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REVIEW ARTICLE

Ciprofloxacin: review on developments in synthetic, analytical, and medicinal aspects

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Abstract

In the current practices of antiinfective therapy, ciprofloxacin is a very popular fluoroquinolone having a broad spectrum of activity and diverse therapeutic prospects. The reasons for its wide use include multiresistant pathogens susceptible only to ciprofloxacin. The available clinical evidence suggests the potentially enhanced efficacy of this drug in the treatment of various community acquired and nosocomial infections, e.g. respiratory tract, urinary tract, and skin infections and sexually transmitted diseases. As compared to other agents of its class, the pharmacokinetic profile of ciprofloxacin demonstrates equivalent or greater bioavailability, higher plasma concentrations, and increased tissue penetration, as reflected in the greater volume of distribution. Various molecular modifications of this drug have been made to further improve its characteristics. Several methods of analytical determination of ciprofloxacin and its metabolites in biological fluids employing various techniques have been reported. The present article is focused on the synthetic development, pharmacotherapeutic, and analytical evaluation vistas of ciprofloxacin.

Keywords: *Ciprofloxacin; fluoroquinolone; analytical; antibacterial*

Introduction

During the past 25 years, antimicrobial agents have been introduced at a rate exceeding our ability to integrate them into clinical practice[1,2]. Since their introduction, fluoroquinolones have become a mainstay in the treatment of serious bacterial infections[3,4]. These are synthetic antibacterial agents structurally related to nalidixic acid[5]. They depict several favorable properties such as excellent bioavailability, good tissue penetrability, and a relatively low incidence of adverse and toxic effects[6]. These drugs are potentially used in the treatment of urinary tract infection and prostatitis. They are also employed against bacterial enteric infections, biliary tract infections, sexually transmitted diseases, and prophylaxis in the immunocompromised neutropenic host[7–9]. One of the most successful and widely used compounds of the class[10], ciprofloxacin, was patented in 1983 by Bayer A.G. and subsequently approved by the United States Food and Drug Administration (US FDA) for use in the United States in 1987. Ciprofloxacin is marketed worldwide, with well over 300 different brand names, and since its introduction, the value of fluoroquinolones for the respective uses has been recognized[11]. The licensed uses for ciprofloxacin in the United States are quite limited, and it is to be considered as a drug of final resort when all other antibiotics have failed. There are 10 approved uses of this drug in the adult population and two approved uses in the pediatric population, as well as a variety of veterinary uses (as documented within the package inserts). Being not approved by the FDA, its other uses can be considered as off-label. Ciprofloxacin may interact with a number of other drugs, some herbal and natural supplements, and certain thyroid medications[12]. Ciprofloxacin (Figure 1) has proved to be a blockbuster drug for Bayer A.G., generating billions of dollars in additional revenue. In 1999, ciprofloxacin was the 11th most prescribed drug in the United States, based on new prescriptions, and ranked 20th in total United States sales. In 1999, Bayer's gross sales of ciprofloxacin in the United States were approximately $1.04 billion. The sale of ciprofloxacin increased dramatically following the anthrax scare of 2001. A deal between the US Government and Bayer Pharmaceuticals was announced to

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purchase 100 million tablets of ciprofloxacin. In 2004, ciprofloxacin and levofloxacin together commanded 65% ($3.3 billion) of global sales. Sales of ciprofloxacin for the first 9 months of 2008 were $242 million, as compared to $324 million for Bayer Aspirin. Some brands of ciprofloxacin are mentioned in Table 1.

Fluoroquinolones are classified on the basis of their spectrum of activity and pharmacokinetic profile. Ciprofloxacin is the most potent fluoroquinolone, active against a broad range of bacteria[15], the most susceptible being the aerobic Gram-negative bacilli, especially the enterobacteriaceae and *Neisseria*[16]. It is a second-generation fluoroquinolone, and has depicted a considerable and myriad spectrum of activity for several infectious conditions. Ciprofloxacin is a very promising and efficacious drug, having potent antibacterial activity along with well-established safety aspects. Since its approval, ciprofloxacin has been extensively studied; more than 250 million patients have been treated successfully worldwide, and its safety profile is well documented in a commendable number of scientific publications[17]. Ciprofloxacin offers a potential alternative for antimicrobial therapy in pediatric populations, such as children with cystic fibrosis[4]. Data from more than 1500 pediatric patients treated with ciprofloxacin for infection related to cystic fibrosis have shown a safety profile in children and adolescents comparable to that in adult patients[18]. *In vitro* susceptibility data for commonly used fluoroquinolones show that the minimum inhibitory concentration (MIC) of ciprofloxacin is distinctly superior to other fluoroquinolones when tested against several Gram-negative bacterial strains. Against *Escherichia coli*, the MIC90 for ciprofloxacin was found to be 0.015–0.25, as compared to MICs90 of 0.12–0.39, 0.06–0.25, and 0.03–0.5 for ofloxacin, levofloxacin, and trovafloxacin, respectively. Similarly, against *Klebsiella pneumoniae*, the MIC90 was found to be 0.05–1.0 for ciprofloxacin when compared to 0.1–0.5 and 0.12–1.0 for levofloxacin and ofloxacin, respectively[19]. In another investigation, Antonio *et al.* found that ciprofloxacin was more efficacious than some other fluoroquinolones such as ofloxacin and pefloxacin in preventing infections due to Gram-negative bacteria in a specific population of neutropenic patients[20]. Further, Yamane *et al.* reported that the activity of levofloxacin against Gram-positive bacteria was either equal to or less than that of ciprofloxacin[21]. In another study, topical ciprofloxacin/dexamethasone therapy was found to be superior to oral amoxicillin/clavulanic acid in acute otitis media with otorrhea[22]. Literature findings also suggest that ciprofloxacin, when given orally, is superior to ampicillin and chloramphenicol in curing typhoid in immunocompromised mice[23].

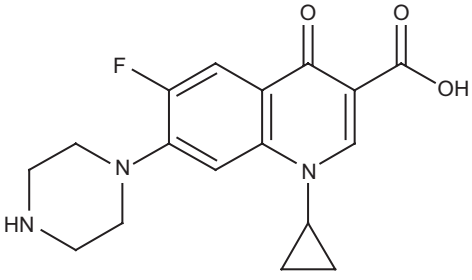


Figure 1. Structure of ciprofloxacin.

Table 1. Major brands of ciprofloxacin in some countries[13,14].

