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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

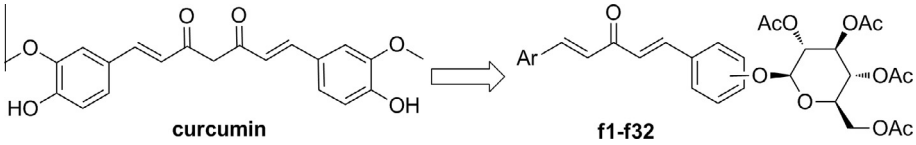
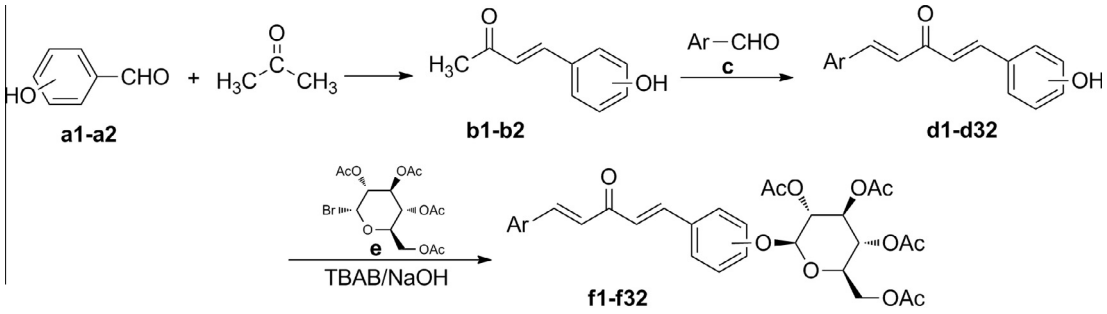


Figure 1. Design of the target compounds.



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*.

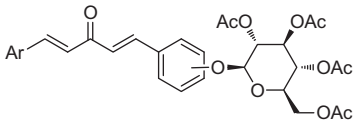
Scheme 1. Synthesis of the target compounds **f1**–**f32**.

evaluated for their antiviral activities in vivo against TMV based on previously described methods,[35] and the commercial agent Ribavirin was the control. Results of preliminary bioassay against TMV were listed in Table 2 and most of the glucopyranoside derivatives exhibited good inactivation activities against TMV with the inhibition rates of 57.0–93.9% at 500 μg/mL. Particularly, compounds **f6**, **f8**, **f10**, **f26**, and **f28** showed excellent inactivation activity (93.9%, 90.6%, 91.7%, 92.3% and 91.0%, respectively) superior to Ribavirin (72.9%) against TMV at 500 μg/mL. Compounds **f1**, **f2**, **f3**, **f4**, **f5**, **f7**, **f13**, **f15**, **f16**, **f20**, **f23**, **f25**, and **f27** had higher inhibition rates (84.1%, 86.7%, 89.7%, 81.4%, 89.1%, 89.4%, 81.5%, 86.8%, 85.3%, 88.1%, 80.0%, 87.2% and 83.1%, respectively) against TMV than the that of Ribavirin (72.9%) at 500 μg/mL. The other compounds moderately inactivated TMV.

On the basis of previous in vivo bioassays, the title compounds exhibited good inactivation activities against TMV. Therefore, to further investigate their inhibitory activity in vivo, the EC_{50} values for all of the synthesized compounds were calculated and summarized in Table 3. Generally, the evaluated compounds favorably inactivated TMV, notably, compounds **f5**, **f6**, **f8**, **f10**, **f13**, **f14**, **f20**, **f24**, **f26**, and **f28** exhibited higher antiviral activity against TMV (the EC_{50} values of 52.9, 55.3, 56.0, 62.8, 60.6, 67.4, 62.3, 57.1, 57.1, and 57.4 μg/mL, respectively) than that of Ribavirin (145.1 μg/mL). SAR indicated antiviral activities of the title compounds shown promising potency against TMV for different aryl groups (style and position) were introduced into novel glucopyranose of derivatives. The data of antiviral activities indicated that the relationships of the antiviral activities with different Ar were deduced. Excellent TMV inactivation was observed when Ar was substituted with 2-ClC_6H_4, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 3-Py, and 4-Py groups, whereas when Ar was substituted with 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, or 4-MeC_6H_4, the corresponding target compounds poorly inactivated TMV. Notably, the compounds bearing electron-withdrawing (2-ClC_6H_4, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$) and heterocyclic groups (3-Py, 4-Py) were found to exhibit significantly higher inactivity effects against TMV than the other groups. Furthermore, most of title compounds bearing the same Ar along with *O*-glucopyranose at C-2-position of benzene showed higher inactivation activities against TMV than the corresponding compounds with *O*-glucopyranose at C-4-position of benzene.

