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Antiviral activity and interaction mechanisms study of novel glucopyranoside derivatives

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ABSTRACT

Novel glucopyranoside derivatives were synthesized and evaluated for their antiviral activities against tobacco mosaic virus (TMV). Bioassay results indicated that some of the target compounds exhibited good in vivo antiviral activities against TMV. Among the title compounds, **f6** showed appreciable inactivation effect against TMV, with the 50% effective concentration value (EC_{50}) of 52.9 μg/mL, which was better than that of ribavirin (145.1 μg/mL). In addition, interaction between **f6** and TMV-CP was characterized by fluorescence spectroscopy, isothermal titration calorimetry (ITC), and microscale thermophoresis (MST). Results showed that **f6** bound to TMV-CP with micromole affinity, and thermodynamic parameters suggested that this interaction was typically endothermic and spontaneous, with 1:1.53 ratio of TMV-CP to **f6**. Thus, the synthesized glucopyranoside derivatives containing 1,4-pentadien-3-one moiety could be promising antiviral agents.

Tobacco mosaic virus (TMV) is a kind of severe plant virus and extremely difficult to control due to its absolute parasitism, which hence endows it with another name 'plant cancer'. So far the activities of all commercialized antiviral agents for plants are around 30–50% at 500 μg/mL.[1] Ribavirin, a successful antiviral agent, is widely used to prevent TMV disease. However, its antiviral activity is consistently less than 50% at 500 μg/mL.[2] In addition, anti-plant virus agent research is not like pharmaceutical research. We all know that many targets of pharmaceutical research, such as the structure and function of target protein, or even the signal transduction pathway of target proteins are already known.[3] But for anti-plant virus agent research, only very few molecular targets are investigated and can be used in agrochemical design and discovering,[4] which on the other hand increases the difficulty of discovery of antiviral molecules for plants. Therefore, it's a challenge for the development of novel, effective, and environmentally safe antiviral agent.[5]

Glycoside, widely distributed in plants, has increasingly aroused attention because of its various pharmacological effects,[6] such as anticancer,[7] antiviral,[8] antiproliferative,[9] anti-HBV,[10] anti-HIV,[11] antihyperglycemic,[12] antimicrobial,[13] antioxidant,[14] and cytotoxic[14] activities. Recently, a large number of natural glycosides were found to exhibit outstanding antiviral activities against TMV.[15–21] Moreover, a number of synthetic glycosides derivatives were found to exhibit antiviral activities against TMV. For example, Dai and co-workers synthesized a series of glycosides derivatives containing 1,5-diacetyl-2,4-dioxohexahydro-1,3,5-triazine moiety with good antiviral activity against TMV.[22] Meanwhile, Wang et al. synthesized a series of novel glycoconjugates of phenanthroindolizidine alkaloids, and found that these compounds exhibited higher antiviral activities against TMV than commercialized antiviral agents.[23]

Curcumin, a non-nutritive and non-toxic compound, was isolated from the plant *Curcuma longa* L. A number of studies documented that curcumin and its derivatives exhibited multiple pharmacological activities, such as antiviral,[24] anti-angiogenic,[25] antimicrobial,[26] anticancer,[27] antioxidative,[28] anti-inflammatory,[29] and anti-HIV[30] activities. Additionally, curcumin and its derivatives have been also found to possess fine activities against plant virus.[31–34] For example, our research group has synthesized a series of 1,4-pentadiene-3-one derivatives containing pyrazole, oxime ester, and quinazoline groups with good antiviral activities.[32]

Abbreviations: EC_{50}, 50% effective concentration; ^1H NMR, ^1H nuclear magnetic resonance; ^{13}C NMR, ^{13}C nuclear magnetic resonance; TMV, tobacco mosaic virus; TBAB, tetrabutylammonium bromide; PEG, polyethylene glycol; TMV-CP, tobacco mosaic virus coat protein; ITC, isothermal titration calorimetry; MST, microscale thermophoresis; DCM, dichloromethane; mp, melting point.

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Notably, a number of quinazolin-1,4-pentadien-3-one derivatives[33] and 4(3*H*)-quinazolinone-1,4-pentadien-3-one derivatives exhibited better protection and curative effects in vivo against TMV than Ningnanmycin.[34] However, all of the synthesized compounds poorly inactivated TMV. Thus, the development of an excellent antiviral agent with a simple structure is needed.