Name of country	Brand name of ciprofloxacin
Australia	C-Flox, Ciloquin, Ciloxan, Ciprol, Ciproxin, Profloxin, Proquin
Canada	Ciloxan, Cipro
Ireland	Biofloxcin, Cifloxager, Ciproxin, Profloxin, Truoxin
New Zealand	Ciloxan, Cipflox, Ciproxin, Topistin, Ufexil
South Africa	Adco-Ciprin, Biocip, Cifloc, Cifran, Ciloxan, Ciploxx, Cipro-Hexal, Ciprobay, Ciprogen, Dynafloc, Orpic, Spec-Topistin
United Kingdom	Ciloxan, Ciproxin
United States	Ciloxan, Cipro
India	Ciloxan, Cipro, Cifran, Ciplox

Ciprofloxacin, a commonly used broad-spectrum antibiotic, has also attracted significant interest of the scientific community due to its antiproliferative and apoptotic activities in several cancer cell lines. It was observed that it can induce time- and dose-dependent growth inhibition and apoptosis of various carcinoma, osteosarcoma, and leukemia cell lines[24]. Aranha *et al.* found that ciprofloxacin may have a profound effect in bladder cancer management. *In vitro* studies on tumor cells derived from transitional cell carcinoma of the bladder revealed a dose- and time-dependent inhibition of cell growth by ciprofloxacin at concentrations that are easily attainable in the urine of patients. These studies provided strong experimental evidence for the use of this fluoroquinolone agent as a potential preventive and/or therapeutic agent for the management of transitional cell carcinoma of the bladder[25]. They further demonstrated suppression of human prostate cancer cell growth by ciprofloxacin associated with cell cycle arrest and apoptosis. This fluoroquinolone showed antiproliferative and apoptosis-inducing activity on prostate cancer cells at the doses generally required for the treatment of antibacterial infections. It was also found that ciprofloxacin did not have any effect on non-tumorigenic prostate epithelial cells. The main advantage of this antibiotic is its relative non-toxicity as compared to current chemotherapy, which is not very effective, for the treatment of advanced hormone resistant prostate cancer[26]. Doxorubicin and docetaxel, two standard antineoplastic agents in hormone-refractory prostate cancer (HRPC) therapy, and ciprofloxacin were evaluated singly and in several simultaneous and sequential drug combination schemes by Pinto and co-workers. Ciprofloxacin exhibited sensitization of HRPC cell lines to doxorubicin and docetaxel treatment in a schedule-dependent manner. It was inferred that ciprofloxacin may play a significant role as a chemosensitizing agent in prostate cancer treatment[27]. Bourikas *et al.* also demonstrated novel antiproliferative and immunoregulatory effects of ciprofloxacin on human intestinal epithelial cells in a concentration- and time-dependent manner[28].

Herold *et al.* reported ciprofloxacin-induced growth inhibition and apoptosis in colon carcinoma cell lines, whereas hepatoma cells remained unaffected. The growth arrest was mediated through the inhibition of DNA synthesis, induction of mitochondrial injury, and subsequent apoptosis. Therefore, due to the encouraging effects of this topoisomerase inhibitor, ciprofloxacin can be explored as a good candidate for such therapies[24]. Moreover, ciprofloxacin is generally used in several large cancer treatment centers for antimicrobial prophylaxis in high-risk patients with prolonged neutropenia, including patients with acute leukemia undergoing remission induction chemotherapy, and recipients of bone marrow transplantation[29,30]. Also, orally administered ciprofloxacin is a safe and effective therapy of many serious infections in cancer patients[31].

Various alterations have been made to improve the antibacterial activity of this drug molecule; however, the development has been primarily focused on the following aspects[10,32,33]:

- Increased activity against resistant strains of microbes, anaerobes, and atypical organisms[34];
- Reduced rate of emergence of resistance[35];
- Improved pharmacokinetics and pharmacodynamic profile[32].

Mode of action

Fluoroquinolones inhibit the bacterial enzyme DNA gyrase, which nicks double-stranded DNA, introduces negative supercoils, and then reseals the nicked end. This is necessary to prevent excessive positive supercoiling of the strands when they separate to permit replication and transcription[36,37]. Ciprofloxacin inhibits the activity of DNA gyrase, an essential adenosine triphosphate-hydrolyzing topoisomerase II enzyme, or it prevents the detachment of gyrase from DNA. The topoisomerases exert their bactericidal activity by interacting with the DNA[38]. During the processes of replication and transcription, an enzyme called helicase unwinds the DNA double helix. The uncoiling process creates tension due to excess supercoiling of the remaining DNA double helix. This tension needs to be relieved if the process is to continue. The topoisomerase II enzyme allows the relaxation of supercoiled DNA by breaking both strands of the DNA chain, crossing them over, and finally resealing them[3].

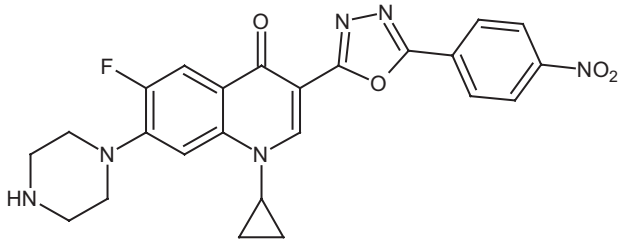
Current synthetic developments

Extensive efforts have been undertaken for the synthetic development and to derive an array of significantly potent analog candidates of this drug. Molecular modification for lead optimization by bioisostearic replacements, homologation of the side chain or branching of the side chain, stereochemistry, and other useful techniques of analogous design and development of ciprofloxacin have given rise to agents with broad-spectrum activity and minimal toxic or side effects[9]. A number of derivatives of ciprofloxacin have been reported that have shown improved activity and potency. Some important examples are described below.

Shaharyar *et al.* synthesized a series of 1-[(sub)]-6-fluoro-3-[(sub)]-1,3,4-oxadiazol-2-yl-7-piperazino-1,4-dihydro-4-quinolones by the reaction of ciprofloxacin with an appropriate acid hydrazide in phosphorus oxychloride. All newly synthesized compounds were evaluated for antiproliferative activity against human lung tumor cell lines (A549). Among the synthesized compounds, 1-cyclopropyl-6-fluoro-3-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)-7-(piperazin-1-yl) quinolin-4(1H)-one **(a)** was found to be the most active compound[39] (Figure 2).

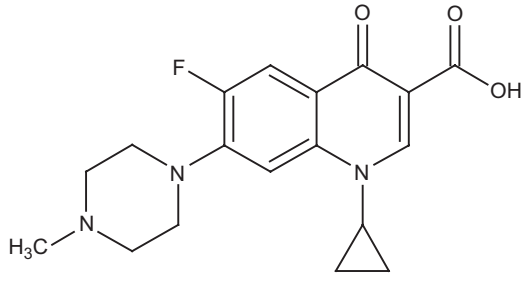
Vila *et al.* reported a number of ciprofloxacin derivatives and tested them against quinolone susceptible and resistant *E. coli*, *Acinetobacter baumannii*, *Stenophotromonas maltophilia*, and *Staphylococcus aureus* strains using a microdilution test. Among these derivatives, 4-methyl-7-piperazine ciprofloxacin **(b)** derivative showed a minimum inhibitory concentration for 50% of the organisms that was 16- and 8-fold lower than that of ciprofloxacin for *A. baumannii* and *S. maltophilia*, respectively[40] (Figure 3).

