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

Jian Zhou [a], Qing-Qing Tao [a], Pei-Yi Wang [a,*], Wu-Bin Shao [a], Zhi-Bing Wu [a], Zhong Li [b], Song Yang [a,b,*]

[a] State Key Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Center for R&D of Fine Chemicals of Guizhou University, Guiyang 550025, China
[b] College of Pharmacy, East China University of Science & Technology, Shanghai 550025, China

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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

* Corresponding authors at: State Key Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Center for R&D of Fine Chemicals of Guizhou University, Guiyang 550025, China.
E-mail addresses: pywang888@126.com (P.-Y. Wang), jhzx.msm@gmail.com (S. Yang).

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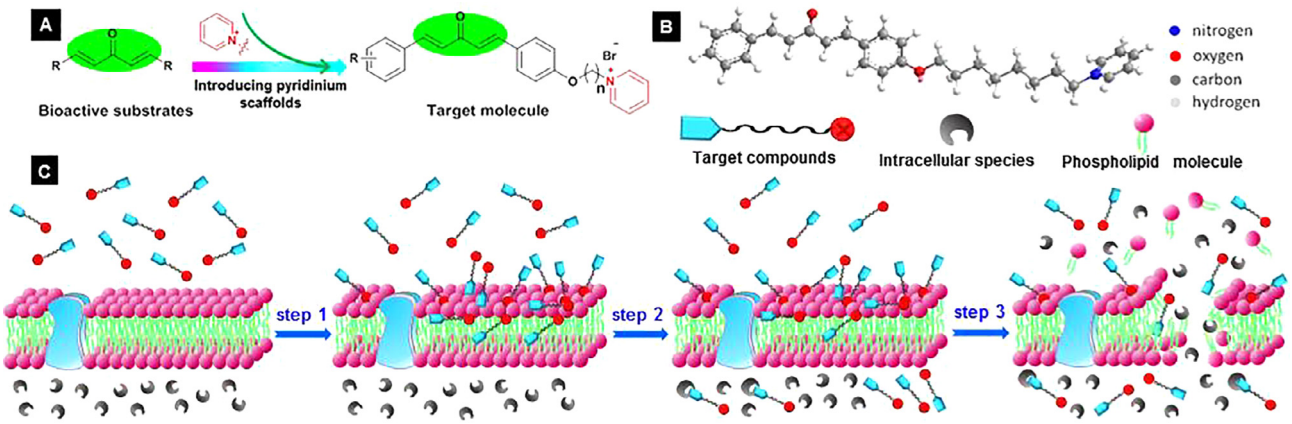
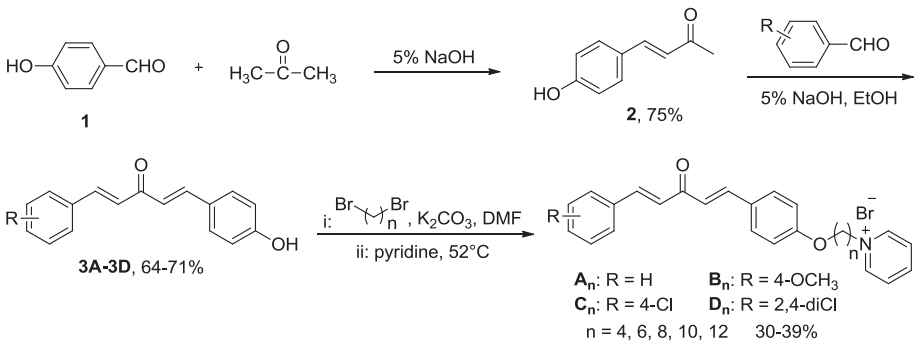


Fig. 1. (A) Design strategy for the target molecules; (B) Simulated structure of compound $\mathbf{A_8}$ (n = 8) using Chem 3D; (C) Proposed action mechanism for the designed compounds against microorganism.

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.

Table 1
Antibacterial activities of target compounds against plant pathogen *Xoo*, *R. solanacearum* and *Xac in vitro*.

