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Synthesis of novel indole derivatives containing double 1,3,4-oxadiazole moiety as efficient bactericides against phytopathogenic bacterium *Xanthomonas oryzae*

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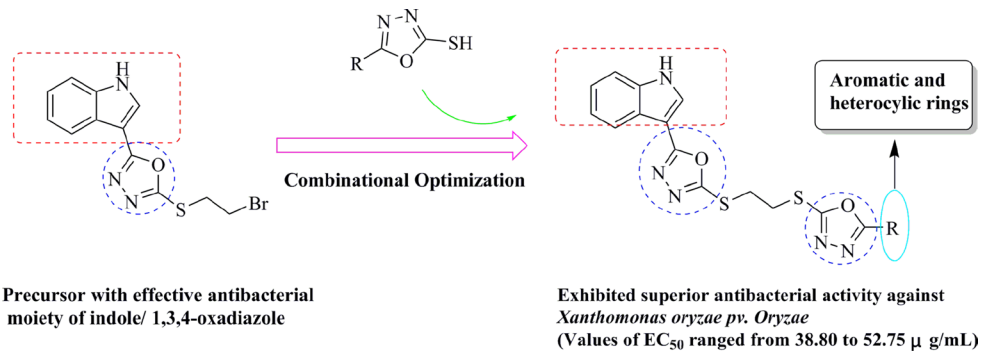
Abstract

A series of novel indole derivatives containing double 1,3,4-oxadiazole moiety was designed, synthesized and evaluated for their antibacterial activities in vitro. These compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, and HRMS. Bioassay results indicated that most of title compounds exhibited excellent antibacterial activities against rice bacterial pathogen *Xanthomonas oryzae* (*Xoo*). For example, compounds **7d**, **7h**, **7i**, **7j**, **7k**, **7l** and **7m** had the half-maximal effective concentration (EC_{50}) values of 52.31, 54.12, 40.65, 38.80, 51.13, 52.75 and 50.66 μg/mL, respectively, which was better than that of commercial product bismerthiazol (BMT) (85.18 μg/mL). The experimental results proved that indole derivatives bearing double 1,3,4-oxadiazole unit are promising candidates for the development of new agricultural bactericides against pathogenic bacterium *Xoo*.

Graphical abstract



Keywords Indole · 1,3,4-Oxadiazole · Antibacterial activity

Introduction

Xanthomonas oryzae (*Xoo*) and *Ralstonia solanacearum* (*Rs*) are pathogenic bacteria for rice bacterial leaf blight and tobacco bacterial wilt, respectively, which do serious harm to global agricultural products and give rise to huge economic losses to farmers all over the world (Carvalho 2006). Rice is a staple crop for much of the world population, as well as a model for cereal biology (Ronald and Leung 2002).

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Extended author information available on the last page of the article

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Taking the phytobacterium *Xoo*, a member of the gamma subdivision of the proteobacteria, as an example, it is one of the most destructive bacterial diseases for the rice crop, which occurs throughout all the growth stages of rice and triggers bacterial blight by invading vascular tissues (Niño-Liu et al. 2006), entering rice leaves through water pores or wounds and moves systemically by invading the xylem, causing a disease known as bacterial blight (Salzberg et al. 2008). The most important bacterial disease of rice in the rice growing countries (Mew 1987) carrying the potential to reduce yields by as much as 50% (Huang et al. 1997). Additionally, the pathogen *Rs*, with a global distribution and an unusually wide host range, is β-proteobacteria and considered as complex species. It was first discovered to cause fatal wilt diseases threatening many important crops such as eggplant, tomato, potato by Smith in 1896 and subsequently tobacco in 1908 (Li et al. 2011). Meanwhile, it is also one kind of highly devastating and widespread soil-borne plant pathogen (Li et al. 2015). When it infects at the growth stage, the tobacco plants are rapid yellowing and wilting of tobacco leaves (Ronald and Leung 2002). At present, several commercial antibacterial agents (i.e., bismerthiazol and thiodiazole copper) are currently available on the market for fighting against the two bacterial diseases. However, poor efficiency, high phytotoxicities and residue levels, adverse effects on the natural environment and growing problems of antibacterial resistance related with the utilization of these bactericides are continuously attracting attention from so many researchers. Therefore, there is an urgent need to develop new and more efficient antibacterial agents in the agrochemical field.

It is well known that the indole moiety which is probably the most widely spread nitrogen heterocycle in nature is very important for its medicinal and biological aspects, thus attracting a lot of scientific attention. It has been found to possess pharmacological and chemotherapeutic properties such as antibacterial (Mahboobi et al. 2006), antifungal (Williams et al. 2005), antidiabetic (Dropinski et al. 2005), antiinflammatory (Karg et al. 2009), antimalarial (Agarwal et al. 2005), antiviral (Chen et al. 2005), and anticancer (Akué-Gédu et al. 2009). Some indole derivatives have been confirmed to have antibacterial activity, such as compounds **1** (Williams et al. 2013), **2** (Li et al. 2016), **3** (Franz et al. 2017), and **4** (Hong et al. 2017) (Fig. 1).

