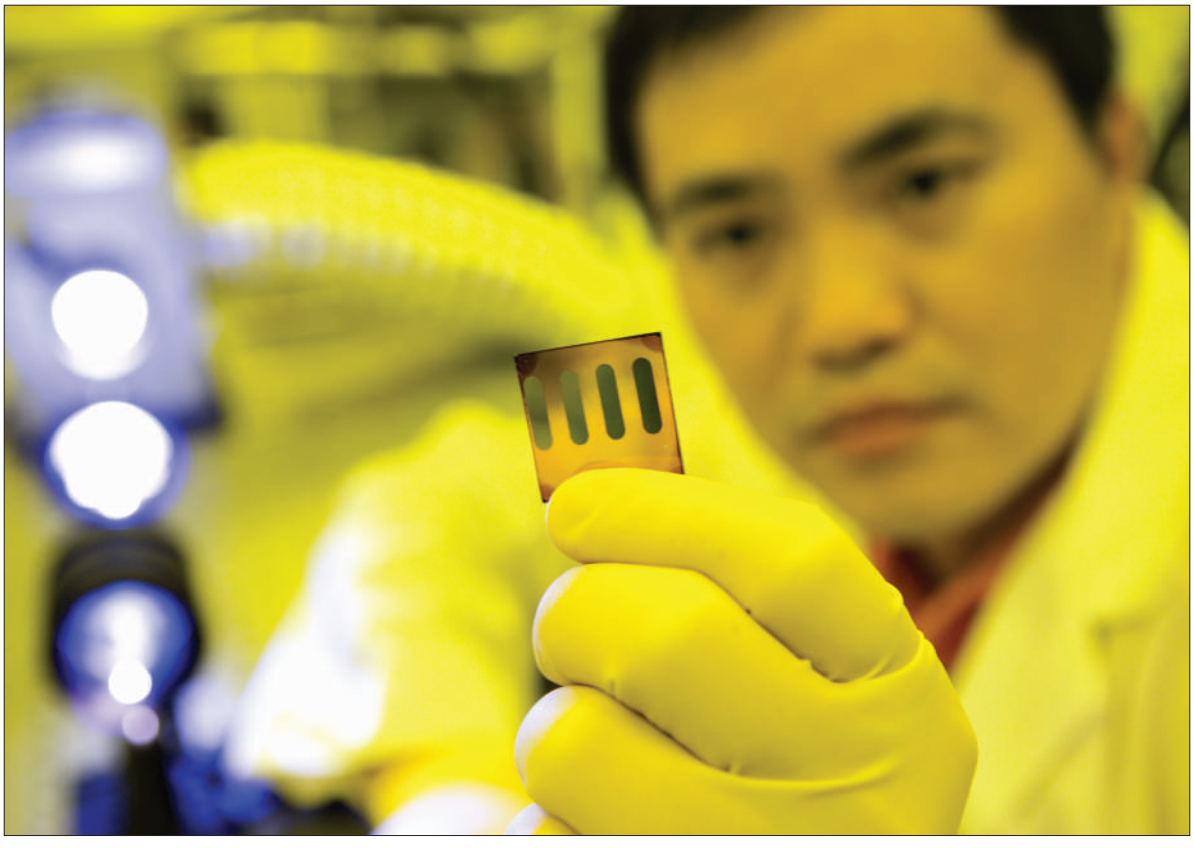

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Research Article
An Improved Antibacterial Activity of Cephalosporin Analogues by Introducing Sulfamoylamino Group

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Abstract

Background and Objective: Antibiotic resistance is increasing globally because of the widespread use of antibiotics. Therefore, there is an urgent need to find new antibiotics with novel structures and more potent activities. This study was aimed to evaluate the antibacterial activity of cephalosporin analogues by introducing a sulfamoylamino group, displayed the relation between the structure and antibacterial activity. **Materials and Methods:** A series of novel cephalosporin analogues were synthesized and the *in vitro* antibacterial activity against Gram-positive bacteria (*S. aureus*, *S. pneumonia* and *S. epidermidis*) and Gram-negative bacteria (*E. coli*, *P. aeruginosa* and *K. pneumonia*) were performed by the standard agar dilution method. **Results:** The synthesized sulfamoylamino-containing cephalosporin analogues exhibited significantly antibacterial activity against the test bacteria. **Conclusion:** The screening result discovered that sulfamoylamino-containing cephalosporin analogues was able to significantly improved the antibacterial activity, which provided us evidence for the further development of potential cephalosporin antibiotics.

