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European Journal of Medicinal Chemistry 44 (2009) 1779–1787

EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY

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Short communication

Synthesis, characterization and structure–activity relationship analysis of novel depsides as potential antibacterials

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Received 29 January 2008; received in revised form 10 April 2008; accepted 15 April 2008
Available online 4 May 2008

Abstract

Twenty-six depsides were synthesized to screen for their antibacterial activity. All of them were reported for the first time. Their chemical structures were clearly determined by ^{1}H NMR, ^{13}C NMR, ESI mass spectra and elemental analyses, coupled with one selected single-crystal structure. All the compounds were assayed for antibacterial activities against three Gram-positive bacterial strains (*Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 6538 and *Streptococcus faecalis* ATCC 9790) and three Gram-negative bacterial strains (*Escherichia coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 13525 and *Enterobacter cloacae* ATCC 13047) by MTT method. Compound 2-(2-methoxy-2-oxoethyl)-phenyl 3-nitrobenzoate (**C10**) and 2-(2-ethoxy-2-oxoethyl)phenyl 3-nitrobenzoate (**C23**) showed powerful antibacterial activities against *B. subtilis* with MIC of 0.78 μg/mL while compound 2-(2-methoxy-2-oxoethyl)phenyl 2-(3,4-diethoxyphenyl)acetate (**C8**) and 2-(2-ethoxy-2-oxoethyl)phenyl 2-(3,4-diethoxyphenyl)acetate (**C21**) exhibited significant antibacterial activities against *E. coli* with MIC of 1.562 μg/mL, which were superior to the positive controls penicillin G and kanamycin B, respectively. On the basis of the biological results, structure–activity relationships were discussed.

Keywords: Depside; Antibacterial; Structure–activity relationship

1. Introduction

Depsides, in the strict sense, are compounds comprised of two or more aromatic rings bound by a phenolic oxygen-ester linkage. They are most often found in lichens, but have also been isolated from higher plants, including species of the Ericaceae, Lamiaceae, and Papaveraceae [1,2]. Some depsides isolated from lichens have been reported to have activity against mycobacteria, Gram-positive bacteria, insects, and nematodes. In addition, several well-characterized depsides exhibit antiproliferative, analgesic, antipyretic, anticancer, anti-HIV-1 integrase and antiviral properties [3–11]. As inhibitors of prostaglandin biosynthesis and leukotriene B4 biosynthesis, depsides are potent nonsteroidal anti-inflammatories [12]. Furthermore, it is reported that members of the macrocyclic salicylate family (a, Fig. 1) [13] are potent inhibitors of the mammalian vacuolar ATPase with a potential novel mode-of-action [14], whereas resorcinylic macrolides (b, Fig. 1) such as radicicol [15] inhibit the molecular chaperone Hsp90 [16]. Recently, a new depside, named jaboticabin (Fig. 1), was demonstrated to inhibit chemokine interleukin (IL)-8 production before and after cigarette smoke treatment of cells [17].

However, few attentions have focused on the antibacterial activity of depsides up to now, especially Gram-negative bacteria. In view of that, we have designed two series of novel depside derivatives which are structurally similar to jaboticabin (Fig. 1), and evaluated their antibacterial activities against three Gram-positive bacterial strains (*Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 6538 and *Streptococcus faecalis* ATCC 9790) and three Gram-negative bacterial strains

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doi:10.1016/j.ejmech.2008.04.019

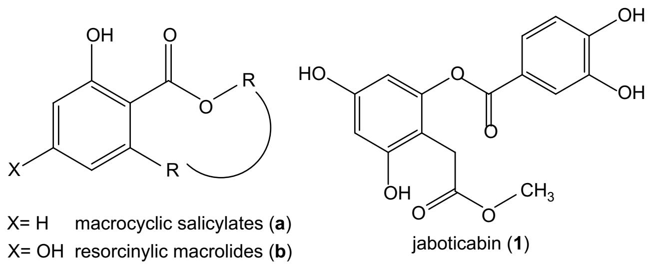


Fig. 1.

(*Escherichia coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 13525 and *Enterobacter cloacae* ATCC 13047) by MTT method. Fortunately, we found that most compounds showed potent antibacterial activity against the six bacterial strains. Most importantly, compounds **C10** and **C23** showed powerful antibacterial activities against *B. subtilis* ATCC 6633 with MIC of 0.78 μg/mL while compounds **C8** and **C21** exhibited significant antibacterial activities against *E. coli* ATCC 35218 with MIC of 1.562 μg/mL, which were superior to the positive controls penicillin G and kanamycin B, respectively (Table 1).

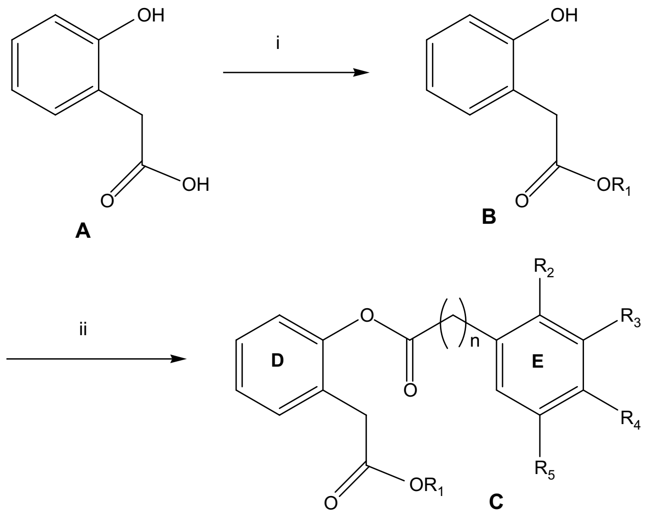
2. Results and discussion

2.1. Chemistry

Twenty-six depsides were synthesized to screen for the antibacterial activity. All of them were reported for the first time. The synthesis of compounds **C1–C26** followed the general pathway outlined in Scheme 1. They are prepared in two steps. Firstly, a solution of 2-hydroxyphenylacetic acid (compound **A**) in methanol or ethanol containing concentrated H_2SO_4 was refluxed overnight [18]. This step can yield the corresponding ester. Secondly, the coupling reaction between the obtained esters and the different substituted phenylacetic acid or benzoic acid was performed through 'step ii' by using *N*,*N*-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in anhydrous CH_2Cl_2 [19]. Then, compounds **C1–C26** were obtained by subsequent purification

Table 1
MICs (minimum inhibitory concentrations) (μg/mL) of the synthetic compounds

