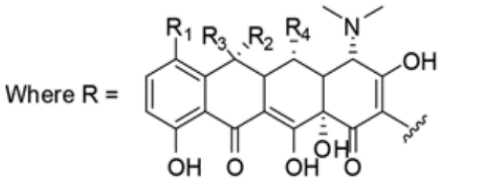
Synthesis of Ciprofloxacin methyleneisatin derivatives



Tetracycline has broad-spectrum antibacterial activity against gram-positive bacteria and gram-negative bacteria, and bacteriostatic activity has been established. Various derivatives of Ciprofloxacin based on tetracycline were synthesized by Sriram and colleagues[62], who used the Mannich reaction to synthesize this compound under the influence of microwave radiation. Their methodology involved reacting compound 10 with formaldehyde and Ciprofloxacin 2 in a microwave, and the resulting compound 11 gave a reasonable yield (5266%). As a result of examining the biological activity of the synthesized Ciprofloxacin derivative 11, excellent anti-HIV and anti-fungal activity.

Mannich base synthesis of Ciprofloxacin using a tetracycline moiety

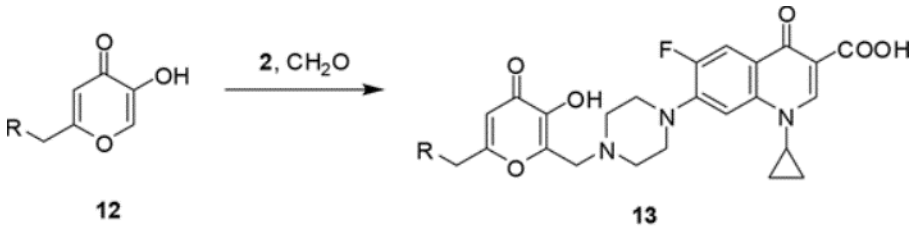




R_1, R_2, R_3, R_4 = H, Me, OH, $N(CH_3)_2$

Kojic acid (an antibacterial agent) is produced by many fungal species, such as Aspergillus and Penicillium. Used to inhibit the growth of E. coli and S. aureus. Studies have shown that not only kojic acid, but also chloric acid has antibacterial activity. Given their importance, Emami et al.[63] reported the synthesis of Mannich base of Ciprofloxacin using kojic acid and chloric acid. Compound 12 was reacted with Ciprofloxacin and formaldehyde. Reaction proceeded smoothly and for kojic acid (R = OH) the product 13 was obtained in 83% yield, whereas chloric acid (R = Cl) gave 77% of the desired Mannich base.[64] Antimicrobial evaluation of these compounds showed that all synthesized compounds were effective against gram-positive and gram-negative bacteria.[65]