Furthermore, 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 (Joshi and Parikh 2014; Desai and Kotadiya 2014; Wang et al. 2016), such as compounds **5** (Bhat et al. 2013), **6** (Desai et al. 2014), **7** (Palekar et al. 2009), and **8** (Xu et al. 2012) (Fig. 1). Meanwhile, Patel and co-workers (Patel et al. 2012) have evaluated the antibacterial activity of a series of 3-(5-sulfanyl-1,3,4-oxadiazol-2-yl)-2H-chromen-2-ones bearing various substituted piperazines and piperidines against two types of Gram-positive bacteria and six types of Gram-negative bacteria.

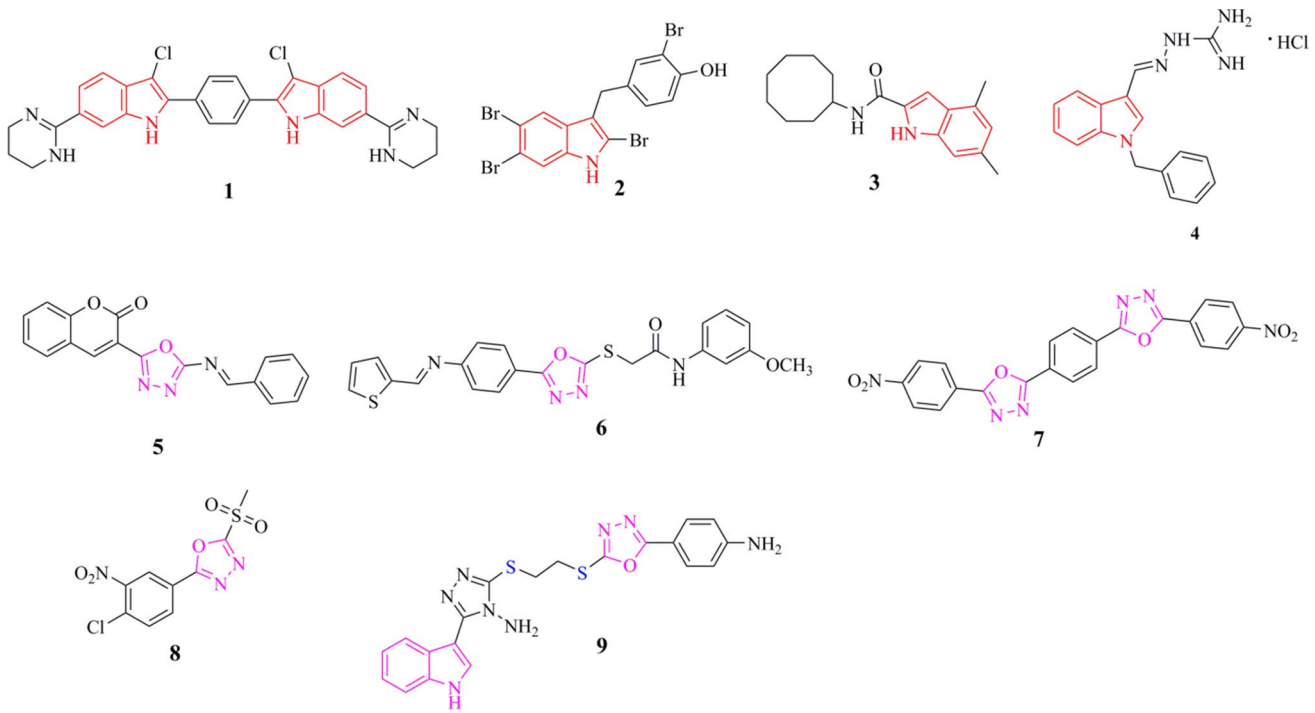


Fig. 1 Chemical structures of cited molecules with antibacterial and antifungal activities

Until now, the method of "active substructure combination" is still quite useful for the development of new bioactive molecules (Guan et al. 2014; Zhu et al. 2016), which means that combining separate pharmacophoric groups into one compound to achieve more potent molecule with biological activity (Saundane et al. 2017). The findings made by Shi et al. (2015) (compound **9**), just one good example of ingenious combination of indole and 1,3,4-oxadiazole heterocycles, exhibits excellent activity against *Staphylococcus aureus* and *Escherichia coli* using the disc diffusion assay. On the basis of previous work, a series of 1,3,4-oxadiazole hybrid derivatives can serve as potential alternative bactericides (Li et al. 2014, 2015; Wang et al. 2016; Xu et al. 2013). The attachment of new indole derivatives containing double 1,3,4-oxadiazole moiety might provide structures with interesting biological activity against *Xoo* and *Rs*. In continuation of our interest, a series of 2-((2-((5-(1H-indol-3-yl)-1,3,4-oxadiazol-2-yl)thio)ethyl)thio)-5-phenyl-1,3,4-oxadiazole were designed and synthesized (Scheme 1) so as to get biologically more potent molecules. The bioassays reveal that most of target compounds exhibited better inhibition activities against *Xoo* than positive controls bismerthiazol (BMT). Among them, **7d**, **7h**, **7i**, **7j**, **7k**, **7l** and **7m** exert excellent inhibition activities against *Xoo* with half-maximal effective concentration (EC_{50}) values ranging from 38.80 to 54.12 μg/mL. The experimental results proved that indole derivatives bearing double 1,3,4-oxadiazole unit are promising candidates for the development of new agricultural bactericides against pathogenic bacterium *Xoo*.