Compounds	Microorganisms					
	Gram-positive			Gram-negative		
	B. subtilis ATCC 6633	*S. aureus* ATCC 6538	*S. faecalis* ATCC 9790	*P. aeruginosa* ATCC 13525	*E. coli* ATCC 35218	*E. cloacae* ATCC 13047
Methyl paraben	6.25	6.25	12.5	6.25	6.25	25
B1	12.5	6.25	12.5	25	12.5	6.25
B2	6.25	12.5	25	12.5	25	12.5
C1	6.25	12.5	12.5	25	25	6.25
C2	12.5	3.125	25	>50	6.25	12.5
C3	6.25	6.25	6.25	25	>50	3.125
C4	3.125	3.125	12.5	12.5	>50	25
C5	1.562	>50	25	25	6.25	>50
C6	>50	25	>50	6.25	>50	>50
C7	25	>50	>50	6.25	>50	6.25
C8	>50	1.562	3.125	3.125	1.562	3.125
C9	12.5	25	>50	12.5	3.125	6.25
C10	0.78	1.562	1.562	6.25	3.125	12.5
C11	>50	3.125	25	>50	25	>50
C12	25	>50	12.5	25	>50	25
C13	>50	>50	>50	6.25	25	>50
C14	12.5	25	6.25	>50	25	12.5
C15	6.25	6.25	12.5	25	>50	6.25
C16	12.5	12.5	>50	25	>50	3.125
C17	3.125	6.25	6.25	>50	6.25	25
C18	1.562	>50	>50	25	6.25	>50
C19	>50	>50	12.5	6.25	25	>50
C20	12.5	25	>50	12.5	>50	6.25
C21	12.5	3.125	1.562	3.125	1.562	3.125
C22	25	>50	>50	12.5	3.125	6.25
C23	0.78	3.125	1.562	6.25	3.125	6.25
C24	>50	6.25	>50	25	6.25	>50
C25	25	>50	25	>50	>50	>50
C26	>50	>50	25	6.25	>50	25
Penicillin G	1.562	1.562	1.562	6.25	6.25	3.125
Kanamycin B	0.39	1.562	3.125	3.125	3.125	1.562
Tetracycline	1.562	1.562	0.78	1.562	6.25	1.562
Vancomycin hydrochloride	0.39	0.78	1.562	>50	>50	>50



C1 $R_1 = CH_3$ $R_2 = H$ $R_3 = H$ $R_4 = F$ $R_5 = H$ n=1
C2 $R_1 = CH_3$ $R_2 = H$ $R_3 = H$ $R_4 = Cl$ $R_5 = H$ n=1
C3 $R_1 = CH_3$ $R_2 = H$ $R_3 = H$ $R_4 = Br$ $R_5 = H$ n=1
C4 $R_1 = CH_3$ $R_2 = H$ $R_3 = Cl$ $R_4 = H$ $R_5 = H$ n=1
C5 $R_1 = CH_3$ $R_2 = H$ $R_3 = Br$ $R_4 = H$ $R_5 = H$ n=1
C6 $R_1 = CH_3$ $R_2 = H$ $R_3 = OCH_3$ $R_4 = H$ $R_5 = H$ n=1
C7 $R_1 = CH_3$ $R_2 = H$ $R_3 = OCH_3$ $R_4 = OCH_3$ $R_5 = H$ n=1
C8 $R_1 = CH_3$ $R_2 = H$ $R_3 = OCH_2CH_3$ $R_4 = OCH_2CH_3$ $R_5 = H$ n=1
C9 $R_1 = CH_3$ $R_2 = H$ $R_3 = H$ $R_4 = CH_3$ $R_5 = H$ n=0
C10 $R_1 = CH_3$ $R_2 = H$ $R_3 = NO_2$ $R_4 = H$ $R_5 = H$ n=0
C11 $R_1 = CH_3$ $R_2 = Cl$ $R_3 = H$ $R_4 = H$ $R_5 = H$ n=0
C12 $R_1 = CH_3$ $R_2 = H$ $R_3 = H$ $R_4 = Cl$ $R_5 = H$ n=0
C13 $R_1 = CH_3$ $R_2 = H$ $R_3 = OCH_3$ $R_4 = H$ $R_5 = OCH_3$ n=0
C14 $R_1 = CH_2CH_3$ $R_2 = H$ $R_3 = H$ $R_4 = F$ $R_5 = H$ n=1
C15 $R_1 = CH_2CH_3$ $R_2 = H$ $R_3 = H$ $R_4 = Cl$ $R_5 = H$ n=1
C16 $R_1 = CH_2CH_3$ $R_2 = H$ $R_3 = H$ $R_4 = Br$ $R_5 = H$ n=1
C17 $R_1 = CH_2CH_3$ $R_2 = H$ $R_3 = Cl$ $R_4 = H$ $R_5 = H$ n=1
C18 $R_1 = CH_2CH_3$ $R_2 = H$ $R_3 = Br$ $R_4 = H$ $R_5 = H$ n=1
C19 $R_1 = CH_2CH_3$ $R_2 = H$ $R_3 = OCH_3$ $R_4 = H$ $R_5 = H$ n=1
C20 $R_1 = CH_2CH_3$ $R_2 = H$ $R_3 = OCH_3$ $R_4 = OCH_3$ $R_5 = H$ n=1
C21 $R_1 = CH_2CH_3$ $R_2 = H$ $R_3 = OCH_2CH_3$ $R_4 = OCH_2CH_3$ $R_5 = H$ n=1
C22 $R_1 = CH_2CH_3$ $R_2 = H$ $R_3 = H$ $R_4 = CH_3$ $R_5 = H$ n=0
C23 $R_1 = CH_2CH_3$ $R_2 = H$ $R_3 = NO_2$ $R_4 = H$ $R_5 = H$ n=0
C24 $R_1 = CH_2CH_3$ $R_2 = Cl$ $R_3 = H$ $R_4 = H$ $R_5 = H$ n=0
C25 $R_1 = CH_2CH_3$ $R_2 = H$ $R_3 = H$ $R_4 = Cl$ $R_5 = H$ n=0
C26 $R_1 = CH_2CH_3$ $R_2 = H$ $R_3 = OCH_3$ $R_4 = H$ $R_5 = OCH_3$ n=0

Scheme 1. (i) CH_3OH or CH_3CH_2OH, H_2SO_4, reflux. (ii) DCC, DMAP, CH_2Cl_2, reflux.

with flash chromatography. All of the synthetic compounds gave satisfactory analytical and spectroscopic data, which were in full accordance with their depicted structures.

2.2. Crystal structure of compound **C13**

Among these compounds, a crystal structure of compound **C13** was determined by X-ray diffraction analysis. Fig. 2 represents the crystal structures of this compound with thermal ellipsoids at 30% probability. It crystallizes in the triclinic, space group $P\bar{1}$ with the following unit cell parameters: $a = 8.721(2)$ Å, $b = 9.892(2)$ Å, $c = 10.006(2)$ Å, $\alpha = 98.07(3)°$, $\beta = 97.57(3)°$, $\gamma = 98.15(3)°$, $V = 836.3(3)$ Å^3, $Z = 2$. The crystallographic data are presented in Table 2, and selected bond lengths/angles and torsion angles are given in Table 3. The bond lengths and angles are all in normal values. The packing diagram in Fig. 3 shows the stacking pattern of compound

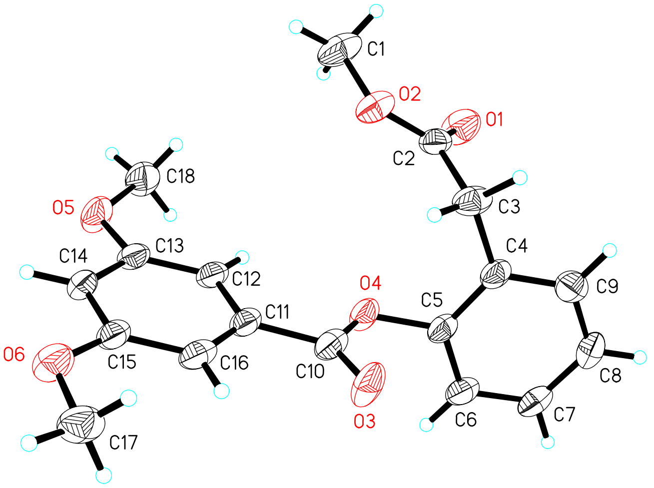


Fig. 2. Molecular structure of compound **C13**. Displacement ellipsoids are drawn at the 30% probability level.

