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Article

Design, Synthesis, and Biological Activity of Novel penta-1,4-dien-3-one Derivatives Containing a *H*-phosphonate Scaffold

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Abstract: A series of penta-1,4-dien-3-one containing a *H*-phosphonate scaffold were designed and synthesized. The structures of all title compounds were determined by ^{1}H-NMR, ^{13}C-NMR, ^{31}P-NMR, and HRMS. Bioassay results showed that several of the title compounds exhibited remarkable antibacterial and antiviral activities. Among these, compounds **3c** and **3o** exhibited substantial antibacterial activities against *Xanthomonas oryzae pv. Oryzae* (Xoo) and *Xanthomonas axonopodis pv. citri* (Xac). In addition, compounds **3c**, **3f**, and **3r** showed remarkable curative activities against tobacco mosaic virus (TMV), with 50% effective concentration (EC_{50}) values of 290.0, 234.0, and 373.6 μg/mL, respectively. These were superior to that of *ningnanmycin* (386.2 μg/mL). Compound **3r** exhibited comparative protective activity against TMV, with an EC_{50} value of 291.1 μg/mL, which was better than that of *ningnanmycin* (297.1 μg/mL). Notably, the solubility of all title compounds improved relative to the lead compound curcumin. These results suggest that penta-1,4-dien-3-one containing a *H*-phosphonate scaffold may be considered as an activator for antibacterial and antiviral agents.

Keywords: penta-1,4-dien-3-one; *H*-phosphonate; antibacterial activities; antiviral activities.

1. Introduction

Pathogenic bacteria, such as rice bacterial leaf blight and citrus canker caused by the pathogens *Xanthomonas oryzae pv. oryzae* (Xoo) [1, 2] and *Xanthomonas axonopodis pv. citri* (Xac) [3, 4], strongly restrain the agricultural output worldwide and are difficult to control in agriculture. Furthermore, vegetables are susceptible to infection with the tobacco mosaic virus (TMV), one of the most severe pathogenic viruses, which causes considerable crop loss [5-7]. To date, the few commercially available bactericides and plant virucides, such as thiodiazole-copper (TC), bismerthiazol (BT), ningnanmycin, and ribavirin not only enhance resistance in the target pathogens, but are also detrimental for both the environment and plant health [8]. Therefore, developing new antibacterial and antiviral agents remains an important task for the medical community.

Pesticides based on natural products show more advantages than synthesized chemicals, e.g., low toxicity, simple decomposition, unique modes of action, and environmental friendliness [9, 10]. Therefore, it is a development trend to search for designs and to synthesize pesticides based on natural products. As an important analog of curcumin isolated from turmeric, penta-1,4-dien-3-one possess numerous potential biological activities, including antibacterial [11], antiviral [12], antifungal [13], and antitumor [14] activities. In a previous study from our group, we synthesized a

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series of penta-1,4-dien-3-one derivatives, most of which exhibited excellent antibacterial and antiviral activities [11, 15, 16].

H-phosphonate and its derivatives possess a wide range of biological activities [17-23] and are therefore widely employed as plant virucides, bactericides, fungicides, herbicides, and plant growth regulators. Because the phosphorus-carbon bond of phosphonates is not susceptible to enzymatic degradation, it possesses more cell permeability, a lipophilic nature, and good physiological stability [24, 25]. Over the past 10 years, a number of papers have reported their synthesis and biological activities [26-29]. *H*-phosphonate has attracted considerate attention in the field of pesticide application.

Motivated by the above-mentioned findings and to continue our efforts for developing highly agrochemicals, we introduced a *H*-phosphonates scaffold into penta-1,4-diene-3-one derivatives, which might generate novel curcumin derivatives with potent biological activities. Thus, 18 penta-1,4-diene-3-one derivatives containing a *H*-phosphonate scaffold were designed, synthesized and evaluated for their antibacterial activities against *Xac* and *Xoo in vitro* and their antiviral activity against TMV *in vivo.*

2. Results and Discussion

2.1. Chemistry.

The synthetic route to penta-1,4-diene-3-one derivatives containing a *H*-phosphonate moiety is schematized in **Scheme 1**. According to previous reports [13, 30], 4-hydroxybenzaldehyde and acetone were used as the starting materials, and reacted with 5% NaOH for 12 h at normal temperature to obtain the intermediate (E)-4-(4-hydroxyphenyl)but-3-en-2-one (**1**). Intermediate **2** was obtained via condensation of intermediate **1** with substituted aldehydes. Finally, the title compounds **3a**-**3r** were synthesized via substitution of intermediates **2** and *H*-phosphonate with Et_3N in CCl_4 at normal temperature for 24 h.