Key words: Antibiotics, bacterial resistance, sulfamoylamino group, cephalosporin, antibacterial activity

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Antibiotics are one of the most effective drug to eliminate or control infectious diseases. In 1940, penicillin was put into use in clinical as the world's first antibiotic[1]. After 80 years of the development, antibiotics have saved millions of lives[2]. β-lactam antibiotics is a breeding fungicides and there are no cell walls in mammalian and fungal. thus, which characterized by strong antibacterial activity and small adverse reactions are widely applied and practical[3,4]. Nowadays, β-lactam antibiotics is the largest variety of antibiotics currently and play a critical role in the treating infection diseases[5]. However, the overuse of antibiotics aggravated the emerging of antibiotic-resistant pathogens, making the original effective antibiotics lose their effect. The treatment of bacterial infections has faced with a new challenge, because of the emergency of bacterial multidrug-resistant and pan-drug resistance[6-8]. One of the effective ways to problem-solving of bacterial resistance is to introduce novel structural group different from previous and develop new antibacterial drugs.

Cephalosporin antibiotics, which were developed in the late 1960s, a class of atypical semisynthetic β-lactam antibiotics[9]. Because of their broad-spectrum, strong antibacterial activities, resistance to β-lactamase, low toxicity and less allergic reactions, cephalosporin have a variety of advantages and play an important role in the treatment of severe infection in hospitals[10]. Currently, more than 60 cephalosporin antibiotics have been put on the market and they have made great contributions to treat bacterial infections[11]. However, with the widespread use of cephalosporin, the bacterial drug resistance has increased and became the most important problem are similar to those of other β-lactam antibiotics[12,13]. There is an urgent need to find new cephalosporin antibiotics with novel structures, long half-life, less side effects and more potent activities[14].

In previous studies, carbapenem are β-lactam antibiotics that have a (3S)-pyrrolidine-3-ylthio moiety side chain, when a sulfonamide or sulfamoylamino group was introduced to 5 -position of pyrrolidine, a significant change in antibacterial activity was available[15-19]. As shown in Fig. 1, compound 2 contain a sulfonamide moiety compared to compound 1 (meropenem), the antibacterial activity of compound 2 is almost the same as that of compound 1 but the stability to DHP-1 superior to meropenem[20]. While compound 3 has a sulfamoylamino structure and the antibacterial activity against Gram-positive bacteria surpassed that of meropenem and displayed better stability[21] to DHP-1. A similar structure was introduced to compound 4, exhibited better antibacterial activity against Gram-positive and Gram-negative bacteria than meropenem and the stability to DHP-I is significantly higher[22].

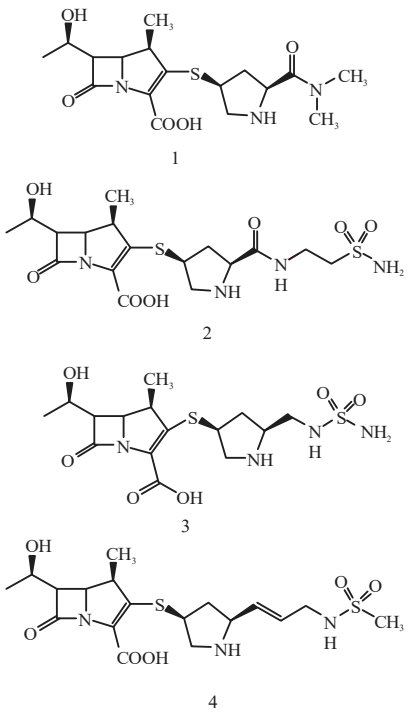


Fig. 1: Carbapenem analogues 1-4

So, in this study, a series cephalosporin analogue with (3S)-pyrrolidine-3-ylthio moiety was designed and synthesized and the antibacterial activity of these analogues by introducing a sulfamoylamino group to 5-position of pyrrolidine was evaluated. The aim is to display the relation between the structure and antibacterial properties and further to discover novel antibacterial potential compounds.

