Synthesis and Antibacterial Activity of Novel 1*H*-indol-2-ol Derivatives

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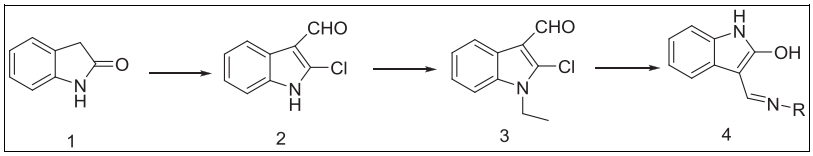

A series of novel 1*H*-indol-2-ol derivatives were synthesized and evaluated their antibacterial activities against rice bacterial leaf blight, tobacco bacterial wilt, and citrus canker caused by *Xanthomonas oryzae pv. oryzae* (*Xoo*), *Ralstonia solanacearum*, and *Xanthomonas axonopodis pv. citri* via the turbidimeter test *in vitro*. Antibacterial bioassay indicated that most compounds demonstrated good inhibitory effect against *Xoo* and *Ralstonia solanacearum*. Especially, compound **4k** demonstrated the best inhibitory effect against *Xoo* with half-maximal effective concentration (EC_{50}) value of 8.27 μg/mL, which was even better than those of commercial agents Bismerthiazol and Thiodiazole copper.

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INTRODUCTION

Indoles are the most ubiquitous components containing nitrogen heterocycle in nature [1,2]. The indole moiety remains at the forefront of biological and medicinal chemistry [3–5]. The most ubiquitous of the bioactive alkaloids known are based on the indole nucleus. Among the nitrogen heterocycles, the partially fused acridine derivatives are important motifs, displaying remarkable pharmaceutical or biochemical activities, such as antitumor [6,7], antifungal, [8] and antibacterial [9]. On the other hand, the indole moiety has been found in various pharmacologically and biologically active compounds [10,11]. Many indole alkaloids are recognized as one of the rapidly growing groups of marine invertebrate metabolites for their broad spectrum of biological properties, such as anticancer [12], antitumor [13], anti-inflammatory [14], hypoglycemic, analgesic, and antipyretic [15,16] activities.

Benzopyrrole, a privileged structure, represents a key motif in heterocyclic chemistry and have shown excellent performances in antibacterial [17], antiviral [18], antifungal [19], inflammatory [20], antianxiety [21], and antitubercular [22] activities. Meanwhile, alcohol derivatives are also known to exhibit a wide spectrum biological activities because the group is an important core found in many biologically active compounds with a wide range of biological activity including antibacterial [23], antifungal [24], insecticidal [25], antiviral [26], herbicidal [27], anticancer [28], anti-HIV-1 [29], antihepatitis [30], antitumor [31], and anti-inflammatory [32] properties.

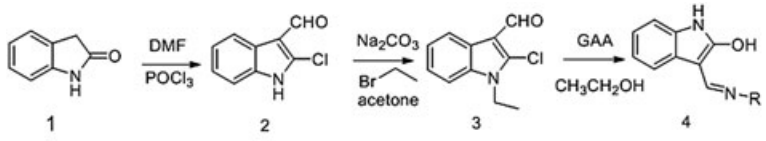
The union of active group is a versatile technology for searching for new broad-spectrum and high-performance bactericide. Herein, we attempt to design and synthesize a series of indol derivatives via union of active group based on the structure–activity relationship, and evaluated their antibacterial activities. It is believed that these indol derivatives have a very promising prospect in bactericide.

RESULTS AND DISCUSSION

Chemistry. The detailed synthetic route for the preparation of 1*H*-indol-2-ol derivatives are summarized in Scheme 1. 2-chloro-1*H*-indole-3-carbaldehyde (**2**) [33] were prepared by indolin-2-one (**1**) on reaction with phosphorus oxychloride and DMF. The key intermediate 2-chloro-1-ethyl-1*H*-indole-3-carbaldehyde (**3**) [34] was synthesized from 2-chloro-1*H*-indole-3-carbaldehyde (**2**) reacting with bromoethane in the presence of sodium carbonate in the acetone. The target compounds (**4**) were synthesized from 2-chloro-1-ethyl-1*H*-indole-3-carbaldehyde (**3**), reacting with different imines and glacial acetic acid in the ethanol at 80°C. The structures of the synthesized compounds were confirmed by HRMS, ^{1}H NMR, ^{13}C NMR.

The structures of compounds **4a–v** were confirmed. The ^{1}H NMR spectrum of **4d** in DMSO-d_6 displayed a singlet at δ 2.54 ppm that corresponds to O = C-CH_3 functionality, a singlet at δ 8.66 ppm that corresponds to −N═CH functionality, a singlet at δ 10.60 that corresponds to Indol 2-OH. A singlet that appeared at δ 10.87 ppm was observed because of the protons of benzpyrrole. The structure of **4d** was also confirmed by its mass spectral data. In high resolution mass spectrum, the molecular ion mass Calcd. $[M + H]^+$:279.11280 Found:279.11221, corresponding to its molecular weight.

Scheme 1. Synthetic route to compound **4a–v**.