The structures of all title compounds were determined by ^{1}H-NMR, ^{13}C-NMR, ^{31}P-NMR, and HRMS, and the spectra data are shown in the Supporting Information. The representative data for **3a** are shown below. In ^{1}H NMR spectra, multiplet signals at δ 7.70–6.99 ppm indicate the presence of protons in olefinic bonds and aromatic nucleuses, and a singlet at δ 3.87-3.89 ppm indicates the presence of $–CH_3$ groups. Absorption signals at δ 188 and 55 ppm in ^{13}C NMR spectra confirm the presences of -C=O- and $–CH_3$ groups, respectively. The HRMS spectra of target compounds show characteristic absorption signals of $[M+H]^+$ ions, which is consistent with their molecular weight.

2.2. Antibacterial Activity of Title Compounds against Xoo and Xac in vitro.

The antibacterial activities of the target compounds **3a**-**3r** against two phytopathogenic bacterial (Xoo and Xac) were tested *in vitro* by the turbidimeter test [31-33]. Commercial agricultural antibacterial TC and BT were used as references, as shown in **Table 1**. Most of the compounds exhibited significant antibacterial activities against Xoo and Xac at 100 or 50 μg/mL.

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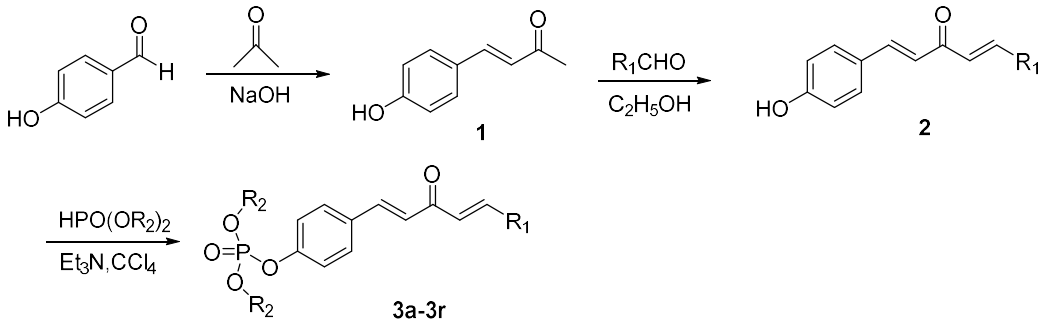

3a: R_1= 4-Cl-Ph, R_2=CH_3; **3b**: R_1= 4-Cl-Ph, R_2=CH_2CH_3; **3c**: R_1= Ph, R_2=CH_3;
3d: R_1= Ph, R_2=CH_2CH_3; **3e**: R_1= 4-F-Ph, R_2=CH_3; **3f**: R_1= 4-F-Ph, R_2=CH_2CH_3;
3g: R_1= 2-OCH_3-Ph, R_2=CH_3; **3h**: R_1= 2-OCH_3-Ph, R_2=CH_2CH_3; **3i**: R_1= Thiophene-2-yl, R_2=CH_2CH_3;
3j: R_1= 3-NO_2-Ph, R_2=CH_2CH_3; **3k**: R_1= 4-NO_2-Ph, R_2=CH_3; **3l**: R_1= 4-NO_2-Ph, R_2=CH_2CH_3;
3m: R_1= Furan-2-yl, R_2=CH_3; **3n**: R_1= Furan-2-yl, R_2=CH_2CH_3; **3o**: R_1= 3-CH_3-Ph, R_2=CH_3;
3p: R_1= 3-CH_3-Ph, R_2=CH_2CH_3; **3q**: R_1= 3-CF_3-Ph, R_2=CH_3; **3r**: R_1= 3-CF_3-Ph, R_2=CH_2CH_3;

Scheme 1. Synthesis of the title compounds 3a–3r.

