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Review article

# Ciprofloxacin derivatives and their antibacterial activities

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ABSTRACT

Bacterial infections represent a significant health threat globally, and are responsible for the majority of hospital-acquired infections, leading to extensive mortality and burden on global healthcare systems. The second generation fluoroquinolone ciprofloxacin which exhibits excellent antimicrobial activity and pharmacokinetic properties as well as few side effects is introduced into clinical practice for the treatment of various bacterial infections for around 3 decades. The emergency and widely spread of drug-resistant pathogens making ciprofloxacin more and more ineffective, so it's imperative to develop novel antibacterials. Numerous of ciprofloxacin derivatives have been synthesized for seeking for new antibacterials, and some of them exhibited promising potency. This review aims to summarize the recent advances made towards the discovery of ciprofloxacin derivatives as antibacterial agents and the structure-activity relationship of these derivatives was also discussed.



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## 1. Introduction

Ciprofloxacin (Fig. 1, developed by Bayer, chemical name 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid) as the second generation

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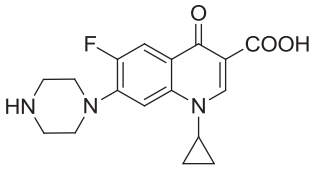


**Fig. 1.** Chemical structure of ciprofloxacin.

fluoroquinolone exhibits notable antimicrobial activity, excellent pharmacokinetic properties and few side effects was introduced into clinical practice for the treatment of various bacterial infections including upper and lower respiratory infections, and some skin, bone, soft tissue infections as well as community acquired pneumonia around three decades [1], and has been recommended as the second-line agents by the WHO for the treatment of tuberculosis (TB) mainly in cases involving resistance or intolerance to first-line anti-TB therapy [2]. Thus, ciprofloxacin derivatives have caused continuous interests.

Numerous ciprofloxacin derivatives which exhibited diverse biological properties such as antibacterial [3], anti-TB [4–7], antifungal [8], anti-HIV [9], anti-malarial [10], anti-tumor [11], anti-ischemic [12], anti-oxidation [13] activities as well as ureases inhibitory [14], imaging [15–18] profiles have been developed in the last 30 years, and the antibacterial property remains the domain research field of ciprofloxacin derivatives.

Bacterial infections, which caused predominately by Gram-positive and Gram-negative organisms, represent a significant health threat globally, and are responsible for the majority of hospital-acquired infections, leading to extensive mortality and burden on global healthcare systems [3,19]. To make the matter worse, the evolution of bacteria new virulent forms like drug-resistant pathogens with different level of resistance the current therapeutic options such as methicillin-resistant *S. aureus* (MRSA), methicillin-resistant *S. epidermidis* (MRSE), vancomycin-resistant *S. aureus* (VRSA), extended-spectrum $\beta$-lactamase (ESBL)-producing *Enterobacter* and *E. coli* have already been emerged and are associated with considerable mortality [20]. Therefore, there is a sense of urgency for new and more effective agents with great potency against both drug-sensitive and drug-resistant pathogens.

This review aims to outline the recent advances of ciprofloxacin derivatives as potential antibacterial drug candidates and summarize the structure-activity relationship (SAR) to provide an insight for rational designs of more active candidates.

## 2. Ciprofloxacin derivatives

It was demonstrated that 3-oxo-4-carboxylic acid core is the active DNA-gyrase binding site, and replacement of the carboxylic acid group results in reduction of the anti-bacterial activity generally [21,22]. The ciprofloxacin hybrids with 4-thiazolidinones replacement of the carboxylic acid of ciprofloxacin exhibited weak anti-bacterial activity which verified that modification of the carboxylic acid at C-3 position resulted in loss of the activity [23,24]. Interestingly, it was observed that when the carboxylic acid of ciprofloxacin was replaced by an aromatic amide group significant enhancements of potency against organisms were achieved compared with the parent ciprofloxacin [25]. Moreover, some of the derivatives were also found to be active against fungi, warrant further exploitations.

