# Synthesis and biological activity of 1,4-pentadien-3-one derivatives containing a triazine scaffold

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## ABSTRACT

**Background:** Literatures revealed that 1,4-pentadien-3-one and triazine derivatives exhibited a wide variety of biological activities. In order to develop highly bioactive molecules, in this study, a series of novel1,4-pentadien-3-one derivatives containing triazine moieties were synthesized and their antibacterial and antiviral activities were investigated.

**Methods.** A series of novel 1,4-pentadien-3-one derivatives containing triazine moieties were synthesized and characterized in detail *via* $^{1}$H NMR, $^{13}$C NMR and HRMS spectra. The antibacterial activities against *Xanthomonas axonopodispv. citri (Xac), Xanthomonas oryzaepv. oryzae (Xoo)* and *Ralstonia solanacearum (R.s)* were evaluated at 100 and 50 $\mu$g/mL using a turbidimeter and *N. tabacun L.* leaves under the same age as that of test subjects. The curative, protective and inactivation activities against tobacco mosaic virus (TMV) at a concentration of 500 $\mu$g/mL were evaluated by the half-leaf blight spot method.

**Results.** The bioassay results showed that some of the target compounds exhibited fine antibacterial activities against *Xac* and *R.s*. Particularly, with half maximal effective concentration ($EC_{50}$) values of some target compounds against *R.s* are visibly better than that of

the positive control bismerthiazol (**BT**). Notably, compound **4a** showed excellent inactivation activity against TMV, the $EC_{50}$ values of 12.5 $\mu$g/mL, which was superior to that of ningnanmycin (**NNM**,13.5 $\mu$g/mL). Besides, molecular docking studies for **4a** with tobacco mosaic virus coat protein (TMV-CP) showed that the compound was embedded well in the pocket between the two subunits of TMV-CP. These findings indicate that 1,4-pentadien-3-one derivatives containing a triazine may be potential antiviral and antibacterial agents.

**Keywords:** 1,4-pentadien-3-one, Triazine, Antiviral, Antibacterial, Molecular docking studies

## INTRODUCTION

Plant pathogens have become one of the world's largest agricultural problems because they exhibit a significant threat not only to agricultural products but also to human health ( *Li et al.,2011; Lorenzo et al.,2017*). Plant pathogens diseases, such as citrus canker, rice bacterial leaf blight and tobacco bacterial wilt, were caused by *Xanthomonas axonopodispv. citri (Xac)*, *Xanthomonas oryzaepv. oryzae (Xoo)* and *Ralstonia solanacearum (R.s)*, respectively. They are difficult to control in agricultural production (*Zou et al., 2011; Li et al., 2017*). In addition, tobacco mosaic virus (TMV) can infect more than 885 plant species, causing nearly $100 million in damage worldwide *(Su et al., 2016; Bos et al., 2000).* Therefore, the discovery and development of new antiviral and antibacterial agents with a novel mode of action are of great importance to the medical community.

1,4-Pentadien-3-one derivatives, derived from plant metabolic products curcumin, were found to have a good range of biological activities such as antiviral *(Zhang et al., 2018)*, antibacterial *(Long et al., 2015)*, anticancer *(Luo et al., 2014)*, anti-inflammatory *(Liu et al., 2014)*, anti-oxidative *(Masuda et al., 2015)*, and anti-HIV activities *(Sharma et al., 2019).* Over the past few years, the synthesis and study of pharmacological activity of 1,4-pentadien-3-one derivatives attracted the attention of many chemists *(Wang et al., 2017; Zhou et al., 2017).* Further study on the structural optimization of 1,4-pentadien-3-one found that introducing benzotriazin-4(3*H*)-one *(Zhang et al., 2018)*, imidazole *(Samaan et al., 2014)*, thiazole *(Wang et al., 2015)*, or chromone *(Chen et al., 2015)* moieties (**Figure 1. A1-A4**), could greatly enhance biological activities. Notably, Chen *et al.* verified the anti-TMV mechanism of 1,4-pentadien-3-one derivatives (**Figure 2. B**), and found 5-position of 1,4-pentadien-3-one nucleus plays a key role in antiviral activities *(Chen et al., 2019).*

