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Design, Synthesis, Antiviral Bioactivity, and Mechanism of the Ferulic Acid Ester-Containing Sulfonamide Moiety

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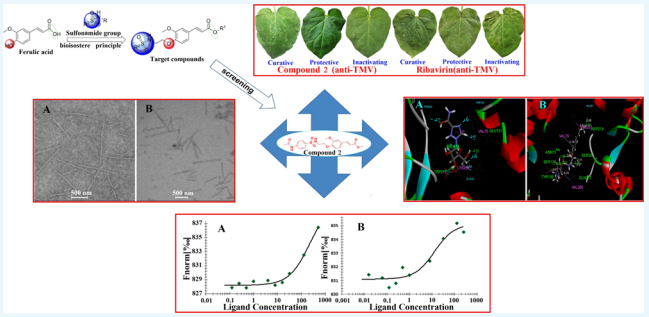
ABSTRACT: Tobacco mosaic virus (TMV) has caused huge economic losses to tobacco, pepper, cucumber, and ornamental crops all over the world. However, few effective antiviral agents were developed and applied to control such plant disease. It is challenging to find an anti-TMV agent which is highly effective, less toxic, and environmentally friendly. In this work, a series of ferulic acid ester-containing sulfonamide moieties were designed and synthesized, and the antiviral activities of these compounds against TMV were evaluated. The anti-TMV biological activity test showed that the target compounds showed excellent anti-TMV activity *in vitro* and *in vivo*. In particular, compound **2** has excellent anti-TMV activity at 500 μg/mL, which is higher than that of the control drug ribavirin. The preliminary mechanism research results showed that compound **2** can obviously destroy the morphology of the virions to show excellent activity. The results show that the ferulic acid ester-containing sulfonamide moiety deserves further research and development.



INTRODUCTION

Plant viruses can cause severe damage to plants, thereby seriously threatening the development of the world economy. One of the most dangerous plant viruses is tobacco mosaic virus (TMV), and it is considered as the most ancient virus in plant virology as it was discovered in 1898.[1,2] It has caused huge economic losses to tobacco, pepper, cucumber, and other ornamentals and flowers all over the world.[3] Moreover, they can use the internal mechanism of the host and you can first spread it, or they can spread it through biological means, such as spreading through aphids.[4] Although traditional chemicals can inhibit TMV within a certain range, they cannot effectively eliminate the virus and are not environmentally friendly. Therefore, the use of traditional chemicals is limited.

To find green and efficient antiplant virus drugs, researchers have conducted screening from natural product sources and chemical synthesis to obtain some effective antiplant virus drugs, such as ningnanmycin and ribavirin (Figure 1).[5−7] However, the ribavirin activity is poor, whereas the field control efficacy of ningnanmycin is not ideal, and the cost is high.[8−10] Therefore, finding new and highly effective environmentally friendly antiplant virus agents remains a major challenge for pesticide researchers.

Natural products have attracted widespread attention from biologists for their specific targets, special modes of action, and environmental protection.[11−13] However, natural products have some drawbacks, such as complex structures, difficult synthesis, and easy decomposition of the active ingredients.[14,15] These drawbacks limit the widespread use of natural products in pesticides. Ferulic acid (Figure 1) is a phenolic acid commonly found in plants and one of the active ingredients in Chinese medicine, such as *Angelica sinensis*, *Ligusticum chuanxiong* Hort, and *Ferula sinkiangensis* K. M. Shen. In addition, ferulic acid is high in wheat and rice brans. Studies have shown that ferulic acid and its derivatives have a wide range of biological activities,[16,17] including bacteriostatic,[18] antiviral,[19−21] anticancer,[22,23] anti-inflammatory,[24] and other activities. A series of ferulic acid derivatives have been designed and synthesized by the research group in the early stage, and the results have shown that the ferulic acid derivatives exhibit good antiplant virus activity. At the same time, sulfonamides have attracted widespread attention from pesticide scientists because of their broad biological properties, such as antibacterial[25] and antiviral activities.[26−29]

