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Antimicrobial evaluation and action mechanism of pyridinium-decorated 1,4-pentadien-3-one derivatives

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ABSTRACT

A type of pyridinium-decorated 1,4-pentadien-3-one derivatives possessing flexible alkyls were designed and synthesized by integrating the key scaffolds of pyridinium cations and 1,4-pentadien-3-one skeleton in a single molecular architecture. Antimicrobial bioassays indicated that some of the target molecules exerted considerable bioactivities against six phytopathogenic strains, especially for *Xanthomonas oryzae pv. oryzae*, the minimal EC_{50} value can reach to 0.504 μg/mL. A plausible action mechanism for this kind of compounds was proposed and confirmed by employing fluorescent spectroscopy, fluorescence microscopy, and scanning electron microscopy. We anticipated that this finding can promote high-efficient lead compounds discovery in the research of antimicrobial chemotherapy.

Microbial infection has become one of the world's largest agricultural issues, not only due to the significant threats they impose on agricultural products, but also the potential risks associated with human health.[1–3] To address this issue, antimicrobial drugs have been extensively developed and widely used to treat infectious diseases and reduce the infection and spread of pathogenic microorganism, such as bismerthiazol (**BT**), thiodiazole copper (**TC**), and streptomycin. However, long-term and abuse of traditional antimicrobial agents had induced the emergence of resistance in the pathogenic microorganism,[4,5] resulting in poor treatment efficacy and even large economic losses, which gives us great challenges to manage this new circumstance. Therefore, developing alternative drugs or rational treatment methods to attack pathogenic microorganism through unique mechanisms or render them unable to resist the treatment is an important research topic for chemists.

Considerable efforts and investment are being devoted to the exploration and development of novel, high-efficient antimicrobial substances, leading to an array of designed compounds with admirable pharmacological activities.[6–9] Particularly, fabrication of bioactive molecules based on naturally occurring products have aroused extensive interest by scientists owing to their privileged performances including inartificial structural features, good physicochemical property, superior biocompatibility, low mammalian toxicity, environmental friendliness, specificity for the target species, and unique modes of action.[10–14] 1,4-Pentadien-3-one derivatives and analogues, derived from plant metabolic products curcumin, were discovered with an impressive array of pharmacological activities such as anticancer, antiviral, and anti-inflammatory.[15–20] Because 1,4-pentadien-3-one moiety performs a key role in the determination of the final bioactivity of target compounds, continuous efforts and repeatedly numerous studies on this functional scaffold opened a new avenue for the discovery of novel, high-efficient bioactive substrates, especially in the anticancer and antiviral fields.[21–25] However, few studies were performed via using this kind of compounds in growth suppression of plant pathogenic microorganism.

As another stimulating key fragment in the exploration and development of novel antimicrobial candidates, pyridinium scaffold has been extensively investigated for the crucial role in reforming the bioactivity of final target compounds due to the positive charge can promote their specificity for the target species.[26–29] Herein, an array of pyridinium-decorated 1,4-pentadien-3-one derivatives were constructed via coupling a key fragment of pyridinium scaffold into 1,4-pentadien-3-one structures linked by flexible alkyls of different lengths (Fig. 1A). The alkyl chains

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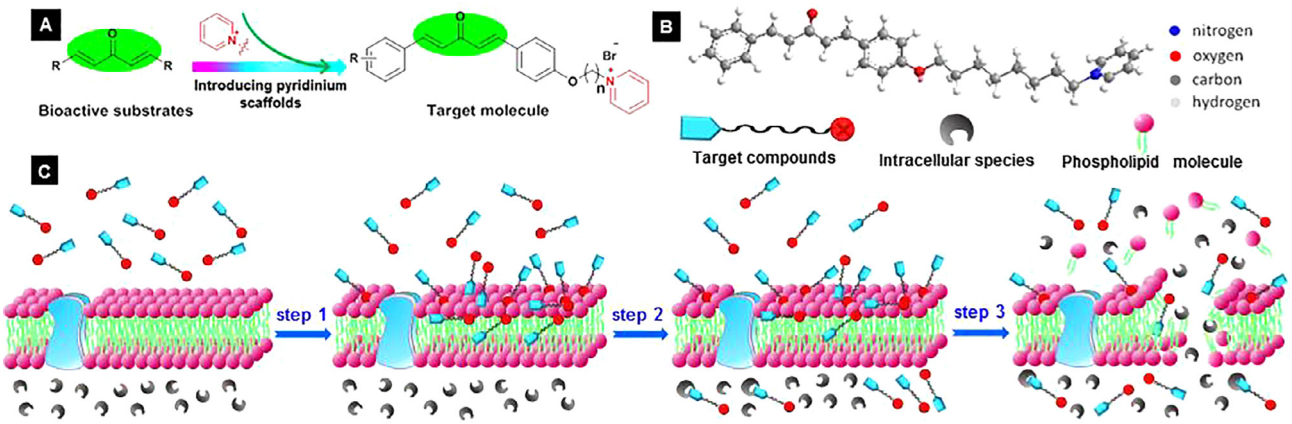
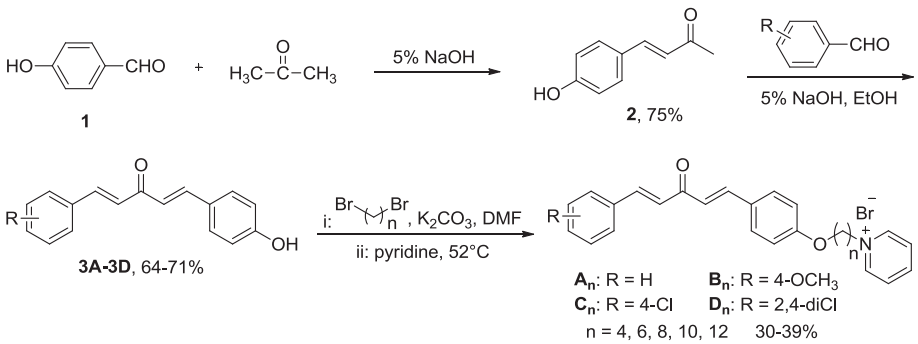


