Chem. Pap.
DOI 10.1007/s11696-017-0189-5

ORIGINAL PAPER

Synthesis and antibacterial activity of oxime ester derivatives containing 1,2,4-triazole or 1,3,4-oxadiazole moiety

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Received: 3 March 2017 / Accepted: 3 May 2017

Abstract A series of oxime ester derivatives containing 1,2,4-triazole or 1,3,4-oxadiazole moiety were designed and synthesized, and their antibacterial activities in vitro against *Xanthomonas axonopodis pv. citri* (Xac) and *Xanthomonas oryzae pv. oryzae* (Xoo) were evaluated. The bioassays showed that all the title compounds exhibit potent antibacterial activity against Xac and Xoo. In particular, the compounds **4a**, **5a**, **5b**, **5c**, **5d**, **5h** and **5i** exhibited remarkable antibacterial activity against Xoo, with the EC_{50} values ranging from 15.15 to 49.34 μg/mL, which were superior to that of *bismerthiazol* (92.61 μg/mL). This study indicated that oxime ester derivatives containing 1,2,4-triazole or 1,3,4-oxadiazole moiety may be used as potential alternative templates in the search for novel antibacterial agents.

Electronic supplementary material The online version of this article (doi:10.1007/s11696-017-0189-5) contains supplementary material, which is available to authorized users.

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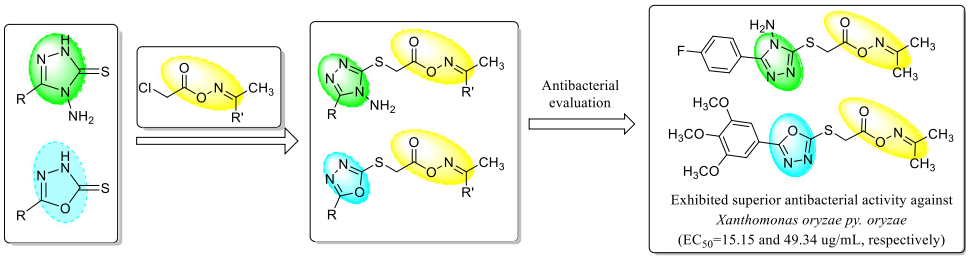
Published online: 08 May 2017

Graphical Abstract



Keywords 1,2,4-Triazole · 1,3,4-Oxadiazole · Oxime ester · Antibacterial activity

Introduction

Plant bacterial diseases cause enormous economic losses and restrict the sustainable development of agriculture. As examples of plant bacterial diseases, rice bacterial leaf blight and citrus bacterial canker, which were, respectively, caused by *Xanthomonas oryzae pv. oryzae* (Xoo) and *Xanthomonas axonopodis pv. citri* (Xac), seriously limit the yields of rice and citrus (Li et al. 2014). Although some bactericides, such as *bismerthiazol* and *thiodiazole-copper*, are available to combat phytopathogenic bacteria, great challenges in pesticide chemistry have been posed due to the rapid emergency of bacteria resistance (Wang et al. 2013; Yan et al. 2016). Consequently, it is vitally urgent to develop novel lead molecules with potent activities against plant bacteria (Xu et al. 2012).

With broad bioactivities including insecticidal (Sun et al. 2010), anticancer (Xue et al. 2006), antiviral (Ouyang et al. 2008), antifungal (Zhao et al. 2013), antibacterial (Liu et al. 2008), and anticonvulsant (Karakurt et al. 2012) properties, oxime esters are important nitrogenous compounds that are vital to agricultural chemistry. As oxime ester derivatives, *aldicarb temic* and *methomyl lannate* are important representative cholinesterase inhibitors that effectively alleviated agricultural disease outbreaks caused by agricultural pests. Recently, Harini et al. 2012 evaluated the antibacterial activity of a series of vanillin-derived piperidin-4-one oxime esters, and found that those target compounds exhibited excellent antibacterial activities against *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Meanwhile, a series of penta-1,4-diene-3-one oxime esters were found to exhibit good antiviral activity against tobacco mosaic virus in our previous research (Wang et al. 2016). Obviously, introducing oxime ester group in lead compounds might generate novel compounds with greater bioactivities.