Foroumadi *et al.* synthesized and evaluated a series of N-[2-(5-bromothiophen-2-yl)-2-oxoethyl] and N-[2-(5-bromothiophen-2-yl)-2-oximinoethyl] derivatives of ciprofloxacin for antimicrobial activity against Gram-positive and Gram-negative microorganisms. Among the synthesized compounds, 7-(4-(2-(5-bromothiophen-2-yl)-2-(hydroxyimino)ethyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **(c)** showed significant activity against Gram-positive bacteria such as *S. aureus*, *S. epidermidis*, and *Bacillus subtilis*[41]. In



(a)

Figure 2. Ciprofloxacin derivative **(a)**.



(b)

Figure 3. Ciprofloxacin derivative **(b)**.

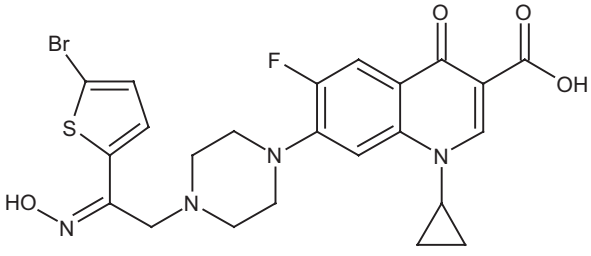
another study, they examined a series of N-(5-benzylthio-1,3,4-thiadiazol-2-yl) and N-(5-benzylsulfonyl-1,3,4-thiadiazol-2-yl) derivatives of piperazinyl quinolone and evaluated them for antibacterial activity against different microorganisms. Among the synthesized compounds, 7-(4-(5-(4-nitrobenzylthio)-1,3,4-thiadiazol-2-yl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **(d)** exhibited high activity against Gram-positive bacteria[42] (Figure 4).

In the proceeding year, Foroumadi *et al.* examined a number of piperazinyl N-substituted ciprofloxacin derivatives for antibacterial activity against Gram-positive and Gram-negative bacteria. Among these derivatives, 1-cyclopropyl-6-fluoro-7-(4-(2-(5-(methylthio)thiophen-2-yl)-2-oxoethyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **(e)** showed significant improvement of potency against staphylococci, maintaining Gram-negative coverage[43]. In the same year, they reported a number of N-(phenethyl)piperazinyl quinolone derivatives bearing a methoxyimino-substituent and evaluated them for antimicrobial activity against Gram-positive and Gram-negative microorganisms. In the series, 1-cyclopropyl-7-(4-(2-(2,4-dichlorophenyl)-2-(methoxyimino)ethyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **(f)** proved to be the most active analog against tested strains[44] (Figure 5).

Talath *et al.* evaluated a series of 7-[4-(5-amino-1,3,4 thiadiazole-2-sulfonyl)]-1-piperazinyl fluoroquinolone derivatives. The compounds were evaluated for their *in vitro* antibacterial activity against some Gram-positive and Gram-negative bacteria and antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ strain by the broth dilution assay method. The compound 7-(4-(5-amino-1,3,4 thiadiazole-2-ylsulfonyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **(g)** showed better antibacterial activity against Gram-positive bacteria as compared to the reference drug ciprofloxacin[45] (Figure 6).

Nieto *et al.* characterized and tested a series of new benzenesulfonamide analogs of ciprofloxacin **(h)**. Quantitative structure–activity relationship (QSAR) studies through Hansch analysis showed a linear correlation of the activity with electronic and steric parameters. Small electron-donor groups increased the *in vitro* activity against Gram-positive bacteria. Hydrophobic properties played a minor role when activity was measured as minimum inhibitory concentration. Finally, according to this QSAR study, the amino and methyl amino derivatives were found to be the most active analogs within this series[46] (Figure 7).

Sriram *et al.* reported a number of 7-substituted ciprofloxacin derivatives and evaluated them for antimycobacterial activity *in vitro* and *in vivo* against *M. tuberculosis* and for inhibition of the supercoiling activity of DNA gyrase from *M. smegmatis*. Preliminary results indicated that compound 7-[4-{(5-bromo-2,3-dioxoindolin-1-yl)methyl}piperazin-1-



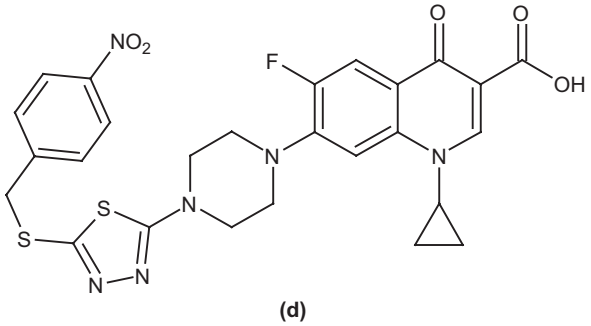
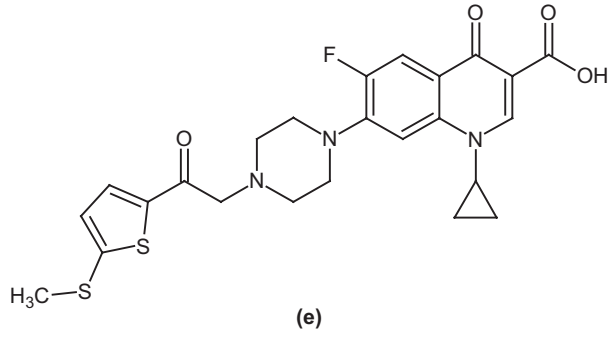


Figure 4. Ciprofloxacin derivatives **(c)** and **(d)**.



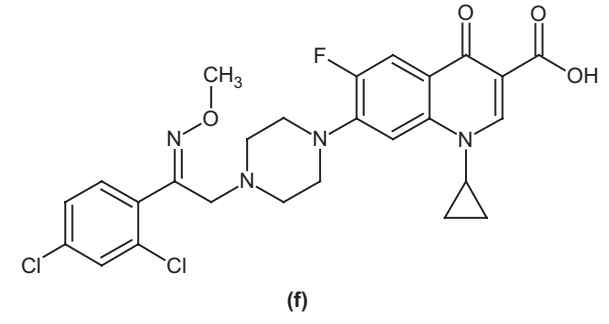


Figure 5. Ciprofloxacin derivatives **(e)** and **(f)**.