MATERIALS AND METHODS

All of solvents and reagents used in experiments come from commercial sources such as Macklin (www.macklin.cn), Adamas-beta (www.adamas-beta.com) and Aladdin (www.aladdin-reagent.com) used without further purification. These cephalosporin analogues were synthesized at Synthesis Lab from October, 2018-July, 2019 and the antibacterial activity was determined at Microbiology Lab in September, 2019.

Synthesized the cephalosporin analogues: The synthesis of cephalosporin analogues by chemical method, according to specific reaction conditions and measured the chemical structure by ^{1}H-NMR and LC-MS.

Evaluation of the antibacterial activity: The antibacterial activity of cephalosporin analogues was determined using experimental disc diffusion method[23]. The compound dissolve and dilute to 250 μg mL^{-1} with sterile water and then double dilution in order. Six strains of Gram-positive and Gram-negative bacteria were inoculated in broth at 37°C and cultured overnight. Quantify with a multi-point inoculators and inoculated 10^5 CFU/point and then incubated at 37°C for 18 h to observe the minimum inhibitory concentration (MIC value, μg mL^{-1}).

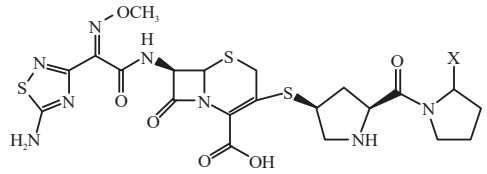
Statistical analysis: The results were analyzed by one-way ANOVA test using SPSS 19.0 with a statistically significant were considered.

RESULTS

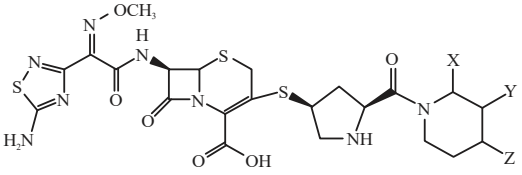
Synthesized the cephalosporin analogues: A series of cephalosporin analogues was synthesized. The molecular structure of these compounds is given in Fig. 2. As shown, cephalosporin analogues 5a-5e have (3S)-pyrrolidine-3-ylthio side chain and introduced a piperidine or pyrrolidine methanol moiety to 5 -position of pyrrolidine. For the purpose of investigating the effect of sulfamoylamino group on antibacterial activity, the hydroxyl of 5a-5e molecular was substituted by sulfamoylamino moiety and obtained cephalosporin analogues 6a-6e for antibacterial activity test.

Antibacterial activity: The *in vitro* antibacterial activity of cephalosporin analogues was determined using experimental disc diffusion method and the results are shown in Table 1.

It could be seen from Table 1, all the samples displayed excellent antibacterial activity against the test bacteria, with Gram-positive and Gram-negative bacteria being approximately equally susceptible. Potent antibacterial activities (generally in the range 1.56-12.5 μg mL^{-1}) were evident for hydroxyl moiety cephalosporin analogues (5a-5e) against both Gram-positive and Gram-negative bacteria. The sulfamoylamino-containing cephalosporin analogues (6a-6e) also exhibited significantly antibacterial activity (generally in the range 0.39-6.25 μg mL^{-1}) against the test bacteria. The MIC value of the tested cephalosporin analogues was slightly lower than the positive control except compound 6a and 6b exhibited the same antibacterial activity against *S. epidermidis* and *E. coli*. It is notable that there exhibits a significantly improved of antibacterial activity while hydroxyl moiety was substituted by sulfamoylamino group at the same position.



