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Synthesis and antiviral evaluation of novel 1,3,4-oxadiazole/thiadiazole-chalcone conjugates

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ABSTRACT

A series of novel 1,3,4-oxadiazole/thiadiazole–chalcone conjugates were synthesized and their in vitro and in vivo antiviral activities were evaluated via microscale thermophoresis method and half-leaf method, respectively. The in vitro results indicated that compounds **7g**, **7l**, **8h**, and **8l** displayed good antiviral activity against TMV, with the binding constant values of 5.93, 6.15, 6.02, and 5.04 μM, respectively, which were comparable to that of Ninnanmycin (6.78 μM) and even better than that of Ribavirin (99.25 μM). The in vivo results demonstrated that compounds **7g**, **7l**, **8h**, and **8l** exhibited remarkable anti-TMV activity with the EC_{50} values of 33.66, 33.97, 33.87 and 30.57 μg/mL, respectively, which were comparable to that of Ningnanmycin (36.85 μg/mL) and superior to that of Ribavirin (88.52 μg/mL). Interestingly, the trend of antiviral activity in vivo was consistent with the in vitro results.

Introduction

Tobacco mosaic virus (TMV), a well-known plant virus can infect at least 400 individual species such as tobacco, cucumber, tomato, and many ornamental flowers.[1,2] The loss caused by TMV is up to $ 100 million worldwide each year.[3] Unfortunately, few effective antiviral agents for completely controlling TMV infection are available. Therefore, the search of novel, highly effective, friendly to environmentally friendly antiviral agents with unique mode of action still remains a challenging task in pesticide research.

TMV is composed of RNA and coat protein (CP) subunits; viral RNA and CP self-assemble readily in vitro to virion.[4] TMV CP can assemble into four main alpha-helices which are joined by a prominent loop proximal to the axis of the virion. This alpha-helices can ensure that the virion remains stable[5,6] and play a positive role in regulating production of subgenomic mRNAs, translation of mRNAs, transcription and translation pathways of TMV RNA and production of one or more viral proteins which are consistent with multi-functionality of CP molecules.[7] Furthermore, we recently reported the crystal structure of a four-layer aggregate of engineered TMV CP.[8,9] The binding constant (K_d) between compound and TMV CP, which is an important parameter for drug discovery, was investigated by microscale thermophoresis (MST). The results revealed that TMV CP was the key functional protein for virus infecting the host,[10–12] and might be a potential action target for development and screening of anti-TMV drugs.

Chalcones, a kind of important natural products in plants,[13,14] have been used in drug and pesticide design in consequence of their various biological activities, such as anticancer,[15–17] antibacterial,[18,19] anti-fungal,[20,21] anti-inflammatory,[22] anti-plasmodial,[23] antiparasitic,[24] and antiviral[14,25] effects. In our previous work, we have reported a series of chalcone derivatives (**A** and **B**, Fig. 1), with remarkable bioactivities against TMV.[11,26] The 1,3,4-oxadiazole/thiadiazole scaffold represented a key motif in heterocyclic chemistry, possessing a variety of biological activities, including antibacterial,[27–29] anticancer,[30] antitubercular,[31] antiviral[32] and other effects. In our previous work, we found that several 1,3,4-oxadiazole/thiadiazole derivatives (**C** and **D**, Fig. 1) displayed good antiviral activities against TMV and the structure–activity relationship (SAR) revealed that 5-phenyl-1,3,4-oxadiazole derivatives showed excellent antiviral action.[33,34] These findings demonstrated that chalcone and 1,3,4-oxadiazole/thiadiazole derivatives exhibited

Abbreviations: TMV, tobacco mosaic virus; ^{1}H NMR, ^{1}H nuclear magnetic resonance; ^{13}C NMR, ^{13}C nuclear magnetic resonance; HRMS, high-resolution mass spectrometer; EC_{50}, half-maximal effective concentration; MST, microscale thermophoresis; SAR, structure–activity relationship; TMV CP, tobacco mosaic virus coat protein.

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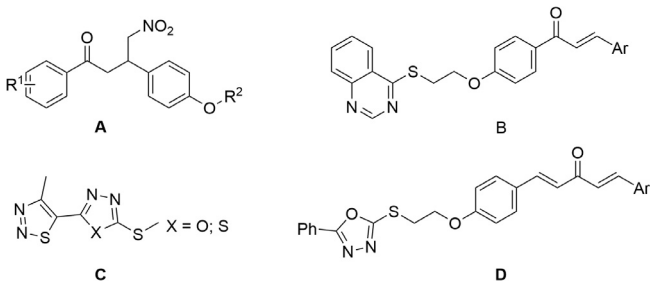


Fig. 1. Structures of the compounds in our previous studies.

good curative and protective effects against TMV, but it was still lack of compounds with high inactivating activity.

As part of our ongoing drug discovery program in developing potential antiviral agents on the basis of natural product chalcone scaffold, we combined 5-phenyl-1,3,4-oxadiazole/thiadiazole and chalcone with 1,2-dibromoethane to generate a series of novel 5-phenyl-1,3,4-oxadiazole/thiadiazole–chalcone conjugates (Fig. 2). In this letter, we report their synthesis, in vitro and in vivo antiviral activity, and preliminary structure–activity relationship analyses.

