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Design, Synthesis, Bioactivity and Mechanism of Dithioacetal Derivatives Containing Dioxyether Moiety

Yanju Wang,[†] Jian Zhang,[†] Fangcheng He,[†] Xiuhai Gan,[†] Baoan Song,*[†] Deyu Hu*[†]

Current address: State Key Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Huaxi District, Guiyang 550025, China.

*Address of the corresponding author

Fax: 0086-851-88292170; E-mail: dyhu@gzu.edu.cn; songbaoan22@yahoo.com

ABSTRACT: The present work designed and synthesized a series of dithioacetal derivatives containing dioxyether, as well as evaluated their antiviral activities against tobacco mosaic virus (TMV). Bioassays demonstrated that the target compounds showed excellent anti-TMV activities *in vivo* and *in vitro*. Compound **24c** has excellent anti-TMV activities, and its curative, protective and inactivating activities for TMV were 50.9%, 58.9% and 81.8%, respectively, which are obviously superior to those of ribavirin (50.2%, 41.3% and 69.5%, respectively). Moreover, the EC_{50} of the inactivating activities of the anti-TMV of compound **24c** is 67.9 mg/L, which is superior to that of ribavirin (149.5 mg/L). Transmission electron microscopy showed that compound **24c** caused great damage to the morphology of TMV particles, causing fracture and bending. Molecule docking model revealed that this compound formed five conventional hydrogen bonds with the active sites of amino acids GLN57, ASN73, TYR139, and SER138. Furthermore, the test results of Fluorescence titration and microscale thermophoresis showed that compound **24c** has a strong binding force with TMV coat protein (TMV CP), with an association constant (K_a) of 1.04×10^5 L/mol and dissociation constant (K_d) of 1.6 ± 0.6 μM. These results indicate that the dithioacetal derivatives containing dioxyether are worthy of further research and development as novel antiviral agents.

KEYWORDS: dithioacetal derivatives, vanillin, dioxyether moiety, antiviral activities, Transmission electron microscopy, interaction, molecule docking

Plant virus disease seriously endangers the growth of crops, causing significant economic losses to agricultural production and seriously affecting the development of agricultural industries.[1] Among them, tobacco mosaic virus (TMV) is a common plant virus that mainly harm crops, such as cucumber, tomato, potato, tobacco and pepper. Given the absolute parasitism of the virus in plant and the shortage of an integral immune metabolic system, the prevention and control of plant virus disease is currently a major problem. The current antiviral agents for controlling plant virus diseases are principally ningnanmycin and ribavirin, but the former has poor field control effect and is costly, while the antiviral activities of the latter is poor.[2,3] A broad-spectrum and efficient agent that can control plant virus disease has not yet been developed.

Natural products are of great interest to biologists because of their low toxicity, easy degradation, environmental friendliness, specific targets, and special modes of action.[4,5,6] The pesticide research based on natural products has become one of the hotspots of pesticide development and utilization in recent years.[7-9] Vanillin (3-methoxy-4-hydroxybenzaldehyde) (Fig. 1) is a flavor component of vanilla beans. It can be found in beets, vanilla beans, benzoin gum, Peru balsam, tolu balsam, and so on. It is an important spice with a strong aroma and a widely used edible flavor. It can be found in vanilla seeds and can also be artificially synthesized. Vanillin has extensive biological activities, such as antibacterial,[10,11] anticancer,[12] antioxidant,[13] antifungal,[14] anti-inflammatory,[15] anti-tumor,[16] antimutagenic,[17] and antiproliferative,[18] antiviral activities,[19] and so on.

Our group reported for the first time vanillin derivatives containing dithioacetal and

discovered that xiangcaoliusuobingmi (Fig. 1) has excellent antiviral activities against CMV and PVY. [19,20] Subsequently, our group designed and synthesized a series of dithioacetal derivatives with prominent antiviral activities against CMV, PVY, and TMV.[21,22] However, no compounds with high inactivating activities for TMV were found. Hence, in the present study, target compounds of dithioacetal derivatives containing dioxyether were designed (Fig. 1) and synthesized (Fig. 2), and their activities against TMV were evaluated via half-leaf method in an attempt to find a new, efficient, and broad-spectrum anti-plant virus compounds as precursors for further derivatization and studying their mechanism of action.

