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Syntheses, antiviral activities and induced resistance mechanisms of novel quinazoline derivatives containing a dithioacetal moiety

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ABSTRACT

A series of novel quinazoline derivatives containing a dithioacetal moiety were designed and synthesized, and their structures were characterized by ^{1}H nuclear magnetic resonance, ^{13}C nuclear magnetic resonance, and high-resolution mass spectrometry. Bioassay results indicated that compound **4b** exhibited remarkable protective activity against cucumber mosaic virus (CMV, EC_{50} = 248.6 μg/mL) and curative activity against potato virus Y (EC_{50} = 350.5 μg/mL), which were better than those of ningnanmycin (357.7 μg/mL and 493.7 μg/mL, respectively). Moreover, compound **4b** could increase the chlorophyll content in plants, improve photosynthesis, and effectively induce tobacco anti-CMV activity.

Abbreviations: ^{1}H NMR, ^{1}H nuclear magnetic resonance; ^{13}C NMR, ^{13}C nuclear magnetic resonance; HRMS, high resolution mass spectrometry; CMV, cucumber mosaic virus; PVY, potato virus Y; DMSO, dimethyl sulfoxide; CC, cellular components; MF, molecular functions; BP, biological processes; COS, chitosan oligosaccharide; DEPs, differential proteomics analysis; GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; PS I, photosystem I; PS II, photosystem II; ATP, adenosine triphosphate; NPR1, nonexpressor of pathogenesis related genes 1; CAT, catalase 1; PR1, related protein 1; ICS1, isochorismate synthase 1; SOD, superoxide dismutase; PAL, phenylalanine ammonia-lyase

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1. Introduction

Cucumber mosaic virus (CMV) and potato virus Y (PVY) are two well-known agricultural viruses, which can infect many plants and cause serious economic losses in annual agricultural production worldwide [1,2]. However, the control effects of existing anti-plant virus reagents against these plant viruses are generally unsatisfactory. For instance, ningnanmycin, one of the successfully registered and widely used as plant virus inhibitor, has only 30%–60% control effect against these plant viruses [3,4]. Thus, the development of potent novel molecules for controlling plant virus disease is still required.

Quinazoline is one important heterocyclic structure found in many synthetic and naturally occurring products [5]. As a natural alkaloid, quinazoline has been the focus of considerable attention because of its potential biological activities in agrochemicals, such as antibacterial [6], antifungal [7], and antiviral activities [8]. In our previous work, several series of quinazoline derivatives were synthesized and exhibited good antiviral activities [9–12]. Among these quinazoline derivatives, when the derivatization site is at position 4 of the quinazoline ring, the compounds showed good activities against tobacco mosaic virus (TMV) and CMV in vivo. For example, a series of 1,4-pentadien-3-one derivatives containing the 4-thioquinazoline moiety were synthesized, and these derivatives exhibited good antiviral activity against CMV. Moreover, we also detected (1*E*,4*E*)-1-aryl-5-(2-(quinazolin-4-yloxy)phenyl)-1,4-pentadien-3-one derivatives with excellent protective activities against TMV in vivo.

Dithioacetal is the sulfur analog of acetal. Recent research on dithioacetal derivatives have mainly focused on synthetic methodology [13–15]. In our previous study, we observed for the first time that the dithioacetal derivatives exhibited remarkable antiviral activities against CMV and PVY, and the compound 2,2′-((4-(chlorobenzyl)oxy)-3-methoxyphenyl)methylene-bis(2-hydroxyethyl) [16] (**6f**, Fig. 1) is being further developed as a potential antiviral agent. On the basis of these facts, we sought to incorporate a dithioacetal substructural unit into the backbone of quinazoline to obtain novel quinazoline derivatives with good antiviral activities. To continue our work on developing novel and promising antiviral agents, a series of novel quinazoline derivatives containing a dithioacetal moiety were designed and synthesized. The antiviral activities of all of the synthesized compounds against CMV and PVY were assessed. Compound **4b** showed excellent antiviral activities, which is related to that compound **4b** can increase the chlorophyll content in plants and improve photosynthesis, and then effectively induce tobacco antiviral activity.