No.	*Xoo*					*R. solanacearum*		*Xac*	
	Inhibition (%)		Regression equation[a]	r	EC_{50} (μg/mL)	Inhibition (%)		Inhibition (%)	
	100 μg/mL	50 μg/mL				100 μg/mL	50 μg/mL	100 μg/mL	50 μg/mL
A_4	100	100	y = 10.882x + 2.320	0.99	1.76 ± 0.05	66.6 ± 2.1	58.2 ± 6.9	89.6 ± 0.3	83.7 ± 3.4
A_6	100	100	y = 13.235x + 6.156	0.97	0.818 ± 0.025	60.9 ± 1.2	57.6 ± 0.6	86.5 ± 2.5	84.4 ± 1.5
A_8	100	100	y = 15.682x + 9.662	0.95	0.504 ± 0.086	72.9 ± 3.5	56.6 ± 4.2	42.9 ± 5.5	39.7 ± 3.6
A_{10}	100	100	y = 26.23x + 9.601	1.00	0.668 ± 0.093	71.8 ± 3.1	48.7 ± 5.9	79.7 ± 2.7	75.2 ± 3.1
A_{12}	100	100	y = 2.142x + 5.238	1.00	0.774 ± 0.256	65.5 ± 3.9	40.6 ± 4.7	88.1 ± 1.3	82.3 ± 1.0
B_4	100	100	y = 4.058x + 5.380	0.96	0.806 ± 0.015	57.9 ± 1.6	48.8 ± 5.2	89.5 ± 0.7	88.2 ± 1.7
B_6	100	100	y = 3.404x + 4.955	0.99	1.03 ± 0.28	72.2 ± 2.6	66.9 ± 2.8	69.4 ± 4.6	62.9 ± 3.8
B_8	100	100	y = 10.381x + 5.560	0.96	0.883 ± 0.025	61.5 ± 3.7	53.2 ± 3.7	90.3 ± 0.8	89.7 ± 0.0
B_{10}	100	100	y = 3.660x + 4.094	0.99	1.77 ± 0.28	51.8 ± 2.4	49.4 ± 4.7	50.6 ± 0.0	34.2 ± 0.8
B_{12}	100	100	y = 5.352x + 3.240	0.99	2.13 ± 0.11	52.8 ± 0.8	35.8 ± 6.1	88.7 ± 0.6	88.2 ± 2.3
C_4	100	100	y = 6.825x-3.080	0.99	1.91 ± 0.51	54.3 ± 2.1	53.8 ± 7.1	87.6 ± 0.6	75.0 ± 2.4
C_6	100	100	y = 2.190x + 2.010	0.99	23.2 ± 1.5	51.1 ± 5.1	45.6 ± 2.6	63.8 ± 4.2	63.2 ± 2.7
C_8	100	100	y = 2.211x + 5.010	1.00	0.990 ± 0.257	33.7 ± 0.5	24.0 ± 3.3	56.6 ± 3.9	45.5 ± 3.8
C_{10}	100	100	y = 3.194x + 1.590	0.99	11.7 ± 0.8	48.5 ± 0.1	38.5 ± 0.2	59.3 ± 1.4	49.5 ± 4.7
C_{12}	100	100	y = 3.667x + 4.960	0.95	1.02 ± 0.09	40.9 ± 7.8	37.6 ± 3.3	56.4 ± 1.7	42.1 ± 1.9
D_4	100	100	y = 2.777x + 2.674	0.99	6.87 ± 0.09	33.9 ± 7.3	26.4 ± 8.9	86.0 ± 2.8	74.9 ± 2.5
D_6	100	100	y = 4.036x + 0.195	1.00	15.5 ± 0.2	38.1 ± 3.8	34.6 ± 3.8	89.2 ± 0.9	82.3 ± 1.3
D_8	100	100	y = 4.124x + 2.614	1.00	3.79 ± 0.22	59.5 ± 2.5	58.3 ± 6.0	31.1 ± 1.4	25.4 ± 9.2
D_{10}	100	100	y = 4.011x + 4.657	0.98	1.20 ± 0.72	33.4 ± 1.1	22.0 ± 5.1	85.1 ± 2.0	76.2 ± 8.1
D_{12}	100	100	y = 2.962x + 3.425	0.99	3.40 ± 0.323	45.2 ± 7.8	41.6 ± 4.9	58.9 ± 2.4	58.8 ± 1.1
HP	100	100	y = 5.233x-1.383	0.97	16.6 ± 0.5	14.4 ± 5.9	0	42.0 ± 5.0	19.2 ± 2.1
BT	53.7 ± 1.2	38.4 ± 3.1	y = 1.499x + 2.052	0.98	92.6 ± 2.1	/	/	/	/
TC	43.1 ± 3.2	30.2 ± 1.5	y = 1.540x + 1.788	0.98	121.8 ± 3.6	51.3 ± 1.5	22.1 ± 1.4	61.2 ± 2.6	36.4 ± 2.3