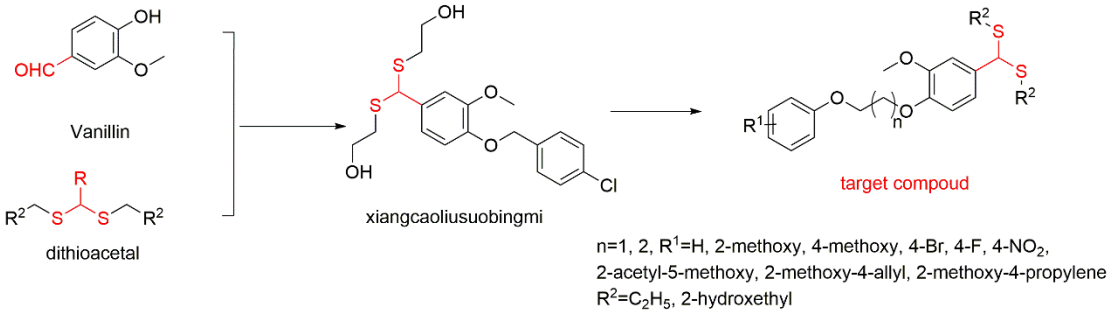
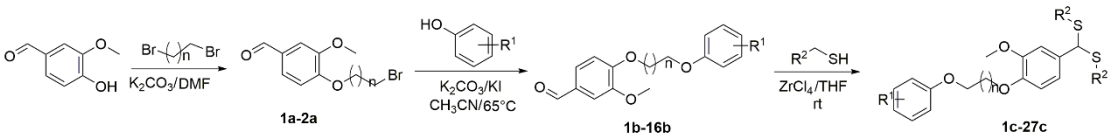


Fig. 1. Design of the target compounds



1c: n=1, R^1=2-methoxy, R^2=C_2H_5
2c: n=1, R^1=2-methoxy-4-allyl, R^2=C_2H_5
3c: n=1, R^1=2-methoxy-4-propylene, R^2=C_2H_5
4c: n=1, R^1=2-acetyl-5-methoxy, R^2=C_2H_5
5c: n=1, R^1=4-F, R^2=C_2H_5
6c: n=1, R^1=H, R^2=C_2H_5
7c: n=1, R^1=4-NO_2, R^2=C_2H_5
8c: n=1, R^1=4-methoxy, R^2=C_2H_5
9c: n=1, R^1=4-Br, R^2=C_2H_5
10c: n=2, R^1=2-methoxy-5-acetyl, R^2=C_2H_5
11c: n=2, R^1=2-methoxy, R^2=C_2H_5
12c: n=2, R^1=H, R^2=C_2H_5
13c: n=2, R^1=4-F, R^2=C_2H_5
14c: n=2, R^1=4-methoxy, R^2=C_2H_5
15c: n=2, R^1=4-NO_2, R^2=C_2H_5
16c: n=2, R^1=4-Br, R^2=C_2H_5
17c: n=1, R^1=2-methoxy, R^2=2-hydroxyethyl
18c: n=1, R^1=2-methoxy-4-allyl, R^2=2-hydroxyethyl
19c: n=1, R^1=2-methoxy-4-propylene, R^2=2-hydroxyethyl
20c: n=1, R^1=4-F, R^2=2-hydroxyethyl
21c: n=1, R^1=H, R^2=2-hydroxyethyl
22c: n=1, R^1=4-NO_2, R^2=2-hydroxyethyl
23c: n=1, R^1=4-methoxy, R^2=2-hydroxyethyl
24c: n=1, R^1=4-Br, R^2=2-hydroxyethyl
25c: n=2, R^1=H, R^2=2-hydroxyethyl
26c: n=2, R^1=4-F, R^2=2-hydroxyethyl
27c: n=2, R^1=4-Br, R^2=2-hydroxyethyl

Fig. 2. Synthetic route of the target compounds **1c–27c**

The anti-TMV activities of the target compounds (Table 1) showed that the protective effect of **3c**, **6c** and **8c** (60.2%, 62.9% and 60.9%, respectively) are better than that of

ribavirin (41.3%). The curative effects of **6c** and **22c** (68.5% and 65.8%, respectively) are superior to that of ribavirin (50.2%). Moreover, the inactivating activities of compounds **9c**, **12c** and **24c** (82.8%, 84.3% and 81.8%, respectively) are better than that of ribavirin (69.5%), and the EC_{50} of inactivating activities of compounds **6c**, **7c**, **9c**, **11c**, **12c**, **13c** and **24c** (95.6, 110.3, 80.1, 140.3, 71.5, 139.6 and 67.9 mg/L, respectively) are superior to that of ribavirin (149.5 mg/L).