**Figure 1.** Chemical structures of bioactive molecules bearing 1,4-pentadien-3-one fragment.

**Figure 2.** The anti-TMV mechanism of 1,4-pentadien-3-one derivatives.

In addition, triazine scaffold has been associated with diversified pharmacological activities *(Irannejad et al., 2010),* such as antioxidant *(Khoshneviszadeh et al., 2016),* antithrombotic *(Tamboli et al., 2015),* antiplatelet *(Konno et al.,1993),* anticancer *(Fu et al., 2017),* thromboxane synthetase inhibition *(Monge et al., 2010),* antimalarial *(Tamboli et al., 2015),* $\alpha$-glucosidase inhibition *(Wang et al., 2016),* antiviral and antibacterial activities *(Tang et al., 2019).* Recently, chemical research on triazine derivatives showed that the heterocyclic nitrogen had tremendous application foregrounds in the development of novel agricultural bactericides and virucides *(Zhang et al., 2018).* Sangshetti *et al*. reported potent inhibitory effect of triazine and their derivatives against three fungals ((Candida albicans (MIC-25), Aspergillus niger (MIC-12.5) and Cryp tococcus neoformans (MIC-25)) similar to miconazole (**Figure 3. C**) *(Sangshetti et al., 2010).* Therefore, triazine group was introduced into the 5-position of 1,4-pentadien-3-one nucleus to build a new molecular structure and their potential biological activities were tested (**Figure 4**).

**Figure 3.** 1,2,4-triazine fragment against three fungals (Candida albicans, Aspergillus niger and Cryp tococcus neoformans).

**Figure 4.** Design strategy of title compounds.

## MATERIALS & METHODS

### Instruments and chemicals

Melting points were determined using an XT-4 digital melting-point apparatus (Beijing Tech. Instrument Co., China) and readings were uncorrected. $^{1}$H NMR , $^{13}$C NMR and $^{19}$F NMR spectra were recorded on a 400 MHz spectrometer (Swiss Bruker) with DMSO and $CDCl_3$ as the solvent and tetramethylsilane as the internal standard. The course of the reaction was monitored by thin-layer-chromatography analysis on silica gel $GF_{254}$ (Qingdao Haiyang Chemical Company, Ltd., Qingdao, China), and spots were visualized with ultraviolet (UV) light. High-resolution mass spectrometry (HRMS) was conducted by using a Thermo Scientific Q Exactive

(Thermo Scientific, Missouri, USA). The molecular docking was performed by using DS-CDocker implemented in Discovery Studio (version 4.5). All reagents and solvents were purchased from Chinese Chemical Reagent Company and were of analytical grade reagents. The synthetic route to1,4-pentadien-3-one derivatives containing triazine moiety was shown in **Figure 5**

**General procedure for the synthesis of intermediates**

A synthetic route to 1,4-pentadien-3-one derivatives containing a triazine moiety was designed and shown in **Figure 5**. According to previously reported methods *(Chen et al., 2019; Tang et al., 2019;, Gan et al., 2017),* intermediates **1** and **2** could be obtained. Using benzyl, biacetyl and thio-semicarbazide as the initial materials in acetic acid and water was stirred at 100-110 $^{o}$C for 6-8 h to obtain the intermediate **3** *(Tang et al., 2019).*

**General procedure for the synthesis of target compounds 4a-4r**

Reaction mixture was added to a solution of intermediate **2** (12 mmol), intermediate **3** (10 mmol) and $K_2CO_3$ (30 mmol) in dimethylformamide and stirred at room temperature for 6-8 h. Upon completion of reaction (indicated by TLC), and ethyl acetate was used to extract three times (30 mL×3). the solvent was removed under reduced pressure. Residue was purified by silica-gel column chromatography using petroleum ether/ethyl acetate (3:1 *v/v*) to obtain target compounds **4a**–**4r**. The $^{1}$H NMR, $^{13}$C NMR, $^{19}$F NMR and HMRS spectra of the target compounds **4a**–**4r** are also provided in the Supporting Information.