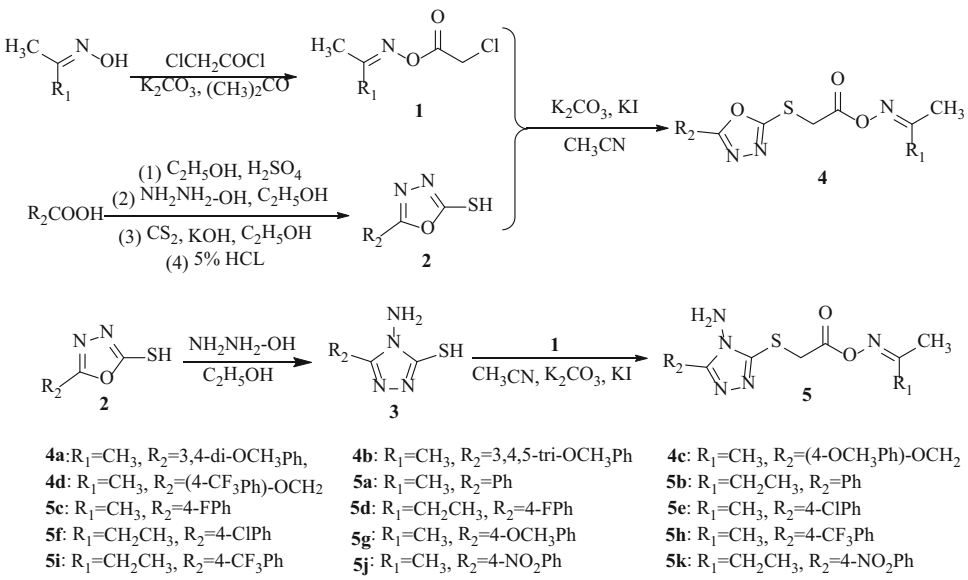
With outstanding characteristics including high activity, unique action mechanism, long duration and broad spectrum, 1,2,4-triazoles are important nitrogenous heterocycles that play a vital role in agrochemical development and arouse great attractions (Li et al. 2013; Hashemi et al. 2015; Murlykina et al. 2015; Paprocka et al. 2015; Chen et al. 2016; Pan et al. 2016). For example, *fluquinconazole* and *flusilazole* are important representative fungicides that inhibit pathogen ergosterol biosynthesis. Recently, a series of 1,2,4-triazolylthioethers containing quinazolinone moiety, which exhibited remarkable antibacterial activities against Xac and Xoo, were synthesized by our group (Yan et al. 2016). Moreover, as another important nitrogenous heterocycles, 1,3,4-oxadiazoles are widely used for developing novel agrochemicals with potent antibacterial and antifungal activities (Xu et al. 2013). Recently, a series of 1,3,4-oxadiazole sulfone derivatives exhibited excellent antibacterial activities against rice bacterial leaf blight and leaf streak, and 1,3,4-oxadiazole derivatives containing 1,4-pentadien-3-one moiety as potent antiviral agents were synthesized in our previous research (Li et al. 2014; Gan et al. 2016).

Considering the above findings, we speculated that introducing oxime ester fragment into 1,2,4-triazole and 1,3,4-oxadiazole might generate novel lead compounds with greater biological activities. Thus, a series of oxime ester derivatives containing 1,2,4-triazole or 1,3,4-oxadiazole moiety were synthesized (Scheme 1), and their antibacterial activities in vitro against Xac and Xoo were evaluated.

Experimental

The melting points (M.P.) of title compounds were determined when uncorrected on an XT-4 binocular microscope (Beijing Tech Instrument Co.). ^{1}H, ^{19}F and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a JEOL-ECX 500 NMR spectrometer (JEOL, Japan) using TMS as the internal standard and DMSO-d_6 as the solvent. Mass spectra studies were recorded on an Agilent organic mass spectrometer (Agilent, USA). Elemental analysis was performed on an Elementar Vario-III CHN analyser (Elementar, German). Unless noted, all solvents and reagents

Scheme 1 Synthetic route of the title compounds **4a**–**4d** and **5a**–**5k**



were purchased from Shanghai Titan Scientific Co., Ltd, and were treated with standard methods. The intermediates **2a**–**2j** were synthesized by the methods described in the literature (Li et al. 2009), and their physical properties and related NMR data are listed in Supporting Information.

General synthetic procedure for 2-chloroacetic acid acetone oxime ester (1a) and 2-chloroacetic acid butanone oxime ester (1b)

The reactions of acetone oxime or butanone oxime with chloroacetyl chloride were carried out in acetone at room temperature to give the intermediates **1a** or **1b** in acceptable yields. The physical properties and related NMR data are listed in Supporting Information.

General synthetic procedure for the intermediates 3a–3f

A mixture of 20.0 mmol of intermediate **2**, 15 mL of 80% hydrazine hydrate, and 60 mL of ethanol was heated under reflux. After the reaction was completed, the solvent was evaporated under vacuum and the solid residue was recrystallized using ethanol to give a white solid of the intermediates **3**. The physical properties and related NMR data of the intermediates **3a**–**3f** are listed in Supporting Information.

General synthetic procedure for title compounds 4a–4d and 5a–5k

Intermediates **2** or **3** (1 mmol), intermediates **1** (1.1 mmol) and K_2CO_3 (1.5 mmol) were added to acetonitrile (50 mL). Then, the reaction mixture was stirred at room temperature for 3–4 h and monitored by TLC (petroleum ether/ethyl acetate, *V*/*V* = 1:2). After the reaction was finished, acetonitrile was evaporated under vacuum, and the residue was subjected to column chromatography with petroleum ether/ethyl acetate (*V*/*V* = 4:1) to obtain title compounds **4** or **5**. The physical properties and analytical data of compounds **4** and **5** are listed in Table 1, and the spectral data of compounds **4** and **5** are listed in Table 2.