Based on the above finding, we aim to introduce a glucopyranoside fragment into the structure of 1,4-pentadien-3-one (Fig. 1) to build a novel family of bioactive compounds inactivated TMV. Therefore, in current work, a serial of novel glucopyranoside derivatives containing 1,4-pentadien-3-one moiety were synthesized. The activities against TMV in vivo were subsequently evaluated, and the bioassays results demonstrated that compounds **f5**, **f6**, **f8**, **f10**, **f13**, **f14**, **f20**, **f24**, **f26**, and **f28** remarkably inactivated TMV, with EC_{50} values of 59.6, 52.9, 55.3, 56.0, 62.8, 60.6, 67.4, 62.3, 57.1, and 57.4 μg/mL, respectively, compared with Ribavirin (145.1 μg/mL). And as an extension of this approach, the structure–activity relationship (SAR) analyses of antiviral activities were also discussed. To further study the underlying mechanisms of inactivation effect between compound **f6** and TMV-CP, their interaction was studied by fluorescence spectroscopy, isothermal titration calorimetry (ITC), and microscale thermophoresis (MST).

The synthetic route of glucopyranoside derivatives containing 1,4-pentadien-3-one moiety **f1**–**f32** was shown in Scheme 1. Using 2 or 4-hydroxybenzaldehydes as the starting materials, the key intermediates **d1**–**d32** were obtained via two consecutive condensation reactions.[34] Then, a mixture of the intermediates **d1**–**d32**, compound **e**, tetrabutylammonium bromide and NaOH were reacted in dichloromethane (DCM) for 6–12 h at 35 °C, and generated the title compounds **f1**–**f32** in 36–87% yields. To optimize the reaction conditions for the preparation of compound **f1**, the synthesis was carried out with different concentrations of NaOH (3%, 4%, 5%, and 6%). As shown in Table 1, a maximum yield of 87% was achieved when the reaction mixture was stirred for 6 h with 5% NaOH. The physical characteristics, IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis data for all the synthesized compounds were reported in Supplementary data and the representative data of **f1** were shown below.

Table 1
Effect of different concentration for synthesis of **f1**

No	Concentration	Solvent	Temperature (°C)	Reaction time (h)	Yield (%)
1	3% NaOH	DCM	35	6	37
2	4% NaOH	DCM	35	6	52
3	5% NaOH	DCM	35	6	87
4	6% NaOH	DCM	35	6	84

(1E,4E)-1-(2-(2,3,4,6-tert-O-acetyl-β-D-glucopyranosyl)phenyl)-5-phenyl-1,4-pentadien-3-one (***f1***): yellow solid, mp 175–178 °C, yield, 87%; IR (KBr, cm^{-1}) *v*: 1759, 1651, 1616, 1602, 1489, 1375, 1228, 1074; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) *δ*: 7.93 (1H, d, *J* = 16.50 Hz, =C*H*–C_6H_4O), 7.77–7.75 (3H, m, =C*H*–C_6H_5, ArH), 7.65 (1H, d, *J* = 8.05 Hz, ArH), 7.43–7.12 (5H, m, CO–C*H*=CH–C_6H_5, ArH), 7.10–7.04 (2H, m, ArH), 7.00 (1H, d, *J* = 16.60 Hz, CO–C*H*=CH–C_6H_4O), 5.51 (1H, t, *J* = 9.75 Hz, 3-H), 5.37 (1H, t, *J* = 9.10 Hz, 2-H), 5.23 (1H, t, *J* = 8.30 Hz, 4-H), 5.12 (1H, d, *J* = 18.35 Hz, 1-H), 4.35–4.23 (2H, m, 6-H), 4.12–4.10 (1H, m, 5-H), 2.09–2.02 (12H, 4s, 4 × CH_3CO); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) *δ*: 189.58, 170.65, 170.19, 169.57, 169.44, 155.61, 143.56, 137.06, 135.10, 131.58, 130.33, 128.89, 128.73, 128.61, 124.97, 123.60, 123.40, 115.40, 99.30, 72.34, 72.17, 70.64, 61.85, 20.70, 20.67, 20.61; Anal. Calcd for $C_{31}H_{32}O_{11}$ (580.19): C, 64.13; H, 5.56; found: C, 64.52; H, 5.72.