[a] Five different concentrations (such as 10, 5, 2.5, 1.25, 0.625 μg/mL, depending on the bioactivity of different compounds, the concentrations were chosen in two times decline trend to make sure the EC_{50} values are inside the concentration ranges tested) of the test compounds and positive control were selected to test the corresponding inhibition rates. By using the SPSS 17.0 software and the obtained inhibition rates at different concentrations, a related regression equation was provided to calculate the related EC_{50} values.

Table 2
Inhibitory effect of target compounds at 50 μg/mL against plant fungal strains *B. cinerea*, *F. oxysporum*, and *S. sclerotiorum in vitro*.

No.	*B. cinerea*	*F. oxysporum*	*S. sclerotiorum*	No.	*B. cinerea*	*F. oxysporum*	*S. sclerotiorum*
A_4	79.4 ± 2.0	11.0 ± 3.6	8.38 ± 2.46	**C_4**	75.4 ± 2.0	11.9 ± 0.8	8.38 ± 2.21
A_6	80.0 ± 2.4	50.0 ± 1.7	47.4 ± 3.0	**C_6**	77.6 ± 2.4	68.7 ± 1.7	64.9 ± 1.3
A_8	74.2 ± 1.8	64.7 ± 2.0	62.6 ± 1.53	**C_8**	18.8 ± 1.7	3.93 ± 6.14	6.11 ± 4.10
A_{10}	76.4 ± 2.0	51.8 ± 0.4	11.0 ± 5.5	**C_{10}**	46.4 ± 8.6	51.2 ± 0.7	24.3 ± 7.1
A_{12}	74.4 ± 1.9	15.9 ± 3.8	9.36 ± 1.48	**C_{12}**	66.9 ± 3.5	12.2 ± 0.6	7.41 ± 3.58
B_4	79.6 ± 0.8	42.0 ± 2.5	43.5 ± 4.06	**D_4**	71.8 ± 2.4	2.39 ± 0.98	11.3 ± 3.9
B_6	53.0 ± 2.3	68.1 ± 2.1	68.8 ± 4.73	**D_6**	67.9 ± 1.6	20.2 ± 2.1	9.68 ± 2.63
B_8	79.4 ± 2.1	54.9 ± 1.7	37.3 ± 0.99	**D_8**	34.1 ± 8.6	21.1 ± 3.0	7.41 ± 3.01
B_{10}	47.4 ± 9.9	18.0 ± 3.1	19.7 ± 1.04	**D_{10}**	56.3 ± 0.4	28.2 ± 7.0	13.9 ± 4.2
B_{12}	3.37 ± 1.49	0	0	**D_{12}**	0.20 ± 0.34	0	6.76 ± 3.57
HM	91.8 ± 3.2	60.1 ± 0.8	50.2 ± 1.5	**CB**	100	100	100

decreased and then increased with adjusting the length of alkyl tailors and resulted in the minimal EC_{50} value up to 0.504 μg/mL, suggesting that even fine-tuning the ratio of hydrophobicity/hydrophilicity can affect their bioactivities. To study the effect of the substitution on the benzene ring towards bioactivity, an array of compounds **B_n**, **C_n**, and **D_n** owning different substituent groups were designed and synthesized. Apparently, the substituents and their electronegativity had a significant influence towards bioactivity, illustrated by comparing the EC_{50} values of compounds **A_4** (1.76 μg/mL, -H), **B_4** (0.806 μg/mL, $-OCH_3$), **C_4** (1.91 μg/mL, -Cl), and **D_4** (6.87 μg/mL, -2,4-diCl), indicating that an electron-donating group may benefit for the anti-*Xoo* activity with n = 4.