Structure-activity relationships (SARs). The activities of the target compounds against TMV showed that the type and position of substituents have a great impact on the anti-TMV curative, protective and inactivating activities. The curative and protective activities are increased when R^1 is H or electron-donating group; for example, the anti-TMV curative activities of the compounds decrease in the following order **6c** > **14c** > **18c** > **1c** (H > 4-OCH_3 > 2-OCH_3-4-CH_2-CH=CH_2 > 2-OCH_3), while the anti-TMV protective activities decrease in the following order **6c** > **8c** > **3c** > **24c** (H > 4-OCH_3 > 2-OCH_3-4-CH_2=CH-CH_3 > 4-Br). However, not all of compounds follow this rule. For example, the curative and protective activities of compound **24c** is superior to those of **11c**, that is, 4-Br > 2-OCH_3. The compounds demonstrate better inactivating activities when the substituent R^1 is H or an electron-withdrawing group, as in the following order **12c** > **24c** > **7c** > **13c** (H > 4-Br > 4-NO_2 > 4-F). However, not all compounds follow this rule; for example, **10c** >**7c** (2-OCH_3-5-$COCH_3$ > 4-NO_2). In addition, the value of *n* is also variable for the anti-TMV activity of the compound. Usually, when *n*=1, the compound has better anti-TMV curative, protective and inactivating activities; for example, the curative activities of the compounds decrease

in the following order: **6c** > **12c**, **5c** > **13c**, **7c** > **15c**, **20c** > **26c**, **24c** > **27c**, but some exceptions have occurred, as in **11c** > **1c**, **14c** > **8c**, **16c** > **9c**, **25c** > **21c**. The general variation rule of protective activities is as follows: **1c** > **11c**, **5c** > **13c**, **6c** > **12c**, **7c** > **15c**, **8c** > **14c**, **9c** > **16c**, **20c** > **26c**, **21c** > **25c**, **24c** > **27c**, but with one exception of **10c** > **4c**.

Table 1. Antiviral activities of target compounds **1c**-**27c** against TMV *in vivo* at 500 mg/L and *in vitro*

Compd.	*In vivo* effect				*In vitro* effect K_d[a] (μM)
	protective activity[a] (%)	curative activity[a] (%)	inactivating activity[a] (%)	EC_{50} for TMV inactivating activity[a] (mg/L)	
1c	50.3±1.4	57.2±2.1	53.3±3.4	346.8±3.7	150.4±27.1
2c	52.1±8.8	52.7±7.5	68.0±0.3	172.4±4.3	85.6±26.5
3c	60.2±4.2	52.9±11.1	65.4±8.9	163.3±2.8	77.2±35.5
4c	27.3±3.3	38.3±9.7	37.2±4.0	718.8±2.1	244.2±155.0
5c	48.8±9.2	51.2±9.2	65.8±7.4	160.6±1.9	72.1±3.4
6c	62.9±6.1	68.5±2.1	77.9±2.7	95.6±1.9	14.4±4.9
7c	42.9±6.4	55.4±4.12	76.6±0.7	110.3±2.5	14.5±3.2
8c	60.9±5.2	43.7±6.4	52.9±7.4	393.9±3.4	166.2±45.5
9c	43.6±9.9	31.5±3.6	82.8±5.6	80.1±2.0	10.8±7.5
10c	47.8±8.9	32.1±7.6	66.9±0.8	160.5±4.6	63.1±31.1
11c	55.6±8.7	23.1±6.2	77.9±2.5	140.3±2.1	44.3±4.5
12c	46.0±7.1	41.4±9.5	84.3±0.2	71.5±3.4	4.4±1.4
13c	28.4±6.7	50.9±8.7	72.0±5.3	139.6±5.2	22.1±9.8
14c	35.8±5.3	59.3±9.3	55.7±4.6	331.8±2.7	140.4±37.1
15c	40.0±6.3	44.3±11.3	67.1±4.4	178.3±4.3	88.3±17.4
16c	30.7±6.3	56.5±11.4	81.1±5.4	245.6±3.6	116.9±63.9
17c	40.9±6.3	52.6±9.7	44.8±2.4	685.3±5.3	198.1±73.5
18c	41.4±7.2	58.9±9.9	58.5±0.4	253.4±2.1	120.5±65.4
19c	44.6±2.8	42.5±6.4	65.0±2.8	190.3±6.2	101.9±67.4
20c	43.6±4.5	51.0±1.8	57.0±1.1	263.5±5.1	123.7±59.7
21c	48.4±9.4	44.8±2.5	54.9±0.5	360.2±4.6	149.5±48.9