This project intends to use the principle of active splicing to introduce a wide range of biologically active sulfonamide structural units into the natural product ferulic acid with good antiplant virus activity to design (Figure 2) and synthesize a series of ferulic acid ester-containing sulfonamide moieties. The anti-TMV activities are tested using the half-leaf method

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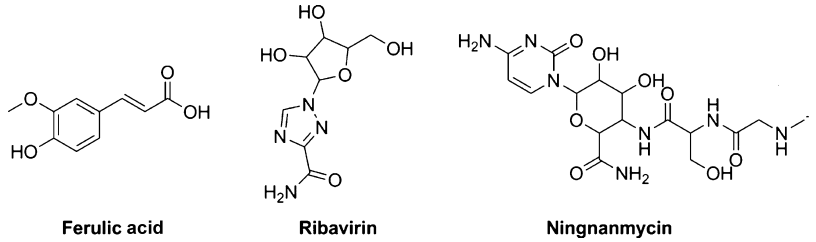


Figure 1. Commercially available antiviral agents of ferulic acid, ribavirin, and ningnanmycin.

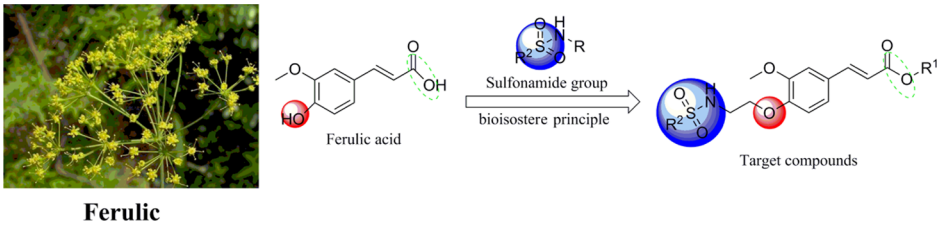
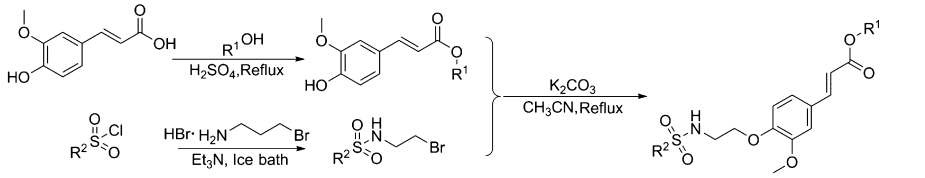


Figure 2. Design ideas of the target compounds. The pictures in the figure, except the picture of ferulic, were taken by the author Xiaoli Ren. Copyright 2020. The picture of ferulic was freely available online, and the image of ferulic is a free domain.



1: R^1=-C_2H_5 ,R^2=4-NO_2 -Ph; **2:** R^1=-CH_3 ,R^2=4-$NHCOCH_3$-Ph; **3:** R^1=-C_2H_5 ,R^2=4-$NHCOCH_3$-Ph ; **4:** R^1=-C_4H_9 ,R^2=4-OCH_3-Ph ; **5:** R^1=-C_2H_5 ,R^2=4-OCH_3-Ph ; **6:** R^1=-CH_3 ,R^2=-CH_3 ; **7:** R^1=-C_2H_5 ,R^2=4-CH_3-Ph; **8:** R^1=-C_4H_9 ,R^2=4-CH_3-Ph; **9:** R^1=-C_4H_9 ,R^2=2-F-Ph; **10:** R^1=-CH_3 ,R^2=2-F-Ph; **11:** R^1=-C_4H_9 ,R^2=2-Cl-Ph; **12:** R^1=-C_2H_5 ,R^2=2,6-di-Cl-Ph; **13:** R^1=-CH_3 ,R^2=-Ph; **14:** R^1=-C_2H_5 ,R^2=4-F-Ph; **15:** R^1=-C_4H_9 ,R^2=2,6-di-F-Ph; **16:** R^1= -CH_3,R^2=4-OCH_3-Ph

Figure 3. Synthetic routes of target compounds **1**−**16**.

to find compounds with high activity and study the preliminary mechanism of action of highly active compounds and viruses.