**Figure 5.** Synthesis route for the target compounds.

**Bioactivity assay**

**Antibacterial activity *in vitro***

The *in vitro* antibacterial activities of target compounds **4a**–**4r** against rice bacterial leaf blight, tobacco wilt and citrus canker caused by the pathogens of *Xanthomonas axonopodispv. citri (Xac), Xanthomonas oryzaepv. oryzae (Xoo) and Ralstonia solanacearum (R.s),* respectively, by the turbidimeter test *(Tang et al., 2019; Zhang et al., 2017).*This test method is provided in the Supporting Information.

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**Antiviral activities *in vivo***

The *in vivo* antibacterial activities of target compounds **4a**–**4r** against tobacco mosaic virus (TMV) by the half-leaf blight spot method *(Chen et al., 2019).*This test method is provided in the Supporting Information.

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**Molecular docking**

The molecular docking was performed by using DS-CDocker implemented in Discovery Studio (version 4.5). This test method is provided in the Supporting Information.

**RESULTS**

**Antibacterial activities *in vitro***

The antibacterial activities of target compounds have been evaluated by the turbidimeter test *(Zhang et al.,2018; Tang et al.,2019)*. Results in **Table 1** indicated that some of synthesized compounds exhibited appreciable antibacterial activities against *Xoo*, *R.s* and *Xac* at the concentrates of 100 $\mu$g/mL. Among these derivatives, **4n** and **4p** exhibited excellent bactericidal effect against *Xoo*, with inhibition rates of 60.5 % and 56.5 %, respectively, which were superior to bismerthiazol (**BT**, 56.1 %). In addition, as **Table 1** demonstrated that the designed compounds displayed certain bactericidal effect toward *R.s*. Studies on the inhibition effect of title compounds suggested that **4a**, **4b**, **4j** and **4k** exerted the excellent inhibition effect against *R.s* with the inhibition rates of 58.2, 53.9, 53.5 and 61.9 %, respectively, which were better than that of **BT** (52.1 %). It was noted that compounds **4k** (91.8 %) and **4l** (95.4 %) exposed better antibacterial activity toward *Xac* than that of **BT** (70.5 % ).

To further understand antibacterial activity of title compounds, the $EC_{50}$ values of some title compounds were calculated and summarized in **Table 2**. Notably, compounds **4a**, **4b**, **4j** and **4k** exerted admirable inhibition effects against *R.s*, with half maximal effective concentration ($EC_{50}$) values of ranging from 0.43-4.76 $\mu$g/mL, which were better than that of **BT** ($EC_{50}$=49.5 $\mu$g/mL). Meanwhile, compounds **4j** and **4k** showed remarkable antibacterial activities against *Xac* with the $EC_{50}$ values of 55.53 and 129.1 $\mu$g/mL, which were better than that of **BT** ($EC_{50}$=153.7 $\mu$g/mL).

**Table 1.** Inhibition effect of the some title compounds against *Xoo*, *R.s* and *Xac*. [a]

**Table 2.** $EC_{50}$ values of some title compounds against *Xoo*, *Xac* and *R.s*.

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**Antiviral activities against TMV *in vivo***

The antiviral activities of the title compounds **4a**–**4r** against tobacco mosaic virus (TMV ) were evaluated by the half leaf method *(Chen et al., 2019)* and the results were summarized in **Table 3** and **Figure 6**. It was found that some of the title compounds exhibited good antiviral activity against TMV *in vivo*. Compounds **4f**, **4k** and **4l** showed remarkable curative activity

against TMV, with values of 53.8, 66.3 and 59.9 %, respectively. Which were better than that of ningnanmycin **(NNM**, 45.7 %). Meanwhile, compound **4h (**61.4 %) exhibited excellent protection activity, also superior to **NNM** (53.4 %). Overall, most of the compounds indicated general inactivation activity against TMV at 500 $\mu$g/mL.