In comparison, the target molecules showed poor to moderate antibacterial efficacy towards *R. solanacearum*. Among them, **A_8**, **A_{10}**, and **B_6** gave the inhibition rates of 72.9, 71.8, and 72.2% at a dosage of 100 μg/mL, respectively, which were better than that **TC** (51.3%). It is mentioned that **B_6** also exerted better antibacterial effect towards *R. solanacearum* with the suppression value of 66.9% (**TC**, 22.1%) at 50 μg/mL. For anti- *Xac* bioassays, compounds **A_4**, **A_6**, **A_{12}**, **B_4**, **B_8**, **B_{12}**, **C_4**, **D_4**, **D_6**, and **D_{10}** exhibited good growth inhibition effects at 100 μg/mL with the rates ranging from 85.1 to 90.3%. Particularly, these compounds still performed considerable antibacterial effects even decreasing the dosage to 50 μg/mL, and resulted in the inhibition values within 74.9 and 89.7%. Based the above result, the designed compounds can be considered as new lead compounds in research of antibacterial fields.

The antifungal activity of target compounds was tested via the poison plate technique against three phytopathogenic fungal strains including *B. cinerea, F. oxysporum*, and *S. sclerotiorum*, meanwhile, the commercial agricultural antifungal hymexazol (**HM**) and carbendazim (**CB**) were used for the positive controls.[36,37] As illuminated in Table 2, target compounds demonstrated poor to good antifungal activity. Compounds **A_4-A_{12}**, **B_4**, **B_8**, **C_4**, **C_6**, and **D_4** showed growth inhibition rates ranging from 71.8 to 80.0% towards *B. cinerea* at 50 μg/mL, which were lower than that of **HM** (91.8%) or **CB** (100%). While compounds **A_8**, **B_6**, and **C_6** were bioactive against *F. oxysporum* and *S. sclerotiorum* with the suppression values of (64.7, 62.6%), (68.1, 68.8%) and (68.7, 64.9%), respectively, which were better than that of **HM** (60.1, 50.2%). It is worth mentioning that compounds **A_8** and **C_6** exerted comprehensive antifungal activity towards the three fungi with the inhibition rates of (74.2, 64.7, 62.6%) and (77.6, 68.7, 64.9%), respectively.