RESULTS AND DISCUSSION

Chemistry. As shown in Figure 3, ferulic acid and alcohol are used as raw materials, concentrated sulfuric acid is used as a catalyst, and alcohol is used as a solvent, and stirring was performed under reflux for 6−8 h to obtain intermediate A. Dichloromethane was used as the solvent, and triethylamine was used as the acid-binding agent using sulfonyl chloride and bromoethylamine hydrobromide as raw materials; the reaction was performed in an ice bath for 4−6 h to obtain intermediate B. Intermediate A (1.0 mmol) was then dissolved in 15 mL of acetonitrile and potassium carbonate (2 mmol) and stirred. Next, different sulfonamides (1.2 mmol) were added and stirred at 80 °C for 8 h to obtain the target compound. Their structures have been identified by ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectrometry (HRMS) (Supporting Information).

Anti-TMV Activity *in Vivo*. The anti-TMV biological activity test showed that the target compound showed excellent anti-TMV activity at 500 μg/mL, and the result is as shown in Table 1. The curative effect activities of compounds **6**, **7**, **12**, and **14** on TMV were 50.3, 57.9, 55.3, and 57.4%, which were significantly better than that of ribavirin (49.3%). The protective activity of compound **2** on TMV was 59.7%, which was significantly better than that of ribavirin (48.6%). The inactivation activity of compound **2** on TMV was 87.3%, which was better than that of ribavirin (72.7%). To further understand the antiviral activity of synthesized compounds, we calculated and summarized the concentration for 50% of maximal effect (EC_{50}) values of them. The EC_{50}

Table 1. Antiviral Activities of Target Compounds 1−16 against TMV *in Vivo* at 500 mg/L[a,d]

compound	curative effect activity[a] (%)	protection effect activity[a] (%)	inactivation effect activity[a] (%)
1	34.0 ± 4.4	31.7 ± 1.4	64.8 ± 8.5
2	39.8 ± 0.8	59.7 ± 6.2	87.3 ± 2.5
3	36.8 ± 8.0	40.4 ± 9.7	68.4 ± 7.0
4	26.9 ± 4.1	31.2 ± 9.2	56.6 ± 10.2
5	30.2 ± 2.6	38.5 ± 7.7	45.1 ± 7.4
6	50.3 ± 1.9	32.7 ± 5.7	59.8 ± 7.4
7	57.9 ± 10.3	53.3 ± 1.3	77.7 ± 8.1
8	31.9 ± 8.6	38.3 ± 7.9	54.6 ± 6.8
9	37.3 ± 2.0	41.0 ± 5.7	76.9 ± 5.4
10	41.4 ± 3.4	49.8 ± 8.3	74.1 ± 7.4
11	35.4 ± 3.2	38.9 ± 6.3	72.1 ± 7.5
12	55.3 ± 2.9	53.7 ± 9.9	65.2 ± 7.6
13	32.8 ± 2.3	53.7 ± 9.2	71.1 ± 8.0
14	50.6 ± 4.7	52.7 ± 8.6	64.6 ± 8.1
15	30.6 ± 2.7	38.7 ± 9.5	43.7 ± 3.8
16	47.1 ± 6.1	55.9 ± 1.9	73.7 ± 8.2
ningnanmycin[b]	56.6 ± 6.8	54.1 ± 3.4	88.3 ± 4.3
ribavirin[c]	49.3 ± 7.5	48.6 ± 2.5	72.7 ± 4.7

[a]Average of three replicates at 500 μg/mL. [b]Ningnanmycin. [c]Ribavirin was used as the control. [d]The ± values represent the standard deviation.