C13, viewed along the *a* axis. The structure is stabilized by intermolecular hydrogen bonds of the types C—H···O and not stabilized by π–π interactions because the distance between two parallel benzene rings is too long (4.701 Å). The intermolecular hydrogen bonds are listed in Table 4. When the angle of C—H···O is comparable to that of O—H···O, the former hydrogen bond is much weaker [20,21]. We also found that methyl hydrogen bond is weaker than aryl hydrogen bond, which is supported by the following discovery: C(14)—H(14A)···O(5)#2 has

Table 2
Crystal structure data for compound **C13**

Compound	**C13**
Formula	$C_{18}H_{18}O_6$
M_r	330.32
Crystal size/mm^3	0.40 × 0.30 × 0.20
Crystal system	Triclinic
Space group	$P\bar{1}$
a/Å	8.7210(17)
b/Å	9.898(2)
c/Å	10.006(2)
α/°	98.07(3)
β/°	97.57(3)
γ/°	98.15(3)
V/Å^3	836.3(3)
Z	2
D_c/ (g/cm^{-3})	1.312
μ/mm^{-1}	0.099
$F(000)$	348
Max. and min. trans.	0.9805 and 0.9615
θ range/°	2.08/25.18
Index range (h, k, l)	−10/10, −11/11, 0/11
Reflections collected/unique	3213/2999
Data/restraints/parameters	2999/0/217
R_{int}	0.0487
Goodness-of-fit on F^2	1.152
R_1,[a] wR_2[b] [$I > 2\sigma(I)$]	0.078/0.219
R_1,[a] wR_2[b]	0.116/0.277
Extinction coefficient	0.099
$(\Delta\rho)_{max}$, $(\Delta\rho)_{min}$ (e/Å^3)	0.270/−0.328

[a] $R = \sum|F_o| - |F_c|/\sum|F_o|$.
[b] $wR = [\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2}$.

Table 3
Selected bond lengths (Å) and torsion angles (°) of compound **C13**

Compound	**C13**
Bond lengths (Å)	
C1–O2	1.437(5)
O1–C2	1.215(5)
O2–C2	1.301(5)
O4–C10	1.344(5)
C10–C11	1.482(5)
O5–C13	1.365(4)
O5–C18	1.425(5)
Bond angles (°)	
O2–C1–H1A	109.5
O1–C2–O2	124.6(4)
C4–C3–H3B	108.8
C15–O6–C17	117.2(3)
O3–C10–C11	125.0(4)
Torsion angles (°)	
C1–O2–C2–C3	177.5(4)
C2–C3–C4–C5	−79.3(5)
C3–C4–C5–C6	−179.6(3)
O4–C5–C6–C7	176.1(3)
C5–O4–C10–O3	−0.7(6)

length 3.343(5) Å and an angle of 144.2°, while C(1)–H(1B)··· O(1)#3 has length 3.436(6) Å and an angle of 148.1°. This may be caused by the sp^2 carbon atom having higher electronegativity than sp^3 carbon atom. In fact, the higher the electronegativity of the atom is, the higher the positive electrical property the hydrogen atom bonded with parent atom has. This results in more powerful hydrogen bond. In the crystal structure of **C13**, there are two benzene rings in the molecule. C(4), C(5), C(6), C(7), C(8) and C(9) forms the first plane with the mean deviation of 0.0032 Å, defined as plane I; Similarly, C(11), C(12), C(13), C(14), C(15) and C(16) forms the second plane with the mean deviation of 0.0041 Å, defined as plane II. The dihedral angle between plane I and plane II is 84.8 (5)°. In addition, the ester group (C(10), C(11), O(3) and O(4)) forms the third plane, defined as plane III. The dihedral angle between plane II and plane III is 2.897(144)°, which suggests that they are nearly co-planar. This indicated that there is a π–π conjugation between the C(=O) group and the benzene ring of plane II. A comparision with over 100 other crystal structures showing the depside motif indicates that the majority has planes II and III co-planar (Cambridge Structural Database). Because of the steric repulsion of the bulky *ortho* substituent, plane I is out of the molecular plane (the plane consisted of plane II and plane III). The same database also shows that this is the first case where the *ortho* substituent is a carboxyethyl group. The X-ray data have been deposited at the Cambridge Crystallographic Data Centre, and the CCDC number is 683433.

2.3. Antibacterial activity

All the compounds prepared were evaluated for their antibacterial activities against three Gram-positive bacterial strains (*B. subtilis* ATCC 6633, *S. aureus* ATCC 6538 and *S. faecalis* ATCC 9790) and three Gram-negative bacterial strain (*E. coli* ATCC 35218, *P. aeruginosa* ATCC 13525 and *E. cloacae* ATCC 13047) activities by MTT method, and the results are shown in Table 1.

Parabens are commonly added in pharmaceutical, cosmetic and food products because of their wide antibacterial

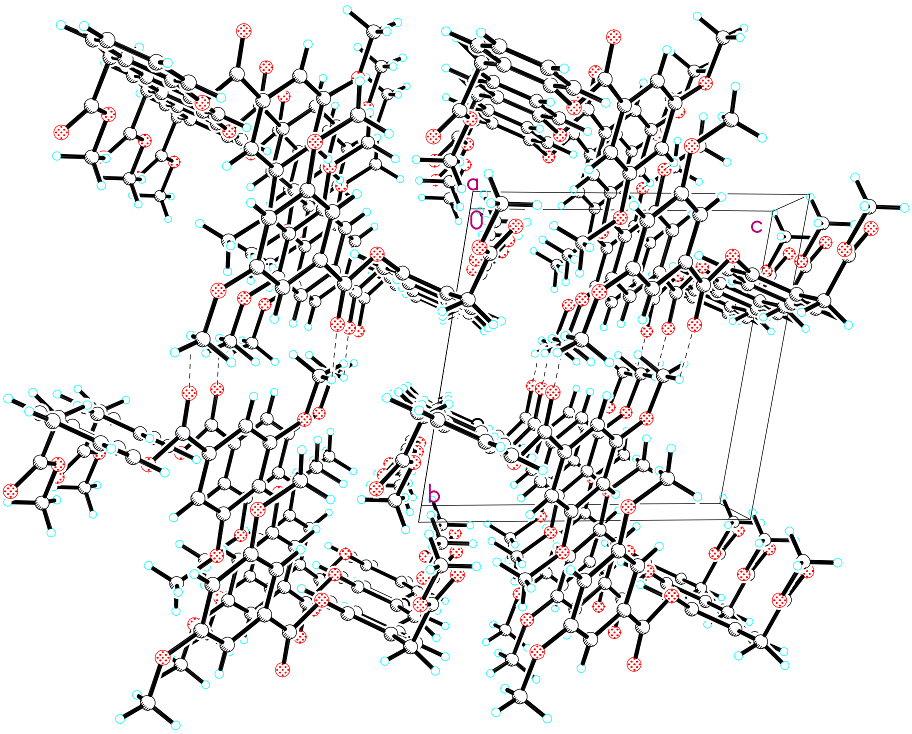


Fig. 3. Packing diagram of compound **C13**, viewed along the *a* axis, showing the intermolecular hydrogen-bonding scheme (dashed lines).

