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Synthesis and antibacterial activity of pyridinium-tailored 2,5-substituted-1,3,4-oxadiazole thioether/sulfoxide/sulfone derivatives

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ABSTRACT

By introducing the pyridinium group into 2,5-substituted-1,3,4-oxadiazole, a series of pyridinium-tailored 2,5-substituted-1,3,4-oxadiazole thioether/sulfoxide/sulfone derivatives were obtained, and their antibacterial activities were evaluated via turbidimeter test in vitro. The bioassays reveal that most of the target compounds exhibit better inhibition activities against pathogen *Xanthomonas oryzae pv. oryzae*, *Ralstonia solanacearum*, and *Xanthomonas axonopodis pv. citri* than positive controls bismerthiazol (**CK_1**) or thiodiazole copper (**CK_2**). Among them, **I-8**, **I-10**, **I-12**, **II-10**, **II-12**, **III-10**, and **III-12** exert excellent inhibition activities against the three pathogenic bacteria with the half-maximal effective concentration (EC_{50}) values ranging from 0.54 to 12.14 μg/mL. Our results demonstrate that pyridinium-tailored 1,3,4-oxadiazole thioether/sulfoxide/sulfone derivatives can serve as potential alternative bactericides for the management of plant bacterial diseases.

Pathogenic bacteria, one of the most serious threats to the agricultural crops and economic crops, can cause many kinds of plant diseases, such as rice bacterial leaf blight, tobacco bacterial wilt, and citrus bacterial canker.[1–3] The three plant diseases are mainly caused by Gram-negative pathogenic bacteria *Xanthomonas oryzae pv. oryzae* (*Xoo*), *Ralstonia solanacearum* (*R. solanacearum*), and *Xanthomonas axonopodis pv. citri* (*Xac*), respectively, and have led to enormous economic losses each year.[4–6] As one of the control measures toward these plant diseases, chemical control, has become a powerful and useful tool in the past decades.[7,8] However, even though a few commercial bactericides have been developed, their poor efficiency, high phytotoxicity, high residue level, negative impact toward the environment, or pathogen resistance are still a major global concern. For example, bismerthiazol, one of the major bactericides for the control of rice bacterial leaf blight, only shows the control efficiency of 25.49% at a high dosage of 200 μg/mL. Furthermore, its application has already resulted in the appearance of bismerthiazol-resistant strains of *Xoo* in Anhui Province, China.[9,10] Therefore, the exploration and development of high-efficient and safe bactericides to prevent and control plant bacterial diseases still remains an arduous task in pesticide science.

In the exploration of novel bactericide, heterocyclic systems containing 1,3,4-oxadiazole have attracted great attentions due to their potent biological activities against bacteria and fungi.[11–15] For example, Patel and co-workers reported a series of 3-(5-sulfanyl-1,3,4-oxadiazol-2-yl)-2*H*-chromen-2-ones bearing various substituted piperazines and piperidines exhibiting noteworthy bioactivities against two types of Gram-positive bacteria and six types of Gram-negative bacteria.[16] Garudachari et al. have evaluated the antibacterial activity of a series of *N*-alkyl-7-(trifluoromethyl)quinolin-4-amine derivatives containing 1,3,4-oxadiazole moiety, and found that the target compounds exerted significant antibacterial activities against *Mycobacterium smegmatis* and *Pseudomonas aeruginosa*.[17] Furthermore, our previous work have demonstrated that 1,3,4-oxadiazole thioether/sulfoxide/sulfone derivatives exhibiting good control efficiency toward plant bacterial diseases, and have led to two antibacterial candidates in commercialization stage.[7,9,18–20] Obviously, heterocyclic compounds containing 1,3,4-oxadiazole are the promising agents in the development of novel high-efficient bactericide.

As another interesting candidate in the development of novel bactericide, pyridinium-functionalized amphiphiles, were found having potent biocidal activities against Gram-negative and Gram-positive bacteria by disrupting the innate defense system of bacterial membrane.[21–24] For example, Kahriman et al. introduced pyridinium moiety bearing different alkyl tails into 1-alkyl-4-oxo-1,4-dihydroquinoline and found that the amphiphile bearing a hexyl tail exhibited the highest bioactivities against

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Gram-negative (*Pseudomonas aeruginosa*) and Gram-positive (*Staphylococcus aureus*) bacteria.[25] Brahmachari et al. have evaluated a series of compounds containing a pyridinium unit as the polar head group and different length of alkyl chain as the hydrophobic part, and found that amphiphiles with pentadecyl or heptadecyl exhibited excellent bioactivities against two types of Gram-positive (*Bacillus subtilis* and *Micrococcus luteus*) and Gram-negative (*Escherichia coli* and *Klebsiella aerogenes*) bacteria.[26] Apparently, pyridinium group can be used as a functional tool to enhance the bioactivity of the target compounds due to its positive charge can facilitate the interaction with anionic cell components and consequently conduce to the disruption of the innate defense system of bacterial membranes. Inspired by those reports, it was proposed that appreciable bioactivity may be achieved through embedding the pyridinium moiety into heterocyclic systems containing 1,3,4-oxadiazole moiety. As shown in Figure 1, a series of 2,5-substituted-1,3,4-oxadiazole thioether/sulfoxide/sulfone derivatives were designed, with the hydrophobic heterocyclic tails and the hydrophilic pyridinium cations linked by different length of alkyl chains. Till now, few studies focused on the usage of this kind of amphiphiles in growth suppression of plant pathogenic bacteria.

