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Synthesis and antiviral bioactivity of novel (1*E*, 4*E*)-1-aryl-5-(2-(quinazolin-4-yloxy)phenyl)-1,4-pentadien-3-one derivatives

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ABSTRACT

A series of novel (1*E*, 4*E*)-1-aryl-5-[2-(quinazolin-4-yloxy)phenyl]-1,4-pentadien-3-one derivatives were designed and synthesized by reacting substituent aldehyde with intermediates **4a**–**f**. Antiviral bioassays indicated that most of the compounds exhibited promising *ex vivo* antiviral bioactivities against tobacco mosaic virus (TMV) and cucumber mosaic virus (CMV) at 500 μg/mL. The relationship between structure and antiviral activity was also discussed. Compounds **5a**, **6e**, and **6g** could possess appreciable protective bioactivities on TMV *ex vivo* by approximately 50% (EC_{50}) at 257.7, 320.7 and 243.3 μg/mL. This study is the first to demonstrate that (1*E*, 4*E*)-1-aryl-5-(2-(quinazolin-4-yloxy)phenyl)-1,4-pentadien-3-one can be used to develop potential virucides for plants.

1. Introduction

Viruses are microorganisms that can act as intracellular parasites, posing the risk of host genome integration. Thus, controlling virus diseases is extremely difficult thus far. In recent years, progress has been made in screening antiviral agents with higher activities via computer-aided drug design, discovery and application of new targets of plant resistance diseases and viral replication, and molecular discovery of new structures with high antiviral activities from natural products in China. Several anti-plant viral agents were used to prevent agricultural diseases in China, a successful anti-plant viral agent was Ningnanmycin, which was isolated from *Strepcomces noursei* var. Xichangensis and commercialized by the Chengdu Institute of Biology, Chinese Academy of Sciences, and was found to be more effective in the treatment of plants virus [1]. Although the agent is useful in treating plants affected by tobacco mosaic virus (TMV) and cucumber mosaic virus (CMV), their use in field trials is largely limited because of their unsatisfactory curative rates and high control costs. Therefore, the search for new antiviral agents remains a great task in pesticide science [2].

Curcumin is the principal curcuminoid of the popular Indian spice turmeric, which is a member of the ginger family. Curcumin and its derivatives have extensive bioactivities, such as antiviral [3,4], antibacterial [5], antioxidative [6,7,8], anti-inflammatory [9], anticancer [10,11], anti-HIV [12], and anti-hyperglycemic actions [13]. The health-promoting effects of food have recently attracted the attention of researchers because food has the potential to prevent disease and promote health in ways not anticipated by traditional nutrition science. Eto et al. reported a new system that allows the simultaneous estimation of the multiple health-promoting effects of curcumin food constituents using informatics [14]. This system was able to simultaneously estimate health-promoting effects with reasonable precision from the same expression data of marker proteins. This novel system should prove to be an interesting platform for the evaluation of the health-promoting effects of food [14]. Despite its broad effects on biological functions, the potential use of curcumin as a therapeutic agent is severely affected by its low water solubility, poor *ex vivo* bioavailability, and rapid metabolism. In recent years, the structure of curcumin has been widely modified, focusing mainly on omitting the active methylene group and one carbonyl group, thereby yielding 1, 4-pentadiene-3-ones with new structures that still exhibit bioactivities. Our group reported several newly synthesized

Abrreviations: TMV, tobacco mosaic virus; CMV, cumber mosaic virus; *C. amaranticolor*, *Chenopodium amaranticolor*; EC_{50}, 50% effective concentration; ^1H NMR, ^1H nuclear magnetic resonance; ^{13}C NMR, ^{13}C nuclear magnetic resonance.