Several of the compounds showed excellent activities against Xoo compared to TC and BT. Among these, the antibacterial activities of compounds **3c**, **3d**, **3f**, **3k**, **3l**, **3m**, and **3o** against Xoo at 100 μg/mL were 94.9, 71.2, 77.2, 68.1, 88.1, 85.3, and 90.8%, respectively, exceeding those of both TC (50.2%) and BT (64.9%). Compounds **3a**, **3c**, **3d**, **3e**, **3k**, **3l**, and **3m** against Xoo at 50 μg/mL were 61.4, 88.8, 61.8, 54.9, 65.2, 83.2, and 56.3%, respectively, which were better than those of both TC (37.2%) and BT (45.2%). Most importantly, the antibacterial activities of compounds **3c**, **3e**, **3g**, and **3o** against Xac at 100 and 50 μg/mL were 90.3 and 78.0%, 90.2 and 81.5%, 90.2 and 75.2%, and 99.5 and 93.5%, respectively, which were significantly superior to those of TC (57.2 and 27.8%) and BT (70.3 and 54.9%).

Table 1. Antibacterial activities of target compounds (**3a–3r**) against plant pathogens *Xac* and *Xoo in vitro*.

Compounds	R_1	R_2	*Xoo* /%		*Xac* /%	
			100 μg/mL	50 μg/mL	100 μg/mL	50 μg/mL
3a	4-Cl-Ph	CH_3	64.9±0.8	61.4±1.8	45.2±0.8	10.0±5.5
3b	4-Cl-Ph	CH_2CH_3	53.2±2.8	48.8±2.4	28.2±2.1	4.9±4.7
3c	Ph	CH_3	94.9±1.1	88.8±0.9	90.3±2.2	78.0±0.8
3d	Ph	CH_2CH_3	71.2±0.6	61.8±4.9	47.4±2.4	42.0±2.3
3e	4-F-Ph	CH_3	63.5±2.0	54.9±4.8	90.2±2.8	81.5±1.1
3f	4-F-Ph	CH_2CH_3	77.2±0.5	45.4±2.0	27.3±4.0	7.7±3.1
3g	2-OCH_3-Ph	CH_3	36.1±1.7	19.3±4.0	90.2±3.1	75.2±1.5
3h	2-OCH_3-Ph	CH_2CH_3	36.7±1.9	25.9±4.5	12.0±3.5	10.4±1.7
3i	2-Thiophene	CH_2CH_3	53.4±1.7	38.0±4.3	45.3±3.7	17.1±2.7
3j	3-NO_2-Ph	CH_2CH_3	47.4±0.9	36.9±2.6	15.4±1.6	4.2±5.8
3k	4-NO_2-Ph	CH_3	68.1±5.9	65.2±4.1	28.6±5.8	26.7±3.5
3l	4-NO_2-Ph	CH_2CH_3	88.1±1.1	83.2±0.4	40.7±5.7	33.3±1.8
3m	2-Furan	CH_3	85.3±3.2	56.3±1.0	50.5±1.6	42.4±1.9
3n	2-Furan	CH_2CH_3	52.7±3.8	33.0±0.7	45.2±3.3	37.5±2.5
3o	3-CH_3-Ph	CH_3	90.8±4.9	47.7±1.3	99.5±2.1	93.5±2.6
3p	3-CH_3-Ph	CH_2CH_3	39.6±3.8	3.5±3.7	29.1±1.6	18.8±1.2
3q	3-CF_3-Ph	CH_3	31.8±1.8	22.1±4.5	58.8±1.8	48.1±4.5

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3r	3-CF_3-Ph	CH_2CH_3	24.9±9.2	7.1±2.2	20.0±1.0	16.0±1.4
Thiodiazole copper[a]	-	-	50.2±0.9	37.2±3.2	57.2±1.3	27.8±3.8
Bismerthiazol[a]	-	-	64.9±3.9	45.2±2.0	70.3±2.8	54.9±5.5

Average of three replicates.[a] The commercial agricultural bactericides, Bismerthiazol and Thiodiazole copper, were used in a comparison of antibacterial activity.