22c	32.9±6.6	65.8±3.1	45.4±1.1	683.5±5.3	190.5±80.4
23c	29.6±2.8	47.0±9.5	63.2±5.0	240.9±6.4	108.6±62.7
24c	58.9±8.8	50.9±2.7	81.8±2.2	67.9±3.1	1.6±0.6
25c	28.3±0.2	48.8±8.5	57.9±7.2	265.8±4.3	136.4±54.7
26c	35.0±7.6	34.2±9.8	66.4±0.97	180.9±2.6	95.1±36.2
27c	35.6±5.3	50.3±2.7	56.9±1.7	260.8±1.9	121.8±76.1
Ribavirin[b]	41.3±2.4	50.2±3.1	69.5±3.2	149.5±2.3	57.6±23.7

Footnotes: [a] Average of three replicates; [b] Ribavirin was used as the control.

The morphological observation of TMV granules by transmission electron microscope (TEM) (Fig. 3) revealed that normal TMV particles were straight, short rod-shaped in structure, and few particles were broken (Fig. 3A). At a concentration of 200 mg/L, TMV particles treated with ribavirin were broken (Fig. 3B), but the TMV particles treated with **24c** had more severe rupture (Fig. 3C). This finding indicates that compound **24c** has a certain destructive effect on the morphology of TMV particles.

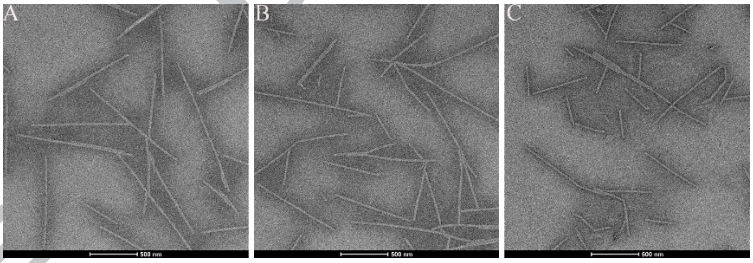


Fig. 3. Effect of compounds **CK** (A), **Ribavirin** (B), and **24c** (C) on the morphology of TMV particles.

Molecular docking was performed using Discovery Studio 4.5 software to investigate the mode of binding of the compounds with TMV CP. Compounds **24c**, **6c** and **4c** were selected to dock with TMV CP and showed prominent to poor inactivating activities against TMV. As shown in the Fig. 4, the binding of the compounds with TMV CP can be attributed to the interaction of compounds with hydrogen and non-hydrogen bonds of TMV CP. First, five conventional hydrogen bonds were formed between compound **24c** and the active sites of amino acids GLN57, ASN73, TYR139, and SER138 with

distance of 2.68, 2.92, 2.62, 2.11, and 3.07 Å, respectively. Among them, compound **24c** formed two conventional hydrogen bonds with TYR139 (2.62 and 2.11 Å, respectively), one carbon hydrogen bond with LYS268 (3.00 Å), and one halogen with GLU222 (2.85 Å), as well as six alkyl or pi-alkyl with VAL75 (5.36 Å), VAL260 (5.15 Å), LYS253 (4.24 and 4.20 Å), VAL251 (5.03 Å), ALA218 (4.30 Å). Second, compound **6c** formed three conventional hydrogen bonds with the active sites of amino acids GLN257 (2.24 Å), ASN73 (1.81 and 2.76 Å), one pi-pi T-shaped with TYR139 (5.80 Å), five alkyl or pi-alkyl with LYS253 (4.72 Å), LYS268 (4.70 Å), VAL75 (4.24 Å), PRO263 (4.57 Å) and ALA74 (5.27 Å). Third, three conventional hydrogen bonds were formed between compound **4c** and the active sites of the amino acids GLY137 (1.65 Å), ASN73 (2.65 and 2.81 Å), one carbon hydrogen bond with THR259 (2.80 Å), one pi-pi stacked with TYR139 (4.24 Å), three alkyl or pi-alkyl with VAL260 (4.86 Å), PRO263 (4.34 Å) and VAL75 (4.46 Å). Finally, the molecular docking results of ribavirin with TMV CP showed that ribavirin formed three conventional hydrogen bonds with LYS268 (2.48 and 1.72 Å) and ARG134 (2.03 Å), seven carbon hydrogen bonds with THR136 (2.64 Å), PRO254 (2.50 Å), GLU222 (2.68 Å), GLU131 (2.73 Å), TRP217 (2.26 Å) and SER255 (2.14 Å), one pi-alkyl with VAL75 (4.54 Å), and one unfavorable donor-donor with ASP219 (1.08 Å).