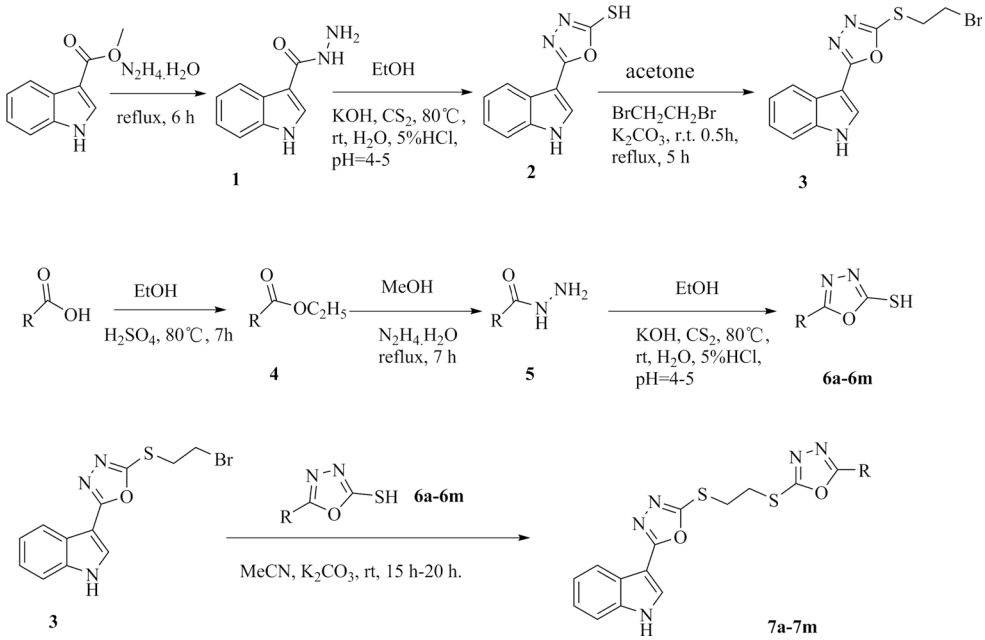
Experimental

All the chemicals were obtained from commercial suppliers and used without further purification (unless otherwise stated). Melting points (M.P.) were determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., China). ^1H and ^{13}C NMR (solvent DMSO-d_6) spectra were measured on a JEOL-ECX 500 NMR spectrometer and Ascend 400 NMR at room temperature using TMS as an internal standard, and chemical shift (δ) was expressed in parts per million (ppm). HRMS-ESI spectra were recorded on Thermo Scientific Q Exactive series.

General synthetic procedure for intermediate 2-((2-bromoethyl) thio)-5-(1*H*-indol-3-yl)-1,3,4-oxadiazole (3)

Briefly, methyl 1H-indole-3-carboxylate as starting material was reacted with $N_2H_4{\cdot}H_2O$ to give 1*H*-indole-3-carbohydrazide **1** which was then subjected to substitution reaction with KOH and CS_2 to generate

Scheme 1 Synthetic route of the title compounds **7a–7m**



7a R = Phenyl
7b R = 2-methylphenyl
7c R = 4-aminophenyl
7d R = 3,4,5-trimethoxyphenyl
7e R = 3-fluorophenyl
7f R = 2-chlorophenyl
7g R= 3-chlorophenyl
7h R = 4-chlorophenyl
7i R = 2,4-dichlorophenyl
7j R = 3,5-dichlorophenyl
7k R = 2-pyridyl
7l R = 3-pyridyl
7m R = 4-pyridyl

5-(1*H*-indol-3-yl)-1,3,4-oxadiazole-2-thiol **2**. Subsequently, it was converted into the corresponding key intermediate **3** through reaction with $BrCH_2CH_2Br$ under CH_3COCH_3/K_2CO_3 system. Additionally, analysis of variance (ANOVA) was used for improving the yield of the intermediate **3**. Different solvents, reaction times, base and temperature were investigated to obtain the best conditions. The results of nine orthogonal tests with four factors and three conditions are shown in Table S1 (Supporting Information). For a complete experiment, 27 tests were carried out for intermediate **3**. The results of orthogonal experimental ANOVA are listed in Table S2 (Supporting Information). The data obtained in all experiments demonstrated that the type of solvent was the most important factor in achieving the highest response value corresponding to A1 (solvent: acetone) B2 (time: 6 h) C2 (temperature: 40 °C) D2 (alkali: K_2CO_3) (Table S1), which was consistent with the optimum results for intermediate **3**. As F ratio > F critical value (Table S2), the response value was influenced by the type of solvent.

General synthetic procedure for intermediates 6a–6m

Taking **6a** as an example, a mixture of benzoic acid (2.5 g, 20.0 mmol), 4 mL sulfuric acid, and 50 mL ethanol was heated under reflux for 7 h (hour, h). After finishing the reaction, it was poured into water and extracted by ethyl acetate, dried with anhydrous Na_2SO_4, and then the solvent of the organic phase was evaporated under vacuum to give colorless liquid **4a**. Then excess 80% $N_2H_4{\cdot}H_2O$ and 15 mL of ethanol were added into the flask containing **4a**, which was heated under reflux about 5 h. After the reaction was completed, it should be cooled into room temperature overnight and the white solid **5a** was given after being filtered, washed with ethanol and dried in open air. Finally, **5a** (1.4 g, 8.0 mmol) was then subjected to substitution reaction with KOH (0.9 g, 15.6 mmol) and CS_2 (1.2 g, 15.0 mmol) to generate intermediate **6a**. At the same time, **6b**–**6m** was synthesized by the methods described in the literature (Shi et al. 2015; Du et al. 2013).

