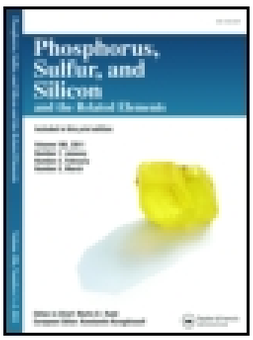

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Synthesis and antiviral activity of novel thioether derivatives containing 1,3,4-oxadiazole/thiadiazole and emodin moieties

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Abstract

A series of novel thioether derivatives containing 1,3,4-oxadiazole/thiadiazole and emodin moieties were designed and synthesized. The structures of the target compounds were confirmed

by ^{1}HNMR, ^{13}CNMR, IR, and elemental analysis. The results of bioactivity analysis showed that most of the target compounds exhibited moderate to good antiviral activity against tobacco mosaic virus (TMV) at a concentration of 500 mg/L. Especially, among the title compounds, **Y2**, **Y8** and **Y10** possessed appreciable curative activity *in vivo*, with inhibition rates of 50.51%, 52.08% and 54.62%, respectively, which were similar to that of Ningnanmycin (53.40%).

Keywords

Thioether derivative;1,3,4-oxadiazole/thiadiazole; emodin; synthesis; antiviral activity; tobacco mosaic virus.

Introduction

Plant diseases, caused by the tobacco mosaic virus (TMV),were found worldwide and infected members of 9 plant families and at least 125 species, including tobacco, tomato, pepper, cucumbers, and a number of ornamental flowers [1]. Therefore, TMV, known as a "plant cancer", is difficult to control. Ningnanmycin, as shown in Figure S 1 (Supplemental Materials), is more effective in TMV. However, the use of Ningnanmycin for field trials is largely limited by its unsatisfactory control efficiency [2].Therefore, it's a significant challenge for the development of a highly efficient, novel, and environmentally antiviral agent.

Emodin, an anthraquinone-based pigment and found in rhubarb, polygonumcuspidatum, aloe, and other polygonaceae medicinal plants, is the most widely distributed one hydroxyanthraquinones [3, 4]. Emodin shows wide range of pharmacological activities, such as antibacterial, anti-inflammatory, anti-oxidation, antitumor, antivirus activities [5--9]. In the agricultural field, emodin also shows good antifungal activity [9], antiviral activity [10], and insecticidal activity [11]. Therefore, studies on the structure modification of emodin have attracted a considerable attention.

1,3,4-Oxadiazole/Thiadiazole,a privileged structure, represents a key motif in heterocyclic chemistry and occupies a prime place in medicinal chemistry due its competence to exhibit a wide range of pharmacological activities. Recently, derivatives of 1,3,4-oxadiazole/thiadiazole have been reported for their antibacterial [12, 13], antifungal [14--15], antiviral[16],

inflammatory [17], antianxiety [18],and anti-tubercular activities [19]. In our previous work, we have reported a series of 1,3,4-oxadiazole/thiadiazole derivatives which showed better antibacterial [12--13], antifungal [14--15],antiviral activities [16].

Meanwhile, thioether groups are known to be associated with a wide range of biological activities, such as antibacterial [20--22], antiviral [23, 24], antitumor [25], and other biological activity. In recent years, study of this group has attracted growing attention from chemists and biologists. In our previous studies, we have also designed and synthesized a variety of thioether derivatives and evaluated for their antiviral activity, the results showed that these compounds displayed excellent antiviral activity against TMV [26, 27].