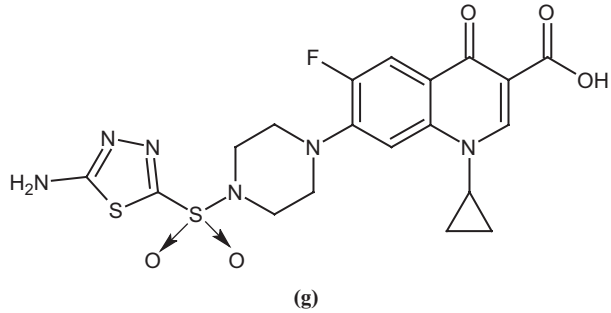
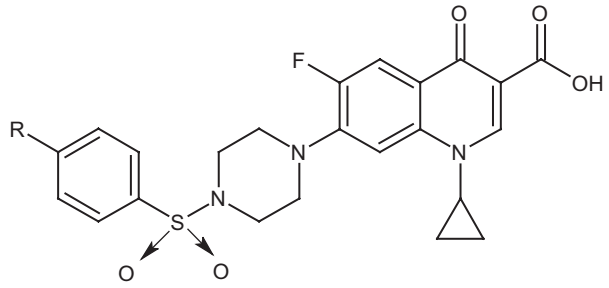


Figure 6. Ciprofloxacin derivative **(g)**.

yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **(i)** showed moderate activity[47] (Figure 8).

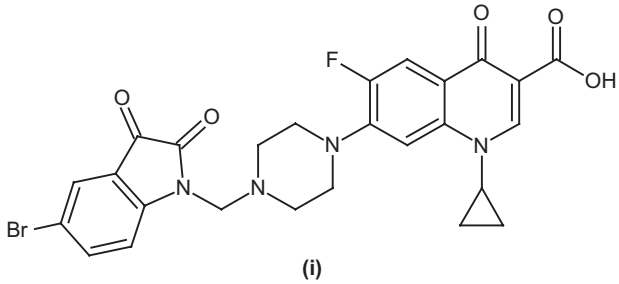
Kerns *et al.* screened a number of symmetric and asymmetric piperazinyl linked dimers of ciprofloxacin. A specific trans butenyl-linked dimer of ciprofloxacin **(j)** showed potent antibacterial activity against drug resistant strains of *S. aureus*[48] (Figure 9).

Imramovsky *et al.* studied a new type of potentially active molecule in which the connection of two active molecules across an easily released bridge is established. The synthesis is based on derivatives that originate from ciprofloxacin **(k)**. The lipophilicity, hydrolysis (stability of the compound), and antitubercular activity as well as the structure lipophilicity and structure–activity relationship were studied[49] (Figure 10).



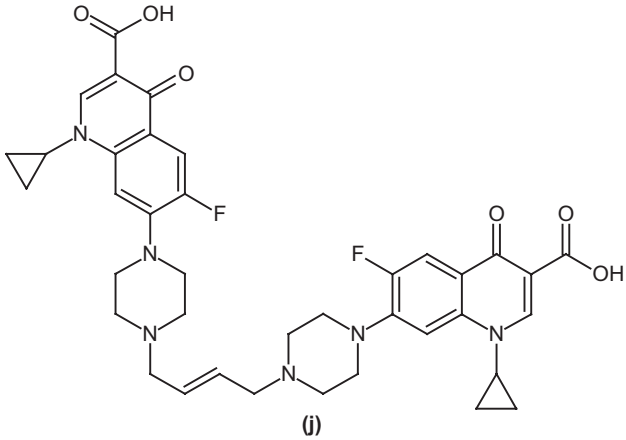
(h)

Figure 7. Ciprofloxacin derivative **(h)**.



(i)

Figure 8. Ciprofloxacin derivative **(i)**.



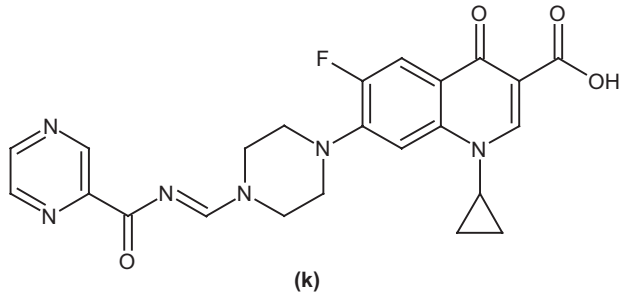
(j)

Figure 9. Ciprofloxacin derivative **(j)**.

Srivastava *et al.* synthesized and evaluated antibacterial activities of a number of substituted 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine quinolones **(l)**. The activities were evaluated against a standard using the *in vitro* MIC assay method. Some of the compounds showed *in vitro* antibacterial activity comparable to that of ciprofloxacin[50] (Figure 11).

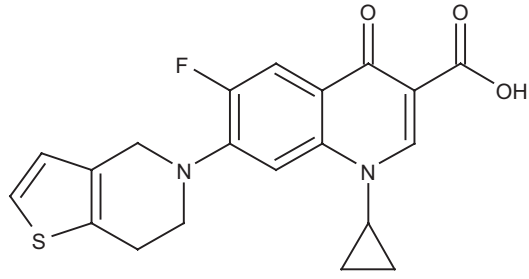
German *et al.* reported ciprofloxacin derivatives as substrate based inhibitors of bacterial efflux pumps. Bacterial efflux pump systems contribute to antimicrobial resistance in pathogenic bacteria. The co-administration of bacterial efflux pump inhibitors with antibiotics is being pursued to overcome efflux-mediated resistance to antibiotics. In this study, they evaluated some derivatives of ciprofloxacin bearing a bis aryl urea efflux pump inhibitor at the C-7 position **(m)**[51] (Figure 12).

Al-Soud *et al.* examined a new class of dihaloquinolones bearing N-aldehydoglycosylhydrazides, mercapto-1,2,4-triazole, oxadiazoline, and α-amino ester precursors. These novel compounds are also conjugated with ciprofloxacin and have shown antimicrobial activity[52].



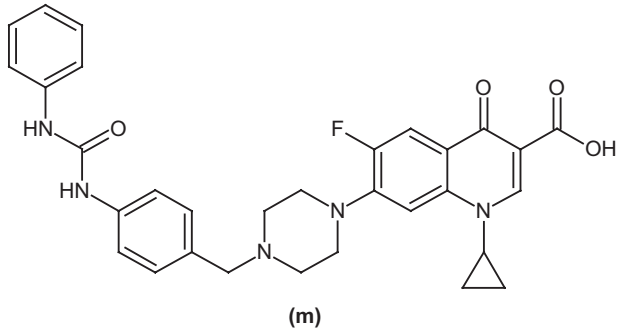
(k)

Figure 10. Ciprofloxacin derivative **(k)**.