Fig. 1. (A) Design strategy for the target molecules; (B) Simulated structure of compound $\mathbf{A_8}$ (n = 8) using Chem 3D; (C) Proposed action mechanism for the designed compounds against microorganism.

orient in a nearly paralleled direction to the 1,4-pentadien-3-one part providing a linear molecule due to the anisotropic feature of the 1,4-pentadien-3-one (Fig. 1B). Within these molecules, the 1,4-pentadien-3-one fragment is probably responsible for binding with the receptors or enzymes of pathogenic microorganism; pyridinium nucleus owning a positive charge, is utilized to interact with anionic cell components via electrostatic interaction; alkyl chain length of the tailor is used to tune the lipophilicity and biocompatibility targeting the microbial membrane.[30,31] A plausible action mechanism for this kind of designed compounds was proposed (Fig. 1C): the target molecules firstly diffuse and attach to microbial surface and begin to deposit through electrostatic interactions between pyridinium cation parts and anionic cell components; then they tend to penetrate through the membrane carrying active 1,4-pentadien-3-one fragments; finally, the cell membrane was disturbed and destroyed by the synergistic effect of these privileged moieties, resulting in the leak of cellular components and subsequent microorganism death. On account of molecular amphiphilic nature and plausible action mechanism, we expected that better bioactive structures would be fabricated through utilizing the strategic cooperation of these privileged moieties. The bioactivities of all the title compounds were tested against three plant bacterial strains including *Xanthomonas oryzae pv. oryzae* (*Xoo*), *Ralstonia solanacearum* (*R. solanacearum*), and *Xanthomonas axonopodis pv. citri* (*Xac*), which belong to gram-negative bacteria, usually composed of a thin peptidoglycan cell wall sandwiched between an inner cytoplasmic cell membrane and a bacterial outer membrane, differed from gram-positive bacteria owning thick peptidoglycan layer in the bacterial cell wall. Meanwhile, three phytopathogenic fungi including *Botrytis cinerea* (*B. cinerea*), *Fusarium oxysporum* (*F. oxysporum*), and *Sclertinia sclerotiorum* (*S. sclerotiorum*) were also evaluated.

The synthetic route and structure of pyridinium-tailored 1,4-pentadien-3-one derivatives were illustrated in Scheme 1. Briefly, a condensation reaction between 4-hydroxybenzaldehyde and acetone gives an intermediate **2** possessing chalcone moiety, [32,33] which subsequently reacts with substituted benzaldehyde to provide the crucial intermediate **3A-3D** bearing 1,4-pentadien-3-one moiety and a hydroxyl group. Finally, the target molecules ($\mathbf{A_n}$, $\mathbf{B_n}$, $\mathbf{C_n}$, $\mathbf{D_n}$, n = 4, 6, 8, 10, 12) were obtained by treating **3** with two-step consecutive reactions with dibromo-substituted alkanes and pyridine. All the molecular structures were confirmed by ^{1}H NMR, ^{13}C NMR, and MS (detailed information see supplementary data).

Antibacterial bioassays against *Xoo*, *R. solanacearum* and *Xac* were carried out as previously described, and the commercial antibacterial agents (**BT** and **TC**) and surfactant (1-hexylpyridinium bromide, **HP**) were co-assayed as positive controls under the same conditions.[34,35] As shown in Table 1, preliminary bioassays revealed that these compounds displayed selectivity and specificity against the three tested strains. It is noted that all the designed molecules can effectively prevent the growth of *Xoo* at 100 μg/mL, even lower the concentration to 50 μg/mL. Further study showed that the EC_{50} values for all the target molecules were ranging from 0.504 to 23.2 μg/mL, suggesting high-efficient antibacterial substances were fabricated by coupling the key fragments of 1,4-pentadien-3-one skeleton and pyridinium moiety in a single molecular architecture. A phenomenon for EC_{50} values of compounds $\mathbf{A_4}$ (1.763 μg/mL), $\mathbf{A_6}$ (0.818 μg/mL), $\mathbf{A_8}$ (0.504 μg/mL), $\mathbf{A_{10}}$ (0.668 μg/mL), and $\mathbf{A_{12}}$ (0.774 μg/mL) against *Xoo* was firstly



Scheme 1. Synthesis route for the target compounds.