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value of compound **2** (Table 2) was 84.8 μg/mL, which was better than that of ribavirin (138.3 μg/mL). Finally, the results

Table 2. EC_{50} of Target Compound Anti-TMV Activity

compound	EC_{50} of inactivation effect activity[a]	compound	EC_{50} of inactivation effect activity[a]
2	84.8 ± 3.2	12	361.2 ± 5.1
6	419.3 ± 3.8	13	198.2 ± 8.3
7	205.8 ± 2.3	14	498.9 ± 4.0
8	542.3 ± 8.9	15	640.2 ± 5.9
9	238.1 ± 5.5	16	175.1 ± 11.6
10	265.5 ± 8.7	ribavirin	138.3 ± 4.2

[a]The ± values represent the standard deviation.

of the above activity tests indicate that the activity of compound **2** is superior to that of the commercially available drug ribavirin.

Transmission Electron Microscopy Observation. As shown in Figure 4, the morphological observation of TMV

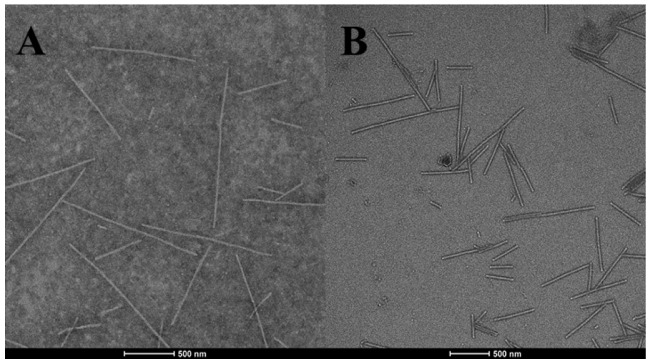

Figure 4. Effects of CK (A) and compound 2 (B) on the morphology of TMV particles.

virions by transmission electron microscopy (TEM) showed that the complete TMV particles were short, straight, and rod-shaped structures (Figure 4A). Compound 2-treated TMV particles ruptured more severely than blank control TMV particles (Figure 4B). The results indicated that compound **2** can cause certain damage to the morphology and structure of TMV virions and cause the virions to lose their ability to infect tobacco.

Molecular Docking. In this study, the molecular docking between compound **2** and TMV-coat protein (TMV-CP) (PDB code: 1EI7) was evaluated. The control agent ribavirin was used as a comparison object in this study. Compound **2** (Figure 5B,D) and ribavirin (Figure 5A,C) are inserted into the active pocket of TMV-CP through amino acid residues. Combined with the analysis of the two-dimensional (2D) and three-dimensional (3D) graphs of molecular docking, we can find that these amino acid residues include tyrosine 139 (TYR139), serine 138 (SER138), serine 255 (SER155), position 75 valine (VAL75), tyrosine at position 72 (TYR139), etc. These amino acid residues play a key role in the self-assembly of TMV-CP (Figure 5). Compound **2** (Figure 5B) showed strong hydrogen bonds with ASP219 (2.46 Å), GLN257 (2.55 Å), SER255 (2.56 Å), ASN 73 (1.54 Å), TYR139 (2.89 Å), and SER 138 (1.66 Å). In addition, some nonbonded interactions (such as π-alkyl and so forth) between certain amino acid residues and compounds are also very important modes of action. For example, π-sigma, alkyl, π-alkyl, and so forth also contribute to disease inactivation. Obviously, compared with the control agent, compound **2** has more hydrogen bonds, and some amino acid residues have more nonbonding than the control agent ribavirin. These binding and nonbinding may enhance the compound for its ability to inhibit the self-assembly process of TMV, thereby achieving the antiviral effect.

Binding Affinity Analysis. The binding affinity of the compound to TMV-CP was studied using microscale thermophoresis (MST), and the desorption constant (K_d) was obtained (Figure 6). Table 3 lists data comparison and analysis. According to the data in the table, compound **2** has a strong binding affinity with TMV-CP, with a K_d value of 12.6 μM, which is significantly better than that of ribavirin (223.0 μM). This result was consistent with the EC_{50} value of compound **2**. These results indicate that compound **2** has better antiviral activity.

