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Article

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Facile Synthesis of Novel Vanillin Derivatives Incorporating a Bis(2-hydroxyethyl)dithioacetal Moiety as Antiviral Agents

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ABSTRACT: A series of vanillin derivatives incorporating a bis(2-hydroxyethyl)dithioacetal moiety was designed and synthesized via a facile method. A plausible reaction pathway was proposed and verified by computational studies. Bioassay results demonstrated that target compounds possessed good to excellent activities against potato virus Y (PVY) and cucumber mosaic virus (CMV), of which, compound **6f** incorporating a bis(2-hydroxyethyl)dithioacetal moiety, exhibited the best curative and protection activities against PVY and CMV *in vivo*, with 50% effective concentration values of 217.6, 205.7 μg/mL and 206.3, 186.2 μg/mL, respectively, better than those of ribavirin (848.0, 808.1 μg/mL and 858.2, 766.5 μg/mL, respectively), dufulin (462.6, 454.8 μg/mL and 471.2, 465.4 μg/mL), and ningnanmycin (440.5, 425.3 μg/mL and 426.1, 405.3 μg/mL, respectively). Current studies provide support for the application of vanillin derivatives incorporating bis(2-hydroxyethyl)dithioacetal as new antiviral agents.

KEYWORDS: vanillin, bis(2-hydroxyethyl)dithioacetal, antiviral activity, potato virus Y, cucumber mosaic virus

INTRODUCTION

Potato virus Y (PVY) and cucumber mosaic virus (CMV) are important destructive plant pathogens. They can infect various crops, such as potato, cucumber, tobacco, pepper, and other economic corps, and cause significant economic loss.[1–3] To date, few antiviral agents can effectively control PVY or CMV because various aphids, which are difficult to control with pesticides, can rapidly inoculate plants.[2,4] Ningnanmycin, dufulin and ribavirin (Figure 1) are widely used for preventing plant viruses. However, their field efficacies are unsatisfactory.[5–7] In recent years, biologists have found several compounds with good antiviral activities,[8–11] but few virucides have yet been used in the field. Thus, a continuing need for the development of new, highly active antiviral agents exists.

Natural products are important sources for the development of new drugs, featuring unique modes of action, low mammalian toxicity, easy decomposition, environmental friendliness, desirable biological activities, and specificity to target species.[12,13] Vanillin (4-hydroxy-3-methoxybenzaldehyde), a natural product derived from orchids (*Vanilla planifolia*, *V. pompona*, or *V. tahitiensis*),[14] has attracted the attention of biologists for several reasons. First, vanillin as a flavoring compound, possesses general bio-safety and has extensive uses in the food, nutraceutical, beverage, and pharmaceutical industries.[15,16] Second, vanillin possesses a simple chemical structure (Figure 1), which may reduce the possibility of difficult synthesis to some extent. Third, vanillin has desirable biological activities,[15] such as antitumor,[17–19] antioxidant,[20,21] antimicrobial,[22,23] antifungal,[24–26] antiinflammatory,[27] antimutagenic,[28] and antiproliferative[29] activities. In addition, vanillin derivatives possess desirable antifungal[30] and antibacterial[31] activities. However, studies on the application of vanillin derivatives in antiviral pesticides have not been reported.

Ketene dithioacetal derivatives also demonstrate various biological properties, such as antiviral,[32] antibacterial,[33] antifungal,[34,35] and insecticidal properties.[36] Isoprothiolane is a commercial fungicide containing a ketene dithioacetal moiety. Bis(2-hydroxyethyl)dithioacetals display a hydrogen-bonded infinite supra-molecular helical structure, which is similar to biological systems,[37] and have attracted considerable interest because of their biocompatibility.[38]

Considering the biosecurity, simple chemical structure, and extensive bioactivities of vanillin and the biocompatibility of bis(2-hydroxyethyl)dithioacetal, we synthesized new simple chemical structures with antiviral activities (Figure 2). These structures include bis(2-hydroxyethyl)dithioacetals, vanillin derivatives incorporating a bis(2-hydroxyethyl)dithioacetal moiety, and vanillin derivatives incorporating a dithioacetal moiety. Their antiviral activities against PVY and CMV were evaluated by using the half-leaf method. The structure-activity relationships (SARs) were investigated on the basis of biological activity.

MATERIALS AND METHODS

General Information. All reagents were purchased from Aladdin Chemicals Co. (Shanghai, China) and were used without further purification. All solvents used in the reactions without further drying and purification. Reaction progress was monitored by thin-layer chromatography on silica gel GF_{254} with UV detection. Melting points were uncorrected and determined on a WRX-4 monocular microscope (Shanghai Yice Apparatus & Equipment Co., Ltd., Shanghai, China), and the thermometer was uncorrected. ^{1}H NMR spectra were obtained by using ECX-500 and Varian Mercury plus 500 MHz spectrometers (JEOL, Tokyo, Japan) with $CDCl_3$ or D_2O as a solvent. Chemical

shifts (δ) were given in parts per million (ppm) and were measured downfield from internal tetramethylsilane. ^{13}C NMR spectra were recorded by using a JEOL ECX–500 spectrometer (125 MHz) with $CDCl_3$ or D_2O as a solvent. Infrared (IR) spectra were recorded on a VECTOR 22 spectrometer (Bruker, Karlsruhe, Germany) using KBr disks. HRMS data were measured on Thermo Scientific Q Exactive (Thermo Scientific, Missour, MO). Density functional theory (DFT) calculations were carried out using the Gaussian 09 package.

General Procedure for Preparation of Bis(2-hydroxyethyl)dithioacetals, 3a–3t. $ZrCl_4$ (2.2 mg, 0.01 mmol) was added to the mixture of aldehyde (1.0 mmol) and 2-mercaptoethanol (140 μL, 2.0 mmol) under solvent-free conditions, and the mixture was stirred for 5–30 min at room temperature. After completing the reaction, 10 mL of water was added into the above reaction mixture. Then, the mixture was extracted with 10 mL of dichloromethane. The organic layer was dried over anhydrous Na_2SO_4. Finally, dichloromethane was removed in a rotary evaporator and the crude product was purified by column chromatography and recrystallization using hexane/EtOAc (1:2, v/v). The representative data for **3a** is shown below.

*2,2'-(phenylmethylene)bis(2-hydroxyethyl)dithioacetal (**3a**)*: Yield: 231 mg (95%); white solid; m.p. 58–60 °C, lit.[37] 59 °C; IR (KBr): 3306 cm^{-1}, (–OH group); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.45 (dd, J = 8.2, 1.0 Hz, 2H, Ar–H), 7.39–7.32 (m, 2H, Ar–H), 7.30 (dd, J = 5.0, 3.7 Hz, 1H, Ar–H), 5.07 (s, 1H, –SCHS–), 3.73 (t, J = 5.8 Hz, 4H, –OCH_2–), 2.84 (dt, J = 14.0, 5.7 Hz, 2H, –SCH_2–), 2.71 (dt, J = 14.0, 5.9 Hz, 2H, –SCH_2–), 2.37 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.9 (1C), 128.8 (2C), 128.2 (1C), 127.6 (2C), 61.25 (2C), 53.0 (1C), 35.5 (2C); HRMS (ESI) *m/z* for

$C_{11}H_{16}O_2NaS_2$ $[M+Na]^+$ calcd. 267.0484, found: 267.0482.