Table 4
Hydrogen-bond geometry (Å, °) in compound **C13**

D–H···A	D–H	H···A	D···A	D–H···A
C17–H(17C)···O(3) #1	0.96	2.57	3.309(6)	134.2
C14–H(14A)···O(5) #2	0.93	2.54	3.343(5)	144.2
C1–H(1B)···O(1) #3	0.96	2.58	3.436(6)	148.1

Symmetry transformations used to generate equivalent atoms: #1 $-x+1$, $-y+1$, $-z+1$; #2 $-x+2$, $-y$, $-z+1$; #3 $-x+1$, $-y$, $-z+2$.

properties, low toxicity, inertness and chemical stability [22]. Moreover, depsides have been reported to have antibacterial activity [3,4]. Enlightened by the above two factors, 2-hydroxyphenylacetic acid which has phenolic hydroxyl group in the *ortho* position was used to synthesize novel depsides with a view to find new antibacterial agents.

Methyl paraben was screened for its antibacterial activity against the six bacterial strains as a reference. As shown in Table 1, methyl paraben showed antibacterial activity with MICs of 6.25 μg/mL, 6.25 μg/mL, 12.5 μg/mL, 6.25 μg/mL, 6.25 μg/mL and 25 μg/mL against *B. subtilis* ATCC 6633, *S. aureus* ATCC 6538, *S. faecalis* ATCC 9790, *P. aeruginosa* ATCC 13525, *E. coli* ATCC 35218 and *E. cloacae* ATCC 13047, respectively. Similarly, the parent compounds (compounds **A** and **B**) used to synthesize the various depsides were also tested for their antibacterial activity against the six bacterial strains and their antibacterial activities are similar with those of methyl paraben (MICs range from 6.25 μg/mL to 25 μg/mL), but are relatively low compared with other described depsides, which indicated that the depside linkage possibly increase the antibacterial activity. These findings are in accordance with those of Ingolfsdottir et al. [5]. These workers found that methyl β-orsellinate and the orsellinic acid esters showed a broad antibacterial spectrum, and the depside linkage is important for antibacterial activity.

Then, studies were performed by modification of the parent compounds to determine how the substituents of the subunits affected the antibacterial activities. As shown in Table 1, compounds **C10** and **C23** displayed potent activity with MIC values of 0.78 μg/mL against *B. subtilis* ATCC 6633, which were superior to the positive control penicillin G. Compounds **C5** and **C18** exhibited significant activity with MIC values of 1.562 μg/mL against *B. subtilis* ATCC 6633, which were comparable to the positive control penicillin G. A comparison of the substitution on **E**-ring demonstrated that 3-position-substituted derivatives have more potent activity against *B. subtilis* ATCC 6633 than the 4-position-substituted ones. Most significantly, the stronger electron-withdrawing substituents the compound contained on **E**-ring at 3-position, the more potent it showed (**C10**, **C23**,**C5**, **C18**, **C4** and **C17**), which was illustrated by the potency order $NO_2 > Br > Cl$. Meanwhile, the derivatives which have electron-donating substituents (such as CH_3, OCH_3, OCH_2CH_3) on **E**-ring exhibited less potent activity against *B. subtilis* ATCC 6633, and their MICs values range from 6.25 μg/mL to 50 μg/mL. Furthermore, Compounds **C8** and **C10** exhibited significant activity with MIC values of 1.562 μg/mL against *S. aureus* ATCC 6538, which were comparable to the positive control penicillin G. Compounds **C2**, **C4**, **C11**, **C21** and **C23** showed moderate activity with MIC values of 3.125 μg/mL against *S. aureus* ATCC 6538. Besides, Compounds **C10**, **C21** and **C23** displayed potent activity with MIC values of 1.562 μg/mL against *S. faecalis* ATCC 9790, which were comparable to the positive control penicillin G. Compound **C8** showed moderate activity with MIC values of 3.125 μg/mL against *S. faecalis* ATCC 9790.

In this paper, compounds prepared were also screened for their antibacterial activity of three Gram-negative bacterial strains. Fortunately, we found that the novel depside derivatives prepared also have antibacterial activity against the three Gram-negative bacterial strains. Compounds **C8** and **C21** exhibited significant activity with MIC values of 3.125 μg/mL against *P. aeruginosa* ATCC 13525, which were comparable to the positive control kanamycin B. Compounds **C6**, **C7**, **C9**, **C13**, **C19**, **C20**, **C22** and **C26** showed moderate activity with MIC values of 6.25 μg/mL against *P. aeruginosa* ATCC 13525. Based on the data obtained, it can be concluded that the derivatives which have electron-donating substituents (such as CH_3, OCH_3, OCH_2CH_3) on **E**-ring exhibited more potent antibacterial activity than those that have electron-withdrawing substituents. In addition, Compounds **C8** and **C21** exhibited potent activity with MIC values of 1.562 μg/mL against *E. coli* ATCC 35218, which were superior to the positive control kanamycin B. Compounds **C9**, **C10**, **C22** and **C23** showed significant activity with MIC values of 3.125 μg/mL against *E. coli* ATCC 35218, which were comparable to the positive control kanamycin B. Besides, Compounds **C3**, **C8**, **C16** and **C21** exhibited moderate activity with MIC values of 3.125 μg/mL against *E. cloacae* ATCC 13047. This work may stimulate an interest in the further development of the novel depsides as potentially useful preservative agents.

3. Conclusions

In this paper, we designed two series of novel depside derivatives and evaluated their antibacterial activities against three Gram-positive bacterial strains (*B. subtilis* ATCC 6633, *S. aureus* ATCC 6538 and *S. faecalis* ATCC 9790) and three Gram-negative bacterial strains (*E. coli* ATCC 35218, *P. aeruginosa* ATCC 13525 and *E. cloacae* ATCC 13047) by MTT method. Compounds **C10** and **C23** showed powerful antibacterial activities against *B. subtilis* ATCC 6633 with MIC of 0.78 μg/mL while compounds **C8** and **C21** exhibited significant antibacterial activities against *E. coli* ATCC 35218 with MIC of 1.562 μg/mL, which were superior to the positive controls penicillin G and kanamycin B, respectively. In addition, a comparison of the substitution on **E**-ring demonstrated that 3-position-substituted derivatives have more potent activity against *B. subtilis* ATCC 6633 than the 4-position-substituted ones. Most significantly, the stronger electron-withdrawing substituents the compound contained on **E**-ring at 3-position, the more potent it showed, which was illustrated by the potency order $NO_2 > Br > Cl$.

4. Experiments

4.1. Crystallographic studies

X-ray single-crystal diffraction data for compound **C13** were collected on a Bruker SMART APEX CCD diffractometer at 293(2) K using Mo Kα radiation ($\lambda = 0.71073$ Å) by the ω scan mode. The program SAINT was used for integration of the diffraction profiles. Structure was solved by direct methods using the SHELXS program of the SHELXTL package and refined by full-matrix least-squares methods with SHELXL [23]. All non-hydrogen atoms of compound **C13** were refined with anisotropic thermal parameters. All hydrogen atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms.