In this study, the inhibitory effect of the synthesized glucopyranoside derivatives containing 1,4-pentadien-3-one moiety were

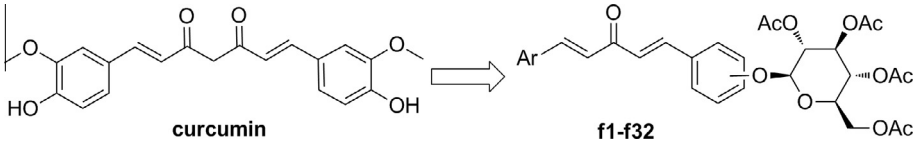
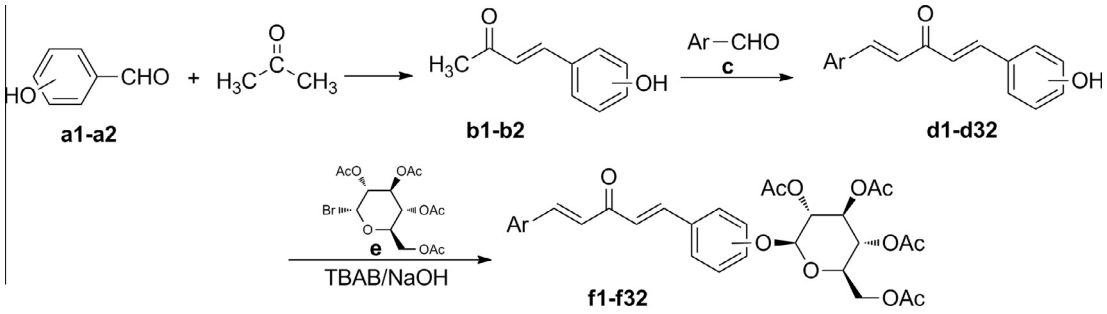


Figure 1. Design of the target compounds.



f_1 Ar=C_6H_5, 2-*O*; **f_2** Ar=C_6H_5, 4-*O*; **f_3** Ar=4-FC_6H_4, 4-*O*; **f_4** Ar=4-FC_6H_4, 2-*O*;
f_5 Ar=2-ClC_6H_4, 4-*O*; **f_6** Ar=2-ClC_6H_4, 2-*O*; **f_7** Ar=3-$NO_2C_6H_4$, 4-*O*; **f_8** Ar=3-$NO_2C_6H_4$, 2-*O*;
f_9 Ar=4-$NO_2C_6H_4$, 4-*O*; **f_{10}** Ar=4-$NO_2C_6H_4$, 2-*O*; **f_{11}** Ar=2-$OMeC_6H_4$, 4-*O*; **f_{12}** Ar=2-$OMeC_6H_4$, 2-*O*;
f_{13} Ar=2-Py, 4-*O*; **f_{14}** Ar=2-Py, 2-*O*; **f_{15}** Ar=4-ClC_6H_4, 4-*O*; **f_{16}** Ar=4-ClC_6H_4, 2-*O*;
f_{17} Ar=4-BrC_6H_4, 4-*O*; **f_{18}** Ar=4-BrC_6H_4, 2-*O*; **f_{19}** Ar=2-FC_6H_4, 4-*O*; **f_{20}** Ar=2-FC_6H_4, 2-*O*;
f_{21} Ar=2-BrC_6H_4, 4-*O*; **f_{22}** Ar=2-BrC_6H_4, 2-*O*; **f_{23}** Ar=2-Th, 4-*O*; **f_{24}** Ar=2-Th, 2-*O*;
f_{25} Ar=3-Py, 4-*O*; **f_{26}** Ar=3-Py, 2-*O*; **f_{27}** Ar=4-Py, 4-*O*; **f_{28}** Ar=4-Py, 2-*O*;
f_{29} Ar=4-$OMeC_6H_4$, 4-*O*; **f_{30}** Ar=4-$OMeC_6H_4$, 2-*O*; **f_{31}** Ar=4-MeC_6H_4, 4-*O*; **f_{32}** Ar=4-MeC_6H_4, 2-*O*.

Scheme 1. Synthesis of the target compounds **f1**–**f32**.