General Procedure for the Preparation of Vanillin Derivatives, 5a–5n. A solution of vanillin (10 mmol) and substituted benzyl chloride (10 mmol) in acetonitrile (40 mL) was heated under reflux for 6 h in the presence of K_2CO_3 (100 mol%) and KI (5 mol%). The mixture was cooled down to room temperature, and the solvent was removed in vacuo. The residue was washed with water and recrystallized using ethanol affording vanillin derivatives. The representative data for **5a** is shown below.

*4-(benzyloxy)-3-methoxybenzaldehyde (**5a**)*: Yield: 232 mg (96%); white solid; m.p. 55–57 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.80 (s, 1H, –CHO), 7.43 (t, J = 4.9 Hz, 3H, Ar–H), 7.38 (ddd, J = 6.1, 4.3, 2.4 Hz, 3H, Ar–H), 7.35–7.28 (m, 1H, Ar–H), 6.98 (d, J = 8.2 Hz, 1H, Ar–H), 5.24 (s, 2H, –OCH_2–), 3.93 (s, 3H, –OCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.0 (1C), 153.8 (1C), 150.2 (1C), 136.1 (1C), 130.4 (1C), 128.8 (2C), 128.3 (1C), 127.3 (2C), 126.7 (1C), 112.5 (1C), 109.4 (1C), 71.0 (1C), 56.1 (1C).

General Procedure for Synthesis of Vanillin Derivatives Incorporating Bis(2-hydroxyethyl)dithioacetal, 6a–6n. $ZrCl_4$ (2.2 mg, 0.01 mmol) was added to the solution of vanillin derivatives (1.0 mmol) and 2-mercaptoethanol (140 μL, 2.0 mmol) in THF (2 mL). Then, the mixture was stirred for 5–30 min at room temperature. After completing the reaction, the solvent was removed in vacuo. CH_2Cl_2 (10 mL) and H_2O (10 mL) were added to the resulting mixture, and the two layers were separated. The organic phase was dried over anhydrous Na_2SO_4, filtered, and then concentrated to obtain the crude product, the crude product was purified by column chromatography and recrystallization using hexane/EtOAc (1:2, v/v). The representative data for **6a** is shown below.

2,2'-(((4-((4-chlorobenzyl)oxy)-3-methoxyphenyl)methylene) bis(2-hydroxyethyl)dithio-

*acetal (**6a**)*: Yield: 393 mg (95%); white solid; m.p. 80–82 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.30 (m, 4H, Ar–H), 7.04 (d, J = 2.1 Hz, 1H, Ar–H), 6.88 (dd, J = 8.2, 2.1 Hz, 1H, Ar–H), 6.76 (d, J = 8.2 Hz, 1H, Ar–H), 5.09 (s, 2H, –OCH_2–), 5.02 (s, 1H, –SCHS–), 3.90 (s, 3H, –OCH_3), 3.73 (q, J = 5.9 Hz, 4H, –OCH_2–), 2.83 (dt, J = 14.0, 5.7 Hz, 2H, –SCH_2–), 2.70 (dt, J = 14.0, 5.9 Hz, 2H, –SCH_2–), 2.28 (s, 2H, –OH, D_2O exchangeable); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.0 (1C), 147.9 (1C), 135.5 (1C), 133.8 (1C), 133. (1C), 128.9 (2C), 128.7 (2C), 120.0 (1C), 113.4 (1C), 110.9 (1C), 70.3 (1C), 61.4 (2C), 56.1 (1C), 53.0 (1C), 35.8 (2C); HRMS (ESI) *m/z* for $C_{19}H_{24}O_4NaS_2$ $[M+Na]^+$ calcd. 403.1008, found. 403.1007.

General Procedure for Synthesis of Vanillin Derivatives Incorporating Dithioacetal, 7–11. A mixture of 1.0 mmol vanillin derivatives and 2.0 mmol 4-chlorothiophenol (or 2.0 mmol 4-fluorothiophenol, 2.0 mmol furfurylmercaptan, 2.0 mmol ethanethiol, and 1.0 mmol dithioglycol) in THF solvent (2 mL) was stirred at room temperature. After complete dissolution, $ZrCl_4$ (2.2 mg, 0.01 mmol) was added to the mixture. The solution was stirred for 5–30 min. After completing the reaction, the solvent was removed in vacuo, treated with H_2O (10 mL) and CH_2Cl_2 (10 mL), and the two layers were separated. Then, the organic layer was dried over anhydrous Na_2SO_4. Finally, dichloromethane was removed in a rotary evaporator and the crude product was purified by column chromatography and recrystallization using hexane/EtOAc (4:1, v/v). The representative data for **7** is shown below.

*((4-((4-chlorobenzyl)oxy)-3-methoxyphenyl)methylene)bis((4-chlorophenyl)sulfane) (**7**)*: Yield: 393 mg (95%); white solid; mp 80–82 °C; IR (KBr): 3065.4, 3002.3, 2961.8, 2930.9, 2876.9, 1515.1, 1465.0, 1411.9, 1385.9, 1333.8, 1264.3, 1240.2, 1144.8, 1092.7,

1035.8, 997.2, 812.0, 732.9 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.33 (m, 4H, Ar–H), 7.25 (d, J = 2.2 Hz, 1H, Ar–H), 7.24–7.23 (m, 3H, Ar–H), 7.22–7.21 (m, 3H, Ar–H), 7.20 (d, J = 2.1 Hz, 1H, Ar–H), 6.88 (d, J = 1.7 Hz, 1H, Ar–H), 6.71 (dd, J = 7.7, 5.1 Hz, 2H, Ar–H), 5.29 (s, 1H, –SCHS–), 5.08 (s, 2H, $–OCH_2–$), 3.82 (s, 3H, $–OCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7 (1C), 147.8 (1C), 135.4 (1C), 134.4 (2C), 134.3 (4C), 133.9 (1C), 132.5 (2C), 132.1 (1C), 129.1 (4C), 128.9 (2C), 128.8 (2C), 120.3 (1C), 113.5 (1C), 111.2 (1C), 70.3 (1C), 60.6 (1C), 56.0 (1C); HRMS (ESI) *m/z* for $C_{27}H_{21}O_2Cl_3NaS_2$ $[M+Na]^+$ calcd. 568.9941, found. 568.9930.

DFT calculations. All geometric structures involved in the reactions were fully optimized without any symmetry constraints using B3LYP hybrid functional in combination with the effective core potential coupled with the LANL2DZ basis set for the Zr atom and the all-electron 6-31G(d) basis set for other atoms (B3LYP/(LANL2DZ, 6-31G(d))). Subsequently, frequencies were computed at the same level to confirm the nature of stationary point on energy surfaces.