In the present study, to aid the development of novel leading compounds with highly active and readily available antiviral agents, we aim to introduce a 1,3,4-oxadiazole/ thiadiazole group into the emodin group, using --SCH_2-- group as a bridge, to build a novel family of bioactive molecules. Herein, 14 novel thioether derivatives containing 1,3,4-oxadiazole/thiadiazole and emodin moieties were designed and synthesized, the structures of the target compounds **Y1**--**Y14** were confirmed by ^{1}HNMR,^{13}CNMR,IR, and MS (HREI) analysis. Bioassays identified that the target compounds possessed moderate to good curative activity against TMV at the concentration of 500 mg/L with the inhibition rates of 31.55%--54.62%. Especially, among the target compounds, compounds **Y2**, **Y8**, and **Y10** possessed appreciable curative activity *in vivo*, with

the inhibition rates of 50.51%, 52.08% and 54.62%, respectively, which were similar to that of Ningnanmycin (53.40%).

Results and Discussion

Chemistry

The synthetic route of the title compounds **Y1--Y14** is illustrated in Scheme 1.

The intermediate **1** was obtained by the hydroxyl methylation of emodin; the reaction mixture of emodin, $(CH_3)_2SO_4$ and $K_2CO_3$was refluxed in acetone for 8 h and cooled down to room temperature. Then the mixture was poured into water and separated to obtain intermediate **1**. The intermediate **1** and NBS were refluxed, using AIBN as a catalyst, for 24 h. The mixture was cooled down to room temperature and then poured into water and separated to obtain intermediate **2**. Meanwhile, intermediate **3** was prepared according to the reported methods [12--13]. Finally, intermediates **2** and **3** were reacted in acetone for 2 h at room temperature and the purified compounds were separated using thin chromatography (dichloromethane/ethyl acetate, 25:3) to afford the target compounds **Y1--Y14**.

To optimize the reaction conditions for the preparation of the target compounds, the synthesis of the target compound **Y1** was used as the model reaction. The effect of different reaction time, reaction temperature, and solvents on the yields of the target compounds was determined and the results were summarized in Table S 1 (Supplemental Materials). As shown in

Table S 1, the highest yield (68%) of the target compound **Y1** was obtained under the following optimal conditions: solvent, acetone; base, K_2CO_3; temperature, 25°C; and time, 2 h. The structures of all target compounds **Y1--Y14** were confirmed by ^{1}H NMR, ^{13}C NMR, IR, and elemental analysis and physical and analytical data of the target compounds **Y1-Y14** were shown in Table S 2 (Supplemental Materials). From the spectral data of compounds **Y1--Y14**, the ^{1}H NMR spectrum showed two characteristic peaks near δ3.98 to 3.94 ppm for the Ar-OCH_3 proton and near δ4.67 to 4.50 ppm for the S--CH_2--Ar proton. The IR spectrum of all the target compounds showed broad absorption bands of around 3100 to 3020 cm^{-1} for Ar--H, and 2964 to 2914 cm^{-1} for CH_2,C = O for in the range of 1675 to 1660 cm^{-1} and C = N for amide in the range of 1600 to 1590 cm^{-1}. As shown in Table S 2, the elemental analysis of all target compounds is in good agreement with the theoretical data.

Antiviral activity

The antiviral activity against TMV of the target compounds**Y1--Y14** was determined using the half-leaf method [28--29]. As shown in Table S3, the bioassay results indicated that all of the target compounds exhibited moderate to good anti-TMV activity at the concentration of 500 mg/L with the inhibition rates of 31.55%--54.62%. Among the target compounds, compounds **Y2**, **Y8** and **Y10** exhibited better curative activity against TMV at 500 mg/L, with the inhibition rates of 50.51%, 52.08% and 54.62%, respectively, which were similar to that of Ningnanmycin (53.40%).

Experimental

General methods

Emodin was purchased from Xi'an Jiatian Biological Technology Co. Ltd. Unless otherwise stated, all reactants and reagents were purchased from commercial suppliers. The melting points were determined on an XT-4 binocular microscope (Beijing Tech Instrument, China) and were not corrected. Mass Spectra were recorded using LC-MS 1100/MSD spectrometer (Agilent, USA). ^{1}HNMR and ^{13}C NMR(solvent $CDCl_3$) spectral analyses were performed on a JEOL ECX 500 NMR spectrometer operated at 500 MHz for ^{1}H NMR, 125 MHz for ^{13}C NMR at room temperature and TMS as the internal standard. Elements were analyzed with an Elemental Vario-III CHN analyzer, and IR spectra were recorded in KBr on a Bruker VECTOR 22 spectrometer. Analytical thin layer chromatography (TLC) was performed on silica gel GF254.

