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Original article

Synthesis and antiviral activities of novel 1,4-pentadien-3-one derivatives bearing an emodin moiety

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ABSTRACT

A series of 1,5-diaryl-1,4-pentadien-3-one derivatives bearing an emodin group were designed and synthesized by the combination of natural products. The antiviral activities against tobacco mosaic virus (TMV) and cucumber mosaic virus (CMV) *in vivo* were evaluated. Some of the derivatives displayed promising curative effect and protective activity against TMV. Compound **D5** showed appreciable curative bioactivity on TMV approximately of 50% at 306.2 μg/mL, which was superior to ningnanmycin (409.3 μg/mL).

1. Introduction

Viruses in crops are infectious particles, posing the risk of host genome integration [1] and leading to serious damage and enormous economic loss in primary agricultural crops, as well as vegetables and tobacco [2]. Taking tobacco mosaic virus (TMV) as an example, it is known as "plant cancer" and causes up to $100 million of economic loss each year worldwide [3]. Controlling viral diseases in plants has been extremely difficult thus far. Hence, the development of new antiviral molecules has attracted more and more attention.

Natural product-based antiviral agents have attracted more attention in recent decades due to their good activity, unique mode of action with low mammalian toxicity, and environmental friendliness [4,5]. Several natural products such as *seco*-pregnane steroids [6], triterpenoid glycosides [7,8], eudesmanolides, [9] triterpene saponins, [10] limonoids [11] *etc.* were found to show strong antiviral activities. In particular, an alkaloid named antofine from *Cynanchum komarovii* [12] showed excellent anti-TMV activity, and a large number of antofine-based agrochemicals with excellent anti-TMV activity were synthesized by Wang and co-workers [13–19]. NK-007, an antofine-based alkaloid demonstrates outstanding antiviral activity and was chosen for further development as a potent anti-TMV agent [20].

1,4-Pentadien-3-one is an important curcumin analogue with numerous potential biological activity [21–24] and serves an important function in discovering new antiviral molecules. In previous works, a series of 1,4-pentadien-3-one analogues containing pyrozole [25], quinazoline [1,26,27], glucopyranoside [28] and 1,3,4-oxadiazole moieties [29] with excellent antiviral activity against TMV and cucumber mosaic virus (CMV) have been reported. Song and co-workers also disclosed a series of 1,4-pentadien-3-one analogues containing rutin, which showed excellent anti-viral activities against TMV and CMV. This is a successful example for design of antiviral molecules by combination of two sub-structures of natural product analogues [30]. Continuing these investigations, the naturally derived molecule emodin has received increasing attention due to its broad spectrum bioactivity [31–36]. Encouraged by those descriptions above, we sought to synthesize some 1,4-pentadien-3-one derivatives bearing an emodin moiety by a combination of two structures of natural products, which may result in new 1,4-pentadien-3-one derivatives with good anti-viral activity. Accordingly, in this work, an attempt was made to link these two structures *via* a methylene ether (Scheme 1). Results of bioassays indicate that most synthesized compounds exhibit good antiviral

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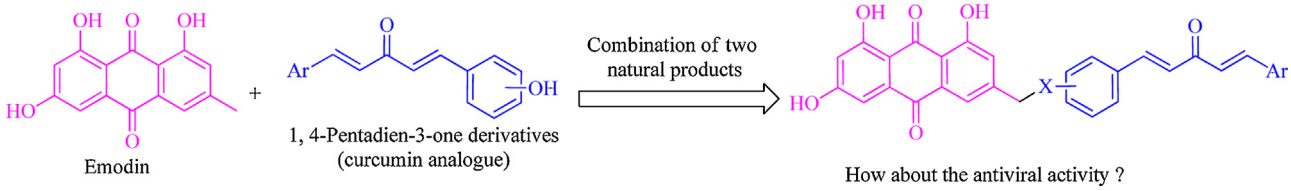

Scheme 1. The molecular design of target compounds.

activities against TMV and CMV. In particular, the EC_{50} value of compound **D5** against CMV was 306.2 μg/mL, which was much better than that of Ningnanmycin (409.3 μg/mL). To the best of our knowledge, this is the first report on antiviral activities of 1,4-pentadien-3-one analogs that includes emodin moieties to date.

2. Experimental

2.1. Synthesis

Unless noted, all solvents and reagents were freshly distilled or purified according to standard procedures. The ^{1}H NMR and ^{13}C NMR spectra (solvent $CDCl_3$ or MeOD or DMSO-d_6) were measured with a JEOL-ECX 500 NMR spectrometer operating at 500 and 125 MHz at room temperature with tetramethylsilane (TMS) as an internal standard, and chemical shifts are expressed in δ (ppm). Mass spectral studies were conducted on an Agilent 5973 organic mass spectrometer. The melting points of the compounds were determined on an XT-4 binocular microscope (Beijing Tech Instrument Co., China) and were not corrected. Analytical thin-layer chromatography (TLC) was performed on silica gel GF254 (400 mesh).