General synthetic procedure for title compounds 7a–7m

The key intermediate **3** (1.0 g, 3.1 mmol) and various derivatives **6a**–**6m** (0.7 g, 3.4 mmol) were reacted under MeCN/K_2CO_3 system (20 mL; 0.8 g, 6.1 mmol) at room temperature and monitored by TLC (petroleum ether/ethyl acetate, V/V = 1:1.5). After the reaction was finished, the mixture was poured into water and the residue was filtered, recrystallized from ethanol with little *N*,*N*-dimethylformamide (the value of $V_{ethanol}/V_{N,N\text{-dimethylformamide}}$ is about 8) to obtain title compounds **7a**–**7m**. The physical properties data of intermediate **3** and compounds **7a**–**7m** were listed in Table 1, and the spectral data of those were listed in Table 2.

Results and discussion

Chemistry

The synthetic route of target compounds **7a**–**7m** was depicted in Scheme 1. Results of physical properties of intermediate **3** and compounds **7a**–**7m** were listed in Tables 1 and 2. Taking **7a** as an example, the ^{1}H NMR spectrum of it in DMSO-d_6 displayed a multiplet at δ 3.77–3.73 ppm that corresponds to –SCH_2CH_2S– functionality, the singlet at δ 8.12 ppm integrating for only one proton was assigned to the –CH in the position 2 of indole. In the ^{13}C NMR spectrum, the –SCH_2CH_2S– carbon signal was found at δ 32.53 and δ 32.50 ppm. The high-resolution mass spectrum (HRMS) of **7a** demonstrated an intense peak at m/z = 422.0739 attributed to the species of $[M+H]^+$.

Antibacterial activity screening of the title compounds against *Rs* and *Xoo* in vitro

Using *Ralstonia solanacearum* (*Rs*, Nanjing Agricultural University, China) and *Xanthomonas oryzae* (*Xoo*, strain PXO99A, Nanjing Agricultural University, China) as the tested bacterial strains, the turbidimetric assay (Yang and Bao 2017; Wang et al. 2017; Xu et al. 2012) was conducted to evaluate antibacterial activities of target compounds **7a**–**7m** and intermediate **3** the same as two commercial agricultural bactericides (namely bismerthiazol (BMT) and thiodiazole copper (TDC)) which were utilized as the control agents against two phytopathogenic bacteria *Xoo* and *Rs*.

Table 1 Physical properties of intermediate **3** and compounds **7a**–**7m**

Compound	Formula	Yield (%)	Appearance	M.P. (°C)
3	$C_{12}H_{10}BrN_3OS$	67	Yellow solid	157–158
7a	$C_{20}H_{15}N_5O_2S_2$	60	White solid	140–141
7b	$C_{21}H_{17}N_5O_2S_2$	49	White solid	164–165
7c	$C_{20}H_{16}N_6O_2S_2$	50	White solid	179–180
7d	$C_{23}H_{21}N_5O_5S_2$	53	White solid	190–191
7e	$C_{20}H_{14}FN_5O_2S_2$	52	White solid	182–183
7f	$C_{20}H_{14}ClN_5O_2S_2$	58	White solid	157–158
7g	$C_{20}H_{14}ClN_5O_2S_2$	60	White solid	150–151
7h	$C_{20}H_{14}ClN_5O_2S_2$	65	White solid	148–149
7i	$C_{20}H_{13}Cl_2N_5O_2S_2$	70	White solid	237–238
7j	$C_{20}H_{13}Cl_2N_5O_2S_2$	76	Gray solid	235–236
7k	$C_{19}H_{14}N_6O_2S_2$	62	White solid	142–143
7l	$C_{19}H_{14}N_6O_2S_2$	63	White solid	143–144
7m	$C_{19}H_{14}N_6O_2S_2$	65	White solid	144–145