General procedure for preparation of the target compounds Y1--Y14

To an oven-dried three-neck 50 mL round-bottom flask fitted with a magnetic stirring bar, emodin (1.0 equiv.), $(CH_3)_2SO_4$ (9.0 equiv.), K_2CO_3 (9.0 equiv.) and acetone (25 mL) was added. The reaction mixture was refluxed for 8 h and cooled down to room temperature, then the mixture was poured into water and separated the precipitate to obtain the intermediate **1**. The intermediate **1** (1.0 equiv.), NBS (1.16 equiv.) and acetone (25 mL) were slowly added a 50 mL three-necked round-bottom flask. The reaction mixture was refluxed with AIBN as catalyst for

24h and then cooled down to room temperature, then the solvent was poured into water and separated to obtain the intermediate **2**. Finally, the target compounds **Y1**--**Y14** were synthesized via condensation of intermediates **2** (1.0 equiv.), and **3** (1.0 equiv.), K_2CO_3 (3.0 equiv.) with KI in acetone (25 mL) at the room temperature for 2h. The purified compounds were obtained from column chromatography on silica gel.

Complete characterization of other compounds and sample ^{1}H and ^{13}C NMR spectra are presented in the Supplemental Materials (Figure S 2 -- S 43)

Characterization of final compounds (Y10)

1,3,8-Trimethoxy-6-(((5-methyl-1,3,4-thiadiazol-2-yl)thio)methyl)anthracene-9,10-dione (Y10). Yield 82.3%, m.p. 181--182°C;^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.82 (s, 1H, Ar-H), 7.42 (s, 1H, Ar-H), 7.30 (s, 1H, Ar-H), 6.75 (s, 1H, Ar-H), 4.57 (s, 2H, S--CH_2), 3.96 (s, 3H, Ar--OCH_3), 3.94 (s, 3H, Ar--OCH_3), 3.94 (s, 3H, Ar--OCH_3), 2.70 (s, 3H, S--C--CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ183.9 (C = O), 181.5 (C = O), 165.7 (Ar--C = N), 163.9 (S--C--S), 163.8 (Ar--C), 161.8 (Ar--C), 159.9 (Ar--C), 142.7 (Ar--C), 136.3 (Ar--C), 134.9 (Ar--C), 123.1 (Ar--C), 119.4 (Ar--C), 119.0 (Ar--C), 118.3 (Ar--C), 105.4 (Ar--C), 102.0 (Ar--C), 56.7 (Ar--OCH_3), 56.5 (Ar--OCH_3), 55.9 (Ar--OCH_3), 37.6 (Ar--CH_2), 15.7 (S--C--CH_3); IR (KBr, cm^{-1}) ν 1669 (C = O str.), 1595 (C = N str.), 1250 (Ar--OCH_3str.), 1070 (C--S str.), 1020 (N--N

str.); MS *m/z*: 443 $[M+H]^+$. Anal. Calcd for $C_{21}H_{18}N_2O_5S_2$: C, 57.00; H, 4.10; N, 6.33; Found: C, 56.66; H, 4.50; N, 6.36.

Conclusion

In summary, we synthesized a series of novel thioether derivatives containing 1,3,4-oxadiazole/thiadiazole and emodin moieties, and the anti-TMV activity of the target compounds **Y1--Y14** were evaluated using the half-leaf method *in vivo*. The results of bioactivity showed that most of synthesized compounds have a certain anti-TMV activity. In particular, compounds **Y2**, **Y8** and **Y10** were found to possess appreciable curative activity against TMV at the concentration of 500mg/L, with inhibitory rates of 50.51%, 52.08% and 54.62%, respectively, which were similar to that of Ningnanmycin (53.40%). To the best of our knowledge, this is the first report on the synthesis and antiviral activity of thioether derivatives containing 1,3,4-oxadiazole/thiadiazole and emodin moieties.