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curcumin analogs, including 1, 4-pentadiene-3-ones containing a phenoxy-substituted group with improved potential to inhibit PC3, BGC-823, and Bcap-37 cells *ex vivo* [15]. Among the synthesized ethers, (1*E*, 4*E*)-4-{[5-(2, 3-dichlorophenyl)-3-one-1,4-pentadieneyl]-phenoxy} ethyl acetate exhibits substantial antiproliferative activity with IC_{50} values ranging from 7.1 μmol/L to 7.3 μmol/L against various human cancer cell lines. Preliminary mechanism of antitumor action by DNA Ladder, Annexin V fluorescein isothiocyanate/propidium iodide double staining, and related studies indicated growth inhibition of PC3, BGC-823, and Bcap-37 cells by induction of tumor cell apoptosis. Nevertheless, to the best of our knowledge, no report exists on the inhibitory effects of (1*E*, 4*E*)-1, 5-diarylpentadien-3-one derivatives bearing a quinazolin pharmacophore on TMV and CMV.

To aid the development of highly active and readily available virus inhibitors, in current study, a series of new (1*E*, 4*E*)-1-aryl-5-(2-(quinazolin-4-yloxy)phenyl)-1,4-pentadien-3-one derivatives were developed and evaluated for their antiviral activities (Fig. 1). The results of bioassay revealed that the title compounds displayed different antiviral activities at 500 μg/mL. Compounds **5a**, **6e**, and **6g** could inhibit TMV *ex vivo* by approximately 50% (EC_{50} for protective effect) at 257.7, 320.7, and 243.3 μg/mL, respectively. Compared with the other compounds, **5r** and **5j** showed more potent antiviral activities. Their antiviral activities against CMV were found similar to that of Ningnanmycin (EC_{50} = 399.0 μg/mL). The present work demonstrates that (1*E*, 4*E*)-1-aryl-5-(2-(quinazolin-4-yloxy)phenyl)-1, 4-pentadien-3-one can be used to develop potential agrochemicals. To the best of our knowledge, this study is the first to report the antiviral activities of (1*E*, 4*E*)-1-aryl-5-(2-(quinazolin-4-yloxy) phenyl)-1, 4-pentadien-3-one derivatives.

2. Results and discussion

2.1. Chemistry

Target compounds **5a**–**z**, **6a**–**h** were synthesized by treatment of the substituted aldehyde with intermediates **4a**–**f** in the present of base (NaOH in water) in acetone at room temperature, as shown in Fig. 2. The key intermediates **4a**–**f** were synthesized by reacting (*E*)-4-(2-hydroxyphenyl)-3-butene-2-ones **3** with substituted 4-chloroquiazoline in the present of K_2CO_3 in CH_3CN at 30 °C–50 °C for 6 h, followed by dropwise addition of water. The resulting precipitate was filtered, washed with water, and then dried. The solid was recrystallized using ethanol to yield intermediates **4a**–**f**.

The structures of all the compounds were confirmed by IR, ^1H NMR, and ^{13}C NMR spectral analyzes and elemental analysis. The IR spectra of the title product **5e** exhibited an absorption wavelength at 3445 cm^{-1}, which indicates the presence of amidic N–CH–N. The stretching frequency at 1653 cm^{-1} was assigned to C=O vibrations, and the characteristic absorptions at 1491 cm^{-1} to 1620 cm^{-1} and 1219 cm^{-1} to 1316 cm^{-1} were attributed to the presence of C=C, N–C, and C–O–C groups, respectively. As indicated by ^1H NMR, all phenyl protons showed multiplets at 7.50 ppm to 6.71 ppm. The main characteristic of the ^1H NMR spectra for the compound was the presence of a high-frequency downfield singlet δ_H 8.45 for N–C–H protons. N–CH_3 absorption peaks showed a singlet at 3.75 ppm. The typical low-intensity carbon resonance frequencies at δ_C 188.61 and δ_C 14.00–36.24 in the ^{13}C NMR spectra of the compounds also confirmed the presence of C=O and CH_3, respectively.