Results and discussion

Chemistry

A series of oxime ester derivatives containing 1,2,4-triazole or 1,3,4-oxadiazole moiety were successfully prepared in our current work. The structures of target compounds were affirmed by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, ESI–MS and elemental analysis. In the ^{1}H NMR spectra of the title compounds, the singles at 1.90–2.00 and 4.20–4.30 ppm reveal the presences of –N=C–CH_3 and –SCH_2– groups, respectively. In the ^{13}C NMR spectra, the typical shifts at near 165–169, 150–155 and 31–32 ppm reveal the presence of –N=C– and C=O, the carbon atoms of 1,2,4-triazole and 1,3,4-oxadiazole, and –S–CH_2– groups. Meanwhile, the E- and Z-isomers of compounds **5b**, **5d**, **5f**, **5i** and **5k** could be obviously observed in ^{1}H NMR and ^{13}C NMR spectra. In MS spectra, the greater abundances of the $[M+H]^+$ ions reveal that the structure of the title compounds is stable.

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

Using *Xanthomonas axonopodis pv. citri* (strain 29-1, Shanghai Jiao Tong University, China) and *Xanthomonas*

Table 1 Physical properties and analytical data of compounds **4a**–**4d** and **5a**–**5k**

Compound	Formula	Yield (%)	Appearance	M.P. (°C)	*Mr.*	*Wi* (calc.)/%		
						Wi (found)/%		
						C	H	N
4a	$C_{15}H_{17}N_3O_5S$	65	White solid	126–127	351.09	51.27	4.88	11.96
						51.63	4.74	12.01
4b	$C_{16}H_{19}N_3O_6S$	58	White solid	106–107	381.10	50.39	5.02	11.02
						50.17	4.98	10.84
4c	$C_{15}H_{17}N_3O_5S$	62	White solid	59–60	351.09	51.27	4.88	11.96
						50.97	5.09	11.77
4d	$C_{15}H_{14}F_3N_3O_4S$	75	White solid	54–55	389.07	46.27	3.62	10.79
						46.44	3.74	10.83
5a	$C_{13}H_{15}N_5O_2S$	48	White solid	155–156	305.09	51.13	4.95	22.94
						51.48	4.84	22.50
5b	$C_{14}H_{17}N_5O_2S$	54	White solid	162–163	319.11	52.65	5.37	21.93
						53.09	5.38	22.04
5c	$C_{13}H_{14}FN_5O_2S$	52	White solid	166–167	323.09	48.29	4.36	21.66
						48.58	4.64	21.72
5d	$C_{14}H_{16}FN_5O_2S$	45	White solid	150–151	337.10	49.84	4.78	27.76
						49.76	4.94	27.63
5e	$C_{13}H_{14}ClN_5O_2S$	55	White solid	132–133	339.06	45.95	4.15	20.61
						46.02	4.23	20.43
5f	$C_{14}H_{16}ClN_5O_2S$	43	White solid	138–139	353.07	47.52	4.56	19.79
						47.54	4.82	19.83
5 g	$C_{14}H_{17}N_5O_3S$	50	White solid	150–151	335.11	50.14	5.11	22.88
						50.31	5.06	21.61
5h	$C_{14}H_{14}F_3N_5O_2S$	47	White solid	266–267	373.08	45.04	3.78	18.76
						44.97	3.76	18.83
5i	$C_{15}H_{16}F_3N_5O_2S$	47	White solid	271–272	387.10	46.51	4.16	18.08
						46.28	4.32	17.96
5j	$C_{13}H_{14}N_6O_4S$	44	White solid	269–270	350.08	44.57	4.03	23.99
						44.61	3.99	24.07
5k	$C_{14}H_{16}N_6O_4S$	49	Yellow solid	271–272	364.10	46.15	4.43	23.06
						46.23	4.51	22.87

oryzae pv. oryzae (strain PXO99A, Nangjing Agricultural University, China) as the tested bacterial strains, the antibacterial activities of title compounds have been evaluated by the turbidimeter test (Yan et al. 2016; Wang et al. 2013; Xu et al. 2012), and the commercial agents *bismerthiazol* were tested as the control. Some compounds with good antibacterial activity against Xoo were tested at five double-declining concentrations (100, 50, 25, 12.5 and 6.25 μg/mL) to obtain the corresponding EC_{50} values. The EC_{50} values of **4a**, **5a**, **5b**, **5c**, **5d**, **5h** and **5i** were calculated and summarized in Table 4.