Antiviral Biological Assay. *Antiviral Biology against PVY.* PVY purification and anti-PVY activity evaluation of the compounds were performed as previously described.[39]

Antiviral Biology against CMV. CMV purification and anti-CMV activity evaluation of the compounds were performed as previously reported.[40, 41]

RESULTS AND DISCUSSION

Chemistry. *Optimization of Reaction Conditions.* We investigated the $ZrCl_4$-catalyzed condensation of benzaldehyde (**1a**) with 2-mercaptoethanol. When benzaldehyde (**1a**) was treated with a catalytic amount of $ZrCl_4$ ([Zr] = 20 mol%) and 2-mercaptoethanol (200 mol%) at room temperature using CH_2Cl_2, toluene, hexane or xylene as a solvent,

the desired product bis(2-hydroxyethyl)dithioacetal derivative (**3a**) was observed in trace. However, when the solvent was replaced with THF, the desired product bis(2-hydroxyethyl)dithioacetal derivative (**3a**) was obtained with a yield of 96%. This result may be associated with the catalytic activity of $ZrCl_4$, which could be activated when $ZrCl_4$ coordinated with THF.[42,43] Then, benzaldehyde (**1a**) was reacted with 2 equiv of 2-mercaptoethanol at room temperature in the presence of 20 mol% $ZrCl_4$ under solvent-free conditions. This reaction gave bis(2-hydroxyethyl)dithioacetal derivative (**3a**) as the sole product in 98% yield. To further optimize the amount of $ZrCl_4$, several trial reactions involving different catalyst amounts were examined. $ZrCl_4$ catalyst (1 mol%) was sufficient for the condensation of benzaldehyde (**1a**) with 2-mercaptoethanol.

*Synthesis of Bis(2-hydroxyethyl)dithioacetals (**3a**–**3t**).* The scope of the reaction was investigated under the optimized conditions (Figure 3). All substituted aldehydes, **1a**–**1t**, using $ZrCl_4$ rapidly reacted, producing to bis(2-hydroxyethyl)dithioacetals **3a**–**3r** in good to excellent isolated yields of 81%–96%. The reactivities of benzaldehyde and aromatic aldehydes containing electron-donating and electron-withdrawing substituents in the ring were investigated. Electron-rich aromatic aldehydes (**1b**–**1f**) exhibited excellent yields in a short reaction time, and electron-withdrawing aromatic aldehydes (**1m**–**1p**) produced slightly lower yields in a longer reaction time. Similarly, 2-naphthaldehyde, cinnamaldehyde, 2-furaldehyde, and 2-thiophenealdehyde were also converted to bis(2-hydroxyethyl) dithioacetals (**3q**–**3t**) with high yields in a short reaction time.

*Synthesis of Vanillin Derivatives Incorporating Bis(2-hydroxyethyl)dithioacetal (**6a**–**6n**), and Dithioacetal (**7**–**11**).* Substitution of vanillin with different substituted benzyl chloride produced vanillin derivatives **5a**–**5n**. Condensation of **5a**–**5n** with 2-

mercaptoethanol yielded corresponding bis(2-hydroxyethyl)dithioacetals **6a**–**6n**. Condensation of **5a** with other sulfydryl compounds produced corresponding dithioacetals **7**–**11** (Figure 4).

Studies on the reaction mechanism. *^{1}H NMR spectra.* To understand the reaction mechanism, $ZrCl_4$-catalyzed reactions of benzaldehyde and 2-mercaptoethanol were performed. The ^{1}H NMR spectra show that after 2-mercaptoethanol reacted with $ZrCl_4$, the hydroxyl hydrogen appeared at δ 4.68, whereas it appeared at δ 3.06 in 2-mercaptoethanol. However, no chemical shift change in sulfydryl hydrogen was observed. The reaction was highly exothermic. Moreover, no change occurred when $ZrCl_4$ reacted with benzaldehyde. Thus, we presumed that $ZrCl_4$ initially reacted with 2-mercaptoethanol to form a Zr···O complex, which resulted in exothermic and chemical shift change. To further observe the coordination mode, $ZrCl_4$ was reacted with 2-mercaptothanol in different molar ratios. Experimental results demonstrated that $ZrCl_4$ was coordinated with 2-mercaptothanol in a 1:2 molar ratio. A plausible reaction pathway based on experimental results above is illustrated as shown in Figure 5.

DFT calculations. DFT results indicated that the coordination of one oxygen of 2-mercaptoethanol with $ZrCl_4$ formed the pentacoordinate **CM1** with a binding energy of –17.08 kcal/mol, and the coordination of two oxygens of 2-mercaptoethanol with $ZrCl_4$ in the *para*-position formed the sexadentate **CM2** with a binding energy of –31.72 kcal/mol. However, the coordination of two oxygens of 2-mercaptoethanol with $ZrCl_4$ in the *ortho*-position formed the sexadentate **CM3** with a binding energy of –35.07 kcal/mol, which is more stable than the other coordination modes. The reaction of 2-mercaptoethanol with benzaldehyde was investigated on the basis of the optimized possible coordination mode

(CM3). Our calculations demonstrated that the reaction proceeded via two steps. In the first step, the addition of a thiol of the complex **A** (**CM3**) to benzaldehyde formed the intermediate **B** (Figure 5), with a Gibbs energy barrier of 34.57 kcal/mol. In the second step, the substitution of another free 2-mercaptoethanol to the hydroxyl of intermediate **B** by its mercapto group formed the intermediate **C** (Figure 5). This step was easily carried out, with a Gibbs energy barrier of only 13.99 kcal/mol. Obviously, the first step is the rate-determining step. Further DFT studies indicated that the coordination of methylene chloride with intermediate **B** formed a weak hydrogen bonding compound, and its binding energy was greater by 1.17 kcal/mol than that of intermediate **C**, indicating that free 2-mercaptoethanol had difficulty reacting with intermediate **B**. This phenomenon may explain the effect of methylene chloride as a solvent on the reaction.

Antiviral Activity. *In Vivo Anti-PVY Activity*. As shown in Table 1, bis(2-hydroxyethyl)dithioacetals **3a**–**3t** exhibited good antiviral activities against PVY *in vivo*. Among these compounds, **3f** derived from vanillin possessed good curative and protective activities with values of 45.2% and 46.5%, respectively, at 500 μg/mL, better than those of ribavirin (40.5% and 43.2%). Vanillin derivatives incorporating a bis(2-hydroxyethyl)dithioacetal moiety possessed good to excellent activities at 500 μg/mL. Compounds **6d**–**6g** and **6i** displayed potent curative activities, with values of 53.7%, 56.7%, 61.3%, 58.7%, and 63.1%, respectively, which were significantly greater than those of ribavirin (40.5%), dufulin (48.2%), and ningnanmycin (50.9%). Compounds **6d**–**6g** showed significant protective activities against PVY, with values of 54.6%, 58.4%, 63.4%, and 59.6% at 500 μg/mL, which were greater than those of ribavirin (43.2%), dufulin (49.5%), and ningnanmycin (52.2%). Interestingly, these compounds could still

maintain potent antiviral activities even at low concentrations. However, the activities of the vanillin derivatives incorporating dithioacetal (**7**–**11**) did not exceed that of the vanillin derivative incorporating bis(2-hydroxyethyl)dithioacetal (**6f**).

