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Novel vanillin derivatives containing a 1,3,4-thiadiazole moiety as potential antibacterial agents

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ABSTRACT

In this study, thirty-four novel vanillin derivatives containing a 1,3,4-thiadiazole structure were obtained and their antibacterial activities were evaluated. The results indicate that most of the title compounds displayed inhibitory effects on *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) and *Xanthomonas oryzae* pv. *oryzicola* (*Xoc*). Among them, compound **29** exhibited excellent antibacterial activities against *Xoo* and *Xoc in vitro*, with the EC_{50} values of 3.14 and 8.83 μg/mL, respectively, much superior to thiodiazole copper (87.03 and 108.99 μg/mL) and bismerthiazol (67.64 and 79.26 μg/mL). Under greenhouse condition, the protective efficiency of compound **29** against rice bacterial leaf blight was 49.34%, and curative efficiency was 40.96%. In addition, compound **29** can reduce the exopolysaccharides production of *Xoo*, increase the permeability of cell membrane and damage cell membrane.

As one of important, indispensable food crops in the world, rice is vulnerable to large number of pathogenic microorganisms during its growth. Among them, rice bacterial leaf blight and leaf streak caused by corresponding pathogenic bacteria *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) and *Xanthomonas oryzae* pv. *oryzicola* (*Xoc*)[1–3] are two destructive bacterial diseases, which cause serious reduction in production.[4–6] At present, only a handful of agrochemicals, such as thiodiazole copper, zinc thiazole, bismerthiazol and zhongshengmycin are used to control these bacterial diseases of rice.[7,8] However, long-term use of these traditional agricultural agents has resulted in increased resistance and brought environmental pollution.[9,10] Therefore, it is still a daunting challenge in management of rice bacterial diseases to develop new, highly-effective, low-toxicity, and environmentally-friendly antibacterial agents.

Natural products always are important leading source for development of pesticide with a wide range of bioactivity and security.[11–13] Vanillin is a natural product from the pods of an orchid (*Vanilla planifolia*), as a secure food additive, it is widely used in food, nutraceutical, beverage and pharmaceutical industry.[14,15] Simultaneously, vanillin and its derivatives possess a wide range of bioactivity, such as antimicrobial,[16] antifungal,[17] anti-inflammatory,[18] antioxidant,[19] anti-alzheimer's,[20] anticancer,[21] antihelminthic,[22] antiviral,[23] and so on. Meanwhile, we found that vanillin derivatives exhibited outstanding antibacterial activities (Fig. 1).[24] In addition, 1,3,4-thiadiazoles are important five-membered heterocyclic compounds with a variety of bioactivity, including antimicrobial,[25] antifungal,[26] insecticidal,[27] antiviral,[28] anticancer,[29] herbicidal.[30] Notably, 1,3,4-thiadiazole moiety is an effective antibacterial group and was used to development for antibacterial agents, such as thiodiazole copper and bismerthiazol. In our previous works, we found that 1,3,4-thiadiazole derivatives exhibited outstanding antibacterial activities.[8,10,31] Based on these, we aimed to introduce 1,3,4-thiadiazole moiety into the skeleton of vanillin (Fig. 1) to obtain some novel vanillin derivatives (Schemes 1 and 2), and evaluate their antibacterial activities against *Xoo* and *Xoc*. Meanwhile, the preliminary mechanism of action was performed in this work.

The title compounds were synthesized via the route outlined in Scheme 1 and 2. As shown in Scheme 1, using different amine compounds as reactant, through substitution, etherification, condensation and reduction to obtain the title compounds **1–9**. As shown in Scheme 2, the title compounds **10–18** were obtained using the vanillin as initiation, through substitution, condensation and reduction reaction, and further substitution to obtain the title compounds **19–26**. Finally, the target products **27–34**, with yield 20.1%–77.6%, were obtained successively by oxidation of corresponding compounds **19–26**. The synthesis and characteristic of the title compounds were shown in Supplementary Data.