To further confirm the antibacterial activities of our target compounds, the EC_{50} values were tested for several compounds, and the results are listed in **Tables 2** and **3**. Compounds **3c**, **3d**, **3f**, **3k**, **3l**, **3m**, and **3o** exhibited remarkable antibacterial activities against Xoo, with EC_{50} values of 22.9, 6.7, 43.5, 16.5, 11.4, 26.5, and 36.1 μg/mL, which were much better than those of BT (78.7 μg/mL) and TC (58.8 μg/mL). Compounds **3c**, **3e**, **3g**, and **3o** exhibited excellent antibacterial activities against Xac, with EC_{50} values of 10.6, 22.1, 18.4, and 10.8, which were significantly superior to those of BT (87.9 μg/mL) and TC (44.5 μg/mL). In particular, compounds **3c** and **3o** exhibited excellent activities against both Xoo (22.9 and 10.6 μg/mL) and Xac (36.1 and 10.8 μg/mL). These results indicate that those compounds should be further studied as potential alternative templates in the search for novel antibacterial agents. When R_1 was Ph (**3c**, **3d**), 4-F-Ph (**3f**), 4-NO_2(**3k**, **3l**), 2-furan (**3m**), and 3-CH_3-Ph (**3o**) groups, the corresponding compounds presented excellent antibacterial activity against Xoo. Moreover, the results showed that Ph (**3c**), 4-F-Ph (**3e**), 2-OCH_3-Ph (**3g**), and 3-CH_3-Ph (**3o**) groups on aromatic rings were favorable for antibacterial activity against Xac.

Table 2. EC_{50} values of the title compounds against Xoo *in vivo* .

Compounds	Toxic regression equation	r	EC_{50}/(μg/mL)
3c	y=2.6313x+1.4206	0.9767	22.9
3d	y=0.4735x+4.6075	0.9951	6.7
3f	y=1.6505x+2.2959	0.9844	43.5
3k	y=1.4894x+3.1874	0.9708	16.5
3l	y=1.1559x+3.7802	0.9916	11.4
3m	y=1.5500x+2.7937	0.9810	26.5
3o	y=1.15798x+2.539	0.9734	36.1
BT[a]	y=1.8133x+1.5622	0.9992	78.7
TC [a]	y=1.5145x+2.3200	0.9993	58.8

[a] The commercial agricultural antibacterial agents Thiodiazole copper (TC) and Bismerthiazol (BT) were used as control agents.

Table 3. EC_{50} values of the title compounds against Xac *in vivo*.

Compounds	Toxic regression equation	r	EC_{50}/(μg/mL)
3c	y=1.2254x+3.7444	0.9916	10.6
3e	y=2.0915x+2.1870	0.9933	22.1
3g	y=1.6197x+2.9497	0.9802	18.4
3o	y=2.2752x+2.6477	0.9921	10.8
BT [a]	y=1.9447x+1.2190	0.9804	87.9
TC [a]	y=1.5561x+2.4354	0.9963	44.5

[a]The commercial agricultural antibacterial agents Thiodiazole copper (TC) and Bismerthiazol (BT) were used as control agents.

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2.3. Antiviral Activity of Title Compounds against TMV in Vivo.

Using N. *tabacum* L. leaves of the same age as the test subjects, the curative and protective activities against TMV *in vivo* at 500 μg/mL were evaluated by the half-leaf blight spot method [31, 34-35]. The commercial agricultural antiviral agent ningnanmycin was used as control and the preliminary bioassays results are listed in **Table 4**. Compounds **3a** to **3r** exhibited from weak to good antiviral activities against TMV. Among these, compounds **3c**, **3f**, and **3r** exhibited excellent curative activities against TMV at 62.5, 62.8, and 56.4%, respectively, which exceeded that of ningnanmycin (56.1%). The protective activities of **3e** and **3r** (58.6 and 58.9%, respectively) against TMV were more potent than that of ningnanmycin (56.2%).

Table 4. Antiviral activities of the test compounds against TMV *in vivo* at 500 μg/mL.

