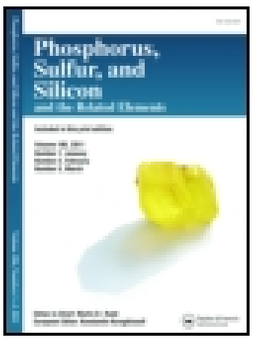

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Synthesis and biological activities of benzothiazole derivatives bearing a 1,3,4-thiadiazole moiety

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ABSTRACT

A series of benzothiazole derivatives bearing a 1,3,4-thiadiazole moiety were designed, synthesized and evaluated for their antibacterial, antifungal and antiviral activities. The bioassay results indicated that most of target compounds showed good antiviral activities against tobacco mosaic virus (TMV) and antibacterial activities against *Xanthomonas oryzae pv. oryzae* (Xoo) and *Ralstonia solanacearum* (Rs). Especially, the anti-Xoo effect of title compounds **5k** (*N*-(5-methoxybenzo[*d*]-thiazol-2-yl)-2-((5-(2-tolyl)-1,3,4-thiadiazol-2-yl)thio)acetamide) and the anti-Rs effect of title compounds **5a** (*N*-(5-nitrobenzo[*d*]thiazol-2-yl)-2-((5-(4-(trifluorom ethyl)phenyl)-1,3,4-thiadiazol-2-yl)thio)acetmide) respectively reached 52.4% and 71.6% at 100 μg/mL, which are superior to that of bismerthiazol (32.0% and 52.3%). In addition, the protective and inactivation activities of title compound **5i** (*N*-(5-methoxybenzo [*d*]thiazol-2-yl)-2-((5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl)thio)acetamide) against TMV were 79.5% and 88.3%, respectively, which are better than that of ningnanmycin (76.4% and 86.8%). The above research showed that benzothiazole derivatives bearing a 1,3,4-thiadiazole moiety may be used as potential molecular templates in searching for highly-efficient antiviral and antibacterial agents.

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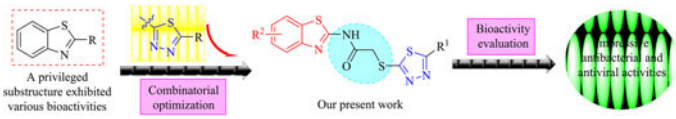
Benzothiazole; 1,3,4-thiadiazole; antibacterial activity; antifungal activity; antiviral activity

GRAPHICAL ABSTRACT



Introduction

Agricultural diseases caused by pathogenic bacteria, viruses and fungi are regarded as the "plant killers" that can result in the significant losses in agricultural output by causing necrotic lesions on leaves, stems or fruits.[1,2] As demaging agricultural bacterial diseases, rice bacterial leaf blight and ralstonia solanacearum, which were respectively caused by *Xanthomonas oryzae pv. oryzae* (Xoo) and *Ralstonia solanacearum* (Rs), are extremely difficult to manage in agricultural production.[3,4] Meanwhile, *tobacco mosaic virus* (TMV) is a classical pathogenic virus that can infects at least 125 agricultural crops including tobacco, tomato, pepper, potato, cucumber and so on.[5,6] Furthermore, wheat scab, apple rot and capsicum wilt, which are respectively caused by *Fusarium graminearum* (Fg), *Oxytetracycline hydrochloride* (Oh) and *Capsicum wilt* (Cw), are severe fungal diseases that are extremely difficult to manage in agricultural production and affect the qualities and outputs of agricultural products. However, long-term uses of existing traditional pesticides, such as bismerthiazol, thiodiazole copper, ningnanmycin, carbendazol and so on, not only lead to the development of pathogens resistance, but also result in a harmful influence on the environment and non-target organisms. Therefore, the discoveries for novel lead compounds with potent agricultural bioactivities are very important in the field of agricultural chemistries.

Benzothiazole derivatives are privileged heterocyclic compounds that play key roles in a search for novel medicines and agrochemicals due to their broad-spectrum bioactivities,[7] such as antifungal,[8] antibacterial,[9] hemostatic,[10] anticancer,[11] antiviral,[12] herbicidal,[13] anti-inflammatory[14] and anti-diabetic activities.[15] In the last decades, some representative benzothiazole derivatives, such as benazolin, benthiavalicarb -isopropyl and dufulin, were developed as commercial agrochemicals that promoted the rapid development of agriculture around the world. In our previous studies, a series of benzothiazole derivatives bearing a oxime ether,[16] phosphonate[17] or cyanoacrylate[18] group were reported for their desirable agricultural bioactivities.