Structure–Activity Relationships. In ferulic acid derivatives containing a sulfonamide moiety, when the substituent on the benzene ring of the sulfonamide is at the 4-position, the anti-TMV therapeutic activity of the electron-donating substituent is superior to that of the electron-withdrawing substituent. For example, compound **7** > compound **14** > compound **1** > compound **5** (4-CH_3-Ph > 4-F-Ph > 4-NO_2-Ph > 4-OCH_3-Ph). At the same time, the anti-TMV protection activity of electron-withdrawing groups is higher than that of electron-donating groups, for example, compound **2** > compound **14** > compound **7** (4-$NHCOCH_3$-Ph > 4-F-Ph > 4-CH_3-Ph).

CONCLUSIONS

In summary, we designed and synthesized ferulic acid ester derivatives containing sulfonamide moieties and tested their anti-TMV biological activities in this work. The test results show that most of the target compounds have good anti-TMV activity. Among them, compound **2** has excellent anti-TMV inactivation activity, with an EC_{50} value of 84.8 μg/mL. Electron microscopy observations showed that compound **2** could cause serious lesion to the morphology of TMV virions, resulting in bending fractures and further inactivation of TMV. The result of the interaction between the MST-titrated compound and TMV-CP found that compound **2** showed significant binding to TMV-CP with K_d = 12.6 μM. The interaction mode between the target compound and TMV-CP was studied through molecular docking, and it was found that compound **2** has excellent binding ability. The above research shows that the compound can better act on virus particles and provide a potential basis for the research of antiviral drugs.

MATERIALS AND METHODS

Chemicals. The reagents used in the experiments were analytically pure reagents and were used without further purification and drying.

Instruments. The melting point of the target product was measured by using a WRX-4 Micro melting point instrument (Shanghai YiCe Apparatus & Equipment Co., Ltd., China). Using $CDCl_3$ and dimethyl sulfoxide-d_6 (DMSO-d_6) as a solvent, ^{1}H NMR and ^{13}C NMR spectra of the target compound were acquired using a Brookfield Ascend-400 spectrometer (Brook, Germany) and a JEOL ECX-500 spectrometer (JEOL, Tokyo, Japan). HRMS data have been

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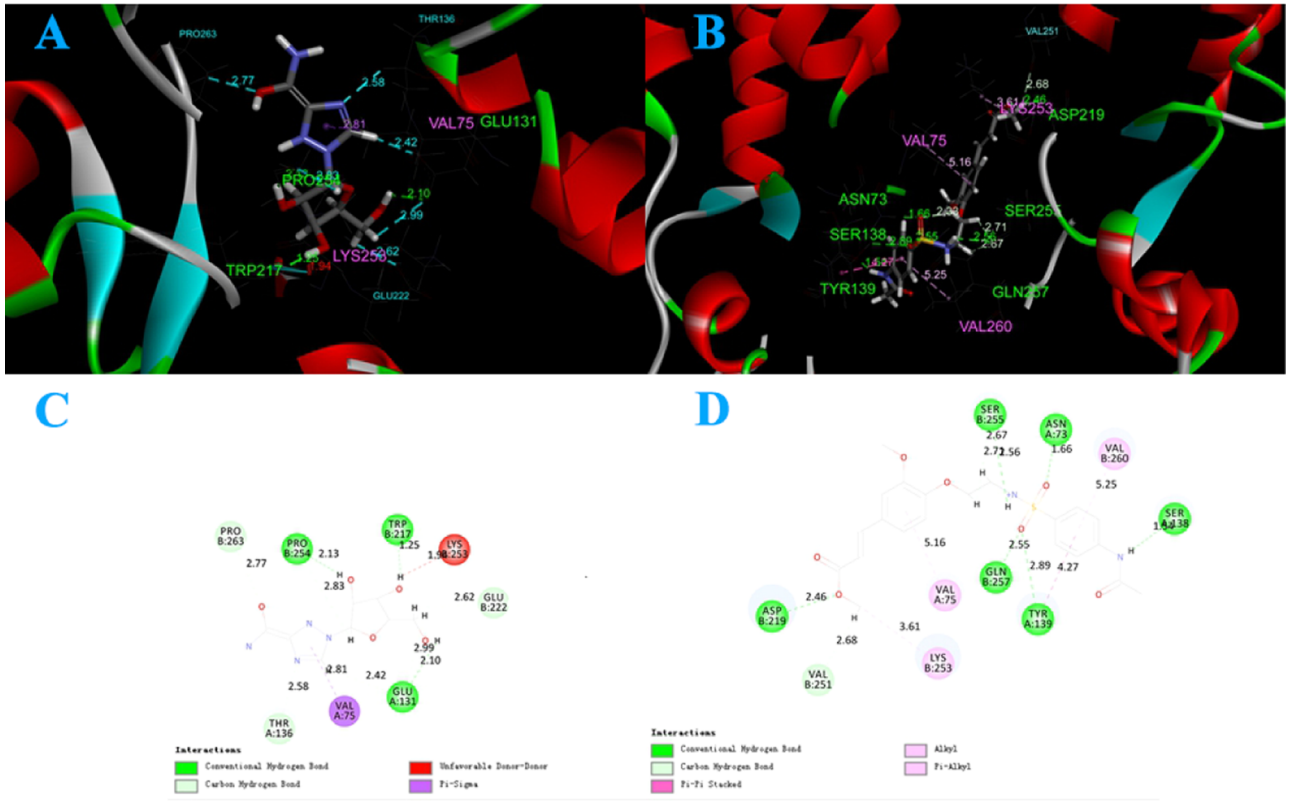