To further confirm the antiviral activities and to study the SARs of the target compounds, the EC_{50} values of some compounds were investigated on the basis of previous bioassays, and the results are listed in Table 2. Compounds **6d**–**6g** and **6i** exhibited remarkable curative activities against PVY, with EC_{50} values of 357.5, 308.4, 217.6, 245.1, and 197.4 μg/mL, which were superior to those of ribavirin (848.0 μg/mL), dufulin (462.6 μg/mL), and ningnanmycin (440.5 μg/mL). Compounds **6d**–**6g** showed significant protective activities against PVY, with EC_{50} values of 352.4, 278.7, 205.7, and 266.7 μg/mL, respectively, which were better than those of ribavirin (808.1 μg/mL), dufulin (454.8 μg/mL), and ningnanmycin (425.3 μg/mL).

In Vivo Anti-CMV Activity. Anti-CMV activity results showed that most of the target compounds displayed obvious inhibitory effects (Table 2). Compounds **6d**–**6h** exhibited excellent curative activities against CMV, with EC_{50} values of 300.6, 270.5, 206.3, 271.6, and 366.7 μg/mL, which were superior to those of ribavirin (858.2 μg/mL), dufulin (471.2 μg/mL), and ningnanmycin (426.1 μg/mL). In addition, compounds **6d**–**6h** exhibited significant protective effects against CMV, with EC_{50} values of 298.4, 260.8, 186.2, 265.3, and 358.6 μg/mL, respectively, which were better than those of ribavirin (766.5 μg/mL), dufulin (465.4 μg/mL), and ningnanmycin (405.3 μg/mL). The anti-CMV activity is consistent with the trend of anti-PVY activity.

SARs. Among simple bis(2-hydroxyethyl)dithioacetals **3a**–**3t**, electron-withdrawing aromatic bis(2-hydroxyethyl)dithioacetals (**3m**–**3q**) exhibited higher activities than

electron-rich aromatics (**3b**–**3e**), and the hydroxy group is favorable for activity (**3f** > **3a**–**3e, 3g–3t**). To study the influence of the substitutions at the –OH position and the SARs under the substituents, vanillin derivatives incorporating bis(2-hydroxyethyl)dithioacetal **6a**–**6n** were prepared. Bioassay results indicated that a benzyl ether could influence the antiviral effect. Among these compounds **6a**–**6n**, halogen atom-substituted benzyl ether containing compounds **6d**–**6i** exhibited better antiviral activities, and chlorine-substituted benzyl ethers are the most favorable for activity (**6d**–**6g** > **6h** and **6i**), especially with the chlorine atom at the *para*-position (**6f** > **6d**, **6e**, and **6g**). To further investigate the effect of different sulfur nucleophilic reagents on the antiviral potency after the substituent group at the –OH position of vanillin was determined, compounds **7**–**11** were synthesized and their antiviral potency was tested. Compared with compounds **7**–**11**, **6f** exhibited higher activity. This phenomenon indicates that the infinite helical structure of bis(2-hydroxyethyl)dithioacetal is favourable for antiviral activity. The main difference in compounds **7**–**11** lies in the sulfur nucleophilic reagent. Compounds **7** and **9** displayed stronger antiviral activities than compounds **10** and **11**. The results indicate that the aryl group is more suitable for antiviral activities than the alkyl group. The antiviral activities of vanillin derivative **5f** were considerably weaker than those of **6d**–**6f** incorporating dithioacetal. This result indicates that bis(2-hydroxyethyl)dithioacetal is indispensable for the antiviral activities of these compounds.

In summary, a series of vanillin derivatives incorporating a bis(2-hydroxyethyl)dithioacetal moiety was designed and synthesized via a new and efficient method. Experimental results indicate that the O···Zr···O complex plays an important role in the formation of bis(2-hydroxyethyl)dithioacetals, which was further verified by

DFT calculations. Bioassay results indicated that most compounds exhibited broad-spectrum and good antiviral activities against PVY and CMV. Compound **6f** displayed superior antiviral activity to the commercial ribavirin, dufulin, and ningnanmycin. These results revealed that vanillin derivatives incorporating bis(2-hydroxyethyl)dithioacetals with an infinite helical structure can be considered as new antiviral agents. Field trials and further investigations on structural optimization, mode of action, and other functions in agrochemicals are currently underway.

ASSOCIATED CONTENT

Supporting Information

Characterization data, ^{1}H, ^{13}C NMR spectra, and high-resolution mass spectra for products **3a**–**3t**, **5a**–**5n, 6a**–**6n**, and **7**–**11** are provided. Supplementary data associated with this article can be found in the online version at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ABRREVIATIONS

304 PVY, potato virus Y; CMV, cucumber mosaic virus; DFT, density functional theory; SAR,
305 structure–activity relationship.

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FIGURE CAPTIONS

Figure 1 Chemical structures of Ningnanmycin, Dufulin, Ribavirin and Vanillin.

Figure 2 Design of the target compounds.

Figure 3 Synthesis of bis(2-hydroxyethyl)dithioacetals using $ZrCl_4$ as a catalyst.

Figure 4 Synthetic route of vanillin derivatives incorporating a bis(2-hydroxyethyl)dithioacetal moiety.

Figure 5 Postulated reaction mechanism.

Table 1 Inhibitory Effect of Target Compounds against PVY and CMV at 500 μg/mL[a]

compd	Anti-PVY		Anti-CMV		compd	Anti-PVY		Anti-CMV	
	curative effect (%)	protection effect (%)	curative effect (%)	protection effect (%)		curative effect (%)	protection effect (%)	curative effect (%)	protection effect (%)
3a	11.6±2.1	10.5±2.3	12.4±3.6	13.1±2.5	**6b**	36.5±1.5	38.0±1.6	38.5±4.1	40.0±3.2
3b	12.6±3.2	13.1±2.6	14.3±2.8	15.2±1.6	**6c**	38.2±2.8	39.5±1.5	41.1±3.4	39.1±2.6
3c	13.1±2.4	14.1±2.9	14.1±3.7	14.9±2.8	**6d**	53.7±1.6	54.6±2.3	56.9±2.3	57.6±3.8
3d	24.6±2.4	23.6±3.5	23.7±2.8	23.6±2.5	**6e**	56.7±1.3	58.4±1.4	58.7±2.6	60.4±3.2
3e	23.4±1.7	22.1±1.6	23.8±2.3	26.4±2.8	**6f**	61.3±1.1	63.4±1.5	62.3±2.6	65.4±3.3
3f	45.2±0.5	46.5±1.8	45.4±1.7	47.8±2.3	**6g**	58.7±2.1	59.6±2.5	58.5±3.1	59.4±2.2
3g	38.3±2.3	35.2±2.7	34.3±3.1	37.3±1.4	**6h**	50.3±2.3	47.7±1.7	55.7±1.8	56.7±2.8
3h	41.6±1.8	42.3±3.3	43.5±2.6	42.4±2.1	**6i**	63.1±2.5	48.3±1.3	47.2±2.2	49.3±1.9
3i	34.2±1.5	35.8±2.6	36.4±1.9	37.3±2.8	**6j**	39.7±2.1	38.4±2.2	36.7±3.2	38.1±3.4
3j	35.7±1.6	37.3±2.2	35.1±2.8	36.1±1.9	**6k**	37.3±1.2	36.4±2.3	35.9±2.2	36.4±3.3
3k	32.7±1.6	32.4±2.7	33.1±1.4	34.9±1.7	**6l**	34.7±2.0	35.9±2.0	36.1±1.9	38.2±2.3
3l	35.8±2.2	32.5±3.1	34.1±2.3	34.3±1.9	**6m**	43.3±2.6	44.3±3.1	44.3±2.2	43.3±2.6
3m	25.4±2.2	26.6±2.8	26.2±2.1	27.2±2.6	**6n**	39.7±2.4	37.4±1.5	40.7±2.6	38.4±4.2
3n	26.6±1.7	25.8±1.5	25.7±2.6	26.5±1.9	**7**	55.6±1.2	56.4±2.2	55.7±3.6	57.5±2.8
3o	28.6±2.7	29.2±1.7	28.5±2.3	27.1±2.6	**8**	47.6±2.4	48.3±3.1	56.4±2.9	49.6±3.4
3p	28.3±1.7	27.7±1.9	27.3±2.4	27.6±2.1	**9**	46.8±2.5	47.2±3.7	47.6±2.0	48.5±3.6
3q	35.8±1.9	36.2±2.4	37.6±3.1	36.4±2.6	**10**	44.8±3.7	45.1±3.0	45.5±2.1	46.2±1.9
3r	38.3±2.4	39.6±3.1	38.2±2.7	40.5±2.4	**11**	43.1±2.9	44.2±3.2	44.9±3.7	45.1±2.6
3s	39.2±2.0	38.7±3.2	39.1±2.5	39.8±1.6	Ribavirin[b]	40.5±2.2	43.2±2.5	39.4±2.5	42.3±1.8
3t	41.0±2.6	41.6±1.8	40.6±3.5	42.4±3.1	Ningnanmycin[c]	50.9±2.3	52.2±2.0	51.3±1.7	53.8±2.3
5f	45.1±1.3	46.1±1.9	46.7±1.9	46.8±1.6	Dufulin[d]	48.2±1.7	49.5±1.3	47.6±1.4	49.4±2.1
6a	42.8±1.5	43.2±1.7	41.8±4.2	42.1±3.5					