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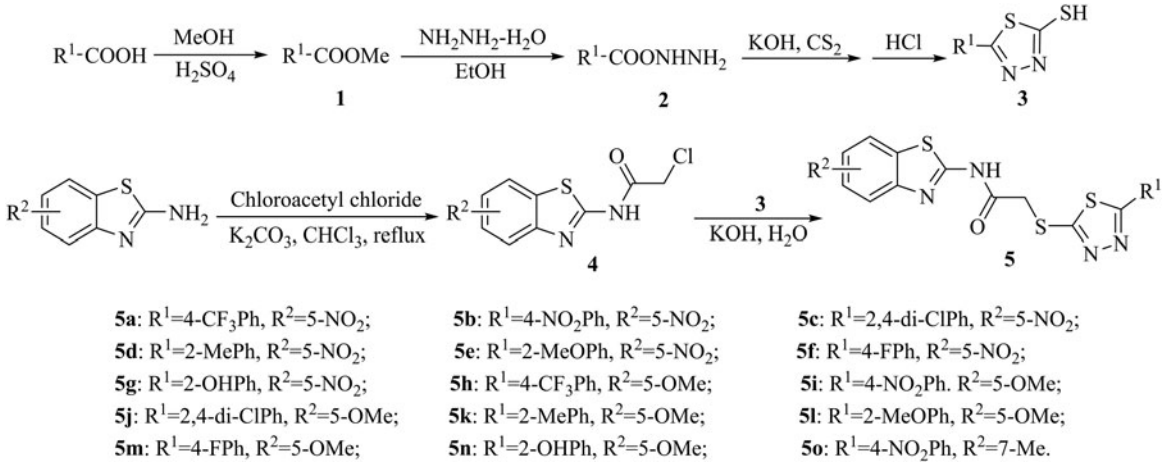

5a: R^1=4-CF_3Ph, R^2=5-NO_2; **5b**: R^1=4-NO_2Ph, R^2=5-NO_2; **5c**: R^1=2,4-di-ClPh, R^2=5-NO_2;
5d: R^1=2-MePh, R^2=5-NO_2; **5e**: R^1=2-MeOPh, R^2=5-NO_2; **5f**: R^1=4-FPh, R^2=5-NO_2;
5g: R^1=2-OHPh, R^2=5-NO_2; **5h**: R^1=4-CF_3Ph, R^2=5-OMe; **5i**: R^1=4-NO_2Ph. R^2=5-OMe;
5j: R^1=2,4-di-ClPh, R^2=5-OMe; **5k**: R^1=2-MePh, R^2=5-OMe; **5l**: R^1=2-MeOPh, R^2=5-OMe;
5m: R^1=4-FPh, R^2=5-OMe; **5n**: R^1=2-OHPh, R^2=5-OMe; **5o**: R^1=4-NO_2Ph, R^2=7-Me.

Scheme 1. Synthetic route of the title compounds.

In addition, 1,3,4-thiadiazole is a pivotal sulfurated fragment that exists in bioactive compounds with anticancer,[19] antinociceptive,[20] anxiolytic,[21] antiviral,[22] anticonvulsant,[23] antibacterial[24] or antifungal[25] activity. Recently, pharmacological studies on 1,3,4-thiadiazole derivatives demonstrated that the sulfurated heterocycles had tremendous application foregrounds in the development of novel agricultural bactericides and virucides. In our preious works, series of 1,3,4-thiadiazole derivatives bearing sulfone,[3] 1,4-pentadiene-3-one[26] and myricetin[27] scaffolds were found to exhibit obvious bioactivities against plant pathogenic bacteria and viruses. In order to continue our studies on searching for novel effective agrichemicals with new action mechanisms, a 1,3,4-thiadiazole group was introduced into the 2-position of benzothiazole nucleus to build a new molecular structure with potent biological activities. Thus, a series of benzothiazole derivatives bearing a 1,3,4-thiadiazole moiety were designed, synthesized (Scheme 1) and evaluated for their antibacterial, antifungal and antiviral activities in this work.