Based on the previous bioassays, the $EC_{50}$ values of some the title compounds were tested and are listed in **Table 4**. Compound **4a** exhibited excellent inactivation activity against TMV, with the $EC_{50}$ values of 12.5 $\mu$g/mL, which was better than that of **NNM** ($EC_{50}$=13.5 $\mu$g/mL). Moreover, compounds **4k** and **4l** exhibited the preferably curative activity against TMV, with $EC_{50}$ values of 11.5 and 12.1 $\mu$g/mL, respectively, which were superior to that of **NNM** ($EC_{50}$=82.2 $\mu$g/mL).

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**Table 3.** Antiviral activities of the target compounds against TMV *in vivo* at 500 $\mu$g/mL

**Table 4.** $EC_{50}$ values of the **4a**, **4d**, **4h**,**4k** and **4l** against TMV *in vivo*

**Figure 6.** Tobacco leaf morphology effects of the NNM and **4k**, **4h** and **4a** against TMV *in vivo* (Right leaf: not treated with compound, Left leaf: smeared with compound).

**Molecular docking studies**

Molecular docking studies (**Figure 7**) for **4a** with tobacco mosaic virus coat protein (TMV-CP) (PDB code:1EI7). Molecular docking results revealed that compound **4a** was the most preferred compound based on the analysis followed by **4d** and so on (**Table 3**). Compound **4a** binding orientation clearly is described by **Figure 7**, it forms one hydrogen bond with PHEA:12 with highest docking score (2.49 Å) among the designed molecules and the glide energy was also less compared to others showing few hydrophobic interactions with specific residues like as TYRA:139, VALA:75, LYSB:268 *etc*.

**Figure 7 .** Three dimensional diagrams of compound **4a** docked with TMV-CP.

**Figure 8.** Two dimensional diagrams of compound **4a** docked with TMV-CP. The two-dimensional diagram contains conventional hydrogen bonds, carbon–hydrogen bonds, Pi-Pi T-shaped bonds and Pi-Alkyl bonds.

**DISCUSSION**

**Structure-activity relationships of antibacterial activities**

The antibacterial results in **Tables 1** and **2** also indicated that the different groups on R had significant effects on the antibacterial activity of the title compounds. Obviously, the presence of -Cl-Ph group can effectively enhance the antibacterial activity against *Xac*. For example, the compounds **4k** and **4l**, which contain R=4-Cl-Ph and R=2-Cl-Ph groups respectively, exhibited $EC_{50}$ values of 55.53 and 129.1 $\mu$g/mL, which were better than that of **BT** ($EC_{50}$=153.7 $\mu$g/mL). Meanwhile, when R was substituted with thiophene-2-yl and 4-Cl-Ph groups, the corresponding compounds **4a**, **4b**, **4j** and **4k** exhibit remarkable antibacterial activities against *R.s*, with the $EC_{50}$ values of ranging from 0.43-4.76 $\mu$g/mL, which were better than that of **BT** ($EC_{50}$=49.5 $\mu$g/mL).

**Structure-activity relationships of antiviral activities**

The antiviral bioassay results indicated that the title compounds showed excellent antiviral activity against TMV. The preliminary SAR results were dropped based on the anti-TMV activity (as shown in **Table 3** and **4**). The results indicated that when R was the 4-$NO_2$-Ph (**4f**), 4-Cl-Ph (**4k**) or 2-Cl-Ph (**4l**) group, the corresponding title compounds exhibited good curative activity. Furthermore, when the R was 4-OMe-Ph group, the protective activity of corresponding compound **4h,** with the $EC_{50}$ values of 32.1 $\mu$g/mL, which was better than that of **NNM** ($EC_{50}$= 82.2 $\mu$g/mL).

## CONCLUSIONS

In short, a series of 1,4-pentadien-3-one derivatives containing a triazine scaffold were synthesized. The obtained bioassay results revealed that some of the title compounds exhibited excellent antibacterial or antiviral activities that were better than the commercial agents. In particular, compound **4a** showed prominent inactivation activity against TMV. Furthermore, compound **4a** had strong binding capability with TMV-CP. These results proved that the 1,4-pentadien-3-one derivatives containing a triazine scaffold possess antiviral and antibacterial agents.

## ADDITIONAL INFORMATION AND DECLARATIONS

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**Conflict of Interest**

The authors declare no conflict of interest.

**Supporting Information**

Supplemental information for this article can be found online.

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