Antibacterial activity of new ciprofloxacin conjugates

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Article Info:

Received Feb 2023
Revised April 2023
Accepted May 2023
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DOI:https://doi.org/10.32947/ajps.v24i4.1080

Abstract:

Numerous antibiotics are no longer effective against certain germs, rendering it harder to treat illnesses and inflicting unnecessary suffering and death on many individuals. This necessitates the introduction of new antibacterial agents to counteract bacterial antibiotic resistance. In a previous published work, new ciprofloxacin conjugates were synthesized by amidification and esterification of the ciprofloxacin core structure. The antibacterial activity of these new ciprofloxacin derivatives was evaluated by clinical and laboratory standard instruments. The Laboratory of Public Health/ Branch of Microbiology in Karbala evaluated their collected strains for each species. All compounds exhibited antibacterial properties, where the inhibition zones were measured and the values reported. Bacterial susceptibility to recently produced chemicals tended to be as follows: *Pseudomonas aeruginosa* is followed by *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Escherichia coli*. The synthesized compounds had stronger antibacterial properties than the ciprofloxacin used as a starting point.

Key words: Ciprofloxacin, Antibiotic, Amidification, Esterification, Antibacterial

النشاط المضاد للبكتيريا لمقترنات السيبروفلوكساسين الجديدة

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الخلاصة:

لم تعد العديد من المضادات الحيوية فعالة ضد بعض الجراثيم، مما يزيد من صعوبة علاج الأمراض ويسبب معاناة ووفاة غير ضرورية للعديد من الأفراد. وهذا يتطلب دخول عوامل مضادة للجراثيم جديدة لمواجهة مقاومة المضادات الحيوية للبكتيريا. في عمل منشور سابق، تم تصنيع معقدات سيبروفلوكساسين جديدة عن طريق تفاعل الاسترة والامايد للبنية الأساسية للسيبروفلوكساسين. تم تقييم النشاط الحيوي لمشتقات السيبروفلوكساسين الجديدة من خلال الأدوات القياسية السريرية والمختبرية. أظهرت جميع المركبات خصائص مضادة للجراثيم، حيث تم قياس منطقة التثبيط وتم تسجيل القيم. ولوحظ ان نمط الحساسية البكتيرية للمركبات المصنعة حديثا كان كالتالي: *Pseudomonas aeruginosa, Escherichia coli*, *Proteus mirabilis,Klebsiella pneumoniae* بالمقارنة مع المادة الأولية، سيبروفلوكساسين، تمتلك المركبات المشتقة فعالية حيوية اعلى بكثير.

الكلمات المفتاحية: سيبروفلوكساسين، مضاد حيوي، أميد، استرة، مضاد للجراثيم

1. Introduction

A class of prokaryotic, include a single-cell microorganisms known as bacteria that are pervasive in the environment and have the potential to cause a wide range of illnesses in humans and other species(1). Bacteria are classified based on their morphological, biochemical and molecular characteristics(2). Bacterial species can be divided into gram-positive and gram-negative groups. For instance, *Staphylococcus aureus* and *Escherichia coli*. Bacterial infections can develop in both people and animals. Symptoms of bacterial infections include fever, chills, discomfort, edema and redness. Antibiotics are effective in treating bacterial illnesses (3). Antibiotic resistance, on the other hand, is a developing issue worldwide(4) . Certain bacteria have acquired resistance to multiple antibiotics, resulting in treatment failure (5,6).

Globally, medical doctors have few alternatives for treating bacterial infections, causing a lot of people to suffer needlessly or to die from diseases that might simply be cured (7). The discovery of novel and effective antibiotic therapies is thus a critical goal in the fight against drug-resistant microorganisms (8,9). For decades, fluoroquinolones have been utilized as broad-spectrum antibacterial drugs (10). Some forms of bacterial illnesses can be successfully treated with them, as researches have shown. Yet, bacterial resistance to these drugs has grown significantly in recent years, making the use of fluoroquinolones difficult or impossible in many clinical cases (11). Studying the structure of the prototypical drug, ciprofloxacin, may provide recognized paths for modification, as shown in figure (1).