The bioassays result in Table 3 indicated that most of the target compounds exhibited important antibacterial activities against Xoo and Xac at 20 and 100 μg/mL. Among the target compounds, the inhibitory rates of compounds **4a**, **5c**, **5i**, **5j** and **5k** against Xac at 200 μg/mL were 99.0, 94.4, 100.0, 100.0 and 94.9%, respectively, which were better than that of the *bismerthiazol* (93.4%). Meanwhile, all target compounds exhibited remarkable antibacterial activities against Xoo at 200 μg/mL, with the inhibitory rates ranging from 76.9 to 100.0%, which are superior to that of *bismerthiazol* (72.3%). In addition, the compounds **4a**, **5c** and **5j** were found to exhibit comparable inhibitory rates against Xac at 100 μg/mL (71.2, 75.7 and 79.9%, respectively) with *bismerthiazol* (69.5%), and the inhibitory rates of compounds **4b**, **5a**, **5b**, **5c**, **5d**, **5f**, **5h**, **5i**

Table 2 Spectral data of compounds **4a**–**4d** and **5a**–**5k**

Compound	Spectral data
4a	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.54 (dd, J = 8.4, 2.0 Hz, 1H, Ph-H), 7.44 (d, J = 2.0 Hz, 1H, Ph-H), 7.16 (d, J = 8.5 Hz, 1H, Ph-H), 4.42 (s, 2H, SCH_2), 3.85 (s, 6H, OCH_3), 1.97 (s, 3H, CH_3), 1.95 (s, 3H, CH_3);
	^{13}C NMR (125 MHz, DMSO-d_6) δ 165.89 (s, C=O), 165.60 (s, Oxadiazole-C), 165.38 (s, C=N), 162.15 (s, Oxadiazole-C), 151.95 (s, Ph-C), 149.11 (s, Ph-C), 120.04 (s, Ph-C), 115.13 (s, Ph-C), 112.04 (s, Ph-C), 109.03 (s, Ph-C), 55.77 (s, OCH_3), 55.70 (s, OCH_3), 33.04 (s, SCH_2), 21.25 (s, CH_3), 16.67 (s, CH_3);
	MS (ESI, *m/z*): 352.1 $[M+H]^+$, 374.1 $[M+Na]^+$, 390.0 $[M+K]^+$
4b	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.23 (s, 2H, Ph-H), 4.44 (s, 2H, SCH_2), 3.87 (s, 6H, OCH_3), 3.75 (s, 3H, OCH_3), 1.97 (s, 3H, CH_3), 1.95 (s, 3H, CH_3);
	^{13}C NMR (125 MHz, DMSO-d_6) δ 165.95 (s, C=O), 165.56 (s, Oxadiazole-C), 165.27 (s, C=N), 162.76 (s, Oxadiazole-C), 153.50 (s, Ph-C), 140.59 (s, Ph-C), 118.07 (s, Ph-C), 103.82 (s, Ph-C), 60.27 (s, OCH_3), 56.19 (s, OCH_3), 33.06 (s, SCH_2), 21.25 (s, CH_3), 16.68 (s, CH_3);
	MS (ESI, *m/z*): 382.0 $[M+H]^+$, 404.1 $[M+Na]^+$, 420.0 $[M+K]^+$
4c	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.02–6.96 (m, 2H, Ph-H), 6.91–6.85 (m, 2H, Ph-H), 5.31 (s, 2H, OCH_2), 4.38 (s, 2H, SCH_2), 3.70 (s, 3H, OCH_3), 1.97 (s, 3H, CH_3), 1.92 (s, 3H, CH_3);
	^{13}C NMR (125 MHz, DMSO-d_6) δ 165.83 (s, C=O), 165.39 (s, C=N), 164.09 (s, Oxadiazole-C), 164.01 (s, Oxadiazole-C), 154.27 (s, Ph-C), 151.14 (s, Ph-C), 116.13 (s, Ph-C), 114.68 (s, Ph-C), 60.06 (s, OCH_2), 55.38 (s, OCH_3), 33.00 (s, SCH_2), 21.25 (s, CH_3), 16.65 (s, CH_3);
	MS (ESI, *m/z*): 352.2 $[M+H]^+$, 374.1 $[M+Na]^+$, 390.1 $[M+K]^+$
4d	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.71 (d, J = 8.7 Hz, 2H, Ph-H), 7.26 (d, J = 8.6 Hz, 2H, Ph-H), 5.52 (s, 2H, OCH_2), 4.39 (s, 2H, SCH_2), 1.97 (s, 3H, CH_3), 1.92 (s, 3H, CH_3);
	^{19}F NMR (471 MHz, DMSO-d_6) δ -59.85 (s, 3F, CF_3);