Table 2 Physical property data of compounds **7a–7m**

Compounds	Spectral data
3	^{1}H NMR (500 MHz, DMSO-d_6) δ 12.05 (s, 1H, indole-NH), 8.19 (s, 1H, indole-CH), 8.05 (d, J = 6.4 Hz, 1H, Ph-H), 7.54 (d, J = 7.4 Hz, 1H, Ph-H), 7.32–7.19 (m, 2H, Ph-H), 3.89 (t, J = 7.5 Hz, 2H, –CH_2–), 3.75 (t, J = 7.5 Hz, 2H, –CH_2–); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.72, 160.43, 136.96, 128.95, 124.43, 123.44, 121.81, 120.64, 113.01, 99.57, 34.49, 31.67; HRMS, ESI (m/z): 323.9802 $[M+H]^+$; 323.9801 calcd $[M+H]^+$ for $C_{12}H_{11}ON_3BrS$
7a	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.12 (s, 1H, indole-CH), 7.98 (d, J = 5.0 Hz, 1H, Ph-H), 7.93 (d, J = 5.0 Hz, 2H, Ph-H), 7.55–7.50 (m, 4H, Ph-H), 7.15–7.18 (m, 2H, Ph-H), 3.77–3.73 (m, 4H, –CH_2CH_2–); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.82, 163.72, 163.58, 160.50, 136.95, 132.45, 129.85, 128.93, 126.95, 124.43, 123.53, 123.41, 121.78, 120.66, 112.97, 99.61, 32.53, 32.50; HRMS, ESI (m/z): 422.0739 $[M+H]^+$; 422.0740 calcd $[M+H]^+$ for $C_{20}H_{16}O_2N_5S_2$
7b	^{1}H NMR (500 MHz, DMSO-d_6) δ 12.02 (s, 1H, indole-NH), 8.16 (s, 1H, indole-CH), 8.03 (d, J = 10.0 Hz, 1H, Ph-H), 7.85 (d, J = 10.0 Hz, 1H, Ph-H), 7.52 (s, 1H, Ph-H), 7.44 (t, J = 7.5 Hz, 1H, Ph-H), 7.39 (s, 1H, Ph-H), 7.33 (s, 1H, Ph-H), 7.26 (d, J = 5.0 Hz, 2H, Ph-H), 3.80–3.76 (m, 4H, –CH_2CH_2–), 2.57 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.89, 163.65, 163.09, 160.39, 137.91, 136.89, 132.10, 131.85, 129.14, 128.86, 126.88, 124.37, 123.33, 122.61, 121.69, 120.60, 112.90, 99.54, 32.44, 31.59, 21.93; HRMS, ESI (m/z): 436.0891 $[M+H]^+$; 436.0896 calcd $[M+H]^+$ for $C_{21}H_{18}O_2N_5S_2$
7c	^{1}H NMR (500 MHz, DMSO-d_6) δ 12.10 (s, 1H, indole-NH), 8.17 (s, 1H, indole-CH), 8.06 (d, J = 5.0 Hz, 2H, Ph-H), 7.64 (d, J = 10.0 Hz, 1H, Ph-H), 7.54 (d, J = 5.0 Hz, 2H, Ph-H), 7.26 (d, J = 5.0 Hz, 2H, Ph-H), 6.67 (d, J = 8.6 Hz, 1H, Ph-H), 5.97 (s, 1H, Ph-H), 3.80–3.63 (m, 4H, –CH_2CH_2–), 2.89 (s, 1H, –NH_2–H), 2.74 (s, 1H, –NH_2–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.62, 162.78, 161.18, 160.44, 152.85, 136.90, 128.89, 128.47, 124.37, 123.33, 121.72, 120.62, 113.98, 112.92, 109.78, 99.54, 32.43, 32.07; HRMS, ESI (m/z): 437.0846 $[M+H]^+$; 437.0849 calcd $[M+H]^+$ for $C_{20}H_{17}O_2N_6S_2$
7d	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.01 (s, 1H, indole-NH), 8.13 (s, 1H, indole-CH), 8.01 (d, J = 5.0 Hz, 1H, Ph-H), 7.50 (d, J = 10.0 Hz, 1H, Ph-H), 7.25–7.22 (m, 2H, Ph-H), 7.17 (s, 2H, Ph-H), 3.84 (s, 6H, –OCH_3), 3.82–3.74 (m, 4H, –CH_2CH_2), 3.70 (s, 3H, –OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.65, 163.59, 163.29, 160.39, 153.81, 140.88, 136.86, 128.79, 124.31, 123.31, 121.66, 120.53, 118.55, 112.85, 104.13, 99.46, 60.60, 56.55, 32.52, 32.42; HRMS, ESI (m/z): 512.1054 $[M+H]^+$; 512.1057 calcd $[M+H]^+$ for $C_{23}H_{22}O_5N_5S_2$
7e	^{1}H NMR (500 MHz, DMSO-d_6) δ 12.04 (s, 1H, indole-NH), 8.20–8.16 (m, 1H, indole-CH), 8.04 (d, J = 5.0 Hz, 2H, Ph-H), 7.77 (d, J = 10.0 Hz, 1H, Ph-H), 7.59–7.52 (m, 2H, Ph-H), 7.43 (d, J = 5.0 Hz, 1H, Ph-H), 7.25 (t, J = 7.5, Hz, 2H, Ph-H), 3.82–3.75 (m, 4H, –CH_2CH_2–); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.00, 163.62, 162.63 (d, J = 245.5 Hz), 160.40, 136.87, 132.15, 128.85, 125.42 (d, J = 8.8 Hz), 124.36 (d, J = 2.6 Hz), 123.32, 123.11, 121.67, 120.59, 119.32 (d, J = 21.1 Hz), 113.79, 113.55, 112.88, 99.52, 32.47, 32.38; HRMS, ESI (m/z): 440.0641 $[M+H]^+$; 440.0646 calcd $[M+H]^+$ for $C_{20}H_{15}O_2N_5FS_2$