The synthesis and structure of pyridinium-functionalized 2,5-substituted-1,3,4-oxadiazole thioether (**I-n**) are shown in Scheme 1. Briefly, the starting material 2,4-dichlorobenzoic acid was treated by three steps including esterification, hydrazidation, and cyclization to give the crucial intermediate 5-(2,4-dichlorophenyl)-1,3,4-oxadiazole-2-thiol,[7–9] which then reacted with dibromo-substituted alkanes to afford bromide-tailored intermediates (**I-nBr**). Finally, these bromide-tailored intermediates were incubated in pyridine at 50 °C to afford the target compounds **I-n** (n = 4, 6, 8, 10, 12). All the structures were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS (detailed information see Supplementary data).

Turbidimeter test[27,28] was carried out to evaluate the antibacterial activities of **I-n** against *Xoo*, *R. solanacearum*, and *Xac* in vitro. And the commercial agricultural antibacterial bismerthiazol (**CK_1**) was selected as the positive control for *Xoo*, as well as thiodiazole copper (**CK_2**) for *R. solanacearum* and *Xac*. As shown in Table 1, **I-n** exhibit better antibacterial activities against *Xoo* than **CK_1** except **I-4**. And their EC_{50} reaches the minimum value 0.54 μg/mL (**I-12**) with the increase in the alkyl length, indicating that suitable hydrophobicity of the amphiphile is favorable for the bioactivities of the target compounds. Meanwhile, **I-n** also show better antibacterial activity against *R. solanacearum* and *Xac* than **CK_2**. EC_{50} values of **I-8**, **I-10**, and **I-12** against *R. solanacearum* are 4.03, 0.94, and 0.75 μg/mL, respectively; EC_{50} values of **I-n** against *Xac* range from 1.62 to 6.98 μg/mL. In our previous work, the EC_{50} value of 2-(methylsulfonyl)-5-(2,4-dichlorophenyl)-1,3,4-oxadiazole was found to be 16.55 μg/mL against *R. solanacearum*,[8] indicating that high-efficient target molecules were successfully obtained as we proposed. In comparison of the bioactivities of **I-8** and **I-8Br** (without pyridinium group), the antibacterial activities are significantly enhanced after introducing the pyridinium group into 2,5-substituted-1,3,4-oxadiazole thioether, suggesting that appreciable bioactivity can be achieved through introducing the pyridinium group into heterocyclic systems. Meanwhile, this study also offers a strategy for us to achieve high-efficient bactericide via manipulating the length of the alkyl chains.

Given the above results that pyridinium tailored 2,5-substituted-1,3,4-oxadiazole thioether exhibit excellent antibacterial

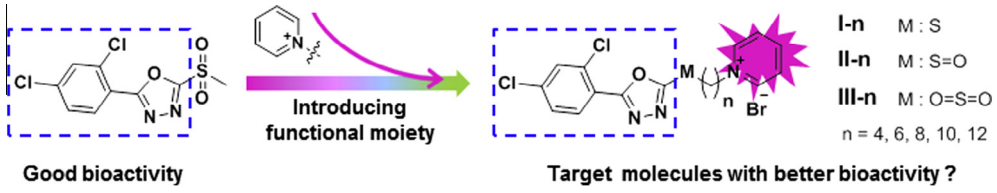
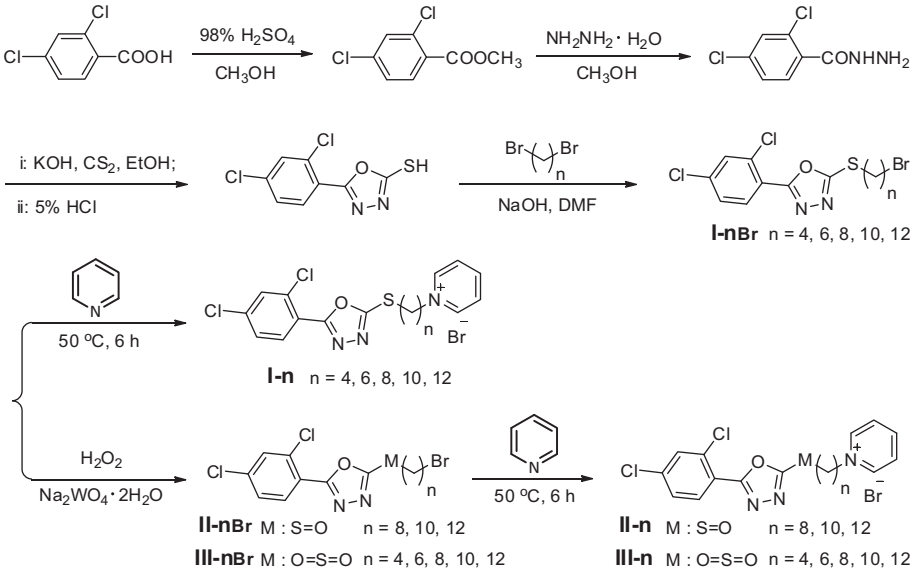


Figure 1. Design route for the target molecules.



Scheme 1. Synthetic route of pyridinium-tailored 2,5-substituted-1,3,4-oxadiazole thioether/sulfoxide/sulfone derivatives.