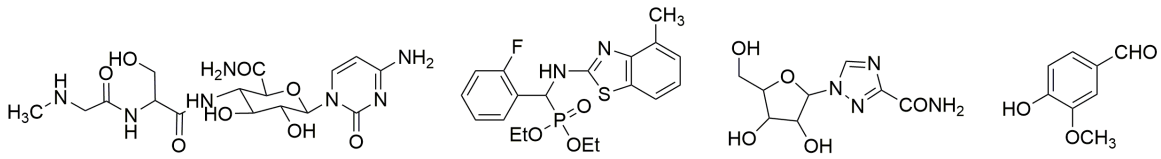
[a]Average of three replicates; [b]Ribavirin, [c]ningnanmycin, and [d]dufulin were used as the control.

443 Table 2 EC_{50} Values of Target Compounds against PVY and CMV[a]

compd	EC_{50} for Anti-PVY		EC_{50} for Anti-CMV	
	curative effect (μg/mL)	protection effect (μg/mL)	curative effect (μg/mL)	protection effect (μg/mL)
3f	726.7±4.8	679.7±2.1	716.8±2.4	658.4±3.1
5f	708.9±3.2	644.4±3.5	652.3±4.4	657.9±5.1
6a	828.8±3.4	598.6±4.8	816.5±3.5	807.6±2.2
6b	1051.5±3.8	841.1±2.6	895.2±3.3	857.8±3.6
6c	872.8±2.1	790.4±1.6	824.6±2.1	885.1±2.5
6d	357.5±4.4	352.4±5.2	300.6±3.3	298.4±4.0
6e	308.4±4.4	278.7±5.2	270.5±3.9	260.8±3.7
6f	217.6±3.6	205.7±2.4	206.3±4.3	186.2±4.5
6g	245.1±2.0	266.7±2.2	271.6±1.8	265.3±2.5
6h	398.4±2.4	521.4±1.9	366.7±2.1	358.6±2.6
6i	197.4±3.9	502.2±2.7	516.7±2.9	467.6±2.3
6j	737.3±4.0	920.9±3.3	968.7±3.6	921.4±3.4
6k	817.3±3.6	1042.3±4.2	982.3±3.8	961.5±2.6
6l	1069.2±3.2	1039.3±3.5	965.1±3.1	906.2±2.4
6m	691.8±1.4	605.4±1.8	603.5±3.2	657.3±2.7
6n	839.4±3.5	839.3±4.0	676.3±3.2	724.3±2.6
7	347.4±2.4	348.0±2.1	346.3±2.8	324.8±4.6
Ribavirin[b]	848.0±2.8	808.1±5.6	858.2±3.0	766.5±3.4
Ningnanmycin[c]	440.5±2.0	425.3±2.4	426.1±4.5	405.3±3.2
Dufulin[d]	462.6±3.8	454.8±2.6	471.2±4.2	465.4±3.4

444 [a]Average of three replicates; [b]Ribavirin, [c]ningnanmycin, and [d]dufulin were used as the control.