The bioassay results indicated that most compounds showed good antibacterial activities against *Xoo* and *Xoc* (Table 1). Of which, compounds **12**, **14**, **17**, **18**, **27**, **28**, and **29** had excellent inhibitory

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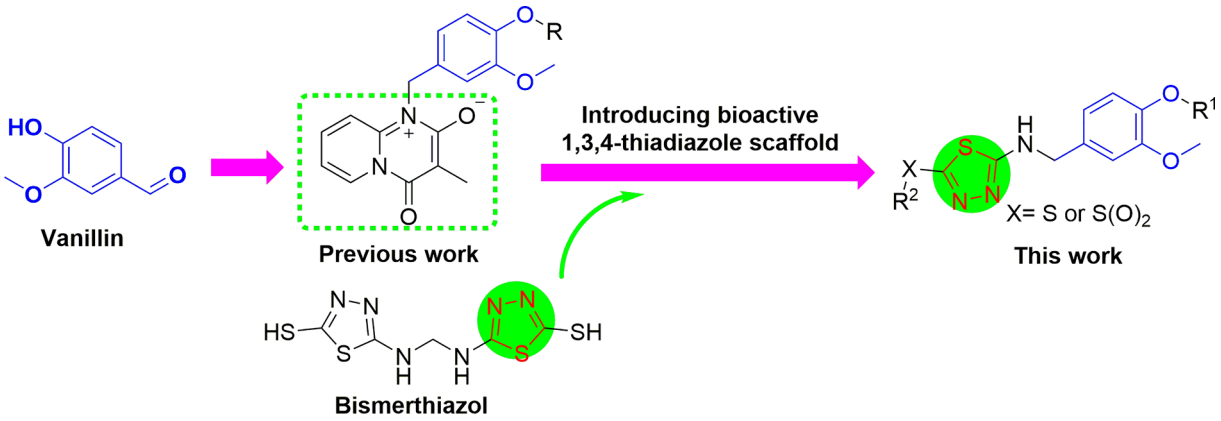
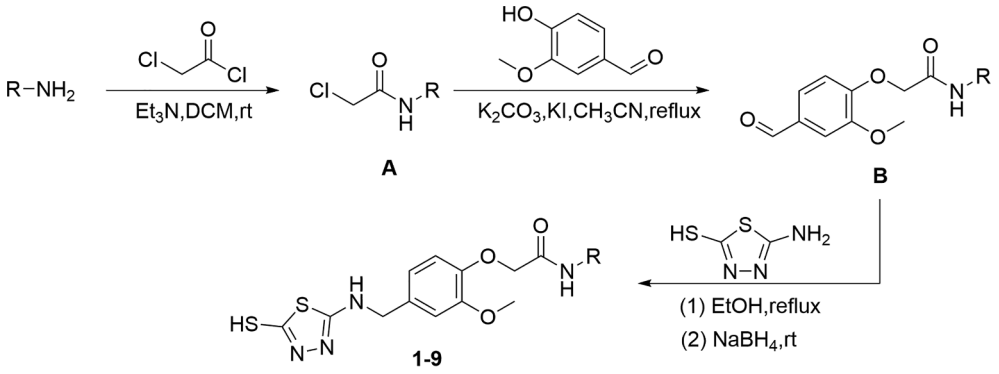
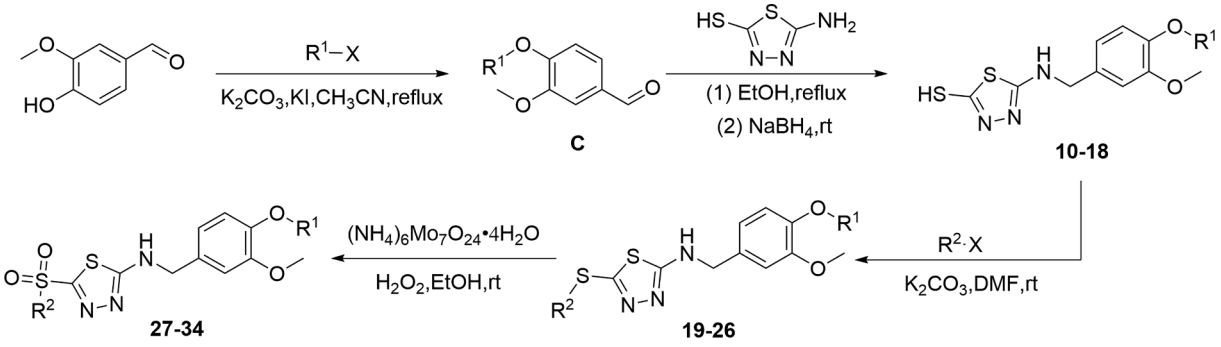


Fig. 1. Design of title compounds.