4a R=3-NO_2Ph; 4b R=2-CH_3OPh; 4c R=3-CH_3COPh;
4d R=4-CH_3COPh; 4e R=CH_3; 4f R=CH_3CH_2;
4g R=$(CH_3)CH$; 4h R=4-CH_3Ph; 4i R=4-CF_3Ph;
4j R=$PhCH_2$; 4k R=3-Cl-4-CH_3Ph; 4l R=2,4-diCH_3Ph;
4m R=2-CH_3CH_2Ph; 4n R=2,6-diCH_3Ph; 4o R=CH_3CH_2OPh;
4p R=2,5-diCH_3OPh; 4q R=3-ClPh; 4r R=3-CH_3Ph;
4s R=4-OHPh; 4t R=4-Cl-3-CF_3Ph; 4u R=2,5-diClPh;
4v R=2-CH_3CH_2OPh;

Antibacterial activity of the synthesized compounds. A series of 1*H*-indol-2-ol derivatives were tested *in vitro* antibacterial activity against *Xanthomonas oryzae pv. oryzae* (*Xoo*), *Ralstonia solanacearum* (*R. solanacearum*), and *Xanthomonas axonopodis pv. citri (Xac)* by the turbidimeter test [25], and the commercial agricultural antibacterial agents Bismerthiazol and Thiodiazole copper were used as references, as shown in Table 1**,** compounds **4a**, **4g**, **4j–l**, **4o**, **4q**, and **4r** possessed excellent antibacterial activity against *Xoo*, with an inhibition rate of 100% at 200 μg/mL, which was even better than those of Bismerthiazol (72%) and Thiodiazole copper (64%). Meanwhile, Table 1 showed that compounds **4a**, **4g**, **4i**, **4k**, **4l**, **4n**, **4o**, and **4s** showed excellent antibacterial activity against *R. Solanacearum,* with an inhibition rate of 100% at 200 and 100 μg/mL, which were better compared with standard drug Bismerthiazol (50%). And in Table 1 showed that compounds **4d**, **4o**, and **4r** showed excellent antibacterial activity against *Xac*, with an inhibition rate of 100% at

Table 1

Antibacterial activity of compounds 7 against *Xanthomonas oryzae pv. oryzae, Ralstonia solanacearum, and Xanthomonas axonopodis pv. citri*.

	Inhibition rate (%)[a]					
	Xanthomomu oryzae pv.oryzae		*tobacco bacterial wilt*		*Xanthomonas axonopodis pv. citri*	
Compd.	200 mg/L	100 mg/L	200 mg/L	100 mg/L	200 mg/L	100 mg/L
4a	100 ± 1.32	60 ± 2.15	100 ± 1.21	100 ± 1.32	0	0
4b	0	0	70 ± 2.10	50 ± 3.10	0	0
4c	60 ± 2.76	28 ± 2.36	39 ± 2.12	30 ± 2.16	0	0
4d	63 ± 3.10	30 ± 2.58	100 ± 3.12	32 ± 3.15	100 ± 1.77	43 ± 2.14
4e	70 ± 2.73	50 ± 2.12	90 ± 2.23	60 ± 1.09	65 ± 2.12	28 ± 1.98
4f	60 ± 1.23	40 ± 3.12	100 ± 2.21	75 ± 1.45	36 ± 2.39	0
4g	100 ± 1.93	70 ± 2.53	100 ± 1.54	100 ± 2.12	51 ± 2.10	50 ± 2.94
4h	63 ± 2.09	0	100 ± 1.33	72 ± 2.44	0	0
4i	64 ± 2.04	0	100 ± 2.31	100 ± 2.43	49 ± 3.09	0
4j	100 ± 2.02	93 ± 2.71	14 ± 3.12	0	67 ± 1.45	31 ± 2.09
4k	100 ± 1.02	100 ± 1.78	100 ± 1.24	100 ± 1.08	50 ± 3.03	42 ± 1.32
4l	100 ± 2.34	95 ± 1.45	100 ± 2.10	100 ± 3.12	0	0
4m	81 ± 2.45	37 ± 3.12	90 ± 1.56	80 ± 2.12	0	0
4n	0	0	100 ± 2.13	100 ± 1.32	56 ± 2.33	50 ± 1.24
4o	100 ± 1.98	80 ± 2.31	100 ± 1.09	100 ± 2.13	100 ± 2.13	24 ± 3.12
4p	26 ± 3.24	24 ± 1.23	100 ± 1.87	75 ± 2.34	78 ± 2.34	62 ± 2.56
4q	100 ± 2.09	62 ± 2.41	80 ± 2.13	70 ± 2.31	90 ± 1.88	63 ± 2.22
4r	100 ± 2.43	75 ± 2.12	100 ± 3.12	97 ± 1.56	100 ± 2.34	53 ± 3.12
4s	88 ± 2.93	62 ± 2.10	100 ± 1.09	100 ± 2.45	50 ± 2.78	43 ± 2.12
4t	0	0	50 ± 1.90	40 ± 3.12	0	0
4u	0	0	70 ± 2.16	66 ± 2.34	0	0
4v	34 ± 2.56	0	0	0	0	0
Bismerthiazol	72 ± 0.65	54 ± 1.23	50 ± 2.11	30 ± 5.41		
Thiediazole Copper	64 ± 2.76	43 ± 3.15			55 ± 3.41	24 ± 2.35

[a]The experiments were repeated three times.

200 μg/mL, which were better compared with standard drug Thiediazole Copper (55%).

As illustrated in the previous bioassays, the half-maximal effective concentration (EC_{50}) values of some of the synthesized compounds as well as for Bismerthiazol and Thiodiazole copper were presented in Tables 2 and 3. Table 2 showed that all of the test compounds showed moderate to excellent activity against *Xoo*, with EC_{50} values of 8.27–168.45 μg/mL. Excitingly, compounds **4a**, **4g**, **4j–l**, **4o**, **4q**, and **4r** showed prominent activity against *Xoo in vitro*, with EC_{50} values of 84.32, 67.56, 56.98, 8.27, 50.00, 60.10, 79.42, and 67.03 μg/mL, respectively, which were even better than that of the commercial bactericide Bismerthiazol (91.54 μg/mL). Table 3 showed that all of the test compounds showed moderate to excellent activity against *R. solanacearum*, with EC_{50} values of 10.25–118.26 μg/mL. Some compounds showed prominent activity against *R. solanacearum in vitro*, which were even better than that of the commercial bactericide Thiediazole Copper (82.17 μg/mL).