4.2. Antibacterial activity

The antibacterial activities of the synthesized compounds were tested against *B. subtilis* ATCC 6633, *S. aureus* ATCC 6538, *S. faecalis* ATCC 9790, *E. coli* ATCC 35218, *P. aeruginosa* ATCC 13525 and *E. cloacae* ATCC 13047 using MH medium (casein hydrolysate 17.5 g, soluble starch 1.5 g, beef extract 1000 mL). The MICs of the test compounds were determined by a colorimetric method using the dye MTT [24]. A stock solution of the synthesized compound (50 μg/mL) in DMSO was prepared and graded quantities of the test compounds were incorporated in specified quantity of sterilized liquid MH medium. A specified quantity of the medium containing the test compound was poured into microtitration plates. Suspension of the microorganism was prepared to contain approximately 10^5 cfu/mL and applied to microtitration plates with serially diluted compounds in DMSO to be tested and incubated at 37 °C for 24 h. After the MICs were visually determined on each of the microtitration plates, 50 μL of PBS containing 2 mg of MTT/mL was added to each well. Incubation was continued at room temperature for 4–5 h. The content of each well was removed and 100 μL of isopropanol containing 5% 1 mol/L HCl was added to extract the dye. After 12 h of incubation at room temperature, the optical density (OD) was measured with a microplate reader at 550 nm. The observed MICs are presented in Table 1. The experiment has been done in triplicate and the results were averaged.

4.3. Chemistry

All chemicals (reagent grade) used were purchased from Aldrich (U.S.A). Separation of the compounds by column chromatography was carried out with silica gel 60 (200–300 mesh ASTM, E. Merck). The quantity of silica gel used was 50–100 times the weight charged on the column. Then, the eluates were monitored using TLC. Melting points (uncorrected) were determined on an XT4 MP apparatus (Taike Corp., Beijing, China). ESI mass spectra were obtained on a Mariner System 5304 mass spectrometer, and ^1H NMR spectra were recorded on a Bruker PX500 or DPX300 spectrometer at 25 °C with TMS and solvent signals allotted as internal standards. Chemical shifts were reported in parts per million (δ). Elemental analyses were performed on a CHN-O-Rapid instrument and were within ±0.4% of the theoretical values.

4.3.1. General procedure for esterification of 2-hydroxy phenylacetic acid

A solution of 2-hydroxyphenylacetic acid (7.6 g, 50 mmol) in methanol or ethanol (50 mL) containing concd H_2SO_4 (5 mL) was refluxed overnight. Water (100 mL) was added, the organic phases were washed with saturated NaCl (100 mL) and dried over Na_2S0_4, and the solvents were evaporated.

*4.3.1.1. Methyl 2-(2-hydroxyphenyl)acetate (**B1**).* White powder, yield 90%, mp: 61–62 °C, ^1H NMR (300 MHz, d_6-DMSO): 3.54 (s, 2H); 3.58 (s, 3H); 6.78 (m, 2H); 7.06 (m, 2H); 9.47 (s, 1H). ^{13}C NMR (DMSO-d_6, δ ppm): 171.9, 155.5, 131.2, 128.2, 121.4, 118.9, 115.0, 51.6, 35.2. MS (ESI): 167.1 ($C_9H_{11}O_3$, $[M+H]^+$). Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07%; Found: C, 65.03; H, 6.10%.

*4.3.1.2. Ethyl 2-(2-hydroxyphenyl)acetate (**B2**).* White powder, yield 86%, mp: 67–68 °C; ^1H NMR (300 MHz, d_6-DMSO): 1.17 (t, $J = 7.1$ Hz, 3H); 3.53 (s, 2H); 4.01 (m, 2H); 6.75 (m, 2H); 7.07 (m, 2H); 9.46 (s, 1H). ^{13}C NMR (DMSO-d_6, δ ppm): 171.6, 155.3, 131.8, 127.9, 121.8, 118.3, 115.4, 51.5, 35.8, 14.3. MS (ESI): 181.1 ($C_{10}H_{13}O_3$, $[M+H]^+$). Anal. Calcd for $C_{10}H_{12}O_3$: C, 65.65; H, 6.71%; Found: C, 65.69; H, 6.74%.

4.3.2. General experimental procedure for the synthesis of compounds ***C1–C26***

To a stirred solution of **B1** (1.66 g, 10 mmol) or **B2** (1.80 g, 10 mmol) in dichloromethane (50 mL) was added different substituted phenylacetic acid or benzoic acid, *N*,*N*-dimethylaminopyridine (248 mg, 2.03 mmol) and *N*,*N*-dicyclohexylcarbodiimide (2.26 g, 11 mmol), Then, the mixture was refluxed overnight. Flash chromatography (acetate: petroleum ether = 1:5 or 1:2) afforded the corresponding depsides as powder or oil.

*4.3.2.1. 2-(2-Methoxy-2-oxoethyl)phenyl 2-(4-fluorophenyl) acetate (**C1**).* Light yellow oil. Yield 89%, ^1H NMR (300 MHz, d_6-DMSO): 3.54 (s, 2H); 3.55 (s, 3H); 3.95 (s, 2H); 7.20 (m, 4H); 7.32 (m, 2H); 7.41 (m, 2H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.8, 169.6, 149.2, 131.7, 130.1, 128.2, 127.1, 126.1, 122.6, 115.2, 51.4, 35.4. MS (ESI): 303.1 ($C_{17}H_{16}FO_4$, $[M+H]^+$). Anal. Calcd for $C_{17}H_{15}FO_4$: C, 67.54; H, 5.00%; Found: C, 67.60; H, 5.05%.

*4.3.2.2. 2-(2-Methoxy-2-oxoethyl)phenyl 2-(4-chlorophenyl) acetate (**C2**).* Light yellow oil. Yield 86%, ^1H NMR (300 MHz, d_6-DMSO): 3.54 (s, 2H); 3.55 (s, 3H); 3.96

(s, 2H); 7.13 (m, 1H); 7.22 (m, 1H); 7.32 (m, 2H); 7.41 (m, 4H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.7, 169.3, 149.1, 132.9, 132.1, 131.5, 128.4, 127.1, 126.1, 122.6, 51.8, 35.3. MS (ESI): 319.1 ($C_{17}H_{16}ClO_4$, $[M+H]^+$). Anal. Calcd for $C_{17}H_{15}ClO_4$: C, 65.06; H, 4.74%; Found: C, 65.09; H, 4.79%.

*4.3.2.3. 2-(2-Methoxy-2-oxoethyl)phenyl 2-(4-bromophenyl) acetate (**C3**).* Light yellow oil. Yield 88%, ^{1}H NMR (300 MHz, d_6-DMSO): 3.55 (s, 2H); 3.59 (s, 3H); 3.95 (s, 2H); 7.14 (m, 1H); 7.22 (m, 1H); 7.32 (m, 4H); 7.56 (d, $J = 1.8$ Hz, 2H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.6, 169.2, 149.0, 133.3, 131.9, 131.6, 128.4, 126.9, 122.5, 114.9, 51.8, 35.2. MS (ESI): 363.0 ($C_{17}H_{16}BrO_4$, $[M+H]^+$). Anal. Calcd for $C_{17}H_{15}BrO_4$: C, 56.20; H, 4.16%; Found: C, 56.14; H, 4.21%.

*4.3.2.4. 2-(2-Methoxy-2-oxoethyl)phenyl 2-(3-chlorophenyl) acetate (**C4**).* Light yellow oil. Yield 84%, ^{1}H NMR (300 MHz, d_6-DMSO): 3.56 (s, 2H); 3.59 (s, 3H); 3.99 (s, 2H); 7.15 (m, 1H); 7.23 (m, 1H); 7.37 (m, 4H); 7.47 (s, 1H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.8, 169.3, 149.1, 136.3, 133.2, 131.7, 130.3, 129.7, 128.4, 127.2, 127.0, 126.2, 122.5, 118.9, 115.0, 51.5, 35.2. MS (ESI): 319.0 ($C_{17}H_{16}ClO_4$, $[M+H]^+$). Anal. Calcd for $C_{17}H_{15}ClO_4$: C, 64.06; H, 4.74%; Found: C, 64.01; H, 4.69%.