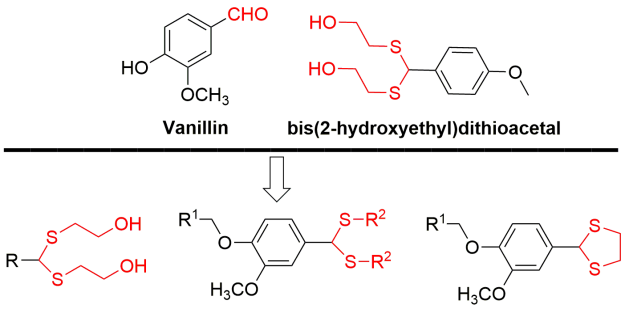
445



446

447 Figure 1

448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Vanillin
HO
S
HO
S
O
bis(2-hydroxyethyl)dithioacetal
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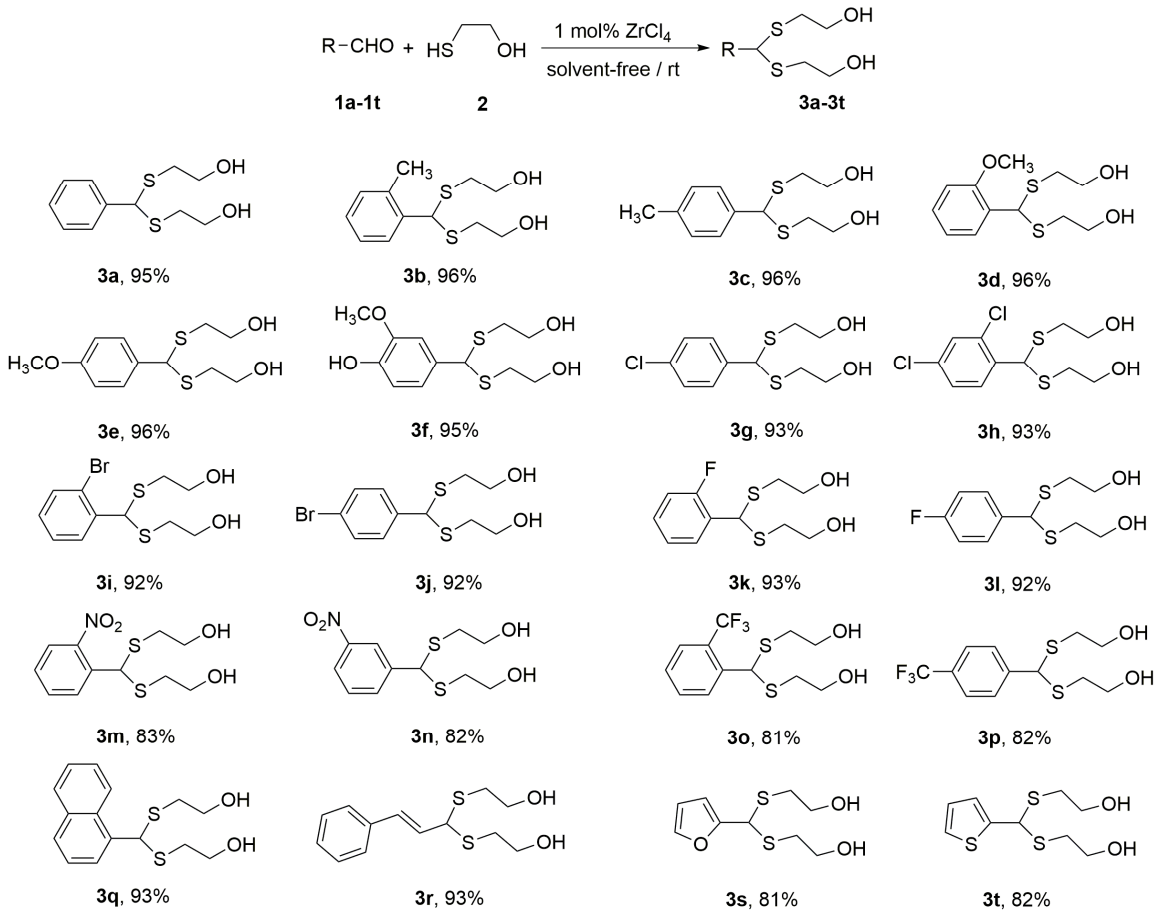
OH
R
S
OH
R1
O
S–R2
S–R2
H3CO
R1
O
S
S
H3CO

Figure 2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solvent-free / rt
R
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2
3a-3t
3a, 95%
3b, 96%
3c, 96%
3d, 96%
3e, 96%
3f, 95%
3g, 93%
3h, 93%
3i, 92%
3j, 92%
3k, 93%
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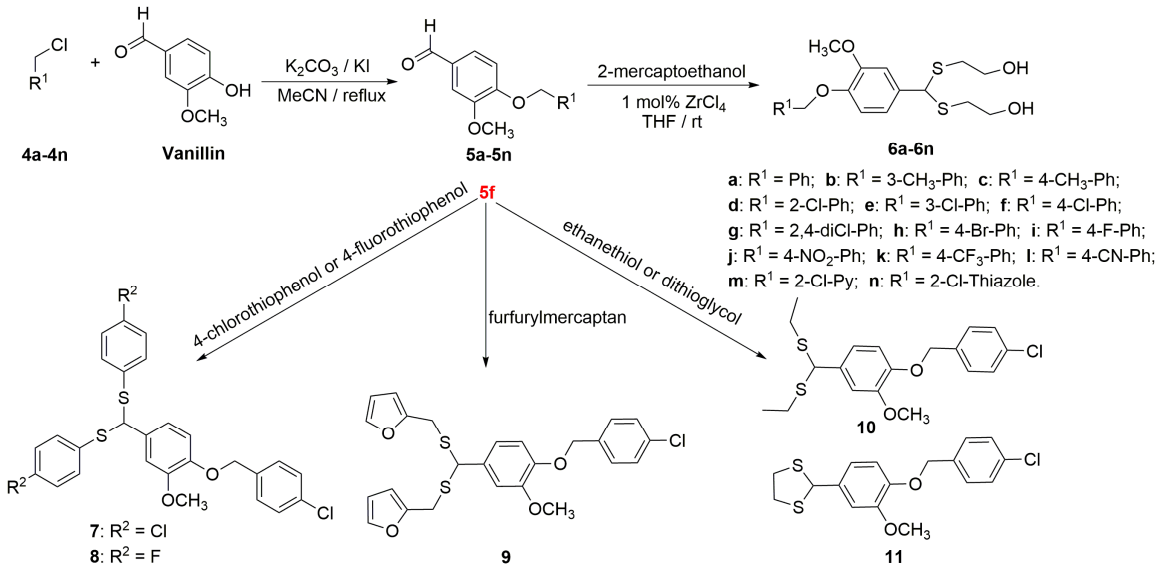
Figure 3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Vanillin
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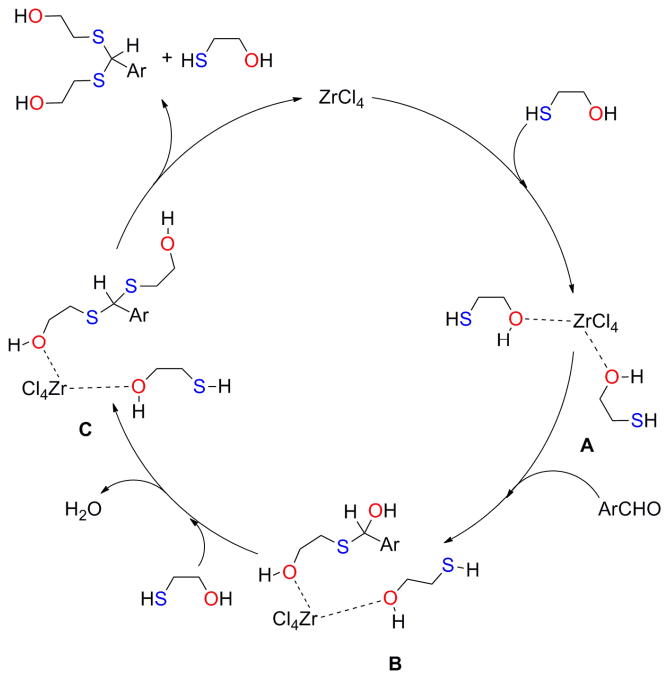
MeCN / reflux
5a-5n
2-mercaptoethanol
1 mol% $ZrCl_4$
THF / rt
6a-6n
a: R^1 = Ph; **b**: R^1 = 3-CH_3-Ph; **c**: R^1 = 4-CH_3-Ph;
d: R^1 = 2-Cl-Ph; **e**: R^1 = 3-Cl-Ph; **f**: R^1 = 4-Cl-Ph;
g: R^1 = 2,4-diCl-Ph; **h**: R^1 = 4-Br-Ph; **i**: R^1 = 4-F-Ph;
j: R^1 = 4-NO_2-Ph; **k**: R^1 = 4-CF_3-Ph; **l**: R^1 = 4-CN-Ph;
m: R^1 = 2-Cl-Py; **n**: R^1 = 2-Cl-Thiazole.
5f
4-chlorothiophenol or 4-fluorothiophenol
furfurylmercaptan
ethanethiol or dithioglycol
7: R^2 = Cl
8: R^2 = F
9
10
11