(l)

Figure 11. Ciprofloxacin derivative **(l)**.



(m)

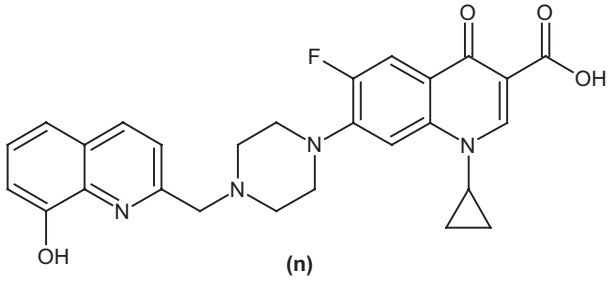
Figure 12. Ciprofloxacin derivative **(m)**.

Zhao *et al.* investigated a number of ciprofloxacin derivatives and evaluated for antimycobacterial activity. A ciprofloxacin derivative **(n)** exhibited 98% inhibition of the growth of *M. tuberculosis*[53] (Figure 13).

Yadav *et al.* afforded piperiazine-substituted ciprofloxacin derivatives by the reaction of ciprofloxacin with benzothiazole **(o)**, thiazole, and diazonium chloride. The *in vitro* antibacterial activities of these compounds were determined by the conventional agar dilution method. The MIC of the test derivatives against the *Staphylococcus* strain indicated that most of the derivatives possessed better activity with respect to ciprofloxacin[54] (Figure 14).

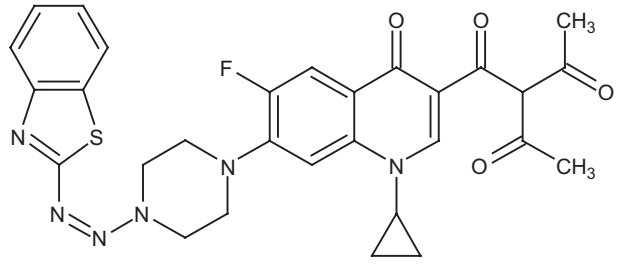
Sriram *et al.* synthesized new ciprofloxacin tetracycline conjugates by reacting appropriate tetracyclines, formaldehyde, and the secondary amino (piperazino) function of ciprofloxacin **(p)** using a microwave irradiation technique and evaluated them for anti-human immunodeficiency virus (HIV) and antimycobacterial activities[55] (Figure 15).

Ye *et al.* reported ciprofloxacin derivatives primarily from 2-methyl-5-nitroimidazole and ciprofloxacin through nucleophilic substitution. The antibacterial activities of the synthesized compounds were evaluated. Nine new compounds were synthesized, some of which have exhibited appreciable antibacterial activity[56].



(n)

Figure 13. Ciprofloxacin derivative **(n)**.



(o)

Figure 14. Ciprofloxacin derivative **(o)**.

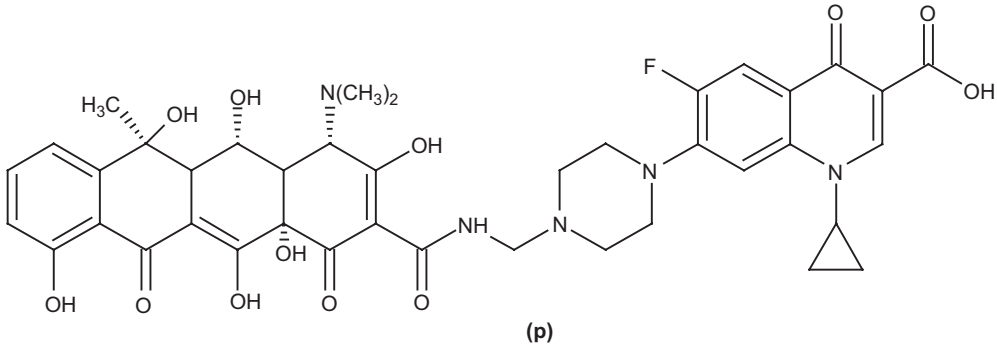
Bani *et al.* studied two new derivatives from the ciprofloxacin fluoroquinoline family, 7-chloro-1-cyclopropyl-6--fluoro-1,4-dihydro-4-oxo-quinoline-3-methylcarbamate and 1-cyclopropyl-7-(4-ethyl-1-piperazinyl)-6-fluoro-1,4-dihydro-(3-oxopyrazolo)[4,3-c]quinoline, and tested them for antibacterial activity. Their molecular and crystal structures were determined. *In vitro* tests revealed lower activities than for ciprofloxacin. Characteristic structural features of these compounds are comparable to data for other known fluoroquinolines[57].

Hu *et al.* discovered a novel antitumor lead compound derived from fluoroquinolone, in which the C-3 carboxyl group of ciprofloxacin was replaced with a heterocyclic ring to form the cyclopropyl fluoroquinolone aminothiadiazole scaffold and which was then reacted with aromatic aldehydes to give the Schiff base compounds. The structures of the new compounds were characterized by elemental analysis and spectral data, and their *in vitro* antitumor activity determined against SMMC-7721, HL60, and L1210 cell lines. The bioactive assay showed that 11 thiadiazole-substituted ciprofloxacin derivatives displayed potential cytotoxicity against the tested cancer cell lines[58].

It is generally believed that the action of fluoroquinolones increases with an increase in lipophilicity. However, in an experiment, Vazquez *et al.* determined the partition coefficients of a homologous series of ciprofloxacin in which a parabolic behavior was observed which evidenced that merely an increase in lipophilicity does not result in enhanced antimicrobial activity[59].

Several reports have also highlighted the interest in increasing the lipophilicity to improve the antitumor efficacy. Azema *et al.* synthesized novel 7-((4-substituted) piperazin-1-yl) derivatives of ciprofloxacin having various lipophilicities, and evaluated them *in vitro* as potential antitumor agents in five human cancer cell lines. The compounds exhibited potent activities[60].

Siddiqui *et al.* prepared a series of ciprofloxacin skeletal variants and screened them for antifungal, antimicrobial, and cytotoxic activities. The structures of these derivatives



(p)

Figure 15. Ciprofloxacin derivative **(p)**.

were confirmed by using spectral techniques such as infrared (IR), ^{1}H nuclear magnetic resonance (NMR), and electron impact mass spectroscopy (EIMS). Cytotoxicity activities of these derivatives were determined in order to establish the effect of substituents on the biological activity[61].

Sharma *et al.* synthesized and evaluated 1-cyclopropyl-6-fluoro-1,4-dihydro-7-4-substituted-piperazin-1-yl-4-oxo-quinoline-3-carboxylates. Compounds exhibited moderate to significant activities[62].