1: R=4-CH_3-Ph
2: R=2,4-diCH_3-Ph
3: R=4-acetamido-Ph
4: R=4-Cl-Ph
5: R=3-Cl-4-F-Ph
6: R=3-CH_3-4-F-Ph
7: R=4-CF_3-Py-2-
8: R=Cyclopentyl
9: R=Isopropyl

Scheme 1. The synthetic route of the title compounds **1–9**.



10: R^1=2-Cl-Py-5-CH_2-
11: R^1=2-Cl-thiazole-5-CH_2-
12: R^1=3-Cl-5-CF_3-2-Py
13: R^1=2-CH_3-Bn
14: R^1=4-Cl-Bn
15: R^1=Ethyl
16: R^1=Propyl
17: R^1=Allyl
18: R^1=2-(methyl aminoacetate)Bn

19: R^1=Allyl,R^2=-CH_3
20: R^1=Allyl,R^2=-CH_2CH_3
21: R^1=Allyl,R^2=-CH_2CH_2Cl
22: R^1=Allyl,R^2=4-Cl-Benzyl
23: R^1=4-Cl-Bn,R^2=-CH_3
24: R^1=4-Cl-Bn,R^2=-CH_2CH_3
25: R^1=2-(methyl aminoacetate)Bn R^2=-CH_3
26: R^1=2-(methyl aminoacetate)Bn R^2=-CH_2CH_3

27: R^1=Allyl,R^2=-CH_3
28: R^1=Allyl,R^2=-CH_2CH_3
29: R^1=Allyl,R^2=-CH_2CH_2Cl
30: R^1=Allyl,R^2=4-Cl-Benzyl
31: R^1=4-Cl-Bn,R^2=-CH_3
32: R^1=4-Cl-Bn,R^2=-CH_2CH_3
33: R^1=2-(methyl aminoacetate)Bn R^2=-CH_3
34: R^1=2-(methyl aminoacetate)Bn R^2=-CH_2CH_3

Scheme 2. The synthetic route of the title compounds **10–34**.

activities against *Xoo*, with the EC_{50} values of 38.74, 33.73, 33.25, 31.78, 16.03, 28.47, and 3.14 μg/mL, respectively, which were much better than thiodiazole copper (87.03 μg/mL) and bismerthiazol (67.64 μg/mL). Meanwhile, compounds **17**, **18**, **27**, **28** and **29** had excellent inhibitory activity against *Xoc*, with the EC_{50} values of 35.49, 26.54, 27.69, 36.47 and 8.83 μg/mL, respectively, superior to

Table 1
The antibacterial activities of the title compounds against *Xoo* and *Xoc in vitro*.[a]