Table 2

Inhibition effect of the compounds against rice bacterial leaf blight.

Compd.	EC_{50}(μg/mL)	Toxic regression equation	*R*
4a	84.32 ± 3.83	y = 0.445 × + 12.478	0.99
4c	168.45 ± 1.97	y = 0.335 × −6.434	0.99
4d	162.05 ± 2.09	y = 0.363 × −8.826	0.99
4e	121.97 ± 5.99	y = 0.293 × +14.260	0.97
4f	150.81 ± 0.98	y = 0.207 × +18.782	0.99
4g	67.56 ± 5.32	y = 0.408 × +22.434	0.96
4j	56.98 ± 4.01	y = 0.974 × −5.501	0.99
4k	8.27 ± 2.48	y = 2.465 × +29.608	0.97
4l	50.00 ± 3.74	y = 0.920 × +4.023	0.99
4m	128.55 ± 3.74	y = 0.440 × −6.565	0.99
4o	60.10 ± 0.80	y = 0.757 × +4.506	0.99
4q	79.42 ± 2.14	y = 0.554 × +6.054	0.99
4r	67.03 ± 3.20	y = 0.731 × +1.088	0.99
4s	107.84 ± 5.48	y = 0.485 × −2.304	0.96
Bismerthiazol	91.54 ± 2.14	y = 1.499 × +2.051	0.98
Thiediazole Copper	124.68 ± 3.32	y = 1.540 × +1.790	0.98

EC_{50}, half-maximal effective concentration.

Table 3

Inhibition effect of the compounds against tobacco bacterial wilt.

Compd.	EC_{50}(μg/mL)	Toxic regression equation	*R*
4a	46.87 ± 3.74	y = 0.960 × +5.033	0.99
4b	118.26 ± 4.21	y = 0.375 × +0.565	0.97
4e	103.97 ± 5.68	y = 0.470 × +1.913	0.96
4f	65.61 ± 3.40	y = 0.777 × −1.023	0.98
4g	55.77 ± 2.91	y = 1.022 × −7.105	0.98
4h	71.43 ± 2.40	y = 0.791 × −6.502	0.99
4i	53.99 ± 3.47	y = 1.065 × −7.504	0.99
4k	10.25 ± 2.13	y = 3.088 × +18.304	0.99
4l	39.08 ± 5.25	y = 0.882 × +13.523	0.99
4m	62.08 ± 3.47	y = 0.814 × −0.534	0.96
4n	40.64 ± 3.73	y = 0.880 × +14.23	0.98
4o	47.44 ± 5.61	y = 0.98 × +3.503	0.98
4p	63.23 ± 3.20	y = 0.708 × +5.321	0.99
4q	52.84 ± 5.34	y = 0.965 × −1.056	0.99
4r	45.55 ± 1.33	y = 0.911 × +8.502	0.99
4s	78.43 ± 2.57	y = 0.765 × −10.0327	0.99
Thiediazole Copper	82.17 ± 4.32	y = 0.505 × +8.503	0.98

EC_{50}, half-maximal effective concentration.

Antibacterial activity and the structure–activity relationships. The 1*H*-indol-2-ol derivatives that have been synthesized are imines of indol. We speculated that the additional electron withdrawing group on the benzene ring in comparison to the benzene ring would contribute substantially to the antibacterial activity. It was noticeable that where compounds were active, it was most commonly against *R. solanacearum*, and that the antibacterial activity lacked potency, rarely extending to the lower rates tested. Although the generally weak activity makes a detailed analysis of structure activity relationships difficult, some broad conclusions can be drawn. The spectrum of antibacterial activity is generally improved by substituting a halogen group onto the benzene ring. For example, while compound **4h** was weak active against antibacterial, the equivalent **4k** also displayed activity against *Xoo* and *R. Solanacearum* at 100 μg/mL, and **4i** was less active against *Xoo* but was active against *R. Solanacearum*, and gave weak activity against other species. This improvement in activity is not seen with all derivatives, however. **4k** was good active against *Xoo* and *R. Solanacearum*, while **4h** was weak active. **4i** was only active against *R. Solanacearum*. More generally, it is noticeable that almost all the derivatives of Compounds with electron donating group on the benzene ring were weak active, while equivalent derivatives of compounds with electron withdrawing group were usually active against *R. Solanacearum*, and sometimes display a broader spectrum of activity (e.g., **4a**).

CONCLUSIONS

A series of indole derivatives containing hydroxy and imine moieties were synthesized and evaluated their antibacterial activities against *Xoo*, *R. solanacearum*, and *Xac* by the turbidimeter test *in vitro*. The bioassays result demonstrated that some of the synthesized compounds exhibited excellent antibacterial activity against *Xoo* and *R. solanacearum*. Among these compounds, compound **4k** against *Xoo*, with EC_{50} value of 8.27 μg/mL, and against *R. Solanacearum,* with EC_{50} value of 10.25 μg/mL, which was better than those of Bismerthiazol and

Thiediazole copper. This work demonstrated that the compound **4k** can be used to develop potential bactericides for plants.