Analytical aspects

In recent years, there has been rapid progress in quinolone research and development, resulting in the production of many clinically important fluoroquinolones, which have been subjected to diverse analytical or assay methods. Various physicochemical properties and analytical methods have been used for the determination of ciprofloxacin in pharmaceutical dosage forms and biological fluids.

Physical properties

Ciprofloxacin occurs as a white powder with bitter taste. It should be stored at 4°C in the dark to minimize photolytically induced degradation. It melts at 313–315°C. Ciprofloxacin is freely soluble in acetic acid, and slightly soluble in water, methanol, ethanol, or acetone. The octanol/water partition coefficient for ciprofloxacin was reported to be lower than 1[63]. The pH–solubility profile shows that the dissociation and isoelectric constants for ciprofloxacin include $pKa_1 = 6.09$, $pKa_2 = 8.62$, and $pI = 7.14$ (isoelectric point, obtained by calculating the average of pKa_1 and pKa_2). This depicts that ciprofloxacin has two ionizable functional groups, the 6-carboxylic group and the N-4 of the piperazine substituent. Since carboxylic acid is normally a stronger acid than the ammonium group, the first ionization constant pKa_1 (6.09) corresponds to the dissociation of a proton from the carboxyl group, while pKa_2 (8.62) corresponds to the dissociation of a proton from the N-4 in the piperazinyl group[64,65]. At the most physiologically relevant pH, the pKa_2 value is 8.25, and significant dissociation of both the 6-carboxylic acid and the basic 10-(1-piperazino) groups occurs, leading to significant fractions of zwitterionic species.

Analytical methodologies

Some important analytical procedures for the determination of ciprofloxacin in pharmaceutical dosage forms and biological fluids have been presented and are discussed in the following text.

Ciprofloxacin content in serum was measured by high performance liquid chromatography (HPLC), in which the samples were analyzed by isocratic reversed phase chromatography on a C-18 column (5 × 100 mm). The mobile phase consisted of acetonitrile–100 mM sodium dihydrogen phosphate (20:80 v/v) adjusted to pH 3.9 with phosphoric acid. Sample elution was monitored with a fluorescence detector, using an excitation wavelength of 280 nm and a 418 nm long pass emission filter[66].

A simple and sensitive HPLC method was developed for the determination of enrofloxacin and ciprofloxacin in canine serum and prostatic tissue. Sample preparation consisted of mixing canine serum with a 1:1 dilution of acetonitrile and 0.1 M sodium hydroxide followed by ultrafiltration through a 10,000 molecular mass cut-off filter. Prostatic tissue was sonicated with the same solution prior to ultrafiltration. Separation of these two quinolones in the ultrafiltrate was accomplished by ion-paired liquid chromatography using a reversed-phase analytical column eluted with an acetonitrile–methanol–water solution. Enrofloxacin and ciprofloxacin were detected by a photometric ultraviolet (UV)-visible detector set at 278.6 nm and confirmed by a photodiode array detector operating from 230 to 360 nm. The limits of detection for enrofloxacin and ciprofloxacin were 4 and 2 ng/mL, respectively[67].

A rapid, accurate, and sensitive method has been developed for the quantitative determination of ciprofloxacin, with high *in vitro* activity against a wide range of Gram-negative and Gram-positive organisms. A Kromasil 100 C-8 250 mm × 4 mm analytical column was used for analysis. Detection was performed with a variable wavelength UV-visible detector at 275 nm, resulting in limits of detection of 0.01 ng per 20 µL injection for ciprofloxacin. A rectilinear relationship was observed up to 5 ng/µL for ciprofloxacin. Separation was achieved within 10 min. The method was applied to direct determination of the fluoroquinolone ciprofloxacin in human blood serum. Sample pretreatment involved only protein precipitation with acetonitrile[68].

Another method of analyzing ciprofloxacin was by using the HPLC technique in which the system consisted of a pump (model LC-600) programmed by a system controller, a UV-visible spectrophotometric detector, and a recorder. The separation was carried out using a Spherisorb C-18 pH stable column (Phase Separations), 15 cm long. The mobile phase consisted of citrate buffer–acetonitrile–methanol (85:10:5 v/v/v) with an apparent pH adjusted to 2.4 with perchloric acid. The flow rate was maintained at 1.5 mL/min, and the column effluent was monitored at 280 nm. Phenacetin was used as the internal standard. Relative standard deviations for within-day and day-to-day precision were within 5%[69].

A thin-layer chromatographic (TLC)–densitometric method has been developed for identification and quantification of ciprofloxacin and an ethylenediamine compound, a desfluoro compound, and fluoroquinolonic acid as ciprofloxacin degradation products in pharmaceutical preparations. By using chloroform–methanol–25% ammonia (43:43:14 v/v/v) as the mobile phase and silica gel 60 high-performance TLC plates as the stationary phase, individual constituents were separated, which were subjected to UV densitometric analysis at 330 nm for fluoroquinolonic acid and at 277 nm for the other compounds. This method gave well-developed peaks allowing easy qualitative and quantitative analysis. Dimethylsulfoxide (DMSO)–methanol (1:1) was used to extract drug constituents. This method showed

high sensitivity (limit of detection 10–44 ng), a wide linearity range (3–20 µg/mL), and good precision (2.32–6.46% relative standard deviation) and accuracy (percentage recoveries 98.62–101.52%) for individual constituents[70].

The biodistribution and pharmacokinetics of the fluorine-18-labeled [^{18}F]ciprofloxacin in tissue were studied non-invasively in humans by means of positron emission tomography (PET). Special attention was paid to characterize the distribution of [^{18}F]ciprofloxacin to select target tissues. Healthy volunteers (n = 12) were orally pretreated for 5 days with therapeutic doses of unlabeled ciprofloxacin. On the 6th day, subjects received a tracer dose (mean injected amount 700 ± 55 MBq, which contained about 0.6 mg of unlabeled ciprofloxacin) of [^{18}F]ciprofloxacin as an intravenous bolus. Thereafter, PET imaging and venous blood sampling were initiated. Time–radioactivity curves were measured for liver, kidney, lung, heart, spleen, skeletal muscle, and brain tissues for up to 6 h after radiotracer administration. The first application of [^{18}F]ciprofloxacin in humans has demonstrated the safety and utility of the newly developed radiotracer for pharmacokinetic PET imaging of the tissue ciprofloxacin distribution. Two different tissue compartments of radiotracer distribution could be identified. From the first compartment consisting of kidney, heart, and spleen, the radiotracer was washed out relatively quickly (half-lives ($t_{1/2}$) 68, 57, and 106 min, respectively). The second compartment comprised liver, muscle, and lung tissue, which displayed prolonged radiotracer retention ($t_{1/2}$ > 130 min). The highest concentrations of radioactivity were measured in the liver and kidney, the main organs of excretion (standardized uptake values (SUVs) 4.9 ± 1.0 and 9.9 ± 4.4, respectively). The brain radioactivity concentrations were very low (<1 kBq/g) and could therefore not be quantified. Transformation of SUVs into absolute concentrations (in micrograms per milliliter) allowed the researchers to relate the concentrations at the target site to the susceptibilities of bacterial pathogens. In this way, the frequent use of ciprofloxacin for the treatment of a variety of infections could be corroborated[17].