	^{13}C NMR (125 MHz, DMSO-d_6) δ 165.84 (s, C=O), 165.39 (s, C=N), 164.26 (s, Oxadiazole-C), 163.47 (s, Ph-C), 160.03 (s, Oxadiazole-C), 127.19 (s, J = 3.8 Hz, Ph-C), 122.83 (s, CF_3), 122.50 (s, Ph-C), 115.43 (s, Ph-C), 59.55 (s, OCH_3), 33.04 (s, SCH_2), 21.25 (s, CH_3), 16.65 (s, CH_3);
	MS (ESI, *m/z*): 412.0 $[M+Na]^+$, 428.1 $[M+K]^+$
5a	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99–7.94 (m, 2H, Ph-H), 7.55–7.49 (m, 3H, Ph-H), 6.23 (s, 2H, NH_2), 4.24 (s, 2H, SCH_2), 1.97 (s, 3H, CH_3), 1.96 (s, 3H, CH_3);
	^{13}C NMR (125 MHz, DMSO-d_6) δ 166.31 (s, C=O), 165.43 (s, C=N), 154.28 (s, Triazole-C), 152.90 (s, Triazole-C), 129.73 (s, Ph-C), 128.57 (s, Ph-C), 127.71 (s, Ph-C), 126.75 (s, Ph-C), 31.96 (s, SCH_2), 21.27 (s, CH_3), 16.68 (s, CH_3);
	MS (ESI, *m/z*): 306.1 $[M+H]^+$, 328.1 $[M+Na]^+$, 344.0 $[M+K]^+$
5b	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.00–7.94 (m, 2H, Ph-H), 7.56–7.50 (m, 3H, Ph-H), 6.23 (s, 2H, NH_2), 4.24 and 4.23 (s, 2H, SCH_2, E-isomer + Z-isomer), 2.36 and 2.31 (q, J = 7.5 Hz, 2H, CH_2, E-isomer + Z-isomer), 1.96 and 1.94 (s, 3H, CH_3, E-isomer + Z-isomer), 1.07 and 1.01 (t, J = 7.6 Hz, 3H, CH_3CH_2, E-isomer + Z-isomer);
	^{13}C NMR (125 MHz, DMSO-d_6) δ 169.53 and 168.75 (s, C=N, E-isomer + Z-isomer), 166.39 and 166.29 (s, C=O, E-isomer + Z-isomer), 154.27 (s, Triazole-C), 152.90 (s, Triazole-C), 129.72 (s, Ph-C), 128.56 (s, Ph-C), 127.71 (s, Ph-C), 126.74 (s, Ph-C), 32.01 and 31.91 (s, SCH_2, E-isomer + Z-isomer), 28.48 and 23.33 (s, CH_2, E-isomer + Z-isomer), 18.90 and 15.05 (s, CH_3, E-isomer + Z-isomer), 10.33 and 9.85 (s, CH_3, E-isomer + Z-isomer);
	MS (ESI, *m/z*): 320.1 $[M+H]^+$, 342.1 $[M+Na]^+$, 358.1 $[M+K]^+$
5c	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.05–7.99 (m, 2H, Ph-H), 7.41–7.35 (m, 2H, Ph-H), 6.23 (s, 2H, NH_2), 4.23 (s, 2H, SCH_2), 1.97 (s, 3H, CH_3), 1.95 (s, 3H, CH_3);
	^{19}F NMR (471 MHz, DMSO-d_6) δ −110.98;
	^{13}C NMR (125 MHz, DMSO-d_6) δ 166.29 (s, C=O), 165.43 (s, C=N), 162.90 (s, J = 247.2 Hz, Ph-C), 153.52 (s, Triazole-C), 152.88 (s, Triazole-C), 130.11 (s, Ph-C), 123.31 (s, J = 3.1 Hz, Ph-C), 115.66 (s, Ph-C), 32.01 (s, SCH_2), 21.27 (s, CH_3), 16.68 (s, CH_3);
	MS (ESI, *m/z*): 324.0 $[M+H]^+$, 346.1 $[M+Na]^+$, 362.0 $[M+K]^+$
5d	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.06–7.99 (m, 2H, Ph-H), 7.41–7.35 (m, 2H, Ph-H), 6.23 (s, 2H, NH_2), 4.24 and 4.23 (s, 2H, SCH_2, E-isomer + Z-isomer), 2.36 and 2.31 (q, J = 7.5 Hz, 2H, CH_2, E-isomer + Z-isomer), 1.96 and 1.94 (s, 3H, CH_3, E-isomer + Z-isomer), 1.07 and 1.01(t, J = 7.5 Hz, 3H, CH_3, E-isomer + Z-isomer);
	^{19}F NMR (471 MHz, DMSO-d_6) δ −110.96;
	^{13}C NMR (125 MHz, DMSO-d_6) δ 169.57 and 168.79 (s, C=O, E-isomer + Z-isomer), 166.40 and 163.91 (s, C=N, E-isomer + Z-isomer), 161.94 (s, J = 247.6 Hz, Ph-C), 153.53 (s, Triazole-C), 152.91 (s, Triazole-C), 130.12 (s, Ph-C), 123.32 (s, J = 3.1 Hz, Ph-C), 115.67 (s, Ph-C), 32.08 and 31.98 (s, SCH_2, E-isomer + Z-isomer), 28.49 and 23.34 (s, CH_2, E-isomer + Z-isomer), 18.91 and 15.06 (s, CH_3, E-isomer + Z-isomer), 10.34 and 9.86 (s, CH_3, E-isomer + Z-isomer);
	MS (ESI, *m/z*): 338.1 $[M+H]^+$, 360.1 $[M+Na]^+$, 376.1 $[M+K]^+$