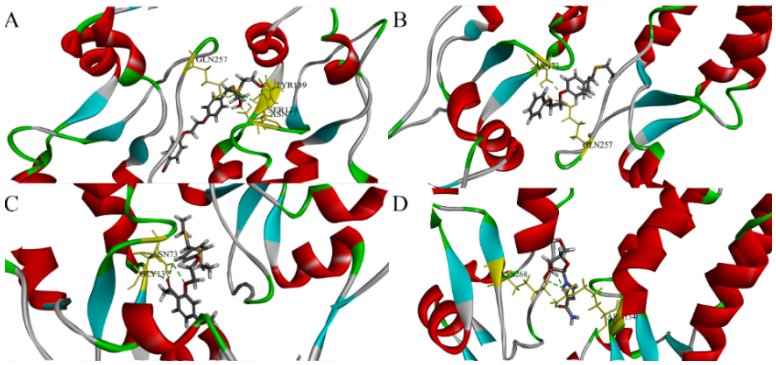


Fig. 4 Molecule docking results of compounds **24c** (A), **6c** (B), **4c** (C), and **Ribavirin** (D) with TMV CP

The interaction of compounds with TMV CP was studied through FT and MST. K_a and K_d values were obtained by FT and MST, respectively, as shown in Table 2 and Figs. 5－6. The results showed that the compound **24c** has powerful adhesion to TMV CP, with $K_a = 1.04\times10^5$ L/mol and $K_d = 1.6 \pm 0.6$ μM. Compound **6c** and TMV CP exhibited moderate binding force strength, with $K_a = 0.85\times10^3$ L/mol and $K_d = 14.4 \pm 4.9$ μM. Ribavirin showed a binding force slightly lower than that of **6c**, with $K_a = 1.04\times10^3$ L/mol and $K_d = 57.6 \pm 23.7$ μM. Compound **4c** showed the lowest binding force, with $K_a = 8.30\times10^2$ L/mol and $K_d = 244.2 \pm 155.0$ μM. These binding constants are consistent with the inactivating activities of EC_{50} of target compounds against TMV.

Table 2 Interaction results of target compounds with TMV CP

Compd.	K_a [a] (L/mol)	K_d [a] (μM)	EC_{50} for TMV inactivating activity [a] （mg/L）
4c	8.30×10^2	244.2±155.0	718.8±2.1
6c	0.85×10^3	14.4±4.9	95.6±1.9
24c	1.04×10^5	1.6±0.6	67.9±3.1
Ribavirin [b]	1.04×10^3	57.6±23.7	149.5±2.3

Footnotes: [a] Average of three replicates; [b] Ribavirin was used as the control.

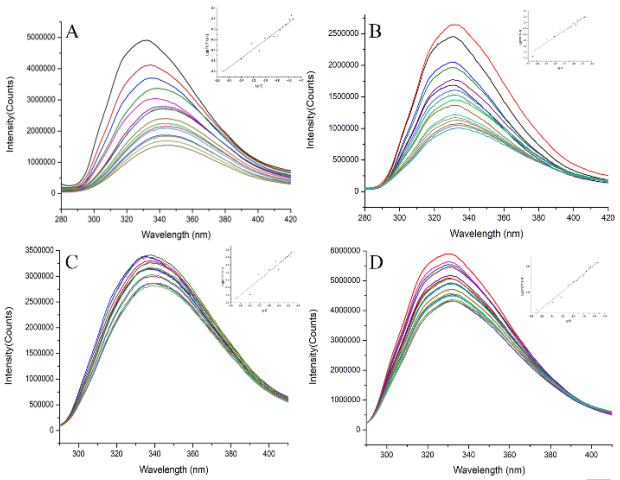


Fig. 5 FT test results of compounds **24c** (A), **6c** (B), **4c** (C), and **Ribavirin** (D) with TMV CP.