EXPERIMENTAL

General procedure. Unless otherwise noted, all common reagents and solvents were used as obtained from commercial supplies without further purifications. The melting points of the products were determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., China) and were not corrected. ^{1}H and ^{13}C NMR (solvent DMSO-d_6) spectra were recorded on a JEOL-ECX 500 NMR spectrometer at room temperature using TMS as an internal standard. HRMS data were measured on Thermo Scientific Q Exactive (Thermo, Missour, USA). TLC was performed on silica gel GF254. All anhydrous solvents were dried and purified according to standard techniques before use.

General procedure for synthesis of 2-chloro-1*H*-indole-3-carbaldehyde (2). Indolin-2-one (6.00 g, 45 mmol) was added to a solution of $POCl_3$ (30 mL) dropwise in DMF (30 mL) at 0°C, then the reaction mixture was stirred to room temperature. After stirring for 24 h, the mixture was poured into ice water. The mixture was filtered and the obtained solids were recrystallized from ethanol to give 2-chloro-1*H*-indole-3-carbaldehyde (**2**).

General procedure for synthesis of 2-chloro-1-ethyl-1*H*-indole-3-carbaldehyde (3). Put 2-chloro-1*H*-indole-3-carbaldehyde (**2**) (5.39 g, 30 mmol) in acetone (30 mL), was added dropwise bromoethane (3.27 g, 30 mmol) and added sodium carbonate (3.18 g, 30 mmol), then the reaction mixture was stirred at room temperature. After stirring for 2 h, the reaction mixture was evaporated under the reduced pressure, and subsequently diluted with water. The mixture was filtered and the obtained solids were recrystallized from ethanol to give 2-chloro-1-ethyl-1*H*-indole-3-carbaldehyde (**3**).

General procedure for synthesis of 3-(((substituted)imino) methyl)-1*H*-indol-2-ol 7a–v. To a solution of 2-chloro-1-ethyl-1*H*-indole-3-carbaldehyde (0.42 g, 2 mmol) in ethanol (20 mL), was added dropwise amine (4 mmol) and glacial acetic acid (2 mL). After heating and stirring for 12 h, the mixture was diluted with water and was filtered and the solid obtained and recrystallized from ethanol to give compounds **4a**–**v**.

3-(((3-nitrophenyl)imino)methyl)-1H-indol-2-ol (4a). Yellow solid; yield 61.9%; m.p. 247–249°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 10.85 (s, 1H, Indol 1-H), 10.55 (s, 1H, Indol 2-OH), 8.69 (s, 1H, −N═CH), 8.34 (m, 1H, Ar-H), 7.84 (m, 2H, Ar-H), 7.66–7.60 (m, 2H, Ar-H), 7.04 (m, 1H, Ar-H), 6.94 (m, 1H, Ar-H), 6.85 (m, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 170.28, 149.49, 142.15, 138.05, 137.53, 131.33, 125.29, 124.46, 123.10, 121.05, 118.24, 117.52, 110.52, 109.79, 102.16; HRMS m/z: ([M + H]$^+$); *Anal*. Calcd. For $C_{15}H_{11}N_3O_3$: 282.08732; found 282.08728.

3-(((2-methoxyphenyl)imino)methyl)-1H-indol-2-ol (4b). Yellow solid; yield 62.5%; m.p. 219–220°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 10.93 (s, 1H, Indol 1-H), 10.46 (s, 1H, Indol 2-OH), 8.63 (s, 1H, −N═CH), 7.66 (m, 1H, Ar-H), 7.59 (m, 1H, Ar-H), 7.10 (m, 1H, Ar-H), 7.05–6.98 (m, 3H, Ar-H), 6.93 (m, 1H, Ar-H), 6.85 (m, 1H, Ar-H), 3.91 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 170.38, 147.99, 137.54, 137.36, 129.57, 124.75, 124.53, 123.63, 121.68, 120.84, 117.58, 113.64, 112.09, 109.66, 100.62, 56.53; HRMS m/z: ([M + H]$^+$); *Anal*. Calcd. For $C_{16}H_{15}O_2N_2$: 267.11280; found 267.11200.

1-(3-(((2-hydroxy-1H-indol-3-yl)methylene)amino)phenyl) ethan-1-one (4c). Yellow solid; yield 64.5%; m.p. 236–237°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 10.81 (s, 1H, Indol 1-H), 10.54 (s, 1H, Indol 2-OH), 8.67 (s, 1H, −N═CH), 7.94 (s, 1H, Ar-H), 7.67 (m, 1H, Ar-H), 7.65–7.61 (m, 2H, Ar-H), 7.52 (m, 1H, Ar-H), 7.05–7.00 (m, 1H, Ar-H), 6.97–6.90 (m, 1H, Ar-H), 6.86 (m, 1H, Ar-H), 2.63 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 198.32, 170.42, 141.04, 138.76, 138.22, 137.71, 130.51, 124.85, 124.65, 123.03, 120.91, 120.89, 117.89, 115.93, 109.73, 100.94, 27.53; HRMS m/z: ([M + H]$^+$); *Anal*. Calcd. For $C_{17}H_{15}O_2N_2$: 279.11280; found 279.11215.

1-(4-(((2-hydroxy-1H-indol-3-yl)methylene)amino)phenyl) ethan-1-one (4d). Yellow solid; yield 58.2%; m.p. 212–214°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 10.87 (s, 1H, Indol 1-H), 10.60 (s, 1H, Indol 2-OH), 8.66 (s, 1H, −N═CH), 7.96 (m, 2H, Ar-H), 7.63 (m, 1H, Ar-H), 7.50 (m, 2H, Ar-H), 7.05 (m, 1H), Ar-H, 6.95 (m, 1H, Ar-H), 6.86 (m, 1H, Ar-H), 2.54 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 196.74, 170.40, 144.58, 138.05, 137.10, 131.74, 130.83, 125.38, 124.33, 121.14, 118.21, 115.75, 109.87, 102.38, 26.99; HRMS m/z: ([M + H]$^+$); *Anal*. Calcd. For $C_{17}H_{15}O_2N_2$: 279.11280; found 279.11221.