General procedures for synthesis of intermediate **B**: A mixture of emodin (2.20 g, 8.14 mmol) and K_2CO_3 (10.13 g, 73.27 mmol) was stirred in acetone (150 mL), and Me_2SO_4 (6.95 mL, 73.27 mmol) was added dropwise. The mixture was heated under reflux for 16 h, concentrated in vacuo, poured into 100 mL of water, and filtered to obtain a light yellow solid **A** (2.51 g, 98.0%). A mixture of **A** (1.60 g, 5.12 mmol), NBS (1.06 g, 5.94 mmol), AIBN (40 mg), and 150 mL CCl_4 was refluxed for 18 h. The light yellow solid was washed with water and filtered. The solid was chromatographed on silica gel (200–300 mesh) with petroleum ether: CH_2Cl_2 gradient (1:1 to 0:1) to obtain a light yellow solid (1.34 g).

General procedures for the preparation of intermediates **C1** to **C18**: 2-hydroxybenzaldehyde or 4-hydroxybenzaldehyde was reacted with acetone in the presence of base (NaOH in water) at room temperature for 18 h. The solution was acidified to obtain (*E*)-4-(2-hydroxyphenyl)-3-buten-2-one or (*E*)-4-(4-hydroxyphenyl)-3-buten-2-one. The key intermediates (1*E*,4*E*)-1,5-diaryl-1,4-pentadien-3-ones (**C1** to **C18**) were synthesized by reacting (*E*)-4-(2-hydroxyphenyl)-3-buten-2-one or (*E*)-4-(4-hydroxyphenyl)-3-buten-2-one with different aldehydes in the presence of base (NaOH in water) at room temperature for 12 h. The pH value of the mixture was adjusted with diluted hydrochloric acid to 5–6 and then filtered to obtain the solid.

General synthetic procedures for compounds **D1** to **D18**: A mixture of **B** (281 μmol), (1*E*,4*E*)-1,5- diaryl-1,4-pentadien-3-one (**C1** to **C18,** 281 μmol), K_2CO_3 (843 μmol), and 10 mg KI was stirred under reflux for about 2 h and concentrated *in vacuo*. The residue was poured into 50 mL water and filtered. The solid was chromatographed on silica gel (200–300 mesh) to obtain 1,3,8-trimethoxy-6-((2/4-((1*E*,4*E*)-3-oxo-5-aryl-1,4-pentadien-1-yl)phenoxy)methyl)-9,10-anthraquinone derivatives. The physical characteristics, ^{1}H NMR and ^{13}C NMR for all the synthesized compounds are listed in the Supporting information.

2.2. Antiviral bioassay against TMV and CMV

Tobacco seeds were provided by the Guizhou Institute of Tobacco. *Chenopodium amaranticolor* seeds were provided by Northwest Agriculture and Forestry University. The curative, protection, and inactivation effects against TMV and the curative effect against CMV *in vivo* were measured according to a previously described procedure [1,2]. The commercial compound ningnanmycin was used as a comparison. Three repetitions were conducted for each sample.

3. Results and discussion

3.1. Chemistry

The synthetic protocol of the 1,4-pentadien-3-one derivatives with an emodin moiety is depicted in Scheme 2. First, 1,3,8-trimethoxy-6-methyl-9,10-anthraquinone (**A**) was obtained with a good yield (up to 98%) by reaction of emodin with Me_2SO_4 in the presence of base (K_2CO_3) in refluxing acetone. Key intermediate 3-(bromomethyl)-1,6,8-trimethoxy-9,10-anthraquinone (**B**) was then synthesized by reacting **A** with NBS in the present of AIBN in CCl_4 under reflux condition for 18 h in good yield [37,38]. AIBN instead of benzoyl peroxide was used to reduce unwanted by-products [37,38]. Second, intermediates **C1** to **C18** were synthesized in good yields *via* two condensation reaction in presence of base (KOH) by the treatment of acetone with different aromatic aldehyde. Finally, the title compounds **D1** to **D18** were readily synthesized by treatment of (1*E*,4*E*)-1,5-diaryl-1,4-pentadien-3-ones with intermediate **B** in alkaline condition (K_2CO_3) in acetone at 50 °C, and KI was added as a catalyst to boost reaction times [1].

The structures of the synthesized compounds (**D1** to **D18**) were established on the basis of the spectroscopic data. As indicated by ^{1}H NMR, the coupling constants of the double bonds' protons were about 16.0 Hz. The position of the doublets may overlap with that of aryl protons. All aryl protons showed multiplets at δ 6.77 to δ 7.89. The main characteristic of the ^{1}H NMR spectra for the compounds was the presence of a singlet δ_H 5.28 for $-CH_2-O-$ protons, which connected the 9,10-anthraquinone part with the 1,4-pentadien-3-one moiety. Three $O-CH_3$ absorption peaks showed singlet at 3.93, 3.97 and 4.00 ppm, respectively. The typical carbon resonance frequencies at δ_C 181.49–189.24, 69.53 and 55.89–56.69 ppm in ^{13}C NMR also confirmed the existence of C=O, $-CH_2-O-$ and three $O-CH_3$, respectively.

3.2. Antiviral activities against TMV

The inhibitory effects of the 1,4-pentadien-3-one derivatives on TMV were evaluated and listed in Table 1. The results indicated that compounds **D1** to **D18** displayed weak to good antiviral activities against TMV. Some of them showed promising curative effect and protective activities, with curative and protective rates ranging from 22.8% to 52.6% and 19.2% to 56.8%, respectively. Particularly, compounds **D3**, **D4** and **D5** showed 48.3%, 50.1%, and 52.6% curative effects at 500 μg/mL, respectively. The protective activity of compounds **D5** and **D11** (55.4% and 56.8%, respectively)