Compound	*Xoo*		*Xoc*	
	50 μg/mL (%)	EC_{50} (μg/mL)	50 μg/mL (%)	EC_{50} (μg/mL)
1	49.15 ± 5.69	51.02 ± 5.54	53.38 ± 3.18	51.81 ± 2.21
2	45.15 ± 2.99	55.9 ± 4.20	41.22 ± 2.37	63.50 ± 2.86
3	48.31 ± 3.46	54.78 ± 2.05	40.33 ± 1.53	62.12 ± 6.22
4	57.80 ± 2.26	40.6 ± 2.85	56.31 ± 3.00	42.53 ± 4.15
5	49.17 ± 3.93	47.78 ± 2.10	36.68 ± 1.71	86.29 ± 4.78
6	35.99 ± 2.10	95.37 ± 3.13	41.90 ± 3.51	64.08 ± 2.09
7	54.71 ± 1.51	51.73 ± 0.89	45.58 ± 2.76	72.13 ± 1.90
8	52.79 ± 0.64	48.63 ± 2.17	50.55 ± 2.52	47.62 ± 2.68
9	62.60 ± 2.10	44.45 ± 2.24	58.32 ± 1.76	45.80 ± 3.11
10	46.18 ± 1.69	51.34 ± 2.04	40.07 ± 1.29	60.72 ± 1.61
11	33.82 ± 0.67	78.94 ± 2.24	34.56 ± 1.13	77.23 ± 1.67
12	58.15 ± 0.72	38.74 ± 2.16	51.09 ± 0.25	46.97 ± 1.96
13	59.47 ± 0.69	40.52 ± 2.57	53.20 ± 1.46	48.17 ± 2.76
14	63.40 ± 2.06	33.73 ± 2.16	56.23 ± 2.23	40.23 ± 1.10
15	39.09 ± 1.67	88.08 ± 2.16	31.83 ± 1.68	89.66 ± 0.76
16	32.92 ± 2.90	80.52 ± 3.38	42.10 ± 1.20	65.66 ± 1.05
17	69.08 ± 1.13	33.25 ± 1.14	57.40 ± 2.94	35.49 ± 1.29
18	68.97 ± 4.53	31.78 ± 2.22	64.47 ± 3.49	26.54 ± 3.30
19	31.46 ± 3.63	100.39 ± 4.57	24.96 ± 1.99	107.15 ± 3.35
20	30.90 ± 3.30	107.8 ± 4.08	19.40 ± 1.84	118.91 ± 1.97
21	45.59 ± 2.30	61.66 ± 4.72	47.51 ± 2.72	61.20 ± 0.47
22	13.85 ± 1.65	190.41 ± 12.21	14.32 ± 1.08	163.17 ± 2.59
23	13.51 ± 3.16	182.31 ± 3.67	14.07 ± 1.44	167.98 ± 2.04
24	15.42 ± 3.93	175.29 ± 2.97	20.73 ± 1.58	176.67 ± 1.38
25	22.41 ± 4.95	138.08 ± 3.84	24.64 ± 1.05	140.29 ± 2.21
26	23.64 ± 1.64	143.93 ± 3.15	22.84 ± 1.26	147.33 ± 3.35
27	85.93 ± 1.52	16.03 ± 1.04	79.65 ± 0.50	27.69 ± 1.30
28	72.93 ± 2.40	28.47 ± 3.65	65.80 ± 3.11	36.47 ± 1.40
29	90.05 ± 1.63	3.14 ± 0.95	81.42 ± 0.96	8.83 ± 1.53
30	51.60 ± 2.33	51.83 ± 2.98	44.00 ± 1.67	70.02 ± 2.30
31	60.84 ± 2.21	31.13 ± 1.24	51.20 ± 2.20	44.20 ± 2.25
32	55.79 ± 2.16	41.31 ± 1.01	45.80 ± 2.29	66.12 ± 2.13
33	55.34 ± 3.75	44.66 ± 4.35	57.28 ± 1.74	44.59 ± 0.87
34	44.20 ± 1.21	59.56 ± 1.93	49.72 ± 1.18	61.33 ± 1.66
Bismerthiazol [b]	40.61 ± 2.49	67.64 ± 2.36	37.19 ± 2.05	79.26 ± 2.66
Thiodiazole copper [b]	31.92 ± 1.94	87.03 ± 2.88	31.98 ± 2.96	108.99 ± 2.80

[a]Average of three replicates. [b]Commercial bactericides bismerthiazol and thiodiazole copper were utilized as positive control agents.

Table 2
Curative and protective activities of compound **29** against rice bacterial leaf blight under at 200 μg/mL *in vivo* (14 days after spraying).

Treatments	Protective effect		Curative effect	
	Disease index (%)[a]	Control efficiency (%)[b]	Disease index (%)[a]	Control efficiency (%)[b]
29	40.93 ± 2.41	49.34 ± 7.14	46.11 ± 0.79	40.96 ± 1.76
Bismerthiazol	34.81 ± 0.74	56.97 ± 3.79	40.37 ± 0.52	48.30 ± 1.75
Thiodiazole copper	43.33 ± 1.11	46.43 ± 5.05	43.70 ± 1.05	43.98 ± 3.97
Negative control	81.11 ± 3.33		78.15 ± 3.67	

[a] Disease index, which is a comprehensive indicator of the overall incidence and severity.
[b] Statistical analysis was conducted by the analysis of variance method.

thiodiazole copper (108.99 μg/mL) and bismerthiazol (79.26 μg/mL). Among the target compounds, compound **29** exhibited the best inhibitory activities against *Xoo* and *Xoc*, and superior to thiodiazole copper and bismerthiazol.