*4.3.2.5. 2-(2-Methoxy-2-oxoethyl)phenyl 2-(3-bromophenyl) acetate (**C5**).* Light yellow oil. Yield 89%, ^{1}H NMR (300 MHz, d_6-DMSO): 3.35 (s, 2H); 3.36 (s, 3H); 4.01 (s, 2H); 7.14 (m, 1H); 7.23 (m, 1H); 7.35 (m, 4H); 7.50 (m, 1H); 7.62 (s, 1H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.7, 169.3, 149.1, 136.6, 132.6, 131.6, 131.1, 130.1, 128.9, 128.2, 127.0, 126.2, 122.6, 119.0, 115.1, 51.5, 35.3. MS (ESI): 363.0 ($C_{17}H_{16}BrO_4$, $[M+H]^+$). Anal. Calcd for $C_{17}H_{15}BrO_4$: C, 56.22; H, 4.16%; Found: C, 56.28; H, 4.20%.

*4.3.2.6. 2-(2-Methoxy-2-oxoethyl)phenyl 2-(3-methoxyphenyl) acetate (**C6**).* Light yellow oil. Yield 83%, ^{1}H NMR (300 MHz, d_6-DMSO): 3.54 (s, 2H); 3.55 (s, 3H); 3.76 (s, 3H); 3.90 (s, 2H); 6.87 (m, 1H); 6.94 (m, 2H); 7.09 (m, 1H); 7.28 (m, 4H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.8, 169.5, 159.6, 149.2, 135.3, 131.6, 131.1, 129.6, 128.2, 127.0, 122.6, 121.8, 115.4, 112.7, 55.1, 51.5, 35.2. (ESI): 363.0 ($C_{18}H_{19}O_5$, $[M+H]^+$). Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77%; Found: C, 68.81; H, 5.73%.

*4.3.2.7. 2-(2-Methoxy-2-oxoethyl)phenyl 2-(3,4-dimethoxyphenyl)acetate (**C7**).* White powder. Yield 85%, mp: 65–66 °C, ^{1}H NMR (300 MHz, d_6-DMSO): 3.49 (s, 2H); 3.51 (s, 3H); 3.72 (s, 3H); 3.73 (s, 3H); 3.82 (s, 2H); 6.84 (m, 1H); 6.90 (m, 1H); 6.94 (m, 1H); 7.08 (m, 1H); 7.18 (m, 1H); 7.30 (m, 2H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.8, 169.8, 149.1, 148.2, 131.6, 128.4, 127.0, 126.3, 126.1, 122.6, 121.8, 113.5, 55.6, 51.8, 35.2. MS (ESI): 345.1 ($C_{19}H_{21}O_6$, $[M+H]^+$). Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85%; Found: C, 66.23; H, 5.89%.

*4.3.2.8. 2-(2-Methoxy-2-oxoethyl)phenyl 2-(3,4-diethoxyphenyl)acetate (**C8**).* Yellow powder. Yield 82%, mp: 92–93 °C, ^{1}H NMR (300 MHz, d_6-DMSO): 1.24 (s, 3H); 1.33 (s, 3H); 3.52 (s, 2H); 3.54 (s, 3H); 3.83 (s, 2H); 3.92 (s, 2H); 3.95 (s, 2H); 6.83 (m, 1H); 6.94 (m, 2H); 7.09 (m, 1H); 7.21 (m, 1H); 7.30 (m, 2H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.8, 169.9, 149.2, 148.4, 147.7, 131.7, 128.5, 12.70, 126.3, 12.61, 122.6, 122.0, 115.3, 113.9, 64.1, 51.8, 35.8, 31.9, 30.6, 25.6, 25.3, 24.6, 15.0. MS (ESI): 373.1 ($C_{21}H_{25}O_6$, $[M+H]^+$). Anal. Calcd for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50%; Found: C, 67.78; H, 6.56%.

*4.3.2.9. 2-(2-Methoxy-2-oxoethyl)phenyl 4-methylbenzoate (**C9**).* White powder. Yield 84%, mp: 59–60 °C, ^{1}H NMR (300 MHz, d_6-DMSO): 2.46 (s, 3H); 3.47 (s, 3H); 3.68 (s, 2H); 7.27 (m, 2H); 7.39 (m, 4H); 7.98 (d, $J = 8.0$ Hz, 2H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.8, 164.0, 149.3, 144.7, 131.6, 129.9, 129.6, 128.5, 127.2, 126.1, 122.8, 51.7, 35.2, 21.4. MS (ESI): 373.1 ($C_{17}H_{17}O_4$, $[M+H]^+$). Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67%; Found: C, 71.87; H, 5.71%.

*4.3.2.10. 2-(2-Methoxy-2-oxoethyl)phenyl 3-nitrobenzoate (**C10**).* White powder. Yield 82%, mp: 69–70 °C, ^{1}H NMR (300 MHz, d_6-DMSO): 3.52 (s, 3H); 3.73 (s, 2H); 7.94 (t, $J = 8.6$ Hz, 1H); 8.51 (m, 1H); 8.58 (m, 1H); 8.76 (m, 1H); 7.31 (m, 1H); 7.43 (m, 3H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.8, 162.4, 148.9, 148.2, 135.7, 131.9, 131.1, 130.6, 127.1, 126.6, 124.2, 122.7, 51.7, 35.2, 24.1. MS (ESI): 316.0 ($C_{16}H_{14}NO_6$, $[M+H]^+$). Anal. Calcd for $C_{16}H_{13}NO_6$: C, 60.95; H, 4.16; N, 4.44%; Found: C, 60.89; H, 4.13; N, 4.48%.

*4.3.2.11. 2-(2-Methoxy-2-oxoethyl)phenyl 2-chlorobenzoate (**C11**).* Light yellow oil. Yield 84%, ^{1}H NMR (300 MHz, d_6-DMSO): 3.51 (s, 3H); 3.71 (s, 2H); 7.31 (m, 2H); 7.43 (m, 2H); 7.58 (m, 1H); 7.67 (m, 2H); 8.06 (m, 1H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.8, 163.1, 149.1, 134.1, 133.0, 131.9, 131.3, 128.8, 128.7, 127.6, 127.2, 126.5, 122.7, 51.8, 35.8. MS (ESI): 305.0 ($C_{16}H_{14}ClO_4$, $[M+H]^+$). Anal. Calcd for $C_{16}H_{13}ClO_4$: C, 63.06; H, 4.30%; Found: C, 63.02; H, 4. 32%.

*4.3.2.12. 2-(2-Methoxy-2-oxoethyl)phenyl 4-chlorobenzoate (**C12**).* White powder. Yield 86%, mp: 82–83 °C, ^{1}H NMR (300 MHz, d_6-DMSO): 3.47 (s, 3H); 3.69 (s, 2H); 7.30 (m, 2H); 7.41 (m, 2H); 7.30 (m, 2H); 7.41 (m, 2H); 7.70 (d, $J = 8.4$ Hz, 2H); 8.10 (d, $J = 8.4$ Hz, 2H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.8, 163.3, 149.1, 139.3, 131.8, 131.7, 129.3, 129.1, 128.6, 128.1, 127.8, 127.2, 126.4, 122.8, 51.8, 35.9. MS (ESI): 305.0 ($C_{16}H_{14}ClO_4$, $[M+H]^+$). Anal. Calcd for $C_{16}H_{13}ClO_4$: C, 63.06; H, 4.30%; Found: C, 63.08; H, 4.29%.