Figure 4

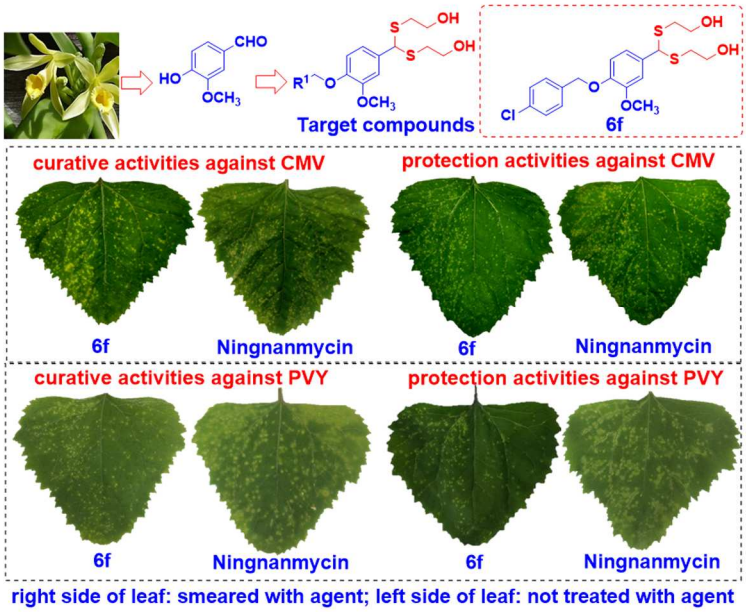


458

459 Figure 5

460

461 Table of Contents Graphic



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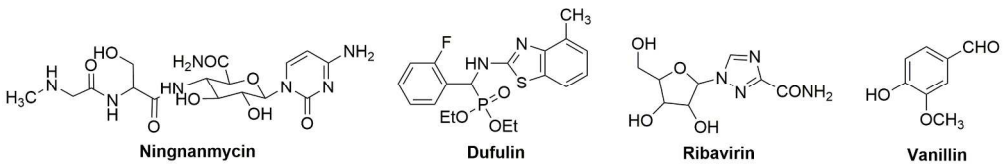

Figure 1 Chemical structures of Ningnanmycin, Dufulin, Ribavirin and Vanillin.

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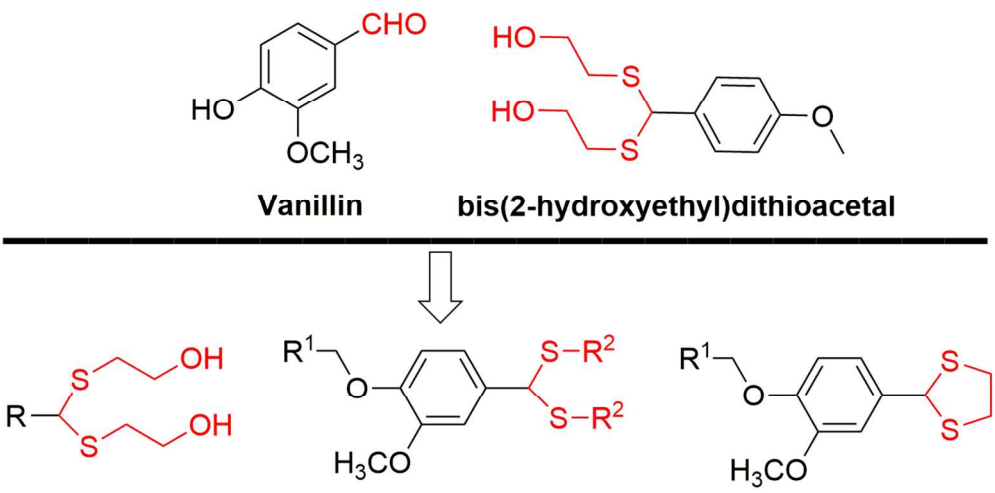

Figure 2 Design of the target compounds.

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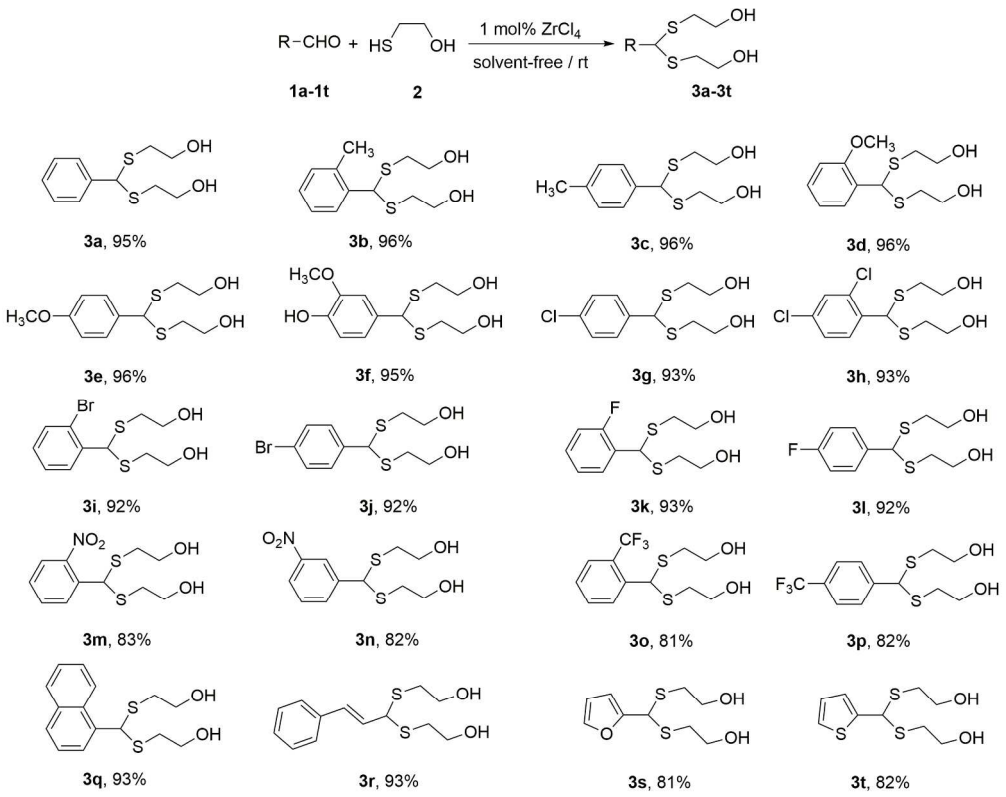

Figure 3 Synthesis of bis(2-hydroxyethyl)dithioacetals using ZrCl4 as a catalyst.