Figure 5. 3D graph of molecular docking results of ribavirin (A) and compound 2 (B) with TMV-CP. 2D graph of molecular docking results of ribavirin (C) and compound 2 (D) with TMV-CP.

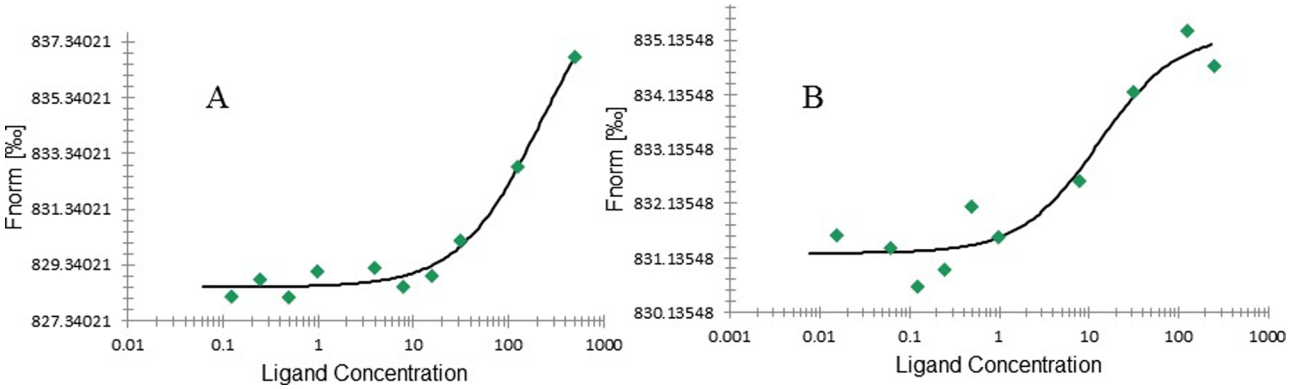

Figure 6. MST test results of compound **2** (A) and ribavirin (B) with TMV-CP.

Table 3. Interaction Results of Target Compounds with TMV-CP[c]

compound	**2**	ribavirin[b]
K_d[a] (μM)	12.6 ± 6.7	223.0 ± 66.2
EC_{50} (μg/mL)	84.8 ± 3.2	138.3 ± 4.2

[a]Average of three replicates at 500 μg/mL. [b]Ribavirin was used as the control. [c]The ± values represent the standard deviation.

validated by Thermo Scientific Q Exactive (Thermo, USA). The morphological structure of virus particles was observed using a Talos F200C electron microscope (FEI, USA).

Preparation of Ferulic Acid Ester (A). Concentrated sulfuric acid was added to the alcohol solution of ferulic acid by the method previously reported,[30] and the reaction system was heated to reflux for 9 h and then cooled to room temperature.