*4.3.2.13. 2-(2-Methoxy-2-oxoethyl)phenyl 3,5-dimethoxybenzoate (**C13**).* White powder. Yield 85%, mp: 86–87 °C, ^{1}H NMR (300 MHz, d_6-DMSO): 3.49 (s, 3H); 3.69 (s, 2H); 3.84 (s, 6H); 6.88 (t, $J = 2.4$ Hz, 1H); 7.20 (d, $J = 2.4$ Hz, 2H); 7.28 (m, 2H); 7.39 (m, 2H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.8, 163.8, 160.8, 149.2, 131.8, 130.9, 128.6, 127.2, 126.3, 122.8, 107.5, 106.1, 55.8, 51.8, 35.9. MS (ESI): 305.0 ($C_{18}H_{19}O_6$, $[M+H]^+$). Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49%; Found: C, 65.41; H, 5.53%.

*4.3.2.14. 2-(2-Ethoxy-2-oxoethyl)phenyl 2-(4-fluorophenyl) acetate (**C14**).* Light yellow oil. Yield 84%, ^{1}H NMR (300 MHz, d_6-DMSO): 3.15 (t, $J = 9.1$ Hz, 3H); 3.52 (s, 2H); 3.96 (s, 2H); 4.02 (q, $J = 8.1$ Hz, 2H); 7.14 (t, $J = 4.0$ Hz, 2H); 7.22 (t, $J = 6.6$ Hz, 2H); 7.32 (m, 2H); 7.42 (q, $J = 5.2$ Hz, 2H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.3, 169.6, 163.2, 160.0, 149.1, 131.7, 131.6, 130.2, 128.4, 128.2, 127.1, 126.1, 122.6, 115.5, 115.2, 60.5, 35.5, 14.1. MS (ESI): 305.0 ($C_{18}H_{18}FO_4$, $[M+H]^+$). Anal. Calcd for $C_{18}H_{17}FO_4$: C, 68.35; H, 5.42%; Found: C, 68.39; H, 5.48%.

*4.3.2.15. 2-(2-Ethoxy-2-oxoethyl)phenyl 2-(4-chlorophenyl) acetate (**C15**).* Light yellow oil. Yield 87%, ^{1}H NMR (300 MHz, d_6-DMSO): 1.13 (t, $J = 8.1$ Hz, 3H); 3.52 (s, 2H); 3.96 (s, 2H); 4.02 (q, $J = 8.4$ Hz, 2H); 7.13 (d, $J = 8.0$ Hz, 1H); 7.22 (m, 1H); 7.32 (m, 2H); 7.42 (m, 4H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.3, 169.4, 149.1, 133.0, 132.2, 131.7, 128.6, 128.4, 127.1, 126.1, 122.6, 60.6, 35.6, 14.1. MS (ESI): 333.0 ($C_{18}H_{18}ClO_4$, $[M+H]^+$). Anal. Calcd for $C_{18}H_{17}ClO_4$: C, 64.97; H, 5.15%; Found: C, 64.91; H, 5.11%.

*4.3.2.16. 2-(2-Ethoxy-2-oxoethyl)phenyl 2-(4-bromophenyl) acetate (**C16**).* Light yellow oil. Yield 82%, ^{1}H NMR (300 MHz, d_6-DMSO): 1.14 (t, $J = 8.1$ Hz, 3H); 3.52 (s, 2H); 3.96 (s, 2H); 4.01 (q, $J = 8.4$ Hz, 2H); 7.13 (d, $J = 8.4$ Hz, 1H); 7.21 (t, $J = 7.5$ Hz, 1H); 7.33 (t, $J = 8.0$ Hz, 4H); 7.56 (d, $J = 8.4$ Hz, 2H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.3, 169.2, 149.1, 133.4, 132.0, 131.6, 131.5, 128.4, 127.1, 126.1, 122.6, 120.6, 60.6, 35.6, 14.2. MS (ESI): 377.0 ($C_{18}H_{18}BrO_4$, $[M+H]^+$). Anal. Calcd for $C_{18}H_{17}BrO_4$: C, 57.31; H, 4.54%; Found: C, 57.38; H, 4.58%.

*4.3.2.17. 2-(2-Ethoxy-2-oxoethyl)phenyl 2-(3-chlorophenyl) acetate (**C17**).* Light yellow oil. Yield 85%, ^{1}H NMR (300 MHz, d_6-DMSO): 1.16 (t, $J = 8.6$ Hz, 3H); 3.54 (s, 2H); 3.99 (s, 2H); 4.06 (q, $J = 10.0$ Hz, 2H); 7.15 (d, $J = 7.9$ Hz, 1H); 7.22 (t, $J = 7.3$ Hz, 1H); 7.37 (m, 5H); 7.48 (s, 1H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.3, 169.2, 149.1, 136.4, 133.2, 131.7, 131.1, 130.4, 129.7, 128.5, 128.4, 127.2, 127.1, 126.2, 122.6, 60.6, 35.5, 14.2. MS (ESI): 333.0 ($C_{18}H_{18}ClO_4$, $[M+H]^+$). Anal. Calcd for $C_{18}H_{17}ClO_4$: C, 64.97; H, 5.15%; Found: C, 64.93; H, 5.12%.

*4.3.2.18. 2-(2-Ethoxy-2-oxoethyl)phenyl 2-(3-bromophenyl) acetate (**C18**).* Light yellow oil. Yield 83%, ^{1}H NMR (300 MHz, d_6-DMSO): 1.17 (t, $J = 8.1$ Hz, 3H); 3.55 (s, 2H); 3.99 (s, 2H); 4.06 (q, $J = 2.0$ Hz, 2H); 7.11 (m, 2H); 7.23 (m, 2H); 7.35 (m, 2H); 7.50 (m, 2H). ^{13}C NMR (DMSO-d_6, δ ppm): 171.4, 170.0, 169.3, 155.6, 149.1, 136.7, 132.7, 131.7, 131.1, 130.7, 130.4, 130.1, 129.6, 129.1, 128.9, 128.4, 128.2, 127.1, 126.2, 122.6, 121.8, 121.5, 118.9, 115.0, 60.6, 60.1, 48.0, 35.5, 14.3. MS (ESI): 377.0 ($C_{18}H_{18}BrO_4$, $[M+H]^+$). Anal. Calcd for $C_{18}H_{17}BrO_4$: C, 57.31; H, 4.54%; Found: C, 57.37; H, 4.59%.

*4.3.2.19. 2-(2-Ethoxy-2-oxoethyl)phenyl 2-(3-methoxyphenyl) acetate (**C19**).* Light yellow oil. Yield 86%, ^{1}H NMR (300 MHz, d_6-DMSO): 1.14 (t, $J = 7.1$ Hz, 3H); 3.52 (s, 2H); 3.76 (s, 3H); 3.91 (s, 3H); 4.03 (q, $J = 6.9$ Hz, 2H); 6.89 (m, 2H); 7.12 (d, $J = 7.9$ Hz, 1H); 7.30 (m, 4H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.3, 169.5, 159.6, 149.2, 135.3, 131.7, 131.2, 129.7, 128.4, 127.1, 126.1, 122.6, 121.9, 115.4, 112.7, 60.5, 55.1, 35.5, 14.3. MS (ESI): 377.0 ($C_{19}H_{21}O_5$, $[M+H]^+$). Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14%; Found: C, 69.54; H, 6.17%.