Analytical procedures that apply chemiluminescence (CL) methods combined with flow injection have some advantages such as sensitivity, speed, ease of use, and use of simple instrumentation. The flow injection chemiluminescence methods have been described for determination of noscapine, propranolol, and ethamsylate in pharmaceutical preparations. A method for the determination of ciprofloxacin was described based on the enhancement by this compound of the weak CL from peroxynitrous acid. The CL reaction of fluoroquinolones with tris(2,2′-bipyridyl) ruthenium(II) [$Ru(bipy)_3^{2+}$] and Ce(IV) were studied in sulfuric acid medium. This method has been used to determine ciprofloxacin hydrochloride in dosage forms and biological fluids[71].

An indirect competitive enzyme-linked immunosorbent assay (ELISA) was developed to detect ciprofloxacin in food-animal edible tissues. Ciprofloxacin was converted by an active ester method into conjugates such as ciprofloxacin–bovine serum albumin (CPFX-BSA) and ciprofloxacin–human serum albumin (CPFX-HSA), which both allowed production of ciprofloxacin-specific rabbit antisera. In the ELISA, CPFX-HSA was coated over the microtiter plate, followed by incubation with standard ciprofloxacin and anti-ciprofloxacin antibody. The indirect competitive ELISA revealed that the antisera have no cross-reactivity with penicillin, gentamicin, neomycin, sulfadiazine, and chlortetracycline. The antisera cross-reacted with enrofloxacin and norfloxacin about 69.8 and 44.6% as much as they did with ciprofloxacin. This ELISA was highly sensitive (0.32 ng/mL) to ciprofloxacin determinations. The coefficients of variation varied from 3.7 to 9.2% over the range of ciprofloxacin concentrations studied. The linear detection range was between 1.6 and 1000 ng/mL. The results suggest that this ELISA is a specific, accurate, and convenient method for the screening of ciprofloxacin residues in food-animal edible tissues[72].

Ciprofloxacin degradation by basidiomycetous fungi was studied by monitoring $^{14}CO_2$ production from [^{14}C]ciprofloxacin in liquid cultures. *Gloeophyllum striatum* was used to identify the metabolites formed from ciprofloxacin. After 8 weeks, mycelia had produced 17 and 10% $^{14}CO_2$ from C-4 and the piperazinyl moiety, respectively, although more than half of ciprofloxacin (applied at 10 ppm) had been transformed into metabolites after 90 h. The structures of 11 metabolites were elucidated by HPLC combined with electrospray ionization mass spectrometry and ^{1}H nuclear magnetic resonance spectroscopy[73].

A molecularly imprinted solid-phase extraction procedure was developed for the simultaneous identification of enrofloxacin and its active metabolite, ciprofloxacin, in milk samples. Water-compatible molecularly imprinted polymers synthesized in a water–methanol system showed a high degree of cross-reactivity for enrofloxacin and ciprofloxacin in aqueous environments. The imprinted particles were applied as selective sorbents in a solid-phase extraction process focusing upon complex milk matrices, which allowed the matrix compounds present in milk samples to be removed effectively. The extracts were sufficiently clean for further chromatographic analysis, and no interference originating from the biological matrix was observed. This method is simple and sensitive, and is therefore an alternative tool to the existing HPLC methods for analyzing residual enrofloxacin and ciprofloxacin in biological samples[74].

Capillary zone electrophoresis (CZE) has been elaborated for separation, identification, and determination of ciprofloxacin and its impurities. For the separation, phosphate buffer pH 6.0 was supplemented with 0.075 M pentane-1-sulfonic acid sodium salt. The elaborated method was validated. The selectivity, linearity, limit of detection (LOD), limit of quantification (LOQ), precision, and accuracy of capillary zone electrophoresis were evaluated. The results obtained by CZE were also compared with those obtained by liquid chromatography. Regarding the validation results, the capillary electrophoresis (CE) method fulfills the current European Pharmacopoeia requirements. The evaluated CE method could be applicable to the analysis of different medicinal products containing ciprofloxacin[75].

In addition to the analytical methods discussed in the preceding text, several other methods[76–81] have been reported by researchers which provide relevant scientific information for determination of ciprofloxacin.

Pharmacokinetic aspects

Pharmacokinetic characteristics, namely absorption, distribution, metabolism, and elimination of ciprofloxacin, are described below.

Absorption

Ciprofloxacin is readily absorbed, but its complete absorption is generally not achieved following oral administration. The absolute bioavailability of oral ciprofloxacin is within a range of 70–80%, with no substantial loss by first pass metabolism[82]. An intravenous infusion of 400 mg ciprofloxacin given over 60 min every 12 h has been shown to produce an area under the serum concentration–time curve (AUC) equivalent to that produced by a 500 mg oral dose given every 12 h[13]. The concentration of ciprofloxacin in brain tissue was 0.87 ± 0.08 mg/kg at a single dose of 200 mg (intravenously, i.v.), suggesting that a dose greater than 200 mg i.v. is required to ensure therapeutic concentrations in brain tissue. Several studies have described the pharmacokinetics of ciprofloxacin in cerebrospinal fluid (CSF). The penetration was excellent when compared with the corresponding serum concentrations, but the absolute CSF concentration was sometimes considered to be subtherapeutic[83]. The relative constancy of the CSF level suggests a slow flux of ciprofloxacin across the blood–brain barrier[84]. Although drug–food interactions may prolong the time required to reach maximum plasma concentration (t_{max}) and thus affect the area under the concentration–time curve, this does not significantly alter the bioavailability of the drug[85]. The pharmacokinetic profile of ciprofloxacin is summarized in Table 2.

Distribution

Ciprofloxacin distribution in the tissues is superior to that of many other drugs of its class because there is little binding to plasma proteins. It has good penetration in various fluids and tissues of the body, except the central nervous system (CNS), after oral administration. A remarkable drug level is achieved in kidney, prostate, liver, and lung. Penetration into the cerebrospinal fluid is poor, except when the meninges are inflamed. The urinary drug concentration is higher than the minimum inhibitory concentration, so it is mainly used in urinary tract infections[9,89]. A small fraction of ciprofloxacin passes from the maternal to the fetal compartment, but this fraction is significantly small, indicating that there is a barrier to the transport of fluoroquinolones in the human placenta[90]. The availability of ciprofloxacin at the interstitial target site is considered to be an important determinant for the effectiveness of antimicrobial therapy and to be the clinical outcome of an infection. In a study, concentrations in the interstitial fluid space at the target sites and AUCs were significantly lower than the corresponding concentrations in plasma for dosages of 400 and 500 mg[91].