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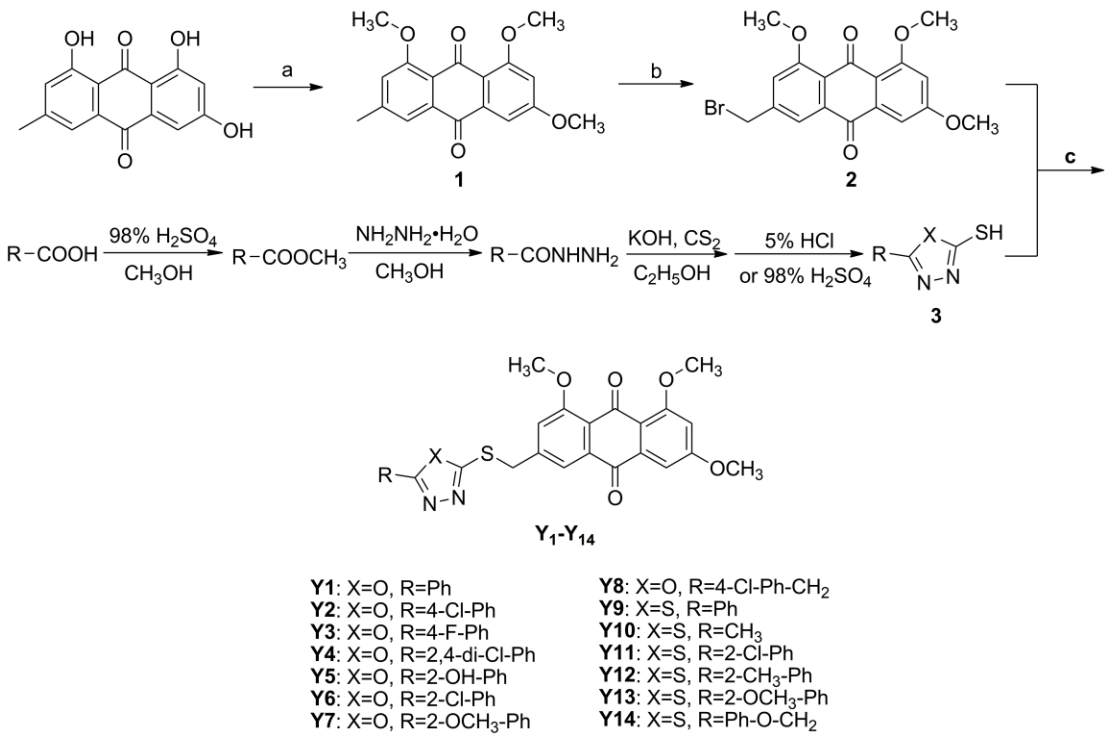

Y1: X=O, R=Ph
Y2: X=O, R=4-Cl-Ph
Y3: X=O, R=4-F-Ph
Y4: X=O, R=2,4-di-Cl-Ph
Y5: X=O, R=2-OH-Ph
Y6: X=O, R=2-Cl-Ph
Y7: X=O, R=2-OCH_3-Ph
Y8: X=O, R=4-Cl-Ph-CH_2
Y9: X=S, R=Ph
Y10: X=S, R=CH_3
Y11: X=S, R=2-Cl-Ph
Y12: X=S, R=2-CH_3-Ph
Y13: X=S, R=2-OCH_3-Ph
Y14: X=S, R=Ph-O-CH_2

Scheme 1: The synthetic route of the target compounds**Y1--Y14**. **a**: $(CH_3)_2SO_4$, K_2CO_3, acetone, reflux, 8 h; **b**: NBS, AIBN, CCl_4, reflux, 24 h; **c**: K_2CO_3, KI, acetone, 2 h.