7f	^{1}H NMR (500 MHz, DMSO-d_6) δ 11.98 (s, 1H, indole-NH), 8.13 (s, 1H, indole-CH), 7.99 (d, J = 10.0 Hz, 1H, Ph-H), 7.92 (t, J = 7.5 Hz, 1H, Ph-H), 7.63 (d, J = 5.0 Hz, 1H, Ph-H), 7.55 (t, J = 5.0 Hz, 1H, Ph-H), 7.47 (d, J = 5.0 Hz, 2H, Ph-H), 7.23–7.19 (m, 2H, Ph-H), 3.78–3.74 (m, 4H, –CH_2–CH_2–); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.16, 163.79, 163.67, 160.34, 136.90, 132.59, 132.10, 131.63, 131.52, 128.34, 128.23, 124.38, 123.36, 121.73, 120.69, 118.72, 112.90, 99.56, 32.52, 32.41; HRMS, ESI (m/z): 456.0347 $[M+H]^+$; 456.0350 calcd $[M+H]^+$ for $C_{20}H_{15}O_2N_5ClS_2$
7g	^{1}H NMR (500 MHz, DMSO-d_6) δ 12.00 (s, 1H, indole-NH), 8.15 (s, 1H, indole-CH), 8.06–7.99 (m, 1H, Ph-H), 7.96–7.86 (m, 2H, Ph-H), 7.62–7.65 (m, 1H, Ph-H), 7.57–7.45 (m, 2H, Ph-H), 7.22–7.25(m, 2H, Ph-H), 3.80–3.73 (m, 4H, –CH_2–CH_2–); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.15, 163.58, 163.14, 159.92, 136.40, 133.99, 131.71, 131.29, 128.37, 125.87, 125.09, 124.88, 123.87, 122.84, 121.20, 120.11, 112.40, 99.04, 32.04, 31.92; HRMS, ESI (m/z): 456.0346 $[M+H]^+$; 456.0350 calcd $[M+H]^+$ for $C_{20}H_{15}O_2N_5ClS_2$
7h	^{1}H NMR (500 MHz, DMSO-d_6) δ 12.01 (s, 1H, indole-NH), 8.15 (d, J = 5.0 Hz, 1H, indole-CH), 8.02–7.91 (m, 2H, Ph-H), 7.68–7.62 (m, 1H, Ph-H), 7.51–7.43 (m, 2H, Ph-H), 7.20–7.23 (m, 3H, Ph-H), 3.85 (t, J = 7.5 Hz, 2H, –CH_2–), 3.71 (t, J = 7.5 Hz, 2H, –CH_2–); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.07, 163.71, 160.37, 151.78, 141.66, 136.92, 128.85, 125.05, 124.76, 124.39, 123.36, 121.73, 120.61, 118.72, 110.66, 99.60, 32.48, 32.42; HRMS, ESI (m/z): 456.0364 $[M+H]^+$; 456.0350 calcd $[M+H]^+$ for $C_{20}H_{15}O_2N_5ClS_2$
7i	^{1}H NMR (500 MHz, DMSO-d_6) δ 12.04 (s, 1H, indole-NH), 8.17 (s, 1H, indole-CH), 8.05 (d, J = 7.5 Hz, 1H, Ph-H), 7.99 (d, J = 10.0 Hz, 1H, Ph-H), 7.84 (s, 1H, Ph-H), 7.58 (d, J = 10.0 Hz, 1H, Ph-H), 7.53 (t, J = 7.5 Hz, 1H, Ph-H), 7.27–7.24 (m, 2H, Ph-H), 3.84–3.80 (m, 4H, –CH_2–CH_2–); ^{13}C-NMR (125 MHz, DMSO-d_6) δ 164.35, 163.70, 163.17, 160.39, 137.56, 136.94, 133.16, 132.74, 131.18, 128.89, 128.60, 124.38, 123.39, 121.76, 121.55, 120.62, 112.95, 99.56, 32.59, 32.48; HRMS, ESI (m/z): 489.9978 $[M+H]^+$; 489.9961 calcd $[M+H]^+$ for $C_{20}H_{14}O_2N_5Cl_2S_2$
7j	^{1}H NMR (500 MHz, DMSO-d_6) δ 12.00 (s, 1H, indole-NH), 8.10 (s, 1H, indole-CH), 7.96 (d, J = 5.0 Hz, 1H, Ph-H), 7.88–7.86 (m, 2H, Ph-H), 7.77 (s, 1H, Ph-H), 7.48 (d, J = 10.0 Hz, 1H, Ph-H), 7.19–7.21 (m, 2H, Ph-H), 3.94–3.64 (m, 4H, –CH_2–CH_2–); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.15, 163.58, 163.14, 159.92, 136.40, 133.99, 131.71, 131.29, 128.37, 125.87, 125.09, 122.84, 121.20, 120.11, 112.40, 99.04, 32.04, 31.92; HRMS, ESI (m/z): 489.9964 $[M+H]^+$; 489.9961 calcd $[M+H]^+$ for $C_{20}H_{14}O_2N_5Cl_2S_2$
7k	^{1}H NMR (500 MHz, DMSO-d_6) δ 11.99 (s, 1H, indole-NH), 8.67 (d, J = 5.0 Hz, 1H, indole-CH), 8.13 (d, J = 5.0 Hz, 1H, pyridine-H), 8.07 (d, J = 10.0 Hz, 1H, pyridine-H), 7.97–7.94 (m, 2H, Ph-H), 7.55–7.52 (m, 1H, pyridine-H), 7.48 (d, J = 5.0 Hz, 1H, Ph-H), 7.21 (t, J = 7.5 Hz, 2H, Ph-H), 3.79–3.73 (m, 4H, –CH_2CH_2–); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.25, 164.67, 163.69, 160.39, 150.74, 142.92, 138.31, 136.93, 128.94, 126.83, 124.41, 123.38, 123.30, 121.76, 120.66, 112.95, 99.60, 32.61, 32.38; HRMS, ESI (m/z): 423.0700 $[M+H]^+$; 423.0692 calcd $[M+H]^+$ for $C_{19}H_{15}O_2N_6S_2$