Compounds.	R_1	R_2	Curative activity(%)[a]	Protective activity(%) [a]
3a	4-Cl-Ph	CH_3	52.9±0.8	27.1±1.9
3b	4-Cl-Ph	CH_2CH_3	36.2±2.9	31.7±2.4
3c	Ph	CH_3	62.5±1.1	29.9±1.0
3d	Ph	CH_2CH_3	50.3±6.2	55.8±4.9
3e	4-F-Ph	CH_3	35.2±2.0	58.6±4.8
3f	4-F-Ph	CH_2CH_3	62.8±0.5	44.4±2.0
3g	2-OCH_3-Ph	CH_3	50.9±1.7	42.0±4.1
3h	2-OCH_3-Ph	CH_2CH_3	34.6±2.1	50.7±4.6
3i	2-Thiophene	CH_2CH_3	26.9±1.8	54.6±4.4
3j	3-NO_2-Ph	CH_2CH_3	45.2±1.5	40.0±2.6
3k	4-NO_2-Ph	CH_3	48.6±5.9	32.5±4.1
3l	4-NO_2-Ph	CH_2CH_3	29.6±1.1	44.5±0.4
3m	2-Furan	CH_3	31.4±3.2	43.7±1.2
3n	2-Furan	CH_2CH_3	43.8±3.8	57.5±0.7
3o	3-CH_3-Ph	CH_3	51.8±4.9	35.8±1.3
3p	3-CH_3-Ph	CH_2CH_3	51.9±3.8	39.9±3.7
3q	3-CF_3-Ph	CH_3	51.6±0.8	46.9±1.8
3r	3-CF_3-Ph	CH_2CH_3	56.4±7.1	58.9±2.2
Ningnanmycin [a]	-	-	56.1±2.5	56.2±6.4

Average of three replicates.

[a] The commercial antiviral agent Ningnanmycin.

To confirm the potential inhibitory capacity of these compounds against TMV, on the basis of our previous bioassays, we further evaluated the EC_{50} of several target compounds against TMV. In **Table 5,** the antiviral curative activities of compounds **3c**, **3f**, and **3r**, with corresponding EC_{50} values of 290.0, 234.0, and 373.6 μg/mL against TMV, were much better than that of ningnanmycin (386.2 μg/mL). The protective activities of **3e** and **3r** (EC_{50} of 324.8 and 291.1 μg/mL) against TMV were better than or near to that of ningnanmycin (297.1 μg/mL). When R_1 was Ph (**3c**), 4-F-Ph (**3f**) and 3-CF_3 (**3r**) groups, the corresponding compounds presented excellent curative activity against TMV. Moreover, good protection activity against TMV was observed when R_1 was 4-F-Ph (**3e**) and 3-CF_3-Ph (**3r**) groups.

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Table5. The EC_{50} values of some compounds against TMV.

Compounds.	curative			protective		
	Regression equation	r	EC_{50} (μg/mL)	Regression equation	r	EC_{50} (μg/mL)
3c	y=1.3788x+1.6048	0.9997	290.0	/	/	/
3f	y=0.8880x+2.8961	0.9966	234.0	/	/	/
3e	/	/	/	y=1.1621x+2.0812	0.9938	324.8
3r	y=1.5902x+1.5423	0.9838	373.6	y=1.0659x+2.3735	0.985	291.1
Ningnanmycy[a]	y=1.3750x+1.4430	0.9999	386.2	y=1.4260x+1.4280	0.9993	297.1

Average of three replicates.

[a] The commercial antiviral agent Ningnanmycin.

3. Experimental

Instruments. All solvents and reagents were purchased from Shanghai Titan Scientific Co., Ltd., were of analytical reagent grade or chemically pure, and were treated with standard methods prior to use. The reactions were monitored by thin-layer chromatography on silica gel GF_{254}. Melting points (m.p.) of all synthesized compounds were determined when left untouched on an XT-4-MP apparatus from Beijing Tech. Instrument Co. (Beijing, China). Using tetramethylsilane (TMS) as the internal standard and chloroform as the solvent, ^{1}H, ^{13}C, and ^{31}P nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Ascend-400 spectrometer (Bruker, Germany) and JEOL-ECX 500 NMR spectrometer (JEOL, Tokyo, Japan) operated at room temperature. High-resolution mass spectral (HRMS) data were performed with Thermo Scientific Q Exactive (Thermo).