3-((methylimino)methyl)-1H-indol-2-ol (4e). Yellow solid; yield 44.2%; m.p. 201–202°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 10.11 (s, 1H, Indol 2-OH), 8.61 (s, −N═CH), 7.84 (m, 1H, Ar-H), 7.37 (s, 1H, Indol 1-H), 7.25 (m, 1H, Ar-H), 6.94–6.83 (m, 2H, Ar-H), 3.08 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 170.06, 149.35, 136.05, 125.96, 122.40, 120.23, 115.31, 109.09, 94.81, 35.77; HRMS m/z: ([M + H]$^+$); *Anal*. Calcd. For $C_{10}H_{10}N_2O$: 175.08659; found 175.08638.

3-((ethylimino)methyl)-1H-indol-2-ol (4f). Yellow solid; yield 48.2%; m.p. 86–87°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 10.01 (s, 1H, Indol 2-OH), 8.11 (s, 1H, −N═CH), 7.69 (m, 1H, Ar-H), 7.39–7.26 (m, 3H, Ar-H), 4.37 (d, J = 7.2 Hz, 2H), 1.31 (d, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 183.82, 136.20, 135.32, 124.41,124.34, 123.82, 120.66, 112.46, 111.39, 39.23,

14.97; HRMS m/z: ([M + H]$^+$); *Anal*. Calcd. For $C_{11}H_{13}ON_2$: 189.10224; found 189.10170.

3-((isopropylimino)methyl)-1H-indol-2-ol (4g). Yellow solid; yield 38.3%; m.p. 85–86°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 10.19 (s, 1H, Indol 1-H), 10.02 (s, 1H, Indol 2-OH), 8.11 (s, 1H, −N═CH), 7.97 (m, 1H, Ar-H), 7.69 (m, 1H, Ar-H), 7.35 (m, 1H, Ar-H), 6.88 (m, 1H, Ar-H), 3.67 (d, J = 13.2, Hz, 1H), 1.27–1.24 (m, 6H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 183.83, 146.51, 135.33, 124.49, 123.83, 120.66, 120.25, 111.39, 109.14, 50.01, 23.94; HRMS m/z: ([M + H]$^+$); *Anal*. Calcd. For $C_{12}H_{15}ON_2$: 203.11789; found 203.11705.

3-((p-tolylimino)methyl)-1H-indol-2-ol (4h). Yellow solid; yield 60.8%; m.p. 268–269°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 10.69 (s, 1H, Indol 1-H), 10.47 (s, 1H, Indol 2-OH), 8.56 (s, 1H, −N═CH), 7.57 (m, 1H, Ar-H), 7.29 (m, 2H, Ar-H), 7.19 (m, 2H, Ar-H), 6.99 (m, 1H, Ar-H), 6.92 (m, 1H, Ar-H), 6.84 (s, 1H, Ar-H), 2.28 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 170.42, 138.71, 138.09, 137.34, 132.71, 130.60, 124.87, 124.34, 120.83, 117.44, 116.37, 109.62, 99.61, 20.86; HRMS m/z: ([M + H]$^+$); *Anal*. Calcd. For $C_{16}H_{15}ON_2$: 251.11789; found 251.11720.

3-(((4-(trifluoromethyl)phenyl)imino)methyl)-1H-indol-2-ol (4i). Yellow solid; yield 46.1%; m.p. 228–229°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 10.83 (s, 1H, Indol 1-H), 10.59 (s, 1H, Indol 2-OH), 8.65 (s, 1H, −N═CH), 8.04 (m, 1H, Ar-H), 7.61 (m, 4H, Ar-H), 7.45 (m, 1H, Ar-H), 6.94 (m, 2H, Ar-H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 170.37, 144.04, 138.05, 137.32, 131.28, 127.34, 125.32, 124.39, 121.10, 118.14, 116.46, 115.66, 109.84, 102.19; HRMS m/z: ([M + H]$^+$); *Anal*. Calcd. For $C_{16}H_{12}ON_2F_3$: 305.08962; found 305.08972.

3-((benzylimino)methyl)-1H-indol-2-ol (4j). Red solid; yield 65.3%; m.p. 189–190°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 10.20 (s, 1H, Indol 1-H), 9.07 (s, 1H, Indol 2-OH), 8.02 (s, 1H, −N═CH), 7.37 (m, 4H, Ar-H), 7.29 (m, 2H, Ar-H), 6.90 (m, 1H, Ar-H), 6.84 (m, 1H, Ar-H), 6.78 (m, 1H, Ar-H), 4.56 (d, J = 6.4 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 170.17, 148.19, 139.73, 136.35, 129.18, 127.93, 125.72, 122.84, 120.37, 115.66, 109.22, 95.73, 52.11; HRMS m/z: ([M + H]$^+$); *Anal*. Calcd. For $C_{16}H_{15}ON_2$: 251.11789; found 251.11769.

3-(((3-chloro-4-methylphenyl)imino)methyl)-1H-indol-2-ol (4k). Yellow solid; yield 50.5%; m.p. 246–247°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 10.64 (s, 1H, Indol 1-H), 10.50 (s, 1H, Indol 2-OH), 8.57 (s, −N═CH), 7.60 (m, 2H, Ar-H), 7.32 (m, 1H, Ar-H), 7.25 (m, 1H, Ar-H), 7.01 (m, 1H, Ar-H), 6.93 (m, 1H, Ar-H), 6.83 (m, 1H, Ar-H), 2.28 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 170.33, 139.94, 138.15, 137.75,137.66, 132.48, 129.99, 124.75,124.73, 120.93, 117.78, 116.18, 115.64, 109.69, 100.71, 19.37; HRMS m/z: ([M + H]$^+$); *Anal*. Calcd. For $C_{16}H_{14}ON_2Cl$: 285.07892; found 285.07822.