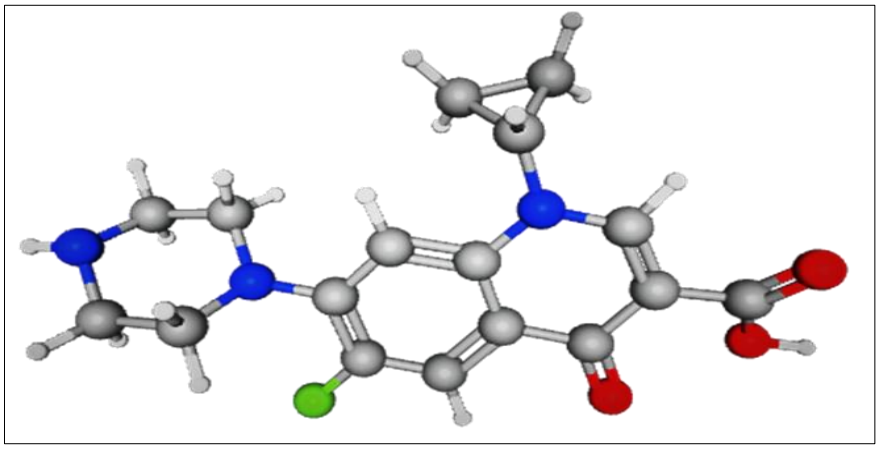


Figure 1: Ciprofloxacin's chemical structure

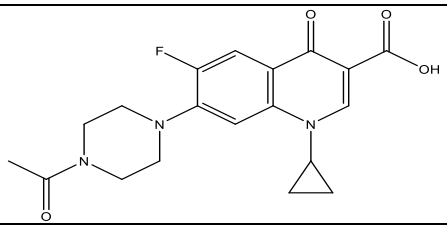
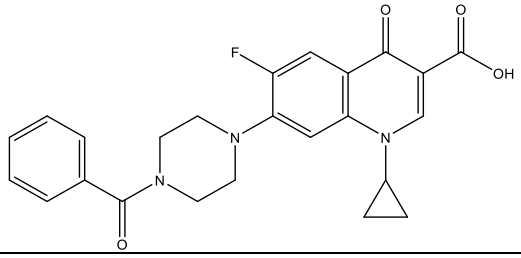
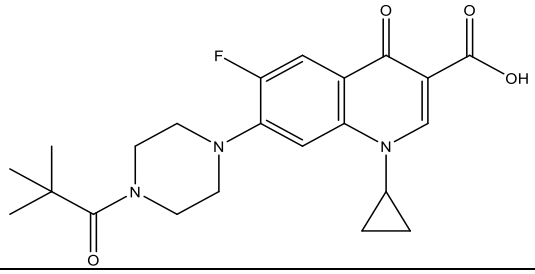
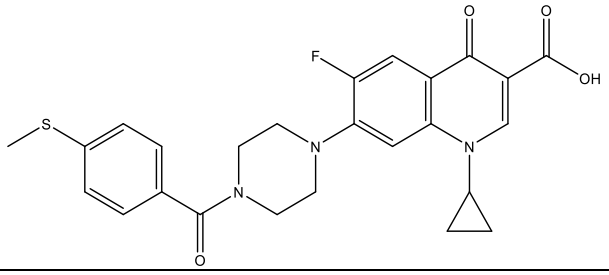
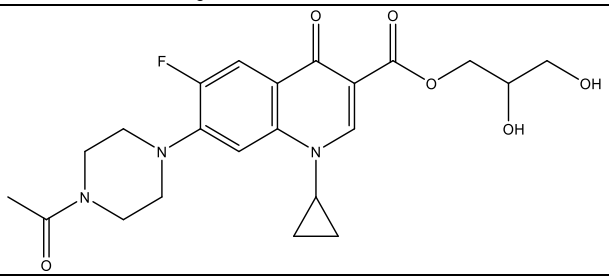
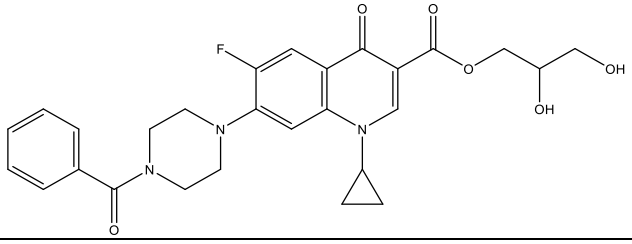
This research's objective is to assess the antibacterial efficacy of ciprofloxacin derivatives that have already been created.

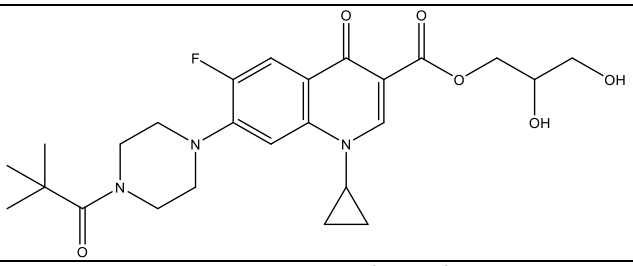
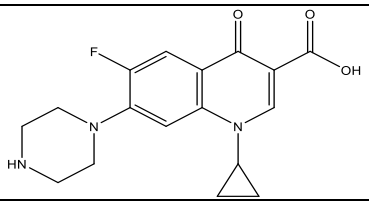
2. Materials and Methods

2.1. Chemicals

The chemical compounds that were chosen for the microbiological testing are listed in Table 1. The synthesis and characterization of these compounds were revealed in a previous work(12) . Ciprofloxacin was utilized as a positive control.