3.1. Chemistry.

3.1.1 Synthesis Procedure for Intermediate **1**.

Aqueous sodium hydroxide solution (9.0 mmol) was added to a solution of 4-hydroxybenzaldehyde (8.2 mmol) and acetone (6 mL) at room temperature. The resulting solution was stirred at room temperature for 12 h. At that time, the resulting dark yellow mixture was acidified by filtration and dried under vacuum to yield (E)-4-(hydroxy-phenyl)-but-3-en-2-one **1** (1.0g). [13, 30].

3.1.2 General Procedure for Preparation of Intermediates **2**

To a stirred solution of (E)-4-(hydroxy-phenyl)-but-3-en-2-one (1.6 g, 0.01 mol) and aromatic aldehyde (0.011 mol) in ethanol (15 mL), a solution of NaOH was added in the form of 10% aqueous solution. The reaction mixture was stirred for 10 h at room temperature. Then, the mixture was diluted with a tenfold volume of water and neutralized with aqueous HCl. The resulting precipitate was separated and recrystallized from ethanol to obtain the yellow solid 1,5-diphenyl-penta-1,4-diene-3-one **2**.

3.1.3 General Procedure for Preparation of Title Compounds **3a–3r**.

A solution of intermediate **2** (1.0 mmol) and Et_3N (3.0 mmol) in CCl_4 (30 mL) was stirred until dissolved. The mixture was stirred in an ice-water bath for 30 min, after adding the mixture of *H*-phosphonate (4.0 mmol) and CCl_4 (6 mL) dropwise. The mixture was then removed from the ice-water bath and stirring continued at room temperature for 24 h. After the reaction was completed (as indicated by TLC), the solvent was removed under depressurization, and the residue was diluted with EtOAc (3×35 mL), and washed with 5% HCl (3×30 mL), and 5% NaOH (3×30 mL),

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respectively. the organic layer was dried by anhydrous Na_2SO_4, the solvent was removed under depressurization, and the residue was purified by column chromatography on silica gel to obtain the title compounds **3a**-**3r**. Representative data for **3a** are listed below.

*4-((1E,4E)-5-(4-chlorophenyl)-3-oxopenta-1,4-dien-1-yl)phenyl dimethyl phosphate (**3a**)* Yellow solid, m.p. 90-91 °C, yield 66%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 15.9, 9.4 Hz, 2H, Ar-2H), 7.60 (d, *J* = 8.7 Hz, 2H, Ar-2H), 7.54 (d, *J* = 8.4 Hz, 2H, Ar-2H), 7.38 (d, *J* = 8.5 Hz, 2H, Ar(4-Cl)-CH=, Ar(4-O)-CH=), 7.27 (d, *J* = 8.6 Hz, 2H, Ar-2H), 7.01 (dd, *J* = 21.4, 15.9 Hz, 2H, Ar(4-Cl)-C=CH, Ar(4-O)-C=CH), 3.88 (d, *J* = 11.4 Hz, 6H, $2CH_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.50, 152.34, 152.29, 142.31, 142.02, 136.53, 133.33, 131.88, 131.87, 131.12, 130.06, 129.63, 129.35, 125.79, 125.44, 120.58, 120.53, 55.18, 55.13. ^{31}P NMR (202 MHz, $CDCl_3$) δ -3.77. HRMS calcd for $C_{19}H_{19}ClO_5P$ $[M+H]^+$ 393.0653, found 393.0645.