The structure and activity relationships were explored on the basis of the inhibitory activity values in Table 1. When title compounds are thiol derivatives, changing substituent on vanillin (R or R^1) did not cause significant effects on antibacterial activity, such as compounds **1**–**18**. When H was replaced with alkyl at the R^2 substituent group caused significantly reduced their antibacterial activities, that is to say the antibacterial activity of thiol derivative is better than that of corresponding thioether derivative, such as compound **14** (-H) > **23** ($–CH_3$) and **24** ($–CH_2CH_3$); **17** (–H) > **19** ($–CH_3$), **20** ($–CH_2CH_3$), **21** ($–CH_2CHCl$) and **22** (4-Cl-Benzyl); **18** (–H) > **25** ($–CH_3$) and **26** ($–CH_2CH_3$). Compared with the same substituent on vanillin and R^2, S was replaced with $S(O)_2$ can significantly enhance the antibacterial activities, for example compound **27** > **19**, **28** > **20**, **29** > **21**, which revealed that the activity of sulfone compound is better than that of the corresponding thioether compound. It maybe that sulfone compounds with privileged structure can react covalently[32–34] or form H-bond[35] with the active sites of certain proteins, and show promising antibacterial active.

Compound **29** exhibited the best antibacterial activities *in vitro*, so, the *in vivo* inhibitory effect of the compound **29** on rice leaf blight caused by *Xoo* was evaluated under greenhouse condition. The results showed that compound **29** demonstrated good controlling effect against rice bacterial leaf blight under greenhouse condition. The protective and curative efficiency was 49.34% and 40.96% at the concentration of

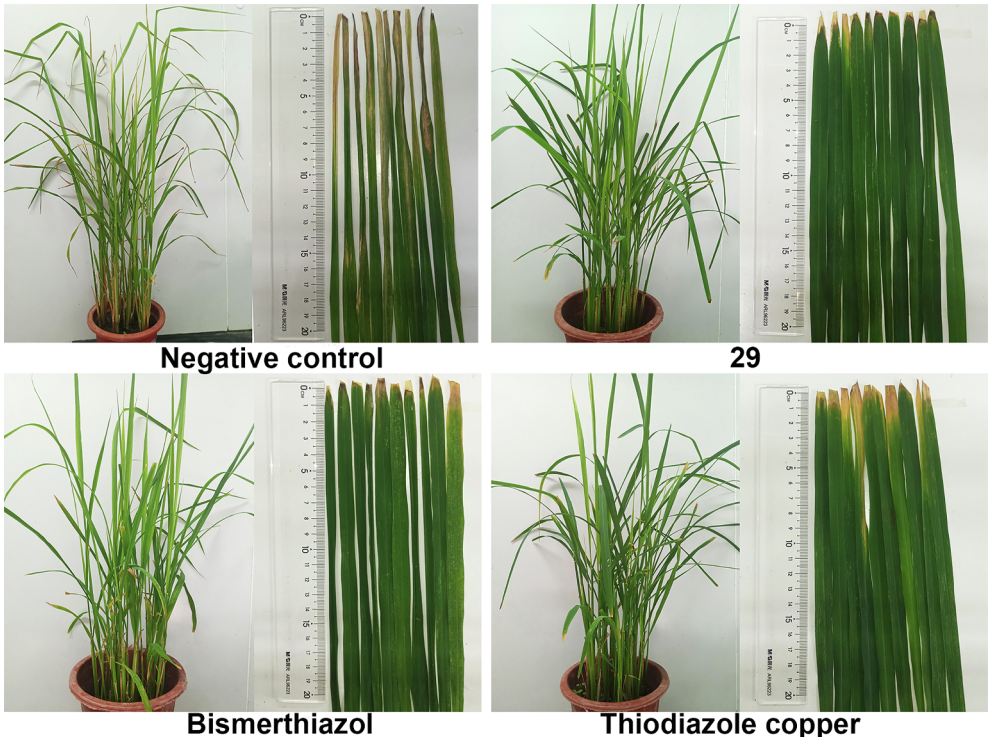


Fig. 2. Protective effect of compound **29** against rice bacterial leaf blight at 200 μg/mL.

