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Design, synthesis and antibacterial evaluation of honokiol derivatives

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ABSTRACT

Staphylococcus aureus is a major and dangerous human pathogen that causes a range of clinical manifestations of varying severity, and is the most commonly isolated pathogen in the setting of skin and soft tissue infections, pneumonia, suppurative arthritis, endovascular infections, foreign-body associated infections, septicemia, osteomyelitis, and toxic shocksyndrome. Honokiol, a pharmacologically active natural compound derived from the bark of *Magnolia officinalis*, has antibacterial activity against *Staphylococcus aureus* which provides a great inspiration for the discovery of potential antibacterial agents. Herein, honokiol derivatives were designed, synthesized and evaluated for their antibacterial activity by determining the minimum inhibitory concentration (MIC) against *S. aureus* ATCC25923 and *Escherichia coli* ATCC25922 *in vitro*. **7c** exhibited better antibacterial activity than other derivatives and honokiol. The structure-activity relationships indicated piperidine ring with amino group is helpful to improve antibacterial activity. Further more, **7c** showed broad spectrum antibacterial efficiency against various bacterial strains including eleven gram-positive and seven gram-negative species. Time-kill kinetics against *S. aureus* ATCC25923 *in vitro* revealed that **7c** displayed a concentration-dependent effect and more rapid bactericidal kinetics better than linezolid and vancomycin with the same concentration. Gram staining assays of *S. aureus* ATCC25923 suggested that **7c** could destroy the cell walls of bacteria at 1 × MIC and 4 × MIC.

Various life-threatening diseases caused by bacterial infections have become a serious public health problem in recent years. *Staphylococcus aureus*, as a major and dangerous human pathogen, is a series of diseases ranging from moderately severe skin infections to fatal necrotizing pneumonia and one of the most frequent causes of morbidity and mortality in worldwide.[1] Therefore, the discovery and development of new antibacterial agents are urgently needed to combat the diseases by *S. aureus* infection.

Natural products are the most valuable source of novel bioactive molecules in antibacterial drug discovery, natural products and/or their semisynthetic derivatives in their origin are the major clinical antibiotics.[2–7] Previous studies reported honokiol, a natural biphenolic compound isolated from the stem bark of *Magnolia officinalis*[8], showed antibacterial activity against several microorganisms such as *Staphylococcus aureus* (MIC: 50 μg/ml)[9], *Streptococcus mutans* (MIC: 10 μg/ml)[10] and *Candida albicans* (MIC: 32 μg/ml).[11] Inspired by antibacterial activity of honokiol, it is significant to find more effective antibacterial honokiol derivatives. Hence, we synthesized a series of novel honokiol derivatives for their initial evaluation as new antibacterial agents (Fig. 1).

Compounds **6a**–**6g** were prepared in a tandem step as described in Scheme 1. The intramolecular iodocyclization of honokiol in the presence of iodine afforded key intermediate **2**.[12] Intermediate **5** was synthesized by hydroxy methylation, chloride reaction and deprotection of the hydroxyl group.[13–16] In the presence of cesium carbonate and potassium iodide, intermediate **5** was reacted with various substituted piperidine or piperazine to afford **6a**–**6g**.[17] Moreover, we also tried to deprotect BOC group to achieve compounds **7a**–**7c** (depicted in Scheme 2). The synthesis of compound **8** was described in Scheme 3.[13]

We obtained total of 12 honokiol derivatives, all derivatives, including honokiol were evaluated for their *in vitro* antibacterial activity against Gram-positive (*S. aureus* ATCC25923) and Gram-negative bacteria (*E. coli* ATCC25922) with linezolid and vancomycin as the positive controls by employing the standard broth microdilution method.[18] The corresponding minimum inhibitory concentration (MIC) values are shown in Table 1.

To the best of our knowledge, little attention has been paid to structural modifications of honokiol as antibacterial agents.[19]