3-(((2,4-dimethylphenyl)imino)methyl)-1H-indol-2-ol (4l). Yellow solid; yield 64.5%; m.p. 192–193°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 10.92 s, 1H, Indol 1-H), 10.51 (s, 1H, Indol 2-OH), 8.66 (s, 1H, −N═CH), 7.84 (m, 1H, Ar-H), 7.59 (m, 1H, Ar-H), 7.50 (m, 1H, Ar-H), 7.18–7.03 (m, 4H, Ar-H), 2.32–2.26 (m, 6H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 170.76, 159.72, 138.82, 137.28, 136.31, 132.03, 128.22, 125.17, 124.72, 124.31, 120.86, 117.49, 113.93, 109.72, 100.02, 20.82, 17.43; HRMS m/z: ([M + H]$^+$); *Anal*. Calcd. For $C_{17}H_{17}ON_2$: 265.13354; found 265.13293.

3-(((2-ethylphenyl)imino)methyl)-1H-indol-2-ol (4m). Yellow solid; yield 48.1%; m.p. 181–182°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 11.11 (s, 1H, Indol 1-H), 10.51 (s, 1H, Indol 2-OH), 8.70 (s, 1H, −N═CH), 7.61 (m, 2H, Ar-H), 7.33–7.22 (m, 2H, Ar-H), 7.02 (m, 2H, Ar-H), 6.93 (m, 1H, Ar-H), 6.88 (m, 1H, Ar-H), 2.78–2.63 (m, 2H), 1.24 (t, J = 7.5 Hz, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 170.80, 138.96, 138.07, 137.40, 131.29, 129.84, 127.84, 124.58, 124.52, 123.67, 120.94, 117.62, 114.45, 109.79, 100.50, 24.21, 14.26; HRMS m/z: ([M + H]$^+$); *Anal*. Calcd. For $C_{17}H_{17}ON_2$: 265.13354; found 265.13348.

3-(((2,6-dimethylphenyl)imino)methyl)-1H-indol-2-ol (4n). Yellow solid; yield 44.3%; m.p. 150–151°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 10.41 (s, 1H, Indol 1-H), 10.27 (s, 1H, Indol 2-OH), 8.04 (s, 1H, −N═CH), 7.46 (m, 1H, Ar-H), 7.20–7.14 (m, 3H, Ar-H), 6.96 (m, 1H, Ar-H), 6.88–6.83 (m, 2H, Ar-H), 2.32 (s, 6H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 170.57, 146.00, 138.82, 136.95, 132.38, 129.27, 126.34, 125.17, 123.83, 120.66, 116.87, 109.49, 98.11, 18.78; HRMS m/z: ([M + H]$^+$); *Anal*. Calcd. For $C_{17}H_{17}ON_2$: 265.13354; found 265.13354.

3-(((4-ethoxyphenyl)imino)methyl)-1H-indol-2-ol (4o). Yellow solid; yield 64.5%; m.p. 212–213°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 10.67 (s, 1H, Indol 1-H), 10.45 (s, 1H, Indol 2-OH), 8.50 (s, 1H, −N═CH), 7.56 (m, 1H, Ar-H), 7.33 (m, 2H, Ar-H), 6.94 (m, 5H, Ar-H), 4.01 (t, J = 6.9 Hz, 2H), 1.32 (t, J = 6.9 Hz, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 170.35, 155.36, 139.26, 137.16, 133.86, 125.02, 124.06, 120.74, 117.91, 117.23, 115.92, 109.55, 98.99, 63.81, 15.24; HRMS m/z: ([M + H]$^+$); *Anal*. Calcd. For $C_{17}H_{17}O_2N_2$: 281.12845; found 281.12772.

3-(((2,5-dimethoxyphenyl)imino)methyl)-1H-indol-2-ol (4p). Yellow solid; yield 52.2%; m.p. 211–212°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 10.92 (s, 1H, Indol 1-H), 10.46 (s, 1H, Indol 2-OH), 8.63 (s, 1H, −N═CH), 7.62 (m, 1H, Ar-H), 7.29 (m, 1H, Ar-H), 7.08–6.98 (m, 2H, Ar-H), 6.93 (m, 1H, Ar-H), 6.86 (m, 1H, Ar-H), 6.58 (m, 1H, Ar-H), 3.85 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 170.37, 154.74, 142.29, 137.62, 137.23, 130.32), 124.67, 124.64, 120.82, 117.73, 113.04, 109.69, 107.52, 100.87, 100.63 (s), 56.97, 56.17; HRMS m/z:

([M + H]$^+$); *Anal*. Calcd. For $C_{17}H_{17}O_3N_2$: 297.12337; found 297.12334.

3-(((3-chlorophenyl)imino)methyl)-1H-indol-2-ol (4q). Yellow solid; yield 40.7%; m.p. 204–205°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 10.68 (s, 1H, Indol 1-H), 10.53 (s, 1H, Indol 2-OH), 8.60 (s, 1H, −N═CH), 7.66–7.57 (m, 2H, Ar-H), 7.38–7.28 (m, 2H, Ar-H), 7.10–7.00 (m, 2H, Ar-H), 6.94 (m, 1H, Ar-H), 6.86–6.81 (m, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 170.34, 142.21, 137.81, 134.84, 131.67, 124.99, 124.59, 122.97, 122.86,120.99, 117.95, 115.61, 115.51, 109.74, 101.34; HRMS m/z: ([M + H]$^+$); *Anal*. Calcd. For $C_{15}H_{12}ON_2Cl$: 271.06327; found 271.06241.