The binding interactions between compound **f6** and TMV-CP were investigated using fluorescence spectroscopy, ITC, and MST analysis to understand the underlying mechanisms. The result of ITC analysis demonstrated that the interaction of one TMV-CP with 1.53 **f6** molecules is typically endothermic (Fig. 2). The ΔG value ($\Delta G \approx -7.63$ kJ/mol) is negative, which indicated that the interaction is spontaneous. The binding constant (K_a) between **f6** and TMV-CP is 1.79×10^5 L/mol, representing a comparatively stronger ligand-protein interaction, which is higher than those of **f18** (2.07×10^4 L/mol) and **f31** (1.76×10^3 L/mol) with moderate (117.8 μg/mL) and poor (397.1 μg/mL) anti-TMV activity, respectively (Table 4). Secondly, in order to verify the result of ITC, the

Table 2
Inhibitory effect of the test compounds (500 μg/mL) against TMV in vivo

Compd			Concentration (μg/mL)	Inactivation activity (%)[a]
	Ar	*O*		
f1	C_6H_5	2-*O*	500	84.1 ± 4.5
f2	C_6H_5	4-*O*	500	86.7 ± 2.3
f3	4-FC_6H_4	4-*O*	500	89.7 ± 2.7
f4	4-FC_6H_4	2-*O*	500	81.4 ± 3.1
f5	2-ClC_6H_4	4-*O*	500	89.1 ± 1.5
f6	2-ClC_6H_4	2-*O*	500	93.9 ± 2.3
f7	3-$NO_2C_6H_4$	4-*O*	500	89.4 ± 2.4
f8	3-$NO_2C_6H_4$	2-*O*	500	90.6 ± 2.8
f9	4-$NO_2C_6H_4$	4-*O*	500	76.9 ± 2.9
f10	4-$NO_2C_6H_4$	2-*O*	500	91.7 + 3.5
f11	2-$OMeC_6H_4$	4-*O*	500	73.1 ± 3.2
f12	2-$OMeC_6H_4$	2-*O*	500	75.5 ± 3.6
f13	2-Py	4-*O*	500	81.5 ± 3.6
f14	2-Py	2-*O*	500	77.0 ± 2.9
f15	4-ClC_6H_4	4-*O*	500	86.8 ± 3.2
f16	4-ClC_6H_4	2-*O*	500	85.3 ± 4.1
f17	4-BrC_6H_4	4-*O*	500	74.5 ± 3.6
f18	4-BrC_6H_4	2-*O*	500	73.2 ± 2.6
f19	2-FC_6H_4	4-*O*	500	73.2 ± 3.3
f20	2-FC_6H_4	2-*O*	500	88.1 ± 1.8
f21	2-BrC_6H_4	4-*O*	500	75.7 ± 3.6
f22	2-BrC_6H_4	2-*O*	500	79.8 ± 2.9
f23	2-Th	4-*O*	500	80.0 ± 4.0
f24	2-Th	2-*O*	500	77.0 ± 2.9
f25	3-Py	4-*O*	500	87.2 ± 3.3
f26	3-Py	2-*O*	500	92.3 ± 2.4
f27	4-Py	4-*O*	500	83.1 ± 3.1
f28	4-Py	2-*O*	500	91.0 ± 1.7
f29	4-$OMeC_6H_4$	4-*O*	500	56.3 ± 0.7
f30	4-$OMeC_6H_4$	2-*O*	500	62.1 ± 2.3
f31	4-MeC_6H_4	4-*O*	500	48.7 ± 3.6
f32	4-MeC_6H_4	2-*O*	500	52.4 ± 1.5
Ribavirin[b]	/	/	500	72.9 ± 2.4

[a] Average of three replicates.
[b] The commercial, agricultural, and antiviral product Ribavirin was used for comparison of activity.