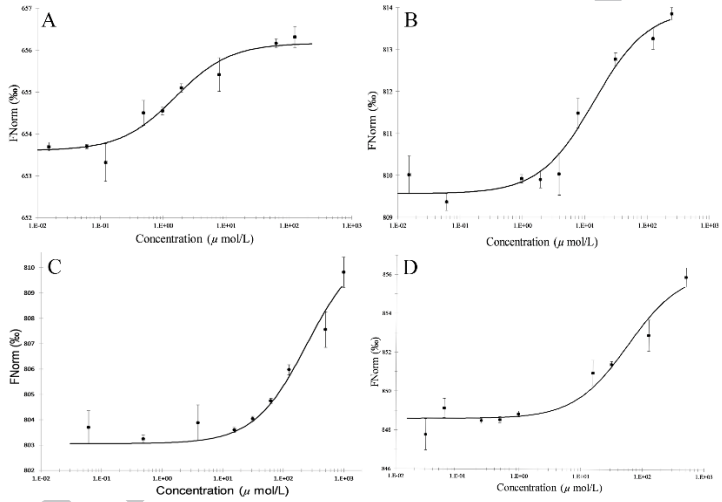


Fig. 6 Microscale thermophoresis (MST) test results of compounds **24c** (A), **6c** (B), **4c** (C) and **Ribavirin** (D) with TMV CP.

In this study, we designed and synthesized a series of dithioacetal derivatives containing dioxyether, as well as evaluated their anti-TMV activities. The biological activities test results indicated that most of the target compounds have excellent anti-TMV curative, protective, and inactivating activities. Especially, compounds **6c**, **9c**, **12c** and **24c** have excellent anti-TMV inactivating activities with EC_{50} values of 95.6, 80.1, 71.5 and 67.9 mg/L, respectively. TEM showed that compound **24c** greatly damaged the morphology of TMV particles, causing fracture and bending, and it has a

certain influence on the shape and size of TMV. Based on the inactivating activities against the TMV of target compounds, the mode of interaction between target compounds and TMV CP was studied by molecular docking, in which compound **24c** was found to have excellent binding ability. In order to derivate molecular docking results, FT and MST were used to further study the interaction of compounds with TMV CP. Compound **24c** demonstrated significant binding with TMV CP, with K_a = 1.04×10^5 L/mol and $K_d = 1.6 \pm 0.6$ μM. This study laid the foundation for the study of antiviral agents.

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Supporting Information

The synthesis, physical analysis, ^{1}H NMR spectra, ^{13}C NMR spectra and high resolution mass spectrum (HRMS) of compounds **1b-16b** and **1c-27c** can be found in the supplementary data.

Abbreviations

TLC, thin layer chromatography; EC_{50}, half-maximal effective concentration; ^{1}H NMR, ^{1}H nuclear magnetic resonance; ^{13}C NMR, ^{13}C nuclear magnetic resonance; TMS, tetramethylsilane; TMV, tobacco mosaic virus; PVY, potato mosaic virus; CMV, cucumber mosaic virus; THF, tetrahydrofuran; SARs, Structure-activity relationships; TEM, Transmission electron microscopy; FT, fluorescence titration; MST, micro-

thermal surge; K_a, association constant; K_d, dissociation constant.

References

1. Tomlinson JA, Epidemiology and control of virus diseases of vegetables. *Ann Appl Biol*. 1987;110:661–681.

2. Wang ZW, Wang L, Ma S, Liu YX, Wang LZ, Wang QM, Design, synthesis, antiviral activity, and SARs of 14-aminophenanthroindolizidines. *J Agric Food Chem*. 2012;60:5825–5831.

3. Wang ZW, Wei P, Liu YX, Wang QM, D and E rings may not be indispensable for antofine: discovery of phenanthrene and alkylaminechain containing antofine derivatives as novel antiviral agents against tobacco mosaic virus (TMV) based on interaction of antofine and TMV RNA. *J Agric Food Chem*. 2014;62:10393–10404.

4. Copping LG, Duke SO, Natural products that have been used commercially as crop protection agents. *Pest Manag Sci*. 2007;63:524–554.

5. Qian XH, Lee PW, Cao S, China: forward to the green pesticides via a basic research program. *J Agric Food Chem*. 2010;58:2613–2623.