Mannich base synthesis of Ciprofloxacin 2 c 12

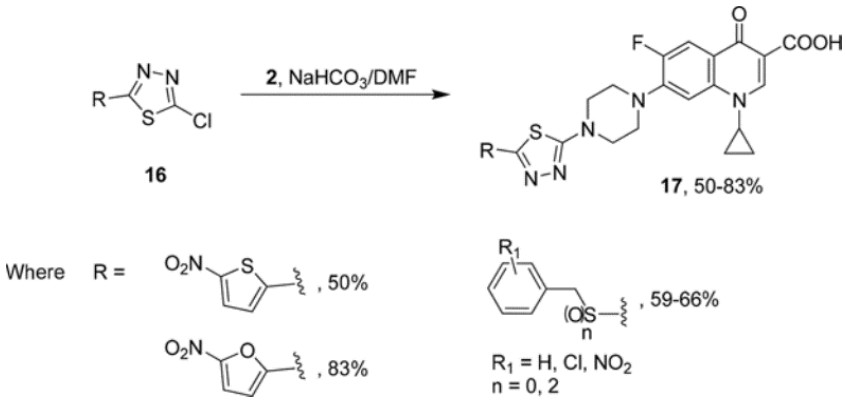


Where R = OH, 83%
= Cl, 77%

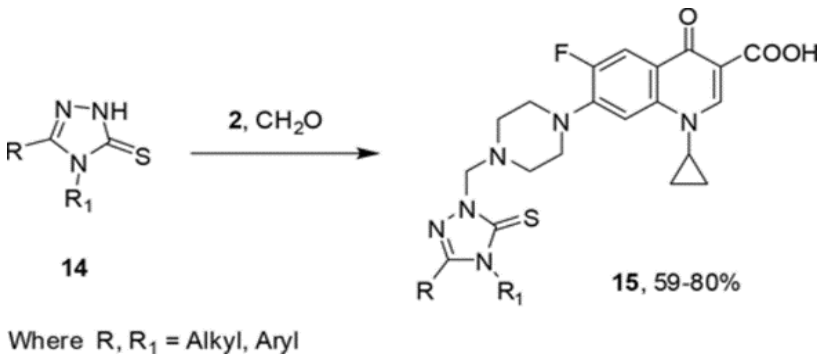
Ciprofloxacin is more effective against gram-negative bacteria this is because it is more permeable than Gram-positive bacteria more permeable to gram-negative bacteria directly through the porous channel.

However, in gram-positive bacteria, it mainly penetrates by passive diffusion.

Also, the affinity for DNA gyrate is higher in gram-negative bacteria than in Gram-positive bacteria. Taking these considerations into account, Plech et al.[60,61] synthesized a structural hybrid of Ciprofloxacin with a 1, 2, 4-triazole fragment that may exhibit increased activity against gram-negative and gram-positive bacteria. In their study, triazole 14 reacted with Ciprofloxacin 2 and formaldehyde according to the Mannich reaction 5. The resulting Mannich base 15 was obtained in a medium to good yield of (5980%). Their results showed that the synthesized compound exhibited Activities against gram-positive bacteria alone. Moreover, some of the synthesized compound also exhibited cytotoxic activity.



Synthesis of Mannich bases of Ciprofloxacin using a 1,2,4-triazole moiety



Synthesis of thiadiazole-based Ciprofloxacin derivatives Sulfonyl fluoroquinolone (NSFQ) is a new class of antimicrobial fluoroquinolones (FQ) containing both sulfonamides and FQs, which exhibit antibacterial activity. Against gram-positive bacteria. Because the antibacterial action of FQ relies on inhibition of bacterial DNA synthesis, sulfase works by inhibiting PABA (paminobenzoic acid), which is used to synthesize the building blocks of DNA. Formed and colleagues synthesized thiadiazole-based Ciprofloxacin derivatives.[66,67] They found that all derivatives synthesized showed equal or higher efficacy against gram-positive bacteria than the standard formulation.

The strategy adopted for the synthesis of These derivatives participate in the reaction of Ciprofloxacin 2 with thiadiazole 16-based compound in the DMF compound 16 in DMF to give intermediate compound 17 in (5083%) yield.

Synthesis of Ciprofloxacin 17 based on Thiadiazole from Thiadiazole 16

Later, Talath and Gadad[68] achieved the synthesis of 7- [4-(5-amino- [1,3,4] thiadiazole-2-sulfonyl) ciprofloxacin 19 by refluxing compound 18 with ciprofloxacin 2 yielding an intermediate in 78% yield which was further hydrolyzed into targeted compound 19 in 82% yield. Biological assay of compound 19 revealed better activity against gram positive bacteria S. aureus, E. faecelis, Bacillus and exhibits similar activity against Corynebacterium as compared to parent drug.

8] CONCLUSION

In summary, different methods involved in attempting to modify the construct to synthesize novel Ciprofloxacin derivatives have been presented in this paper. The important pharmacological interventions of Ciprofloxacin and current analytical methods for its determination or its determination in different formulations and biological fluids were discussed. Ciprofloxacin has emerged as a promising and effective drug, with innumerable antibacterial activity. It should be emphasized that further scientific and technological advances are needed in pharmacology, pharmaceutical chemistry and analytical technique for precise control of the quality and therapeutic profile of this potent medicinal agent.

9] Conflicts of interests

No conflicts of interest.

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