Table 2 (continued)

Compounds	Spectral data
7l	^{1}H NMR (500 MHz, DMSO-d_6) δ 12.02 (s, 1H, indole-NH), 9.15 (d, J = 5.0 Hz, 1H, indole-CH), 8.74–8.77 (m, 1H, pyridine-H), 8.38–8.28 (m, 1H, pyridine-H), 8.17 (d, J = 5.0 Hz, 1H, Ph-H), 8.03 (m, 1H, Ph-H), 7.67–7.47 (m, 2H, Ph-H), 7.23–7.27 (m, 2H, Ph-H), 3.85–3.77 (m, 4H, –CH_2–CH_2–); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.90, 163.74, 163.35, 160.13, 152.57, 147.28, 136.60, 134.20, 128.60, 124.39, 124.07, 123.05, 121.43, 120.31, 119.83, 112.61, 99.24, 32.29, 32.09; HRMS, ESI (m/z): 423.0693 $[M+H]^+$; 423.0692 calcd $[M+H]^+$ for $C_{19}H_{15}O_2N_6S_2$
7m	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1H, indole-NH), 8.76 (d, J = 5.0 Hz, 2H, pyridine-H), 8.17 (d, J = 5.0 Hz, 1H, indole-CH), 8.00–8.04 (m, 1.7 Hz, 1H, pyridine-H), 7.86–7.89 (m, 1.6 Hz, 2H, Ph-H), 7.62–7.38 (m, 1H, Ph-H), 7.24–7.26 (m, 1.4 Hz, 2H, Ph-H), 4.15–3.59 (m, 4H, –CH_2CH_2–); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 164.95, 164.21, 163.65, 160.42, 151.27, 136.87, 130.48, 128.88, 124.33, 123.35, 121.71, 120.54, 120.44, 112.90, 99.50, 32.55, 32.35; HRMS, ESI (m/z): 423.0689 $[M+H]^+$; 423.0692 calcd $[M+H]^+$ for $C_{19}H_{15}O_2N_6S_2$

Table 3 Inhibition effect of the target compounds **7a**–**7m** against two phytopathogenic bacteria *Xoo* and *Rs*

Compounds	Inhibition rate[a] (%)			
	Xoo		*Rs*	
	200 μg/mL	100 μg/mL	200 μg/mL	100 μg/mL
3	90.0 ± 4.1	54.2 ± 3.5	61.5 ± 4.1	34.2 ± 2.1
7a	74.2 ± 6.7	44.8 ± 4.9	51.5 ± 6.2	29.2 ± 2.4
7b	46.4 ± 3.7	29.3 ± 4.5	37.3 ± 5.9	19.7 ± 2.2
7c	68.2 ± 7.8	38.0 ± 3.2	69.5 ± 5.2	43.9 ± 2.7
7d	98.1 ± 0.3	65.4 ± 2.8	69.6 ± 2.8	38.5 ± 4.9
7e	72.1 ± 4.3	41.0 ± 3.1	37.3 ± 5.9	19.7 ± 2.0
7f	75.6 ± 5.8	30.2 ± 4.9	56.1 ± 8.2	48.1 ± 1.9
7g	74.8 ± 0.9	29.5 ± 7.2	67.0 ± 1.4	41.8 ± 3.2
7h	93.2 ± 0.8	81.4 ± 5.7	71.8 ± 1.7	43.7 ± 2.5
7i	99.6 ± 4.1	86.4 ± 3.2	74.9 ± 4.1	52.8 ± 2.5
7j	100 ± 2.8	80.0 ± 4.3	95.9 ± 4.2	79.8 ± 2.4
7k	98.2 ± 2.0	70.1 ± 3.3	66.4 ± 6.2	33.7 ± 7.5
7l	97.9 ± 1.9	68.8 ± 5.2	69.7 ± 0.8	37.4 ± 8.3
7m	98.7 ± 2.1	69.3 ± 3.4	67.6 ± 1.3	36.5 ± 5.3
BMT[b]	77.4 ± 1.5	53.4 ± 2.3	80.2 ± 3.1	45.9 ± 1.3
TDC[b]	NT	NT	75.2 ± 3.1	52.9 ± 0.7

NT not tested

[a]The average of three trials

[b]Commercial agricultural bactericides bismerthiazol (BMT) and thiodiazole copper (TDC) were used as control agent

As shown in Table 3, most of the target compounds exhibited comparable or even better antibacterial activity against the pathogen *Xoo*. For example, compounds **7d**, **7h**, **7i**, **7j**, **7k**, **7l**, and **7m** had the inhibition rate of 98.1, 93.2, 99.6, 100, 98.2, 97.9 and 98.7% against this bacterium at 200 μg/mL, respectively, which was more active than the control agent BMT (77.4%). Additionally, intermediate 3 and the above nine compounds were also found to possess higher inhibition capability against the pathogen *Xoo* (relative to BMT), at 100 μg/mL. Moreover, intermediate **3** only exhibited better antibacterial activity towards this bacterium (with the inhibition rate of 90.0 and 54.2% at the above two concentrations, respectively), which adequately proved the necessity for introduction of indole moiety and 1,3,4-oxadiazole group into target compounds. Further introduction of substituted benzene ring with 1,3,4-oxadiazole moiety (**6a**–**6m**) linked with the intermediate **3** largely improved the activity of these compounds against *Xoo* compared with intermediate **3**, which demonstrated that **6a**–**6m** segment provide a structural advantage. Different from the bacterium *Xoo*, a large majority of the target compounds did not have noticeable antibacterial activity against the *Rs*, except compound **7j** (better than standard drug BMT and more active than control drug than TDC) at 200 μg/mL and compounds **7f**, **7i**, **7j** (better than BMT), **7i** (comparable activity with TDC) at 100 μg/mL. Among them, compounds **7j** and **7i** show better activity than the others. Notably, 3,5-dichloro substituted compound **7j** was found to possess a potent inhibition activity against the bacterium *Rs* (79.8%) even at 100 μg/mL, which was far better than two control agents BMT and TDC (45.9 and 52.9%, respectively). On the basis of previous bioassays, all test compounds showed moderate to excellent activity against *Xoo*.