Table 2 continued

Compound	Spectral data
5e	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.03–7.98 (m, 2H, Ph-H), 7.64–7.58 (m, 2H, Ph-H), 6.25 (s, 2H, NH_2), 4.24 (s, 2H, SCH_2), 1.97 (s, 3H, CH_3), 1.95 (s, 3H, CH_3);
	^{13}C NMR (125 MHz, DMSO-d_6) δ 166.27 (s, C=O), 165.43 (s, C=N), 153.33 (s, Triazole-C), 153.20 (s, Triazole-C), 134.55 (s, Ph-C), 129.39 (s, Ph-C), 128.71 (s, Ph-C), 125.60 (s, Ph-C), 32.02 (s, SCH_2), 21.27 (s, CH_3), 16.68 (s, CH_3);
	MS (ESI, *m/z*): 340.0 $[M+H]^+$, 362.0 $[M+Na]^+$, 378.0 $[M+K]^+$
5f	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.01 (m, 2H, Ph-H), 7.64–7.58 (m, 2H, Ph-H), 6.25 (s, 2H, NH_2), 4.24 (s, 2H, SCH_2), 2.36 and 2.31 (q, J = 7.5 Hz, 2H, CH_2, E-isomer + Z-isomer), 1.96 and 1.94 (s, 3H, CH_3, E-isomer + Z-isomer), 1.07 and 1.00 (t, J = 7.5 Hz, 3H, CH_3, E-isomer + Z-isomer);
	^{13}C NMR (125 MHz, DMSO-d_6) δ 169.55 and 168.77 (s, C=O, E-isomer + Z-isomer), 166.36 and 166.26 (s, C=N, E-isomer + Z-isomer), 153.33 (s, Triazole-C), 153.21 (s, Triazole-C), 134.55 (s, Ph-C), 129.38 (s, Ph-C), 128.71 (s, Ph-C), 125.60 (s, Ph-C), 32.08 and 31.98 (s, SCH_2, E-isomer + Z-isomer), 28.48 and 23.33 (s, CH_2, E-isomer + Z-isomer), 18.90 and 15.05 (s, CH_3, E-isomer + Z-isomer), 10.33 and 9.85 (s, CH_3, E-isomer + Z-isomer);
	MS (ESI, *m/z*): 354.1 $[M+H]^+$, 376.1 $[M+Na]^+$, 392.0 $[M+K]^+$
5g	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.91 (d, J = 8.7 Hz, 2H, Ph-H), 7.07 (d, J = 8.7 Hz, 2H, Ph-H), 6.19 (s, 2H, NH_2), 4.22 (s, 2H, SCH_2), 3.82 (s, 3H, OCH_3), 1.97 (s, 3H, CH_3), 1.95 (s, 3H, CH_3);
	^{13}C NMR (125 MHz, DMSO-d_6) δ 166.36 (s, C=O), 165.43 (s, C=N), 160.36 (s, Ph-C), 154.15 (s, Triazole-C), 152.34 (s, Triazole-C), 129.26 (s, Ph-C), 119.14 (s, Ph-C), 114.02 (s, Ph-C), 55.34 (s, OCH_3), 32.00 (s, SCH_2), 21.30 (s, CH_3), 16.70 (s, CH_3);
	MS (ESI, *m/z*): 336.1 $[M+H]^+$, 358.1 $[M+Na]^+$, 374.0 $[M+K]^+$
5h	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.22 (d, J = 8.2 Hz, 2H, Ph-H), 7.91 (d, J = 8.4 Hz, 2H, Ph-H), 6.31 (s, 2H, NH_2), 4.26 (s, 2H, SCH_2), 1.98 (s, 3H, CH_3), 1.96 (s, 3H, CH_3);
	^{19}F NMR (471 MHz, DMSO-d_6) δ −61.15;
	^{13}C NMR (125 MHz, DMSO-d_6) δ 166.26 (s, C=O), 165.48 (s, C=N), 153.78 (s, Triazole-C), 153.11 (s, Triazole-C), 130.63 (s, Ph-C), 129.85 (s, Ph-C), 128.32 (s, Ph-C), 125.56 (s, Ph-C), 123.99 (s, CF_3), 32.02 (s, SCH_2), 21.28 (s, CH_3), 16.70 (s, CH_3);