3.2. Bioassays:Antibacterial Bioassays

The antibacterial effects of the target compounds against Xac (strain 29-1, Shanghai Jiao Tong University, China) and Xoo (strain PXO99A, Nangjing Agricultural University, China) were evaluated by the turbidimeter test [31-33]. The title compounds were dissolved in 150 μL of dimethylformamide (DMSO) and diluted with water containing Tween-20 (0.1%) to obtain final concentrations of 100 and 50 μg/mL. DMSO in sterile distilled water served as blank control, and the commercial agent thiadiazole-copper was used as positive control. Approximately 1 mL of the sample liquid was added to a 15 mL tube, 4 mL of nutrient broth (NB, 1.5 g of beef extract, 0.5 g of yeast powder, 5.0 g of glucose, 2.5 g of peptone, and 500 mL of distilled water, pH 7.0 to 7.2) media. Then, approximately 40 μL of Xoo or Xac bacterium solution were added. The inoculated test tubes were incubated at 28 ± 1 °C and continuously shaken at 180 rpm for 24-48 h. The growth of the cultures was monitored with a spectrophotometer by measuring the optical density at 595 nm (OD_{595}) given by corrected turbidity values. The relative inhibitory (*I* %) are calculated by the following formula, where C_{tur} represents the corrected turbidity value (OD_{595}) of bacterial growth on untreated NB (blank control) and T_{tur} represents the corrected turbidity values (OD_{595}) of bacterial growth on treated NB.

$$\text{Inhibition rate } I\ (\%) = (C_{tur} - T_{tur}) / C_{tur} \times 100$$

Several of the target compounds were tested against Xoo and Xac at five double-declining concentrations (100, 50, 25, 12.5, and 6.25 μg/mL), and their corresponding EC_{50} values were obtained via software SPSS 17.0 (SPSS, Chicago, IL). Each experiment was computed at least three times.

3.3. Bioassays: Antiviral Bioassays

3.3.1. Purification of TMV

The upper leaves of *N. tabacum* cv. K326 were selected and inoculated with TMV, using previously reported methods for TMV purification [36].

3.3.2. Curative Activities of Compounds against TMV In Vivo

Using *N. tabacum* L. leaves of the same age as the test subjects, the TMV virus were dipped and inoculated on the whole leaves, which were scattered with silicon carbide beforehand [34, 35]. After about 60 min, the leaves were washed with water, and after drying, the compound solution was smeared onto the left side of leaf, and the solvent was smeared onto the right side. The local lesion numbers were counted after 3 to 4 days. Each compound was tested three times.

3.3.3. Protective Activities of Compounds against TMV In Vivo

The compound solution was smeared on the left side of leaf, while the solvent was smeared on the right side [34, 35]. The leaves were inoculated with virus 12 h later. Then, the leaves were washed with water after inoculation for 2 h. The local lesion numbers were counted after 3 to 4 days. Each compound was conducted three times.

4. Conclusions

In summary, with the aim to develop a novel, highly-efficient, and environmentally benign virucide, we introduced a *H*-phosphonate scaffold into penta-1,4-diene-3-one to synthesize 18 curcumin derivatives. Their antibacterial activities against Xac and Xoo *in vitro* and their antiviral activity against TMV *in vivo* were evaluated. Bioassay results showed that several of the title compounds exhibited good antibacterial and antiviral activities. Among these, compounds **3c**, **3d**, **3f**, **3k**, **3l**, **3n**, and **3o** exhibited appreciable antibacterial activities against Xoo, with EC_{50} values of 22.9, 6.7, 43.5, 16.5, 11.4, 26.5, and 36.1 μg/mL, respectively. These were significantly better than those of commercial agents BT and TC (78.7 and 58.8 μg/mL). Compounds **3c**, **3e**, **3g**, and **3o** showed excellent antibacterial activities against Xac, with EC_{50} values of 10.6, 22.4, 18.4, and 10.8 μg/mL, respectively, which were obviously superior to those of commercial agents BT and TC (87.9 and 44.5 μg/mL). In addition, compounds **3c**, **3f**, and **3r** showed remarkable curative activities against TMV, with EC_{50} values of 290.0, 234.0, and 373.6 μg/mL, respectively, which were better than that of ningnanmycin (386.2 μg/mL). Compound **3r** exerted comparative protective activity against TMV, with an EC_{50} value of 291.1 μg/mL, which was better than that of ningnanmycin (297.1 μg/mL). Given the above results, these penta-1,4-diene-3-one derivatives, containing a *H*-phosphonate scaffold, should be further studied as potential alternative templates in the search for novel antibacterial and antiviral agents.

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