Table 3
The EC_{50} values of compounds **f1–f32** against to TMV in vivo

Compd	Ar	O	EC_{50}[a] (μg/mL)	Compd	Ar	O	EC_{50}[a] (μg/mL)
f1	C_6H_5	2-O	98.4 ± 1.0	**f18**	4-BrC_6H_4	2-O	117.8 ± 2.5
f2	C_6H_5	4-O	75.2 ± 2.7	**f19**	2-FC_6H_4	4-O	181.1 ± 3.1
f3	4-FC_6H_4	4-O	94.2 ± 3.1	**f20**	2-FC_6H_4	2-O	67.4 ± 0.9
f4	4-FC_6H_4	2-O	84.4 ± 3.5	**f21**	2-BrC_6H_4	4-O	97.0 ± 1.1
f5	2-ClC_6H_4	4-O	59.6 ± 2.4	**f22**	2-BrC_6H_4	2-O	72.6 ± 3.5
f6	2-ClC_6H_4	2-O	52.9 ± 2.9	**f23**	2-Th	4-O	84.5 ± 3.5
f7	3-$NO_2C_6H_4$	4-O	81.9 ± 1.8	**f24**	2-Th	2-O	62.3 ± 0.8
f8	3-$NO_2C_6H_4$	2-O	55.3 ± 2.6	**f25**	3-Py	4-O	73.5 ± 3.2
f9	4-$NO_2C_6H_4$	4-O	110.8 ± 3.5	**f26**	3-Py	2-O	57.1 ± 2.7
f10	4-$NO_2C_6H_4$	2-O	56.0 ± 1.4	**f27**	4-Py	4-O	75.0 ± 1.8
f11	2-$OMeC_6H_4$	4-O	154.0 ± 3.5	**f28**	4-Py	2-O	57.4 ± 0.9
f12	2-$OMeC_6H_4$	2-O	132.0 ± 1.7	**f29**	4-$MeOC_6H_4$	4-O	384.1 ± 1.2
f13	2-Py	4-O	62.8 ± 1.3	**f30**	4-$MeOC_6H_4$	2-O	326.3 ± 0.9
f14	2-Py	2-O	60.6 ± 2.7	**f31**	4-MeC_6H_4	4-O	397.1 ± 2.1
f15	4-ClC_6H_4	4-O	108.6 ± 2.7	**f32**	4-MeC_6H_4	2-O	365.6 ± 2.7
f16	4-ClC_6H_4	2-O	105.5 ± 4.0	Ribavirin[b]	/	/	145.1 ± 2.6
f17	4-BrC_6H_4	4-O	122.7 ± 1.6	/	/	/	/

[a] Average of three replicates.
[b] The commercial, agricultural, and antiviral product Ribavirin was used for comparison of activity.

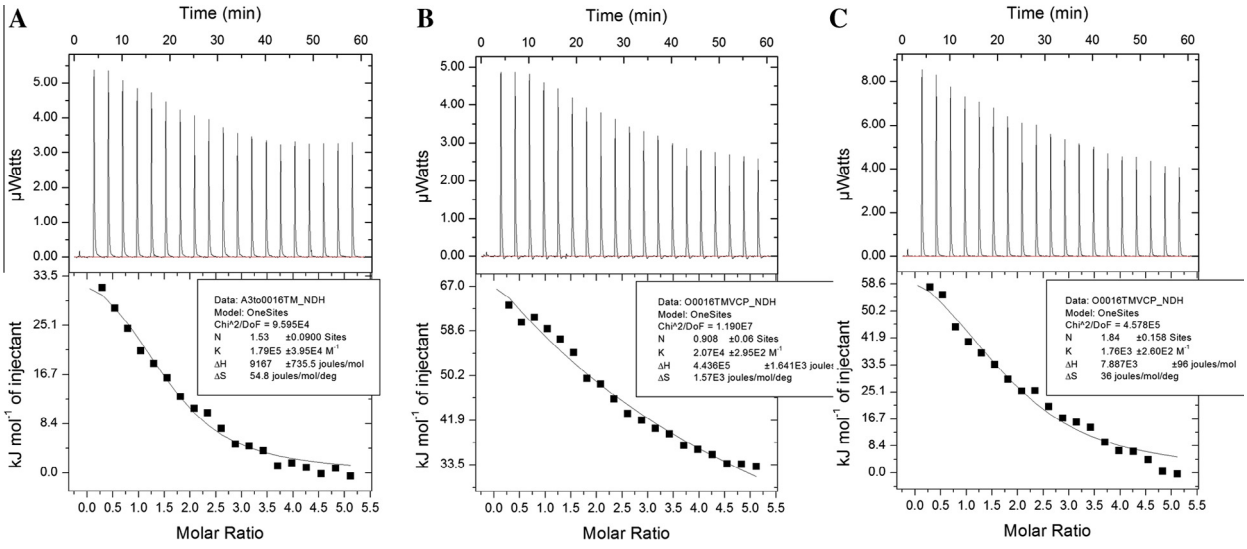


Figure 2. (A) Results of isothermal titration calorimetry for **f6** binding to TMV-CP; (B) results of isothermal titration calorimetry for **f18** binding to TMV-CP; (C) results of isothermal titration calorimetry for **f31** binding to TMV-CP.

Table 4
The binding constant (K_a) of **f6**, **f18**, and **f31**

Compd	ITC (L/mol)	MST (L/mol)	Fluorescence spectroscopy (L/mol)
f6	1.79×10^5	1.10×10^5	3.93×10^5
f18	2.07×10^4	1.07×10^4	5.50×10^4
f31	1.76×10^3	7.69×10^3	3.67×10^3

K_a between compound **f6** and TMV-CP were investigated using MST. As shown in Figure 3 and Table 4, the result of MST measurements was similar to ITC findings and the K_a between **f6** and TMV-CP is 1.10×10^5 L/mol at 25 °C, which is higher than those of **f18** (1.07×10^4 L/mol) and **f31** (7.69×10^3 L/mol). Finally, fluorescence spectrum measurement was also further confirmed the results of MST and ITC. It was found that the K_a of **f6** is 3.93×10^5 L/mol, which is higher those of **f18** (5.50×10^4 L/mol) and **f31** (3.67×10^3 L/mol) (Fig. 4 and Table 4). The result indicated that compound **f6** has a strong affinity with TMV-CP protein.