	MS (ESI, *m/z*): 374.1 $[M+H]^+$, 396.1 $[M+Na]^+$, 412.1 $[M+K]^+$
5i	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.22 (d, J = 8.1 Hz, 2H, Ph-H), 7.91 (d, J = 8.2 Hz, 2H, Ph-H), 6.32 (s, 2H, NH_2), 4.27 and 4.26 (s, 2H, SCH_2, E-isomer + Z-isomer), 2.37 and 2.32 (q, J = 7.5 Hz, 2H, CH_2, E-isomer + Z-isomer), 1.97 and 1.95 (s, 3H, CH_3, E-isomer + Z-isomer), 1.07 and 1.01 (t, J = 7.6 Hz, 3H, CH_3, E-isomer + Z-isomer);
	^{19}F NMR (471 MHz, DMSO-d_6) δ −61.16;
	^{13}C NMR (125 MHz, DMSO-d_6) δ 169.52 and 168.76 (s, C=O, E-isomer + Z-isomer), 166.29 and 166.19 (s, C=N, E-isomer + Z-isomer), 153.64 (s, Triazole-C), 153.05 (s, Triazole-C), 130.61 (s, Ph-C), 128.27 (s, Ph-C), 125.52 (s, Ph-C), 124.01 (s, CF_3), 119.42 (s, Ph-C), 32.12 and 32.01 (s, SCH_2, E-isomer + Z-isomer), 28.42 and 23.28 (s, CH_2, E-isomer + Z-isomer), 18.83 and 14.98 (s, CH_3, E-isomer + Z-isomer), 10.26 and 9.78 (s, CH_3, E-isomer + Z-isomer);
	MS (ESI, *m/z*): 388.1 $[M+H]^+$, 410.1 $[M+Na]^+$, 426.1 $[M+K]^+$
5j	^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.41–8.35 (m, 2H, Ph-H), 8.34–8.29 (m, 2H, Ph-H), 6.36 (s, 2H, NH_2), 4.28 (s, 2H, SCH_2), 1.98 (s, 3H, CH_3), 1.96 (s, 3H, CH_3);
	^{13}C NMR (125 MHz, DMSO-d_6) δ 166.21 (s, C=O), 165.48 (s, C=N), 154.29 (s, Triazole-C), 152.59 (s, Triazole-C), 147.83 (s, Ph-C), 132.72 (s, Ph-C), 128.57 (s, Ph-C), 123.82 (s, Ph-C), 32.08 (s, SCH_2), 21.27 (s, CH_3), 16.69 (s, CH_3);
	MS (ESI, *m/z*): 351.0 $[M+H]^+$, 373.1 $[M+Na]^+$, 389.1 $[M+K]^+$
5k	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.40–8.35 (m, 2H, Ph-H), 8.34–8.29 (m, 2H, Ph-H), 6.37 (s, 2H, NH_2), 4.28 (s, 2H, SCH_2), 2.37 and 2.32 (q, J = 7.5 Hz, 2H, CH_2, E-isomer + Z-isomer), 1.97 and 1.95 (s, 3H, CH_3, E-isomer + Z-isomer), 1.07 and 1.01 (t, J = 7.7 Hz, 3H, CH_3, E-isomer + Z-isomer);
	^{13}C NMR (125 MHz, DMSO-d_6) δ 169.59 and 168.81 (s, C=O, E-isomer + Z-isomer), 166.31 and 166.21 (s, C=N, E-isomer + Z-isomer), 154.31 (s, Triazole-C), 152.59 (s, Triazole-C), 147.82 (s, Ph-C), 132.73 (s, Ph-C), 128.57 (s, Ph-C), 123.82 (s, Ph-C), 32.14 and 32.03 (s, SCH_2, E-isomer + Z-isomer), 28.49 and 23.34 (s, CH_2, E-isomer + Z-isomer), 18.91 and 15.06 (s, CH_3, E-isomer + Z-isomer), 10.34 and 9.86 (s, CH_3, E-isomer + Z-isomer);
	MS (ESI, *m/z*): 365.1 $[M+H]^+$, 387.1 $[M+Na]^+$, 403.1 $[M+K]^+$