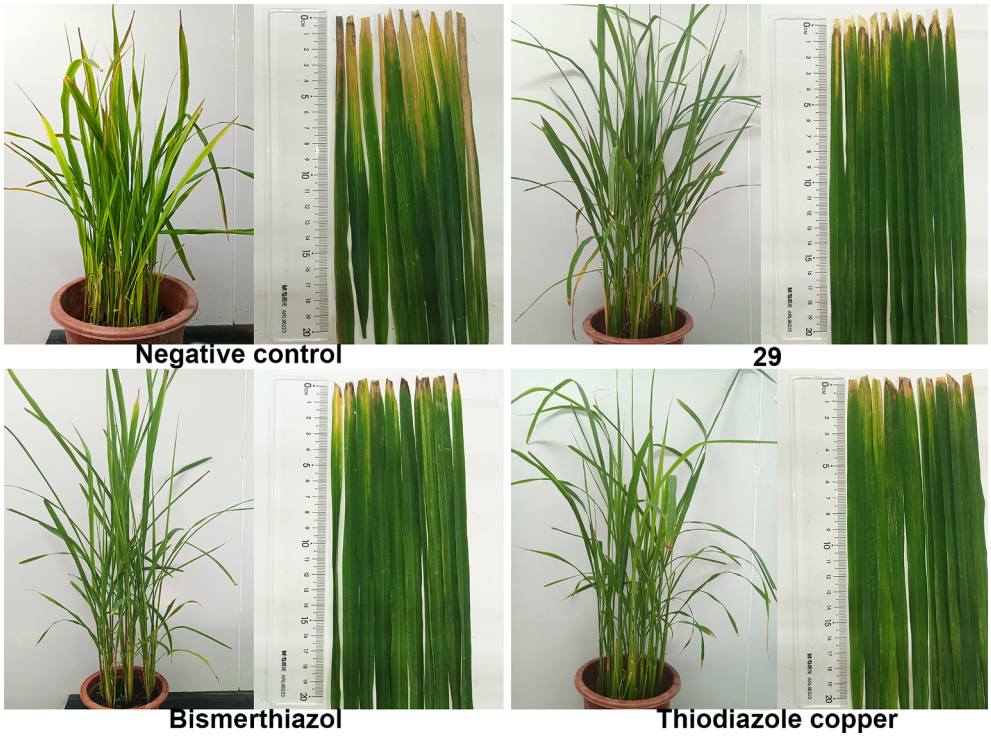


Fig. 3. Curative effect of compound **29** against rice bacterial leaf blight at 200 μg/mL.

200 μg/mL, respectively (Table 2, Fig. 2 and Fig. 3), as well as commercial agents thiodiazole copper (46.43% and 43.98%), and bismerthiazol (56.97% and 48.30%).

Exopolysaccharides are not only a barrier to resist adverse external conditions, but also one of the vital virulence factors of *Xoo*.[36] The effect of compound **29** on the exopolysaccharides of *Xoo* was tested and the result was shown in Fig. 4A. The results showed that compound **29** inhibited the production of exopolysaccharides at the concentration of 50, 25, and 5 μg/mL, with rates of 85.7%, 54.6% and 24.4%, respectively, which can weaken the pathogenicity of *Xoo*.

The effect of compound **29** on the cell membrane permeability of *Xoo* was shown in Fig. 4B. After treatment with compound **29**, the relative permeability of *Xoo*'s cell membrane increased following time and concentration. Especially, the relative permeability increases