6. Cantrell CL, Dayan FE, Duke SO, Natural products as sources for new pesticides. *J Nat Prod*. 2012;75:1231–1242.

7. Du G, Han JM, Kong WS, Zhao W, Yang HY, Yang GY, Gao XM, Hu QF, Chalcones from the flowers of rosa rugosa and their anti-tobacco mosaic virus activities. *B Kor Chem Soc*. 2013;34:1263–1265.

8. Song HJ, Liu YX, Liu YX, Wang LZ, Wang QM, Synthesis and antiviral and fungicidal activity evaluation of *β*-Carboline, dihydro-*β*-carboline, tetrahydro-*β*-

carboline alkaloids, and their derivatives. *J Agric Food Chem*. 2014;62:1010–1018.

9. Xie DD, Xie Y, Ding Y, Wu J, Hu DY, Synthesis of chiral chalcone derivatives catalyzed by the chiral cinchona alkaloid squaramide. *Molecules*. 2014;19:19491–19500.

10. Yadav R, Saini D, Yadav D, Synthesis and evaluation of vanillin derivatives as antimicrobial agents. *Turk J Pharm Sci*. 2018;15:57–62.

11. Kiran K, Ashok D, Rao BA, Sarasija M, Rao AS, Synthesis, characterisation, and antibacterial activity of some novel vanillin related hydrazone derivatives bearing 1,2,3-triazole ring. *Russ J Gen Chem*. 2017;87:1288–1294.

12. Gu MM, Li M, Gao D, Liu LH, Lang Y, Yang SM, Ou HL, Huang B, Zhou PK, Shang ZF, The vanillin derivative 6-bromine-5-hydroxy-4-methoxybenzaldehyde induces aberrant mitotic progression and enhances radio-sensitivity accompanying suppression the expression of PLK1 in esophageal squamous cell carcinoma. *Toxicol Appl Pharm*. 2018;348:76–84.

13. Scipioni M, Kay G, Megson I, Lin PKT, Novel vanillin derivatives: synthesis, *anti*-oxidant, DNA and cellular protection properties. *Eur J Med Chem*. 2018;143:745–754.

14. Illicachi LA, Montalvo-Acosta JJ, Insuasty A, Quiroga J, Abonia R, Sortino M, Zacchino S, Insuasty B, Synthesis and DFT calculations of novel vanillin-chalcones and their 3-aryl-5-(4-(2-(dimethylamino)-ethoxy)-3-methoxyphenyl)-4, 5-dihydro-1H-pyrazole-1-carbaldehyde derivatives as antifungal agents. *Molecules*. 2017;22:1476.

15. Kim ME, Na JY, Park YD, Lee JS, Anti-neuroinflammatory effects of vanillin through the regulation of inflammatory factors and NF-κB signaling in LPS-stimulated

microglia. *Appll biochem biotech*. 2018;5:1–10.

16. Jantaree P, Lirdprapamongkol K, Kaewsri W, Thongsornkleeb C, Choowongkomon K, Atjanasuppat K, Ruchirawat S, Svasti J, Homo-dimers of vanillin and apocynin decrease metastatic potential of human cancer cells by inhibiting the FAK/PI3K/Akt signaling pathway. *J Agric Food Chem*. 2017;65:2299–2306.

17. Keshava C, Keshava N, Whong WZ, Nath J, Ong TM, Inhibition of methotrexate-induced chromosomal damage by vanillin and chlorophyllin in V79 cells. *Teratog Carcinog Mutagen*. 1997;17:313–326.

18. Carrasco GR, Keppner WS, Hieke M, Lange L, Schneider G, Schubert ZM, Proschak E, Spänkuch B, Vanillin-derived antiproliferative compounds influence Plk1 activity. *Bioorg Med Chem Lett*. 2014;24:5063–5069.