In terms of the experimental results, the EC_{50} (half-maximal effective concentration) values of the above-mentioned nine compounds with remarkable antibacterial activity and intermediate **3** against the pathogen *Xoo* were further determined. As shown in Table 4, almost all of the target compounds did exhibit much lower EC_{50} values relative to control drug BMT. Specifically, compounds **7d**, **7h**, **7i**, **7j**, **7k**, **7l** and **7m** had an EC_{50} value of 52.31, 54.12, 40.65, 38.80, 51.13, 52.75 and 50.66 μg/mL, respectively, which was obviously better than control BMT (85.18 μg/mL). In addition, the experimental results showed that the inhibition rate value was linear with the corresponding concentration in the range of 12.5–200 μg/mL depicted by "Toxic regression equation" in Table 4 and good linearity was obtained (Correlation coefficient (a number between −1 and +1 calculated so as to represent the linear dependence of two variables or sets of data) > 0.9128).

Table 4 EC_{50} values of target compounds **7d**, **7h**, **7i**, **7j**, **7k**, **7l**, **7m** and intermediate **3** against the pathogen *Xoo*

Compounds	EC_{50}^{a} (μg/mL)	Toxic regression equation	Correlation coefficient (r)
3	69.52 ± 0.3	$y = 2.1227x + 1.0897$	0.9758
7d	52.31 ± 2.2	$y = 2.8168x + 0.1590$	0.9541
7h	54.12 ± 1.5	$y = 2.5479x + 0.5836$	0.9823
7i	40.65 ± 1.3	$y = 3.6529x - 0.8779$	0.9580
7j	38.80 ± 2.1	$y = 4.0354x - 1.4117$	0.9128
7k	51.13 ± 1.4	$y = 2.8627x + 0.1086$	0.9616
7l	52.75 ± 1.5	$y = 2.7516x + 0.2611$	0.9662
7m	50.66 ± 1.3	$y = 2.9096x + 0.0402$	0.9568
BMT[b]	85.18 ± 3.4	$y = 1.7838x + 1.5567$	0.9958

[a]The average of three trials

[b]The commercial bactericide bismerthiazol (BMT) was used as control agent

Structure–activity relationship analysis of antibacterial activities

A preliminary structure–activity relationship analysis was conducted, which showed that the final compounds with electron-donating substituents (e.g., 2-CH_3 and 4-NH_2) were unfavorable for their antibacterial activities against the pathogen *Xoo* excluding compound **7d** (EC_{50} = 52.31 μg/mL) containing –OCH_3. Generally, the presence of strongly electron-withdrawing substituent (such as 4-F, 4-Cl, 2,4-di-Cl, 3,5-di-Cl) was observed to enhance antibacterial activity against the pathogen *Xoo*. Surprisingly, the position of the substitutions (concerning these electron-withdrawing substitutions) in the benzene ring also produced a remarkable influence on their antibacterial activities against the *Xoo*, such as compounds **7f** vs. **7g** vs. **7h**, so as to the number of same substitution on the benzene ring, such as compounds **7f** vs. **7i** (or **7j**), **7g** vs. **7i** (or **7g**), **7h** vs. **7i** (or **7j**).

Conclusions

In summary, we have synthesized a series of novel indole derivatives **7a**–**7m** containing double 1,3,4-oxadiazole moiety groups. Turbidity test (Wang et al. 2013) was carried out to evaluate the antibacterial activities of intermediate **3** and target compounds **7a**–**7m** against *Xoo* and *Rs* in vitro. The results indicated that the intermediate **3** of indole derivative containing single 1,3,4-oxadiazole moiety exhibited antibacterial activity against *Xoo*. Moreover, the antibacterial activities of compounds **7d**, **7h**, **7i**, **7j**, **7k**, **7l** and **7m** against *Xoo* were much higher than those of intermediate **3** or control agents. More importantly, **7i** and **7j** exert excellent inhibition activities against *Xoo* with the lowest EC_{50} values. Although the compounds **7a**–**7m** showed moderate antibacterial activities against *Rs*, **7j** was found to possess a potent inhibition activity against the bacterium *Rs*, which was far better than two control agents BMT and TDC. Further introduction of substituted benzene ring with 1,3,4-oxadiazole moiety (**6a**–**6m**) linked with the intermediate **3** largely improved the activity of these compounds against *Xoo* compared with intermediate **3**. Given the above results that novel indole derivatives exhibited excellent antibacterial activities, we found out that double 1,3,4-oxadiazole moiety will enhance the bioactivities of the final products. Meanwhile, the structure–activity relationships reveal that the bioactivities of the target compounds are enhanced with the electron-withdrawing substituent.

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