Table 1. Chemical compounds used in microbiological tests

Code	The chemical name of compounds	Chemical Structure
A	7-(4-acetylpiperazi-n-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid(13)	
B	7-(4-benzoylpiperazi-n-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	
T	1-cyclopropyl-6-fluoro-4-oxo-7-(4-pivaloylpiperazi-n-1-yl)-1,4-dihydroquinoline-3-carboxylic acid(13)	
M	1-cyclopropyl-6-fluoro-7-(4-(4-(methylthio)benzoyl)--1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	
AE	2,3-dihydroxypropyl 7-(4-acetylpiperazi-n-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate(14)	
BE	2,3-dihydroxypropyl 7-(4-benzoylpiperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinolin-e-3-carboxylate	

TE	2,3-dihydroxypropyl 1-cyclopropyl-6-fluoro-4-oxo-7-(4-pivaloylpiperazi-n-1-yl)-1,4-dihydroquinoline-3-carboxylate	
C	Ciprofloxacin	

2.2. Biological Activity and Bacterial Strains

Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae and *Proteus mirabilis* were among the clinical isolates of Gram-negative bacteria that were examined in the *in vitro* testing. The Laboratory of Public Health/ Branch of Microbiology in Karbala evaluated their collected strains for each species. The bacteria were cultivated in Mueller-Hinton agar for 24 hours at 37°C. Using the micro-dilution approach, the minimum inhibitory concentrations (MICs) of certain drugs were identified (15)

3. Results

All chemicals examine2d in this study showed to have antibacterial activities. However, these substances were often more effective against Gram-negative bacteria. The following pattern of microorganism susceptibility to substances was noted: *Escherichia coli* followed by *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* while *Proteus mirabilis* was the less one. Table 2 displays the outcomes for the examined substances.

Table 2. Inhibition zone (in cm) of ciprofloxacin derivatives

No.	Compound	Bacterial inhibition zone			
		E. coli	***P. aeruginosa***	***K. pneumoniae***	***P. mirabilis***
1	A	3.66	3.51	3.3	3.2
2	B	3.89	3.7	3.52	3.33
3	T	3.97	3.81	3.66	3.5
4	M	3.79	3.7	3.5	3.22
5	AE	4.1	4	3.88	3.8
6	BE	3.5	3.4	3.39	3.29
7	TE	4.1	3.88	3.79	3.61
8	C	2.5	2.41	2.33	2.29