3-((m-tolylimino)methyl)-1H-indol-2-ol (4r). Yellow solid; yield 48.0%; m.p. 210–211°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 10.70 (s, 1H, Indol 1-H), 10.50 (s, 1H, Indol 2-OH), 8.60 (s, 1H, −N═CH), 7.59 (m, 1H, Ar-H), 7.23 (m, 3H, Ar-H), 7.01 (m, 1H, Ar-H), 6.94–6.83 (m, 3H, Ar-H), 2.33 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 170.47, 140.37, 139.76, 138.50, 137.45, 130.04, 124.79, 124.43, 124.41, 120.88, 117.56, 116.76, 113.57, 109.68, 100.03, 21.62; HRMS m/z: ([M + H]$^+$); *Anal*. Calcd. For $C_{16}H_{15}ON_2$: 251.11789; found 251.11719.

3-(((4-hydroxyphenyl)imino)methyl)-1H-indol-2-ol (4s). Yellow solid; yield 62.6%; m.p. 256–257°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 10.65 (s, 1H, Indol 1-H), 10.42 (s, 1H, Indol 2-OH), 9.34 (s, 1H,Ar-OH), 8.46 (s, 1H, −N═CH), 7.53 (m, 1H, Ar-H), 7.22 (m, 2H, Ar-H), 7.01–6.94 (m, 1H, Ar-H), 6.90 (m, 1H, Ar-H), 6.83 (m, 1H, Ar-H), 6.80–6.77 (m, 2H, Ar-H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 170.35, 154.30, 139.50, 137.01, 132.52, 125.09, 123.87, 120.71, 118.11, 117.07, 116.62, 109.52, 98.50; HRMS m/z: ([M + H]$^+$); *Anal*. Calcd. For $C_{15}H_{13}O_2N_2$: 253.09715; found 253.09729.

3-((((4-chloro-3-(trifluoromethyl)phenyl)imino)methyl)-1H-indol-2-ol (4t). Yellow solid; yield 41.5%; m.p. 252–253°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 10.76 (s, 1H, Indol 1-H), 10.55 (s, 1H, Indol 2-OH), 8.60 (s, 1H, −N═CH), 7.95 (m, 1H, Ar-H), 7.75–7.60 (m, 3H, Ar-H), 7.03 (m, 1H, Ar-H), 6.95 (m, 1H, Ar-H), 6.85 (m, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 170.20, 140.37, 138.06, 137.42, 133.10, 125.27, 124.47, 121.44, 121.01, 118.15, 115.84, 109.79, 102.11; HRMS m/z: ([M + H]$^+$); *Anal*. Calcd. For$C_{16}H_{11}ON_2ClF_3$: 339.05065; found 339.04987.

3-(((2,5-dichlorophenyl)imino)methyl)-1H-indol-2-ol (4u). Yellow solid; yield 34.0%; m.p. 257–258°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 11.16 (s 1H, Indol 1-H), 10.63 (s, 1H, Indol 2-OH), 8.73 (s, 1H, −N═CH), 7.98 (m, 1H, Ar-H), 7.63 (m, 1H, Ar-H), 7.54 (m, 1H, Ar-H), 7.15–7.02 (m, 2H, Ar-H), 6.97 (m, 1H, Ar-H), 6.88 (m, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 170.59, 138.46, 138.28, 136.55, 133.83, 131.67, 125.70, 124.03, 123.26, 121.24, 119.58, 118.46, 114.91, 110.03, 103.43; HRMS m/z: ([M + H]$^+$); *Anal*. Calcd. For $C_{15}H_{11}ON_2Cl$: 305.02429; found 305.02390.

3-(((2-ethoxyphenyl)imino)methyl)-1H-indol-2-ol (4v). Yellow solid; yield 55.9%; m.p. 233–234°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: δ 11.05 (s, 1H, Indol 1-H), 10.39 (s, 1H, Indol 2-OH), 8.63 (s, 1H, −N═CH), 7.68–7.56 (m, 2H, Ar-H), 7.08 (m, 1H, Ar-H), 7.01 (m, 3H, A-H), 6.92 (m, 1H, Ar-H), 6.88–6.84 (m, 1H, Ar-H), 4.19–4.10 (m, 2H), 1.42 (m, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 170.40, 147.26, 137.55, 137.23, 129.92, 124.98, 124.63, 123.53, 121.74, 120.81, 117.53, 113.43, 113.31, 109.67, 100.55, 64.81, 15.21; HRMS m/z: ([M + H]$^+$); *Anal*. Calcd. For $C_{17}H_{17}O_2N_2$: 281.12845; found 281.12775.