*4.3.2.20. 2-(2-Ethoxy-2-oxoethyl)phenyl 2-(3,4-dimethoxyphenyl)acetate (**C20**).* Light yellow oil. Yield 85%, ^{1}H NMR (300 MHz, d_6-DMSO): 1.16 (t, $J = 7.1$ Hz, 3H); 3.53 (s, 2H); 3.74 (s, 3H); 3.76 (s, 3H); 3.86 (s, 2H); 4.02 (q, $J = 4.2$ Hz, 2H); 6.94 (m, 3H); 7.11 (m, 1H); 7.22 (m, 1H); 7.32 (m, 1H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.4, 169.9, 149.2, 148.9, 148.2, 131.6, 131.2, 128.4, 128.2, 127.1, 126.2, 126.1, 122.6, 121.8, 118.9, 115.0, 113.4, 112.0, 60.5, 55.7, 35.5, 14.3. MS (ESI): 377.0 ($C_{20}H_{23}O_6$, $[M+H]^+$). Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19%; Found: C, 67.09; H, 6.23%.

*4.3.2.21. 2-(2-Ethoxy-2-oxoethyl)phenyl 2-(3,4-diethoxyphenyl)acetate (**C21**).* Yellow oil. Yield 81%, ^{1}H NMR (300 MHz, d_6-DMSO): 1.13 (t, $J = 7.1$ Hz, 3H); 1.31 (q, $J = 2.4$ Hz, 3H); 1.33 (q, $J = 2.4$ Hz, 3H); 3.50 (s, 2H); 3.82 (s, 2H); 3.99 (m, 6H); 6.84 (m, 1H); 6.93 (m, 2H); 7.11 (m, 1H); 7.22 (m, 1H); 7.32 (m, 1H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.3, 169.9, 149.2, 148.3, 147.6, 131.6, 128.4, 127.1, 126.3, 126.1, 122.6, 121.9, 115.1, 113.6, 64.0, 60.5, 35.5, 15.0, 14.1. MS (ESI): 387.1 ($C_{22}H_{27}O_6$, $[M+H]^+$). Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78%; Found: C, 68.36; H, 6.74%.

*4.3.2.22. 2-(2-Ethoxy-2-oxoethyl)phenyl 4-methylbenzoate (**C22**).* Yellow powder. Yield 85%, mp: 55–56 °C, ^{1}H NMR (300 MHz, d_6-DMSO): 1.01 (t, $J = 7.1$ Hz, 3H); 2.43 (s, 3H); 3.64 (s, 2H); 3.91 (q, $J = 8.1$ Hz, 2H); 7.28 (m, 2H); 7.41 (m, 4H); 7.99 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.4, 166.9, 163.0, 149.0, 134.3, 132.9, 132.7, 132.0, 131.4, 131.0, 130.8, 130.6, 128.7, 127.7, 127.4, 127.2, 126.5, 122.7, 60.5, 36.0, 14.0. MS (ESI): 299.1 ($C_{18}H_{19}O_4$, $[M+H]^+$). Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08%; Found: C, 72.43; H, 6.03%.

*4.3.2.23. 2-(2-Ethoxy-2-oxoethyl)phenyl 3-nitrobenzoate (**C23**).* White powder. Yield 88%, mp: 73–74 °C, ^{1}H NMR (300 MHz, d_6-DMSO): 0.99 (t, $J = 7.1$ Hz, 3H); 3.71 (s, 2H); 3.94 (q, $J = 7.1$ Hz, 3H); 7.31 (m, 1H); 7.42 (m, 3H); 7.93 (t, $J = 8.0$ Hz, 1H); 8.52 (d, $J = 7.9$ Hz, 1H); 8.59 (d, $J = 8.3$ Hz, 1H); 8.76 (m, 1H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.4, 162.4, 149.0, 148.2, 136.0, 131.9, 131.1, 130.7, 128.6, 127.2, 126.6, 124.2, 122.8, 60.6, 36.1, 14.0. MS (ESI): 330.0 ($C_{17}H_{16}NO_6$, $[M+H]^+$). Anal. Calcd for $C_{17}H_{15}NO_6$: C, 62.00; H, 4.59; N, 4.25%; Found: C, 62.07; H, 4.62; N, 4.28%.

*4.3.2.24. 2-(2-Ethoxy-2-oxoethyl)phenyl 2-chlorobenzoate (**C24**).* White powder. Yield 86%, mp: 77–78 °C, ^{1}H NMR (300 MHz, d_6-DMSO): 1.01 (t, $J = 6.9$ Hz, 3H); 3.69 (s, 2H); 3.94 (q, $J = 7.1$ Hz, 3H); 7.30 (m, 2H); 7.41 (m, 3H); 7.67 (m, 2H); 8.08 (d, $J = 7.5$ Hz, 1H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.4, 163.7, 160.8, 149.2, 131.8, 130.9, 128.5, 127.3, 126.3, 122.8, 107.6, 106.0, 60.5, 55.8, 36.1, 13.9. MS (ESI): 319.0 ($C_{17}H_{16}ClO_4$, $[M+H]^+$). Anal. Calcd for $C_{17}H_{15}ClO_4$: C, 64.06; H, 4.74%; Found: C, 64.08; H, 4.78%.

*4.3.2.25. 2-(2-Ethoxy-2-oxoethyl)phenyl 4-chlorobenzoate (**C25**).* Yellow oil. Yield 85%, ^{1}H NMR (300 MHz, d_6-DMSO): 0.99 (t, $J = 7.1$ Hz, 3H); 3.68 (s, 2H); 3.92 (q, $J = 7.1$ Hz, 2H); 7.29 (m, 2H); 7.41 (m, 2H); 7.68 (m, 2H); 8.12 (m, 2H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.8, 163.3, 149.1, 139.3, 131.8, 131.7, 129.3, 129.1, 128.6, 128.1, 127.8, 127.2, 126.4, 122.8, 51.8, 35.9, 14.2. MS (ESI): 319.0 ($C_{17}H_{16}ClO_4$, $[M+H]^+$). Anal. Calcd for $C_{17}H_{15}ClO_4$: C, 64.06; H, 4.74%; Found: C, 64.11; H, 4.78%.

*4.3.2.26. 2-(2-Ethoxy-2-oxoethyl)phenyl 3,5-dimethoxybenzoate (**C26**).* White powder. Yield 88%, mp: 75–76 °C, ^{1}H NMR (300 MHz, d_6-DMSO): 1.01 (t, $J = 7.1$ Hz, 3H); 3.67 (s, 2H); 3.84 (s, 6H); 3.93 (q, $J = 7.1$ Hz, 2H); 6.88 (t, $J = 2.4$ Hz, 1H); 7.21 (d, $J = 2.4$ Hz, 2H); 7.28 (m, 2H); 7.40 (m, 2H). ^{13}C NMR (DMSO-d_6, δ ppm): 170.4, 164.0, 149.3, 144.8, 131.8, 130.0, 129.7, 128.5, 127.4, 126.2, 122.9, 60.5, 36.1, 21.4, 14.0. MS (ESI): 345.1 ($C_{19}H_{21}O_6$, $[M+H]^+$). Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85%; Found: C, 66.23; H, 5.87%.

Acknowledgements

The work was co-financed by a grant (Project 30772627) from National Natural Science Foundation of China, and by High Technique Research (BG2007330): Development of Agricultural Biofungicide and #61630; Baoman agent.

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