Preparation of Sulfonamide (B). According to the reported method,[31] triethylamine was added to a dichloromethane solution of sulfonyl chloride and bromoethylamine hydrobromide, and the reaction system was placed in an ice water bath for 6 h to obtain intermediate B.

General Procedure for the Synthesis of Compounds ***1*****–*****16.*** Intermediate A, intermediate B, and potassium carbonate were stirred in 15 mL of acetonitrile at reflux for 6–10 h. The reaction system was quenched with saturated brine and then extracted three times with 50 mL of an organic solvent. The substitution data of compound **2** are shown below.

Methyl (E)-3-(4-(2-((4-acetamidophenyl)sulfonamide)-ethoxy)-3-methoxyphenyl)acrylate. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.28 (s, 1H), 7.77 (s, 1H), 7.71 (s, 3H), 7.66 (d, J = 6.3 Hz, 1H), 7.55 (d, J = 15.9 Hz, 1H), 7.32 (d, J = 1.7 Hz, 1H), 7.17 (d, J = 8.3 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H),

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6.53 (d, J = 16.0 Hz, 1H), 3.97 (t, J = 5.6 Hz, 2H), 3.77 (s, 3H), 3.68 (s, 3H), 3.06 (t, J = 5.2 Hz, 2H), 2.04 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.44, 167.44, 150.19, 149.58, 145.12, 143.25, 134.37, 128.15, 127.74, 123.23, 119.03, 115.97, 113.33, 111.27, 67.57, 56.10, 51.79, 42.24, 24.60. HRMS (ESI): calcd for $C_{21}H_{24}N_2O_7KS$ ([M + K]$^+$), calcd, 487.09358; found, 487.09216.

Antiviral Activity Assay. TMV was extracted according to methods in the literature.[32] The model plant was selected according to the half-leaf method in the literature[33] to evaluate the activity of the synthesized compound for treatment, protection, and inactivation. The curative activity is to first select a five-leaf stage model plant with better growth as the test object, spread a uniform layer of emery on the tobacco leaf surface, and then inoculate the virus by rubbing. After half an hour, rinse off the emery on the surface of the leaves with water, and then let the water on the surface of the leaves dry. The test compound solution was applied to the left half of the lobe, and the right half of the lobe was coated with a blank solution as a control. After 3−4 days, there are obvious disease spots on the leaves. Record the number of disease spots on the left and right halves of the leaves. The protective activity is to first apply pesticide treatment to the model plants. After 24 h, the virus was inoculated by rubbing. For passivation activity, the virus and the test compound were mixed for 0.5 h, and then, the mixed solution was applied to the right half of the model plant, and the left half was inoculated with the same dose of the virus solution. The calculation method of the inhibition rate is as follows

$$X = \frac{\mathrm{CK} - R}{\mathrm{CK}} \times 100 \quad (1)$$

where X (%) is the percentage of inhibition rate, R is the number of spots on the leaf, CK is the number of spots on the blank control, 0 = no activity, and 100 = complete inhibition. All experiments were repeated three times under the same conditions, including the positive control: the commercial drug ribavirin.

TEM Analysis. The impact of compound **2** on TMV morphology was evaluated by TEM.

Molecular Docking. The interaction model of compound **2** with TMV-CP was studied using AutoDock 4.0 software.

Microscale Thermophoresis. The binding force of compound **2** with TMV-CP was analyzed using MST to obtain the dissociation constant (K_d). Ningnanmycin and ribavirin were used as positive controls. All tests were repeated three times.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c02421.

Characterization data and related spectra (PDF)

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Author Contributions

X.R., X.L., L.Y., and D.H. conceived and designed the study. X.R. performed the experiments. X.R., X.L., and L.Y. analyzed and interpreted the data. X.R., L.Y., and D.H. wrote the manuscript. X.R., X.L., L.Y., and D.J. provided material support. D.H. supervised and funded the acquisition for this work. All authors have read and reviewed the manuscript.

Notes

The authors declare no competing financial interest.

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