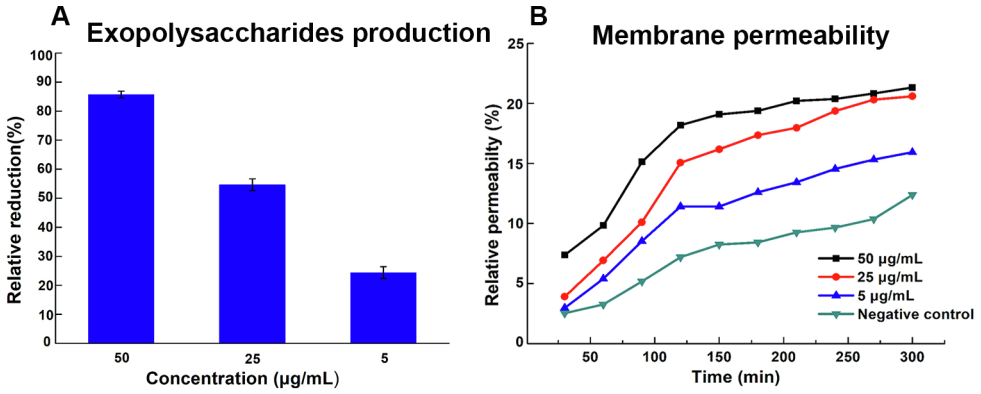


Fig. 4. A: changes in the exopolysaccharides production, B: cell membrane permeability.

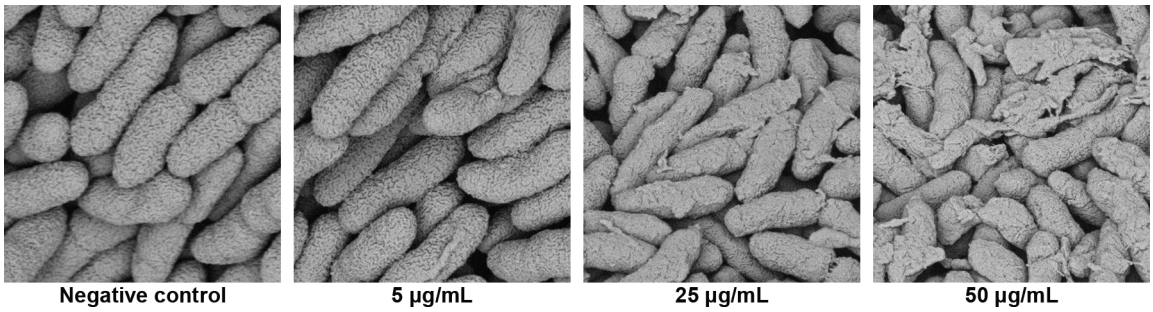


Fig. 5. Scanning electron microscopy images for *Xoo* after treatment with the compound **29** at the concentrations of 5, 25, and 50 μg/mL.

quickly within the first 120 min after treatment, and increases slowly from 150 to 300 min. After treatment for 300 min at concentrations of 50, 25, and 5 μg/mL, the corresponding relative permeability was 21.32%, 20.59%, and 15.94%, respectively, which were higher than that of negative control (12.38%). This result indicated that compound **29** may damage the cell membrane of *Xoo*, cause electrolyte leakage of intracellular, thereby causing cell weakness or apoptosis.

The surface morphology of *Xoo* treated with compound **29** was observed by scanning electron microscope (Fig. 5). The cells of the negative control were intact and had no wrinkles on the surface. After treatment with compound **29**, the cell surface was wrinkled. With the increase of the concentration of the compound, the cells deform, even shrivel and rupture. So, compound **29** may damage *Xoo*'s cell membrane, causing *Xoo* to be unhealthy or apoptotic, which is the primary reason of this compound exhibited excellent antibacterial activity *in vitro*.

In summary, thirty-four novel vanillin derivatives containing a 1,3,4-thiadiazole moiety were constructed, and their antibacterial activities were systematically evaluated. Compound **29** demonstrated the best inhibitory to *Xoo* and *Xoc in vitro*, much better than that of commercial antibacterial agents thiodiazole copper and bismerthiazol. Meanwhile compound **29** exhibited good protective and curative effects on rice bacterial leaf blight *in vivo*. Compound **29** reduced the exopolysaccharides production of *Xoo*, and broke cell membranes, thereby reduced the pathogenicity of *Xoo*. These results demonstrated that novel vanillin derivatives containing 1,3,4-thiadiazole moiety can be used as promising new antibacterial agents for controlling bacterial diseases on rice.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Materials and Methods, ^{1}H and ^{13}C NMR spectra, and HRMS can be found in the Supplementary Data. Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2020.127113.

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