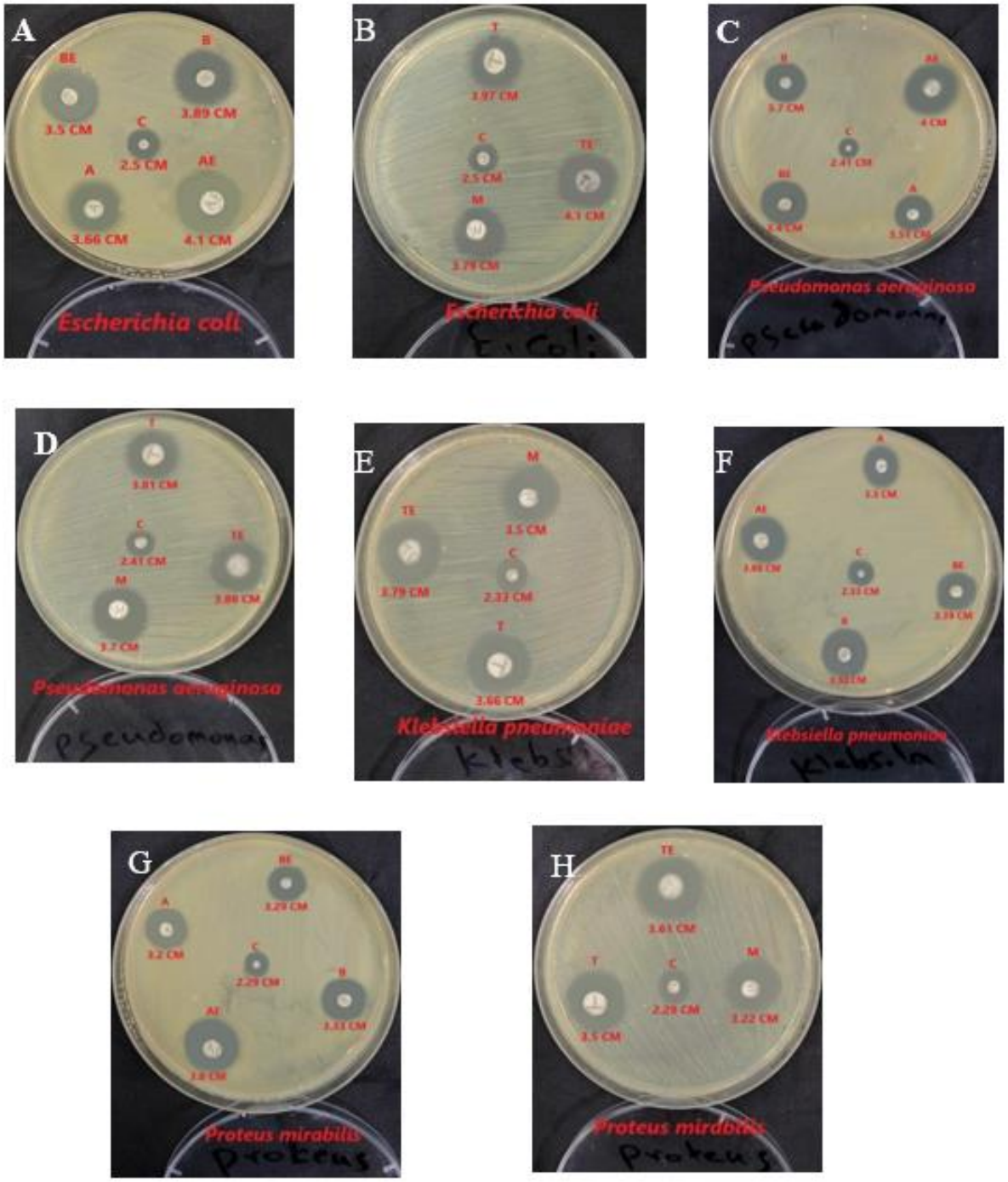


Figure 2: Bacterial inhibition zones, Where A, C, E, and G are the inhibition zones for Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae and Proteus mirabilis, respectively for the compounds A, B, AE, and BE. While B, D, F, and H are the inhibition zones for Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, and Proteus mirabilis, respectively for the compounds T, TE, and M.

4.Discussion

In the current work, the compounds A, B, T and M [acetyl, benzoyl, trimethyl acetyl and 4-(methyl thio) benzoyl group] were respectively added to the C-7 side chain's N atom by amidation reaction. Adding these bulky groups to the N atom led to an increase in the lipophilicity of these compounds. Thus, the activities of compounds almost doubled comparable to the original compound. This is consistent with the studies of Sharma (2017) and Dang (2012) on the structure-activity relationship (SAR) of fluoroquinolones, which shown that the N-substitution possesses an appreciated impact (16,17). For instance, the antibacterial efficiency, spectrum, and safety are significantly influenced by the basic group at the C-7 position(18,19). It is generally accepted that increase in lipophilicity corresponds to ~~the~~ increase in the activity of fluoroquinolones. In compounds AE, BE and TE, a condensation reaction was successfully conducted via the esterification of the carboxylic acid group with a polar triose sugar (glycerol). This has led to a significant enhancement in the solubilization, thus dramatically increasing its activity, which is also consistent with the studies of Shuo Wang (2012) who showed that ester derivatives of the broad-spectrum antibiotic ciprofloxacin would lead to a significant enhancement in solubilization, thus increasing its effectiveness(20).

In summary, the modification of both sides of ciprofloxacin, the amine side and carboxylic side, enabled the successful manipulation of lipophilicity and hydrophilicity, and the desired balance was achieved. Thus, this balance enhanced the penetration of these derivatives compared to the original drug, so the synthesized compounds, by acting on bacterial DNA gyrase, inhibited the relaxation of supercoiled DNA and promoted the breakage of double-stranded DNA better than ciprofloxacin (21).

5.Conclusion

Due to structural modification, the synthesized compounds (A, B, T, M, AE, BE and TE) had a higher antibacterial activity by inhibiting the bacterial DNA gyrase. Targeting the alpha subunits of DNA gyrase prevents it from supercoiling the bacterial DNA, which prevents DNA replication compared to the ciprofloxacin starting material

Acknowledgement:

The authors would like to express their appreciation to the Medicinal Chemistry lab at the College of Pharmacy, Mustansiriyah University and the Public Health Laboratory of Microbiology at Karbala Governorate for facilitating the conduct of this study.

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