Antibacterial activity. The antibacterial activities of some title compounds against *Xoo*, *R. Solanacearum*, *and Xac* were evaluated by the turbidimeter test. Dimethylsulfoxide in sterile distilled water served as a blank control, Bismerthiazol and Thiodiazole copper served as positive controls. Approximately 40 μL of solvent M210 (8.0 g of casein enzymatic hydrolysate, 5.0 g of sucrose, 4.0 g of yeast powder, 3.0 g of K_2HPO_4, 0.3 g of $MgSO_4$•$7H_2O$ and 1000 mL of distilled water; pH = 7.0) containing *Xoo, R. solanacearum* and *Xac* was added to 5 mL of solvent M210 containing the test compounds and positive controls. The inoculated test tubes were incubated at 28 ± 1°C and continuously shaken at 180 rpm for 24 h. The growth of the cultures was monitored on a microplate reader by measuring the optical density at 595 nm (OD_{595}) given by $\text{turbidity}_{\text{corrected values}} = OD_{\text{bacterial wilt}} - OD_{\text{no bacterial wilt}}$, and then the inhibition rate I was calculated by $I\ (\%) = (C_{tur} - T_{tur})/C_{tur} \times 100$. C_{tur} is the corrected turbidity values of bacterial growth on untreated M210 (blank control), and T_{tur} is the corrected turbidity values of bacterial growth on treated M210. Some of the title compounds tested against five double declining concentrations method were expressed by EC_{50}. The average EC_{50} was computed from at least three separate analyses for growth inhibition using the basic EC_{50} program version SPSS 17.0.

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REFERENCES AND NOTES

[1] Cacchi, S.; Fabrizi, G. Chem Rev 2005, 105, 2873.

[2] Humphery, G. R.; Kuethe, J. T. Chem Rev 2006, 106, 2875.

[3] Takada, S.; Ishizuka, N.; Sasatani, T.; Makisumi, Y.; Jyoyama, H.; Hatakeyama, H.; Asanuma, F.; Hirose, K. Chem Pharm Bull 1984, 32, 877.

[4] Ishizuka, N.; Sato, T.; Makisumi, X. Chem Pharm Bull 1990, 38, 1396.

[5] Makisumi, Y.; Sasatani, T. U.S. Patent No. 4,910,318, 1990.
[6] Inman, W. D.; O'Neill-Johnson, M.; Crews, P. J Am Chem Soc 1990, 112, 1.
[7] Gimenez-Arnau, E.; Missailidis, S.; Stevens, M. F. G. Anticancer Drug Des 1998, 13, 431.
[8] Zhang, M. Z.; Mulholland, N.; Beattie, D.; et al. Eur J Med Chem 2013, 63, 22.
[9] McCarthy, P. J.; Pitts, T. P.; Gunawardana, G. P.; Kelly-Borges, M.; Pomponi, S. A. J Nat Prod 1992, 55, 1664.
[10] Casapullo, A.; Bifulco, G.; Bruno, I.; Riccio, R. J. J Nat Prod 2000, 63, 447.
[11] Zhang, M. Z.; Chen, Q.; Yang, G. F. Eur J Med Chem 2015, 89, 421.
[12] Bao, B.; Sun, Q.; Yao, X.; Hong, J.; Lee, C. O.; Sim, C. J.; Im, K. S.; Jung, J. H. J. J Nat Prod 2005, 68, 711.
[13] Kouko, T.; Matsumura, K.; Kawasaki, T. Tetrahedron 2005, 61, 2309.
[14] Kaniwa, K.; Arai, M. A.; Li, X.; Ishibashi, M. Bioorg MedChem Lett 2007, 17, 4254.
[15] Zhu, S.; Ji, S.; Su, X.; Sun, C.; Liu, Y. Tetrahedron Lett 2008, 49, 1777.
[16] Farghaly, A. M.; Habib, N. S.; Khalil, M. A.; Sayed, O. A. E.; Alexandria, J. Pharm Sci 1989, 3, 9.
[17] Chitra, G.; Franklin, D. S.; Guhanathan, S. Journal of Macromolecular Science, Part A 2017, 54, 151.
[18] Abdel-Gawad, H.; Mohamed, H. A.; Dawood, K. M.; et al. Chem Pharm Bull 2010, 58, 1529.
[19] Dandia, A.; Singh, R.; Khaturia, S.; Mérienne, C.; Morgant, G.; Loupy, A. Bioorg Med Chem 2006, 14, 2409.
[20] Winter, C. A.; Risley, E. A.; Nuss, G. W. J Pharmacol Exp Ther 1963, 141, 369.
[21] Kerzarea, D. R.; Khedekar, P. B. J Pharm Sci Bioscientific Res 2016, 6, 144.
[22] Karthikeyan, S. V.; Perumal, S.; Shetty, K. A.; Yogeeswari, P.; Sriram, D. Bioorg Med Chem Lett 2009, 19, 3006.
[23] Yamamoto, Y.; Kurazono, M. Bioorg Med Chem Lett 2007, 17, 1626.
[24] Ryu, C. K.; Lee, J. Y.; Park, R. E.; et al. Bioorg Med Chem Lett 2007, 17, 127.
[25] Hayashi, H.; Takiuchi, K.; Murao, S. Agric Biol Chem 1989, 53, 461.
[26] Giampieri, M.; Balbi, A.; Ml, M. Antiviral Res 2009, 83, 179.
[27] Matschke, J.; Macháčková, I. Biologia plantarum 2002, 45, 375.
[28] Aggarwal, B. B.; Ichikawa, H. Cell Cycle 2005, 4, 1201.
[29] Ragno, R.; Coluccia, A.; La Regina, G. J Med Chem 2006, 49, 3172.
[30] Zhao, C.; Zhao, Y.; Chai, H. Bioorg Med Chem 2006, 14, 2552.
[31] Bradlow, H.; Sepkovic, D. W.; Telang, N. T. Ann N Y Acad Sci 1999, 889, 204.
[32] Winter, C. A.; Risley, E. A. Journal of pharmacology and Experimental Therapeutics 1963, 141, 369.
[33] Majumder, S.; Bhuyan, P. J. Synlett 2011, 2011, 173.
[34] Gao, W.; Gao, D.; Guo, H. Chem Res Chin Univ 2009, 25, 465.

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