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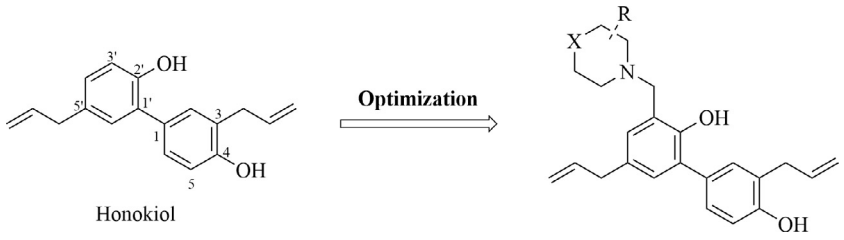
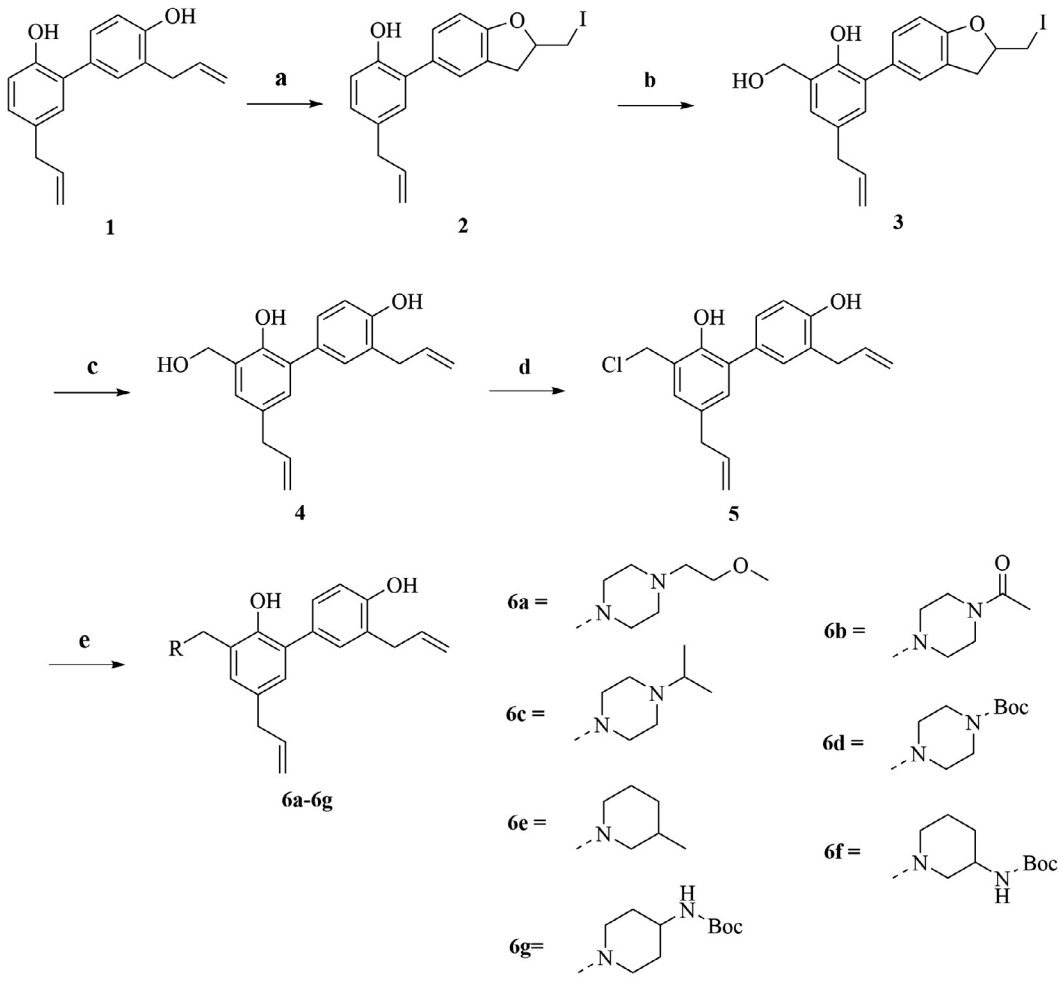


Fig. 1. Design strategy for honokiol derivatives.



Scheme 1. Synthesis of **4** and **6a**–**6g**. Reagents and conditions: (a) I_2, EtOH/H_2O (1:9, v/v), 50 °C, 12 h, 65.87%; (b) HCHO (37% in water), NaOH, EtOH/ H_2O (1:1, v/v), 50 °C, overnight, 53.04%; (c) Zn, AcOH, EtOH, reflux, 8 h, 68.02%; (d) $SOCl_2$, CH_2Cl_2, rt, 49.74%; (e) Cs_2CO_3, KI, MeCN, 80 °C, 24–59%.

Herein we explored the structure–activity relationship of the honokiol derivatives as antibacterial agents. Twelve analogues which were introduced diverse groups to the 5- or 3′-position(s) of honokiol have been synthesized. Compared the MIC values of compounds **4** and **8** with honokiol, we find that the hydroxymethyl group reduced antibacterial activity. For example, **4** and **8** had two fold MIC values of honokiol against *S. aureus* (ATCC 25923). Hence, the hydroxymethyl group is not conducive to improve the antibacterial activity. At the same time, the data acquired show that 4-hydroxy play a crucial role on antibacterial activities. Inspiringly, the introduction of piperidine or piperazine to the 3′-position of honokiol was in favor of enhancing antibacterial activity. However, piperidine or piperazine possessing larger substituent, such as **6a**–**6g**, performed lower antibacterial activity. On the contrary, compounds **7a**–**7c** showed better antibacterial activity possibly because of smaller substituent than other derivatives. Nonetheless, compound **6e** possessing methyl, has lower antibacterial activity. Therefore, the category of substituent was also important. Obviously, piperidine ring with an amino group is helpful to improve antibacterial activity. For example, MIC values of **7b** and **7c** are 16 and 8 (μg/ml) respectively. In addition, the location of amino group is crucial for antibacterial activity. The antibacterial activity of amino group in *para*-position differs from that in *meso*-position. For instance, the MIC value of **7c** is double compared to that of **7b** against *S. aureus* (ATCC 25923). It is particular worth mentioning here that the antibacterial activity of **7c** is better than honokiol.

7b and **7c** were selected to further test *in vitro* antibacterial activity against various bacteria strains including 11 g-positive