The synthetic route is depicted in Scheme 1. The 5-phenyl-1,3,4-oxadiazole/thiadiazole-2-thiols **3/4** were prepared by literature methods.[29] Chalcones **5a–5m** were synthesized by Claisen–Schmidt condensation reaction of *p*-hydroxy-benzaldehyde and substituted acetophenones.[26] The key intermediates **6a–6m** were obtained according to previous report.[11] The 5-phenyl-1,3,4-oxadiazole/thiadiazole–chalcone conjugates were prepared from 5-phenyl-1,3,4-oxadiazole/thiadiazole-2-thiols **3/4** and chalcones **6a–6m** via thioetherification.[34] The target compounds were characterized by ^{1}H NMR, ^{13}C NMR and HRMS, the experimental details and data are presented in the supplementary data file. The main characteristic of the ^{1}H NMR spectra of **7a** as a representative compound was the appearance of two triplet peaks at δ_H 4.45 and 3.69 ppm, which is the O–CH_2– and S–CH_2– proton absorption peak, respectively. The low-frequency downfield doublets at δ_H 8.00–6.96 ppm indicated =C–H and phenyl protons, of which, the two doublets at δ_H 7.76 (d, 1 H, J = 15.5 Hz) and δ_H 7.37 (d, 1 H, J = 15.5 Hz) ppm demonstrated that the configuration of the double bond of chalcone is "*E*". Typical chemical shifts of ^{13}C NMR spectra at around δ_C 166.16 and 163.90 ppm indicated the presence of the 1,3,4-oxadiazole moiety, while peaks at around δ_C 188.87, 66.06, and 31.60 ppm are confirmed the presence of C=O, –OCH_2–, and –SCH_2–, respectively. HRMS found $[M+H]^+$ mass to be 463.08820, which accord with the calculated value for $C_{25}H_{20}O_3N_2ClS$ $[M+H]^+$ 463.08777.

In this study, the in vitro anti-TMV activity of the target compounds was performed via the MST method. The commercially available agents Ribavirin and Ningnanmycin were used as positive control and the results are listed in Table 1. According to Table 1, most of the compounds displayed good antiviral activity against TMV due to the interactions between the target compounds and TMV CP. Compounds **7f** (Ar = 4-F-C_6H_4), **7g** (Ar = 2,4-diCl-C_6H_3), **7l** (Ar = thiophene), **8h** (Ar = Ph), **8 l** (Ar = thiophene), and **8m** (Ar = furan) exhibited strong combining capacity to TMV CP, with the K_d values of 8.78, 5.93, 6.15, 6.02, 5.04, and 8.89 μM, respectively, which were better than that of Ribavirin (99.25 μM), lead compounds B (68.58 μM) and D (19.36 μM), but similar to that of Ningnanmycin (6.78 μM). SAR analyses indicated that electron-withdrawing groups were favorable for combining capacity of compound, these findings were evidenced by the activity order of

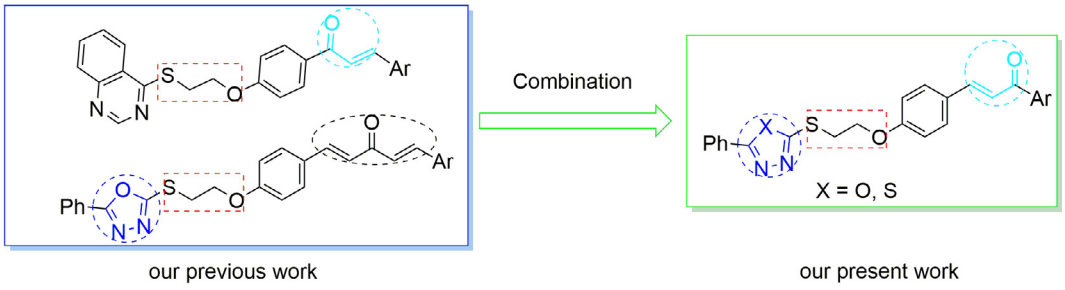
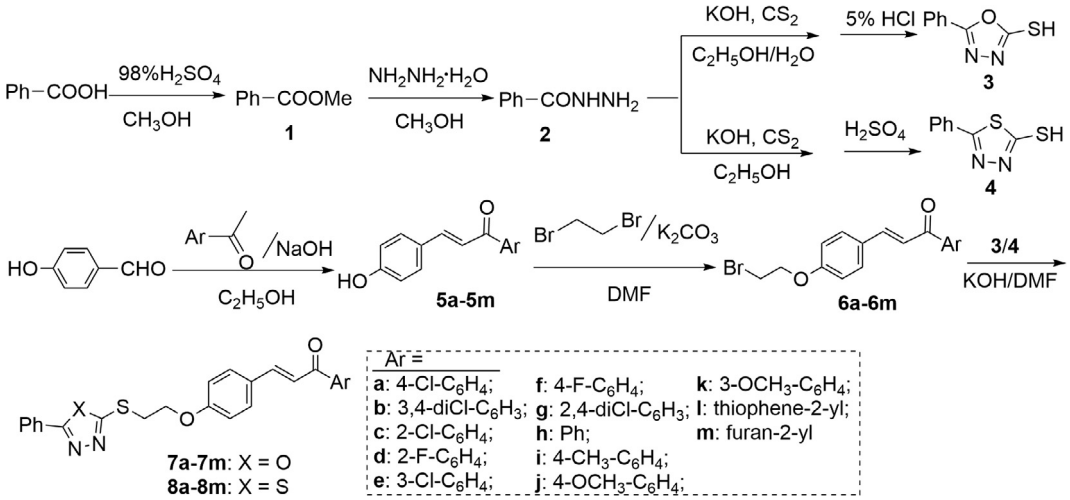


Fig. 2. Design of novel 1,3,4-oxadiazole/thiadiazole–chalcone conjugates.



Scheme 1. Synthetic route of novel 1,3,4-oxadiazole/thiadiazole–chalcone conjugates.