Table 2. Pharmacokinetic properties of ciprofloxacin[82,86–88].

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 (μg h/mL)	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

Metabolism and elimination

Ciprofloxacin differs widely in the degree to which it is metabolized and eliminated in the liver or by renal excretion. The metabolism is inactivating, and is primarily by glucuronide conjugation at the 3-carboxylic group. The piperazine ring is readily metabolized, and this results in decreased antimicrobial activity[9]. Elimination occurs by both renal and non-renal routes, but the primary route of elimination is via the renal route by glomerulus filtration and tubular secretion[86]. Thus, in patients with renal impairment and in geriatrics, dosage adjustment is required. The secondary route of excretion is via the liver[82]. Ciprofloxacin is poorly cleared by both peritoneal dialysis and hemodialysis.

Some change in pharmacokinetics is observed in diseased conditions, although diarrhea or cutaneous infections in human beings do not alter the oral absorption of ciprofloxacin. In the case of bacteremia, serum concentrations remain sufficient for effective treatment of Gram-negative infections, although differences can be observed in different analogs. The metabolism of ciprofloxacin to oxociprofloxacin is reduced in hepatic cirrhosis[92,93].

Adverse effects

With a few exceptions, the adverse effects of ciprofloxacin have not too severe consequences when compared to the beneficial features. Toxicity is mild at therapeutic doses, and generally limited to gastrointestinal disturbances such as nausea, vomiting, and diarrhea[94]. Although resistance to this class of antibiotics in pneumococci is rare, nevertheless some reports indicate that resistance to ciprofloxacin is increasing[95,96]. Recently, ciprofloxacin has been reported to be an effective therapeutic for anthrax[97,98]; however, a large dose is needed due to the blood–brain barrier (BBB), and heavy use of ciprofloxacin in such cases has been suspected to induce aseptic meningitis[99] and arthritis damage[100] and hence, there is a need to increase uptake by the brain[101]. Ciprofloxacin is still effective as antibiotic prophylaxis for prostate biopsies, but there is an increase in infective complications and resistance[102]. Skin photosensitivity reactions have been reported during treatment with ciprofloxacin[85,89].

The greatest concern with ciprofloxacin use in children is potential bone and joint damage[4]. Central nervous system effects are the second most common type of adverse events associated with ciprofloxacin therapy. Dizziness, insomnia, and mood alterations have frequently been observed during treatment. Seizures or hallucination have also been described[85,89,94,101]. Rarely, anaphylaxis and agranulocytosis have been reported[89]. The use of ciprofloxacin to treat multidrug resistant tuberculosis in children has led to the emergence of invasive pneumococcal diseases[103]. Incidences of the most common drug-related adverse events occurring with the ciprofloxacin are given in Table 3.

Drug interactions

Absorption of ciprofloxacin by the oral route of administration is decreased by the presence of antacids containing magnesium, aluminum, and other agents such as sucralfate[94]. Ciprofloxacin also interacts with multivalent cation-containing products. Exceptionally, ranitidine does not alter the oral absorption of ciprofloxacin[4]. These interactions of ciprofloxacin with antacids might be hazardous during the treatment of a serious infection[104]. A more disturbing interaction occurs between ciprofloxacin and theophylline or other methylxanthines such as caffeine. This interaction, which involves isoenzyme 1A2 of the cytochrome P-450 pathway, appears to be most pronounced, the occurrence of which can raise the serum theophylline concentration to a large extent. The clinical consequence of this interaction requires dose reduction and serum concentration monitoring of the xanthines[105]. Elevated serum levels of cyclosporine have been reported with concomitant use of ciprofloxacin. The serum concentration of antineoplastic drugs decreases due to the interaction with ciprofloxacin[4]. A significant decrease in clearance along with increased serum concentration of ciprofloxacin is observed by interaction with azlocillin, cimetidine, and probenecid. Drugs that cause the urine to become alkaline, such as sodium bicarbonate, carbonic anhydrase inhibitors, and citrates, reduce the solubility of ciprofloxacin and may increase the possibility of crystalluria[4,104–106].

Table 3. Incidences of adverse events with ciprofloxacin[87].

Adverse event	Percentage occurrence
Nausea	5.2
Diarrhea	2.3
Taste perversion	0.02
Headache	1.2
Dizziness	<1.0
Phototoxicity	0.4

Clinical indications

Ciprofloxacin is effective in a broad range of infections including those difficult to treat. Because of the wide-spectrum bactericidal activity, oral efficacy, and good tolerability, it is being extensively employed for blind therapy of infections, but should not be used for minor cases or where Gram-positive organisms are primarily suspected[4,101,107,108]. Some clinical indications of ciprofloxacin are summarized in Table 4.

It is pertinent to mention here that, although effective in clinical trials, ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae*[13,14].

Conclusion

Significant pharmacological interventions of ciprofloxacin and current analytical methodologies for its determination or identification in various formulations and biological

Table 4. Summarized uses of ciprofloxacin in infectious diseases[13,14,109–119].

Clinical indication	Infection-causing organisms
Urinary tract infections	*Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, or *Enterococcus faecalis*
Acute uncomplicated cystitis in females	*Escherichia coli* or *Staphylococcus saprophyticus*
Chronic bacterial prostatitis	*Escherichia coli* or *Proteus mirabilis*
Lower respiratory tract infections	*Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, or *Streptococcus pneumoniae*
Acute sinusitis	*Haemophilus influenzae*, *Streptococcus pneumoniae*, or *Moraxella catarrhalis*
Skin and skin structure infections	*Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* (methicillin-susceptible), *Staphylococcus epidermidis*, or *Streptococcus pyogenes*
Bone and joint infections	*Enterobacter cloacae*, *Serratia marcescens*, or *Pseudomonas aeruginosa*
Infectious diarrhea	*Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*, *Shigella boydii*[a], *Shigella dysenteriae*, *Shigella flexneri*, or *Shigella sonnei*
Typhoid fever	*Salmonella typhi*
Uncomplicated cervical and urethral gonorrhea	*Neisseria gonorrhoeae*
Pyelonephritis	*Escherichia coli*

[a]When antibacterial therapy is indicated.

fluids have been discussed. Ciprofloxacin has emerged as a promising and efficacious drug, having a myriad spectrum of antibacterial activity. It is emphasized that further scientific and technological advancements in pharmacology, medicinal chemistry, and analytical techniques are required to accurately control the therapeutic and quality profile of this potent medicinal agent.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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