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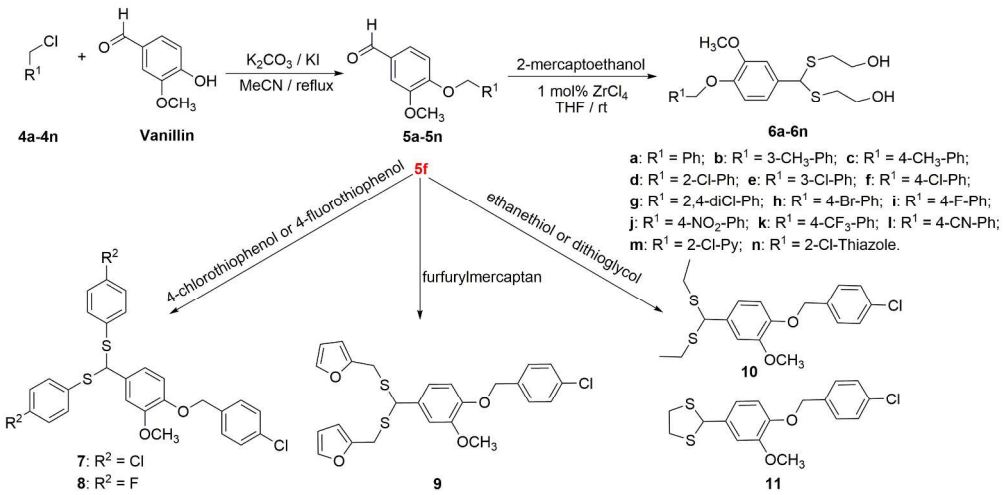

Figure 4 Synthetic route of vanillin derivatives incorporating a bis(2-hydroxyethyl) dithioacetal moiety.

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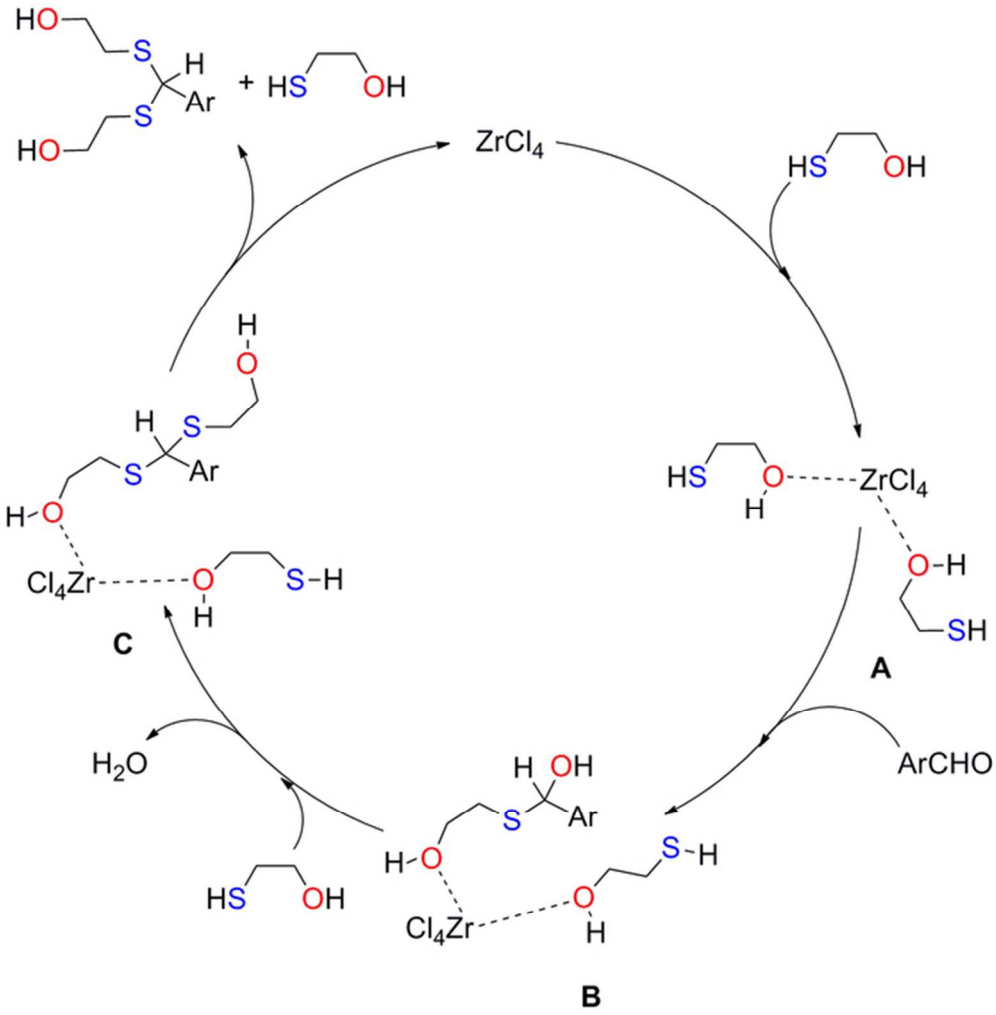

Figure 5 Postulated reaction mechanism.

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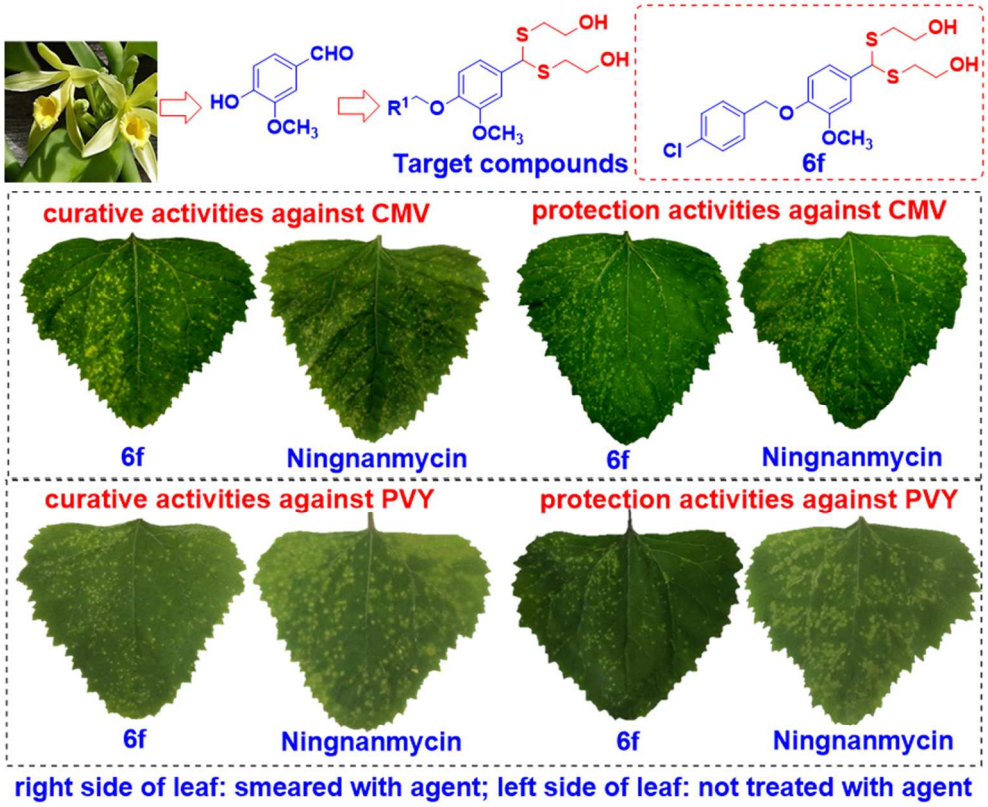

TOC Graphic

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