5a: X=(S) CH_2OH
5b: X=(R) CH_2OH
6a: X=(S) $CH_2NHSO_2NH_2$
6b: X=(R) $CH_2NHSO_2NH_2$



5c: X=CH_2OH, Y=H, Z=H
5d: X=H, Y=CH_2OH, Z=H
5e: X=H, Y=H, Z=CH_2OH
6c: X=$CH_2NHSO_2NH_2$, Y=H, Z=H
6d: X=H, Y=$CH_2NHSO_2NH_2$, Z=H
6e: X=H, Y=H, Z=$CH_2NHSO_2NH_2$

Fig. 2: Cephalosporin analogues 5a-e, 6a-e

Table 1: *In vitro* antibacterial activity (μg mL^{-1}) of the cephalosporin analogues

Compounds	*S. aureus*	*S. pneumonia*	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*K. pneumonia*
5a	3.13	3.13	1.56	6.25	12.5	1.56
5b	3.13	1.56	1.56	6.25	12.5	1.56
5c	6.25	3.13	3.13	12.5	12.5	1.56
5d	6.25	6.25	6.25	12.5	12.5	1.56
5e	3.13	6.25	3.13	12.5	12.5	1.56
6a	1.56	0.78	0.78	3.13	6.25	0.39
6b	1.56	0.78	0.78	3.13	6.25	0.39
6c	1.56	1.56	1.56	6.25	6.25	0.39
6d	3.13	1.56	3.13	6.25	6.25	0.39
6e	1.56	1.56	1.56	6.25	6.25	0.78
Cefpirome	0.78	0.39	0.78	3.13	3.13	0.195

DISCUSSION

The antibacterial activity of cephalosporin analogues 5a-5e, 6a-6e and positive control both displayed excellent antibacterial activity against the test Gram-positive and Gram-negative bacteria and the antibacterial activity of 6a-6e was significantly superior to 5a-5e since hydroxyl moiety was substituted by sulfamoylamino group. It indicated that have a positive effect of antibacterial activity of cephalosporin by introducing a sulfamoylamino group to molecular structure. As in previous reports, Shin *et al.*[20] found that sulfonamide moiety was introduced to molecular structure got a methyl-substituted carbapenem compound, exhibited better stability to DHP-1. Researchers recorded sulfamoylamino moiety was introduced to molecular structure got new carbapenem compound, displayed better antibacterial activity and the stability to DHP-1 is significantly higher better. It showed the possibility that sulfamoylamino moiety may be beneficial for the antibacterial activity of antibiotics[21,22]. Previous assertion by Zhao *et al.*[24] and Badampudi *et al.*[25] revealed that sulfamoylamino moiety was introduced to molecular structure got the improved antibacterial activity. New research has provided more evidence, Kumar *et al.*[26] and Elgemeie *et al.*[27] also affirmed that the structure-activity relationship between sulfamoylamino structure and antibacterial activity, introduction of a sulfamoylamino group provided compounds with significantly improved antibacterial activity.

Although its mechanism of action is not clear, one possible reason is that sulfamoylamino have stronger cohesion with bacterial protein than hydroxyl and form stronger hydrogen bonds which provided stronger antibacterial activity. The antibacterial activity of 6a-6e slightly below the positive control at most test bacteria, it can be speculated that a larger molecular backbone causes partially offset the binding force. It is obvious that introduction of sulfamoylamino groups to compound lead to the improvement of antibacterial activity.

The results provided us strong evidence to further understand the structure-activity relationship cephalosporin and valuable information to find new cephalosporin antibiotics with novel structures and activities that are more potent.

CONCLUSION

The screening result discovered that the sulfamoylamino was introduced to 5 -position of pyrrolidine of cephalosporin were able to significantly improved the antibacterial activity against the test bacteria, compared with hydroxyl cephalosporin analogues. It is displayed that the introduction of sulfamoylamino groups can enhance the antibacterial activity of cephalosporin analogues. The result is consistent with that of β-lactam antibiotics carbapenem as described by previous studies, indicating that sulfamoylamino groups can enhance the antibacterial activity of β-lactam antibiotics. The valuable result of this provided us an evidence for the further develop of antibacterial research and providing potential antibiotics for problem of bacterial resistance.

SIGNIFICANCE STATEMENT

This study discovered the possible interaction effect between sulfamoylamino and bacterial protein, which may be beneficial for the antibacterial activity of β-lactam antibiotics. This study will help the researcher to understand the mechanism of action of sulfamoylamino-containing β-lactam antibiotics that many researchers were not able to explore. Thus, a new theory on sulfamoylamino group was introduced to β-lactam antibiotics will able to significantly improve the antibacterial activity may be arrived at.

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