2. Results and discussions

2.1. Chemistry

The synthetic route of compounds **4a–4x** is depicted in Scheme 1. Intermediate **2** was synthesized according to the previously presented method in the literature [9]. Intermediate **3** was prepared according to the method previously presented in the literature [8]. Target compounds **4a–4x** were synthesized by condensation of 1 equivalent of aldehyde and 2 equivalent of thiol, with $NaHSO_4{\cdot}SiO_2$ as the catalyst. Notably, in the syntheses of these types of compounds, we previously used $ZrCl_4$ as catalyst and obtained a good yield (usually greater than 95%). However, in the syntheses of **4a–4x**, the yield when using $ZrCl_4$ as catalyst is usually only approximately 50%. When $ZrCl_4$ was replaced with $NaHSO_4{\cdot}SiO_2$ as the catalyst, the yield considerably increased (isolation yield was usually greater than 80%). In addition, compared with $ZrCl_4$, $NaHSO_4{\cdot}SiO_2$ has many advantages as catalyst in the reaction, such as water insensitivity, inexpensive, and could be used repeatedly. The structures of all compounds were confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS.

2.2. Biological activity

2.2.1. Antiviral activities of compounds *4a–4x*

In this study, the antiviral activities of target compounds **4a–4x** against CMV and PVY were evaluated using previously presented methods [16–18], and the commercial agent Ningnanmycin and compound **6f** were used as post control. The results of the bioassay against CMV and PVY were shown in Table 1 and indicate that most of the title compounds exhibited good to excellent curative activities in vivo. Compounds **4b**, **4i**, **4o**, and **4p** showed excellent curative activities against CMV at 500 μg/mL with inhibition rates of 58.3%, 56.5%, 58.2%, and 56.0%, respectively, which were better than those of Ningnanmycin (50.0%) and **6f** (54.2%). Compound **4b** showed excellent protective activities against CMV with inhibition rate of 61.1%, which was better than those of Ningnanmycin and **6f**. Moreover, compounds **4b**, **4h**, **4i**, and **4o** exhibited similar or even higher curative activities (i.e., 53.5%, 51.7%, 53.7% and 51.9%, respectively) against PVY than that of **6f** (52.0%) and better than that of Ningnanmycin (46.5%). Compounds **4b**, **4h**, **4i**, **4q**, and **4s** exhibited comparative protective activities (i.e., 52.0%, 52.2%, 54.3%, 52.3%, and 51.3%, respectively) against PVY to that of **6f** (54.5%) and better than that of Ningnanmycin (47.3%).

On the basis of a preliminary biological evaluation, the EC_{50} values of the curative and protective activities against CMV and PVY of some

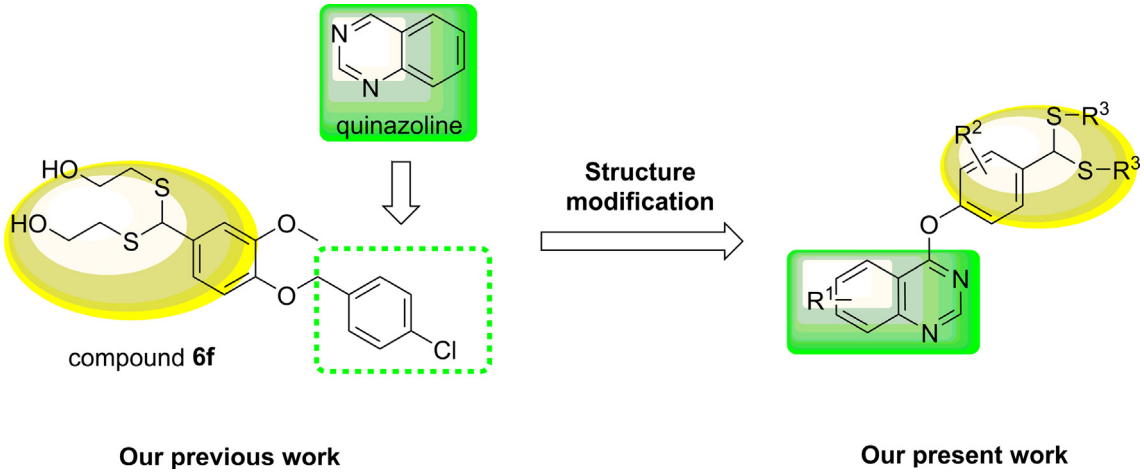

Fig. 1. Design of the title compounds **4a–4x**.