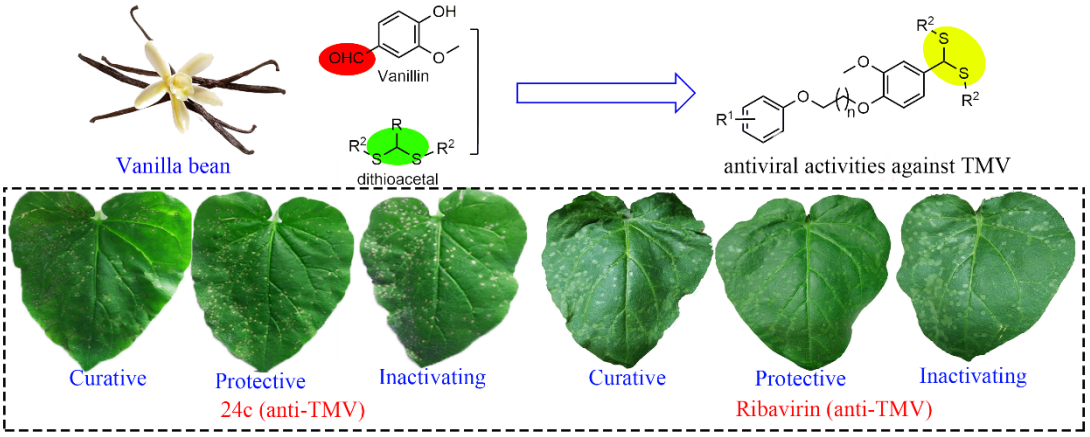
19. Zhang J, Zhao L, Zhu C, Wu ZX, Zhang GP, Gan XH, Liu DY, Pan JK, Hu DY and Song BA, Facile synthesis of novel vanillin derivatives incorporating a bis (2-hydroxyethyl) dithioacetal moiety as antiviral agents. *J Agric Food Chem* 2017;65:4582–4588.

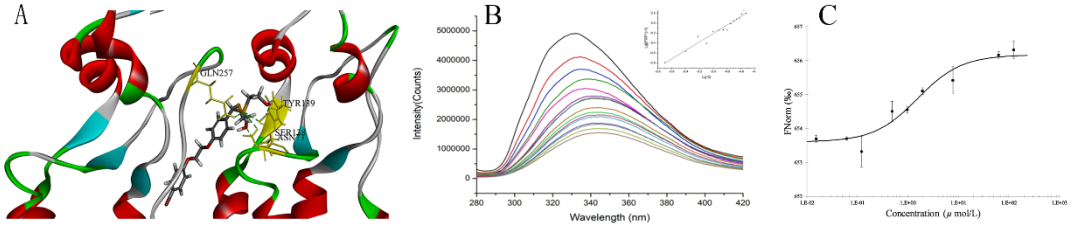
20. Shi J, Yu L, Song BA, Proteomics analysis of xiangcaoliusuobingmi-treated *capsicum annuum* L. infected with cucumber mosaic virus. *Pestic Biochem Phys*. 2018;149:113–122.

21. Chen J, Shi J, Yu L, Liu DY, Gan XH, Song BA, Hu DY, Design, synthesis, antiviral bioactivity, and defense mechanisms of novel dithioacetal derivatives bearing a strobilurin moiety. *J Agric Food Chem*. 2018;66:5335–5345.

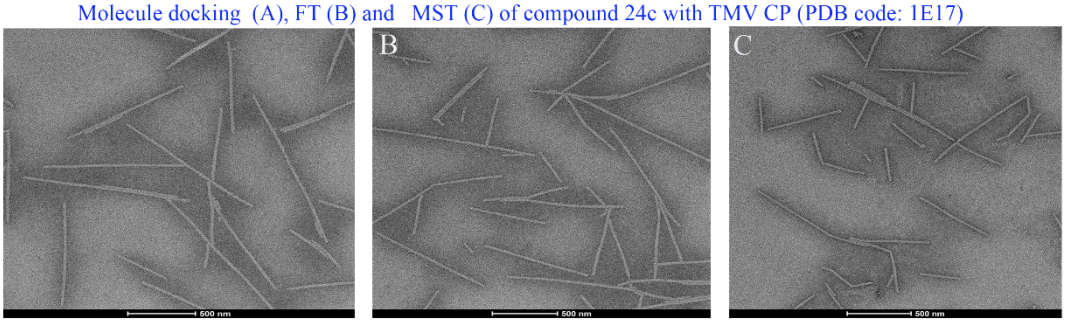
22. Xie DD, Shi J, Zhang AW, Lei ZW, Zu GC, Fu Y, Gan XH, Yin LM, Song BA, Hu

DY, Syntheses, antiviral activities and induced resistance mechanisms of novel quinazoline derivatives containing a dithioacetal moiety. *Bioorg Chem*. 2018;80:433–443.





Molecule docking (A), FT (B) and MST (C) of compound 24c with TMV CP (PDB code: 1E17)



TMV TMV+Ribavirin TMV+24c

The observation of TMV particles morphology by TEM