Three ciprofloxacin derivatives featured an ester group (methyl, ethyl or propyl ester) in place of the original carboxyl group of the ciprofloxacin were assessed for their *in vitro* activities against methicillin susceptible *S. aureus* (MSSA) and MRSA by Bartzatt et al. [26]. The Log *P* for ciprofloxacin and three esters **1a-c** (Fig. 2) were −0.701, −0.441, −0.065 and 0.437, and dermal permeability coefficient ($K_p$) values were increased as length of the ester carbon chain extended, suggesting this kind of esters may have greater penetration and higher efficacy in the treatment of bacterial infections of skin and soft tissues, consequently, have a substantial potential for the clinical treatment of MRSA and MSSA infections.

Several fluoroquinolones **2a-j** (Fig. 2) holding different alkyl subsitiuents at N-1 position of core structure and $N^4$-position of piperazinyl were tested for their antibacterial activities, and the preliminary results exhibited that all derivatives displayed considerable activity [27,28]. The relative contribution order of substituents at N-1 position to the activity was cyclopropyl > -Et > fluoroethyl ≈ *t*-Bu > -Me > 2,4-difluorophenyl > $-CF_3$. The most potent $N^4$-methyl ciprofloxacin **2a** (MIC: ≤0.0063–0.78 μg/mL) was 2-≥8-fold more potent than the reference norfloxacin (MIC: 0.05–3.12 μg/mL) against two Gram-positive (*S. aureus* and *S. pneumoniae*) and two Gram-negative (*P. aeroginosa* and *E. coli*), could act as a lead for further exploitation. Introduction of $N^4$-carboxymethyl into ciprofloxacin (**3a**) boost up the antibacterial activity slightly [29], while $N^4$-formyl (**3b**) led to decrease the antibacterial activity to some extent [30].

Five *N*-acylated ciprofloxacin derivatives **4a,b** (Fig. 2) were examined for their *in vitro* activities against some Gram-positive, Gram-negative organisms and mycobacteria by Miller et al. [31]. SAR revealed that all trimethyl lock ciprofloxacin quinone derivatives **4b** (MIC: <0.05–12.5 μM) were more potent than *N*-acyl derivatives **4a** (MIC: <0.05->100 μM) against all tested microbial, suggesting that the quinone motif played a key role for the enhanced activity. In general, the trimethyl lock ciprofloxacin quinone derivatives **4b** possessed equal or enhanced *in vitro* activity against Gram-positive strains compared to the parent ciprofloxacin, and the most active **4bc** with MIC <0.05 and 0.2 μM against *S. aureus* and *M. luteus* was more potent than ciprofloxacin (MIC: 0.47 and 8 μM). Further study indicated that compound **4bc** may act through a dual-action mechanism by serving as a prodrug and as a covalent thiol-containing enzyme inhibitor, could act as a lead for further modification.

Cormier and Seebach et al. found that *N*-acylated ciprofloxacin **5** (Fig. 2) were highly effective against Gram-positive and Gram-negative bacteria, and several possessing MIC ≤ 1.0 μg/mL against MRSA and *Bartonella* species [32,33]. An analysis of spontaneous mutation frequencies revealed that compared with the existing fluoroquinolone antibacterials, *N*-acylated ciprofloxacin **5** showed very low potential for resistance in MRSA. Mode of action profiling indicated that modification of the piperazinyl nitrogen by acylation did not alter the effect of these derivatives towards their bacterial target [32]. Further investigation suggested that these *N*-acylated derivatives were highly effective at killing intracellular bacteria, indicating the suitability of these derivatives for therapeutic treatment [32].

Eleven ciprofloxacin hybrids **6** (Fig. 2) containing bulky arenesulfonyl fragment were investigated *in vitro* for their antibacterial activities against two Gram-positive and two Gram-negative organisms by Abdel-Aziz et al. [34]. The most active **6a** with MIC of ≤0.25 μg/mL was comparable to ciprofloxacin (MIC: ≤0.25 μg/mL) against all tested strains, also showed a similar binding mode to ciprofloxacin with additional classical and nonclassical hydrogen bonds.

In spite of the antibacterial activity of ciprofloxacin carbamide **7a** was comparable to the parent ciprofloxacin, the majority of ciprofloxacin carbamides **7** were less potent than ciprofloxacin, suggested that in these derivatives the presence of additional moieties at the C-7 position of ciprofloxacin seems not to be beneficial to their bactericidal abilities against the tested strains