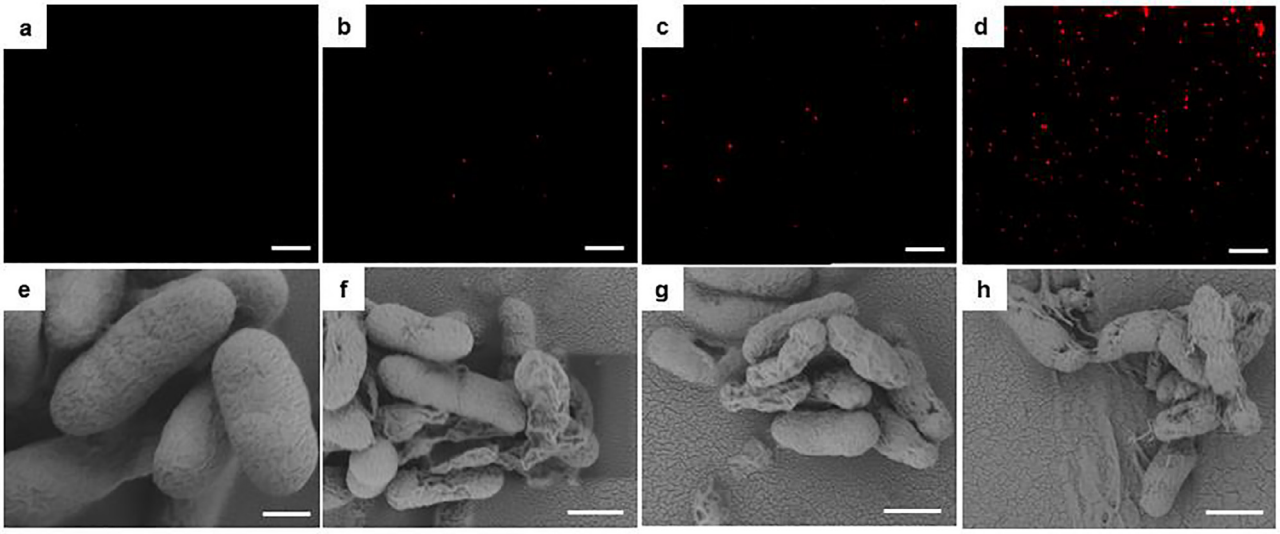


Fig. 2. FM images for *Xoo* stained with 5.0 μL PI (10 μg/mL) after incubated in different concentration of compound **B_4** (a) 0 μg/mL, (b) 12.5 μg/mL, (c) 25 μg/mL, and (d) 100 μg/mL; SEM images for *Xoo* after incubated in different concentration of compound **B_4** (e) 0 μg/mL, (f, g) 10 μg/mL, and (h) 50 μg/mL. Scale bar for (a, b, c, d) are 25 μm, (e) is 250 nm, (f, g, h) are 500 nm.

This study revealed that the designed compounds can be taken into account as novel lead compounds in the development and exploration of antifungal drugs.

To study the antibacterial action mechanism toward *Xoo*, fluorescent spectroscopy, fluorescence microscopy (FM), and scanning electron microscopy (SEM) were employed. Propidium iodide (PI), a non-fluorescent dye, which can form PI-DNA complex producing strong red fluorescence, was usually used to evaluate cell viability or DNA content, while it can't cross the membrane of intact live bacteria.[38] Concentration dependence of fluorescent spectroscopy demonstrated that the fluorescent intensity at 613 nm was enhanced along with increasing the dosage of compound **B_4**, indicating that the cell membrane was gradually destroyed and resulted in the formation of more PI-DNA complex to produce fluorescence (Fig. S1a). It is noted that the fluorescent intensity reached the equilibrium as the concentration attained to 120 μg/mL (Fig. S1b), which was ascribed to the constant amount of *Xoo*. Fluorescent images for *Xoo* showed that the red fluorescent bacteria gradually increased with the improvement of concentration of compound **B_4** (Fig. 2a–d), which was consistent with the finding from fluorescent spectroscopy. Concentration dependence of SEM images further confirmed this type of designed compounds can damage the cell membrane by the cooperation of these privileged scaffolds. In comparison with the control (without treating with compound **B_4**, Fig. 2e), the morphologies of *Xoo* were transformed from well-rounded to corrugated or broken after treating with 10 μg/mL of compound **B_4** (Fig. 2f and g). Meanwhile, pore-like shape was observed on the bacterial surface. As the concentration reached to 50 μg/mL, few intact bacteria was observed (Fig. 2h), which validated the proposed mechanism (Fig. 1C).

In conclusion, a series of pyridinium-tailored 1,4-pentadien-3-one compounds were designed and constructed through fusing the pyridinium cation into 1,4-pentadien-3-one derivatives. Preliminary bioassays suggested that target compounds could effectively and specifically prevent the growth of *Xoo* and afforded the minimal EC_{50} value of 0.504 μg/mL. Moreover, the possible action mechanism for title compounds was proposed and confirmed by employing fluorescent spectroscopy, fluorescence microscopy, and scanning electron microscopy. Considering their simple structures and conveniently synthetic protocols, we anticipated that this finding can motivate high-efficient lead compounds discovery in the development and exploration of antimicrobial chemotherapy.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bmcl.2018.04.034.

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