In summary, a series of novel glucopyranoside derivatives were designed, synthesized, and evaluated for their antiviral activities in vivo against TMV. Bioassay results indicated the title compounds exhibited good antiviral activities against TMV. Notably, compounds **f6** exhibited excellent inactivation activity against TMV, with EC_{50} value of 52.9 μg/mL, which was better than that of ribavirin (145.1 μg/mL). Moreover, interaction between **f6** and TMV-CP was characterized by fluorescence spectroscopy, ITC, and MST. Results showed that **f6** bound to TMV-CP with micromole affinity, and thermodynamic parameters indicated that the

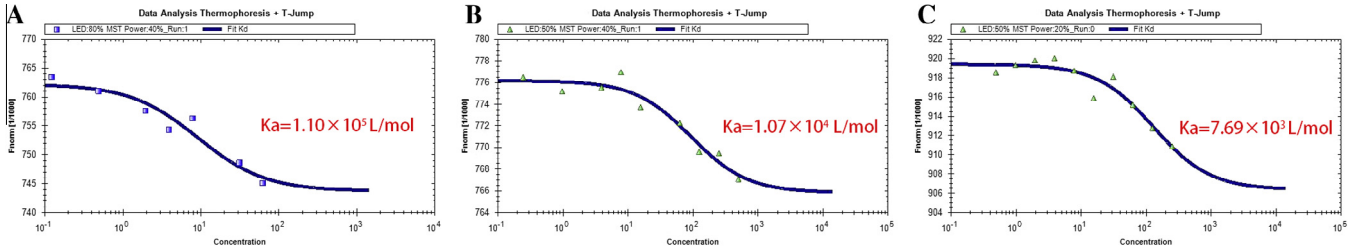


Figure 3. (A) MST measurements for the binding of TMV-CP and **f6**; (B) MST measurements for the binding of TMV-CP and **f18**; (C) MST measurements for the binding of TMV-CP and **f31**.

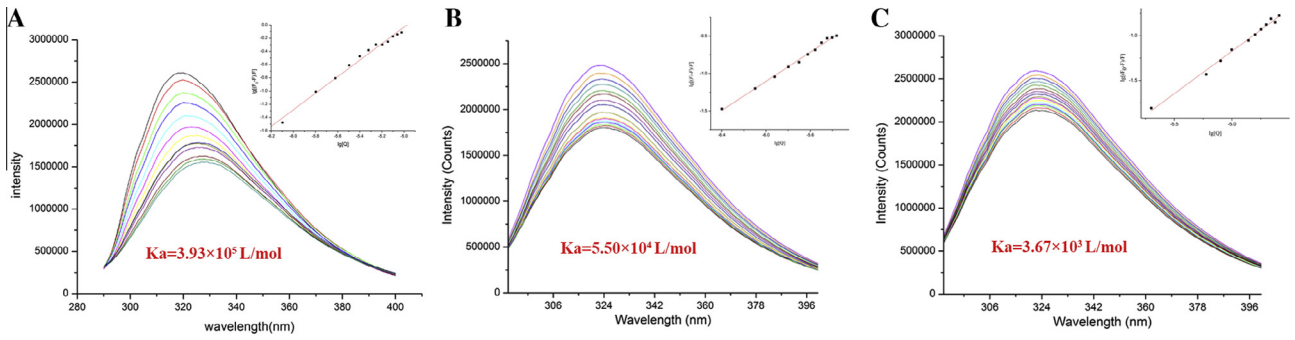


Figure 4. (A) Fluorescence emission spectra of TMV-CP in the presence of **f6** with different concentrations. λ_{ex} = 278 nm. Inset: the linear relationship for quenching TMV-CP by **f6**; (B) fluorescence emission spectra of TMV-CP in the presence of **f18** with different concentrations. λ_{ex} = 278 nm. Inset: the linear relationship for quenching TMV-CP by **f18**; (C) fluorescence emission spectra of TMV-CP in the presence of **f31** with different concentrations. λ_{ex} = 278 nm. Inset: the linear relationship for quenching TMV-CP by **f31**.

interaction was typically endothermic and spontaneous, with 1:1.53 ratio of TMV-CP to **f6**. Further study on the action mechanism of inactivation effect is currently underway.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.07.068.

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