2.2. Antiviral activity

2.2.1. Ex vivo antiviral activities of *5a–z, 6a–h* against TMV

The inhibitory effects of the title compounds on TMV were studied. The results of the preliminary bioassays were compared with those of Ningnamycin virucide and listed in Table 1. From the table, it can be seen that compounds **5a**–**z**, **6a**–**h** indicated weak to good antiviral activities against the tested virus. The title compounds **5a**–**z**, **6a**–**h** exhibited curative, inactivation, and protective rates ranging from 1.2% to 62.7%, 3.4% to 75.3%, and 5.3% to 72.0%, respectively. Compounds **5a**, **5b**, **5n**, **5q**, **5s**, **6e**, and **6h** exhibited significant protective effects against TMV, showing higher inhibitory activities (72.0%, 64.2%, 64.8%, 65.8%, 68.2%, 71.9%, and 74.2%, respectively) at 500 μg/mL than Ningnamycin (64.0%) at 500 μg/mL. Compounds **5a**, **5b**, **5n**, **5q**, **5s**, **6e**, and **6g** were shown to inactivate efficacy at 70.7%, 75.3%, 73.8%, 69.3%, 73.9%, 68.3%, and 68.2%, respectively, and they exhibited slightly lower inactivation activities than Ningnanmycin (87.2%) at 500 μg/mL. Compounds **5a**, **5b**, **5j**, **5n**, **6c**, **6e**, and **6g** exhibited good curative activities on TMV at 40.7%, 45.4%, 51.9%, 54.7%, 45.2%, 62.7%, and 54.7%, respectively, and they showed the same curative activity level as the standard reference Ningnanmycin at 500 μg/mL (55.4%). The variation among the different substitutes on R_1 and R_2 greatly affected the antiviral activities of the compounds against TMV. For example, when R_1 was 6-CH_3 and R_2 was 4-nitrophenyl, an apparent increase in antiviral activity was found. By contrast, when R_2 was 4-nitrophenyl and R_1 was introduced to 8-CH_3 and H, the corresponding compounds **5p** and **5c** at 500 μg/mL inhibited TMV at 20.3% and 45.4%, respectively. Further toxicity bioassays revealed that **5a**, **5j**, **5q**, **5s**, **6e**, and **6g** showed remarkable protective effects against TMV, with EC_{50} values of 257.7, 346.7, 349.8, 333.9, 320.7 and 243.3 μg/mL, respectively. These compounds possessed good protective activities against the tested virus and were even superior to the commercial agent Ningnamycin (EC_{50} = 370.8 μg/mL). This finding suggests that **5a**, **6e**, and **6g** may be promising lead structures for the discovery of new antiviral agents.

2.2.2. Ex vivo antiviral activities of the title compounds against CMV

Ex vivo antiviral tests of **5a**–**z**, **6a**–**h** against CMV were conducted, and the results are summarized in Table 2. The title compounds **5b**, **5c**, **5e**, **5g**, **5r**, **5n**, **6c**, **6e** and **6g** showed good protective effects against CMV, with efficacy rates of 56.1%, 55.6%, 55.2%, 57.2%, 58.5%, 62.8%, 55.1%, 54.0%, and 55.2%, respectively, which were close to that of Ningnamycin (60.1%). The protective rates of the other compounds ranged from 10.9% to 48.9%, which were lower than that of the positive control Ningnamycin (60.1%). The curative

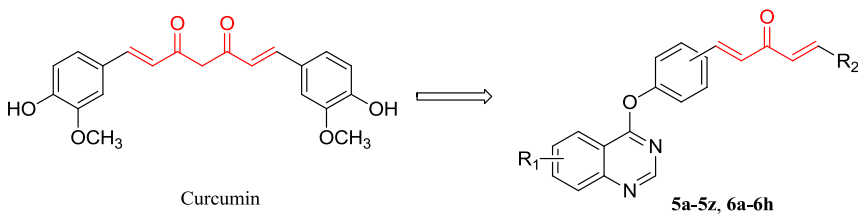

Fig. 1. Design of the target compounds.