and **5k** against Xoo at 100 μg/mL ranged from 59.1 to 100.0%, which are better than that of *bismerthiazol* (57.9%). Table 4 indicates that the compounds **4a**, **5a**, **5b**, **5c**, **5d**, **5h** and **5i** had the EC_{50} values reached 15.15–49.34 μg/mL, which were superior to that of *bismerthiazol* (92.61 μg/mL).

Structure–activity relationship analysis of antibacterial activities

As indicated in Tables 3 and 4, most of the title compounds showed good antibacterial activities against Xac and Xoo. Results in Tables 3 and 4 indicates also that most of the

Table 3 Antibacterial activities of the title compounds **4a–4d** and **5a–5k**

Compound	Inhibition rate (%)[a]			
	Xac		Xoo	
	200 μg/mL	100 μg/mL	200 μg/mL	100 μg/mL
4a	99.0 ± 4.3	71.2 ± 3.7	89.8 ± 4.6	49.8 ± 5.5
4b	73.5 ± 4.2	31.8 ± 2.7	96.9 ± 5.2	77.1 ± 4.6
4c	72.5 ± 0.9	59.4 ± 7.9	79.6 ± 1.2	40.8 ± 4.9
4d	66.1 ± 7.9	45.0 ± 9.9	82.6 ± 7.4	48.7 ± 1.1
5a	80.1 ± 0.4	56.6 ± 3.3	100.0 ± 1.0	100.0 ± 1.2
5b	86.9 ± 5.3	62.3 ± 2.7	100.0 ± 0.6	100.0 ± 0.8
5c	94.4 ± 7.7	75.7 ± 0.4	100.0 ± 1.2	100.0 ± 1.5
5d	91.3 ± 0.9	69.5 ± 5.8	100.0 ± 0.6	94.9 ± 7.3
5e	72.3 ± 1.9	37.5 ± 4.2	76.9 ± 6.1	46.8 ± 2.5
5f	75.5 ± 4.8	53.2 ± 4.7	85.8 ± 8.0	59.4 ± 9.6
5 g	90.1 ± 1.1	40.9 ± 9.1	93.9 ± 4.4	46.4 ± 1.7
5h	84.2 ± 6.1	55.0 ± 1.6	100.0 ± 0.8	100.0 ± 0.5
5i	100.0 ± 1.8	62.1 ± 2.9	100.0 ± 1.1	100.0 ± 1.2
5j	100.0 ± 1.4	79.9 ± 3.4	100.0 ± 1.4	51.5 ± 8.0
5k	94.9 ± 7.5	68.2 ± 2.6	100.0 ± 0.7	59.1 ± 1.0
Bismerthiazol[a]	93.4 ± 4.3	69.5 ± 1.6	72.3 ± 4.3	57.9 ± 6.1

[a] Average of three replicates

[b] The commercial antibacterial agents *bismerthiazol* were used as positive control

Table 4 Inhibitory effect of compounds **4a**, **5a–5d**, **5h** and **5i** against Xoo in vitro

Compound	R_1	R_2	Toxic regression equitation	r	EC_{50} (μg/mL)
4b	CH_3	3,4,5-tri-OCH_3Ph	$y = 1.8222x + 1.9147$	0.9499	49.34
5a	CH_3	Ph	$y = 2.5484x + 1.8975$	0.9549	16.50
5b	CH_2CH_3	Ph	$y = 2.8224x + 1.3153$	0.9550	20.24
5c	CH_3	4-FPh	$y = 2.3106x + 2.2723$	0.9114	15.15
5d	CH_2CH_3	4-FPh	$y = 2.1817x + 1.9563$	0.9318	24.84
5h	CH_3	4-CF_3Ph	$y = 2.5563x + 1.7917$	0.9249	17.99
5i	CH_2CH_3	4-CF_3Ph	$y = 2.4156x + 2.0223$	0.9042	17.09
Bismerthiazol[a]	–	–	$y = 1.4990x + 2.0520$	0.9800	92.61

Average of three replicates

[a] The commercial antibacterial agents *bismerthiazol* was used as positive control

compounds with the same substituted groups showed better antibacterial activities against Xoo than Xac. As examples of this presentation, the compounds **4b**, **5a**, **5b**, **5c**, **5d**, **5h** and **5i** exhibited fine antibacterial activities against Xoo at 100 μg/mL, with the inhibitory rates of 77.1, 100.0, 100.0, 100.0, 94.9, 100.0 and 100.0%, respectively, which are better than those against Xac at 100 μg/mL (31.8, 56.6, 62.3, 75.7, 69.5, 55.0 and 62.1%, respectively). In addition, the presence of 1,2,4-triazole fragments improved the antibacterial activities of the title compounds. For example, the 1,2,4-triazole derivatives **5a**, **5b**, **5c**, **5d**, **5h** and **5i** exhibited remarkable antibacterial activity against Xoo, with the EC_{50} values of 16.50, 20.24, 15.15, 24.84, 17.99 and 17.09 μg/mL, which were superior to that of the 1,3,4-oxadiazole compound **4b** (49.34 μg/mL). Furthermore, when R_2 was substituted with Ph, 4-FPh and 4-CF_3Ph group, the corresponding compounds **5a, 5b, 5c, 5d, 5h** and **5i** showed remarkable antibacterial activity against Xoo, with the EC_{50} values ranging from 15.15 to 24.84 μg/mL, which were superior to that of *bismerthiazol* (92.61 μg/mL).

Conclusions

In summary, aiming to discover novel compounds with potent antibacterial activity against Xac and Xoo, we have synthesized a series of oxime ester derivatives containing

1,2,4-triazole or 1,3,4-oxadiazole moiety. Biological testing data showed that all the title compounds exhibited potent antibacterial activity against Xac and Xoo. In particular, the compounds **4a**, **5a**, **5b**, **5c**, **5d**, **5h** and **5i** exhibited remarkable antibacterial activity against Xoo, with EC_{50} values ranging from 15.15 to 49.34 μg/mL, which were superior to that of *Bismerthiazol* (92.61 μg/mL). Further study on the antibacterial mechanism is currently underway.

Acknowledgements The authors gratefully acknowledge the National Nature Science Foundation of China (No. 21462012), the Special Fund for Outstanding Scientific and Technological Candidates of Guizhou Province (No. 201535) and the Innovation Fund for Graduate Student of Guizhou University (No. 2016076).

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