Results and discussion

Chemistry

The synthestic route to title compounds *N*-(benzo[*d*]thiazol-2-yl)-2-((5-phenyl- 1,3,4-thiadiazol-2-yl)thio) acetamide derivatives (5**a**–5**o**) was described in Scheme 1. According to the reported methods described in the reported literatures,[28,29] the key intermediates **3** (substituted 1,3,4-thiadiazole-2-thiols) was synthesized by three steps including esterification, amidation and cyclization reactions. Intermediates **4** (substituted 2-chloro-*N*-(benzo[*d*]thiazol-2-yl)acetamides) were prepared by a substitution reaction of benzo[*d*]thiazol-2-amine derivatives with chloroacetyl chloride in chloroform.[30,31] Finally, the substituted 1,3,4-thiadiazole-2-thiol (**3**) was reacted with substituted 2-chloro-*N*-(benzo[*d*]thiazol-2-yl)acetamide (**4**) in water under 70 °C for 3 h to obtain a benzothiazole derivatives bearing a 1,3,4-thiadiazole moiety (**5**) with a good yield.

A series of benzothiazole derivatives bearing a 1,3,4-thiadiazole moiety were identified by ^{1}H NMR, 13C NMR, IR and elemental analyses. In the ^{1}H NMR spectra, the absorption peaks at 9.04-6.95 ppm reveal the existence of aromatic protons of title compounds. At the same time, the characteristic singlets at 13.44–12.58 and 4.46–3.77 ppm are attributed to the absorptions of –NH– and $-CH_2-$ groups, respectively. The chemical shifts at 166.35–157.45 and 38.43–36.08 ppm in the 13C NMR spectra confirm the existences of C = O and $-CH_2-$ fragments, respectively. In the IR spectra, signals at 1765–1667 and 1597–1547 cm^{-1} are allocated to the characteristic vibrations of C = O and C = N– fragments, respectively. In addition, the tested values of elemental analyses are consistent with the calculated values of title compounds.

Antifungal and antibacterial activities in vitro

The antifungal effects of target compounds **5a–5o** against Fg, Oh and Cw were evaluated at 50 μg/mL by a mycelial growth rate method.[32,33] The commercial fungicide carbendazol was tested as a positive control under the same conditions, and the results are summarized in Table S1 (Supplemental Materials). As shown in Table S1, the antifungal effects against Fg, Oh and Cw ranged 13.6–26.2%, 7.7–26.3% and 11.4–31.8%, respectively, which are inferior to that of carbendazol (100.0%, 100.0% and 100.0%).

The antibacterial effects of target compounds against *Xoo* and *Rs* were also evaluated at 100 μg/mL by a turbidimeter test.[34,35] The commercial bactericide thiadiazole-copper was tested as a positive control under the same conditions, and the antibacterial bioassay results are shown in Table S1 (Supplemental Materials). Table S1 indicated that some target compounds exhibited considerable antibacterial effects against Xoo and Rs. Particularly, the anti-Xoo effects of compounds **5d**, **5e**, **5f**, **5k**, **5l** and **5m** at 100 μg/mL were 41.2%, 42.7%, 32.7%, 52.4%, 42.3% and 38.7%, respectively, which are superior to that of bismerthiazol (32.0%). At the same time, the title compounds **5a**, **5f**, **5h** and **5m** exhibited obvious anti-Rs effects at 100 μg/mL, with corresponding inhibition rates of 71.6%, 64.7%, 66.5% and 65.3%, respectively, which are better than that of bismerthiazol (52.3%).

Structure-activity relationships of antibacterial activities

Table S1 (Supplemental Materials) showed that the changes of substituted groups could greatly effect the inhibition effects against plant bacteria, and some structure activity relationships analyses were discussed as below. First, the 4-CF_3Ph and 4-FPh groups on the R^1 position are favorable for the anti-Rs acvitities of target compounds. For example, the 4-FPh and 4-CF_3Ph moieties on the R^1 position were advantageous for their antibacterial activities against Rs. For instance, compounds 5**a** (R^1=4-CF_3Ph, R^2=5NO_2), 5**f** (R^1=4-FPh, R^2=5-NO_2), 5**h** (R^1=4-CF_3Ph, R^2=5-OMe) and 5**m** (R^1= 4-FPh, R^2=5-OMe) exhibited important anti-Rs effects at 100 μg/mL, with corresponding inhibition rates of 71.6%, 64.7%, 66.5% and 65.3%, respectively, which are better than that of the other substituent groups. At the same time, the 2-MePh, 2-MeOPh and 4-FPh groups on the R^1 position are favorable for the anti-Xoo acvitities of target compounds. For example, the anti-Xoo effects of compounds **5d** (R^1=2-MePh, R^2=5-NO_2) and **5k** (R^1=2-MePh, 5-OMe), **5**e (R^1=2-MeOPh, R^2=5-NO_2) and **5l** (R^1=2-MeOPh, R^2=5-OMe), **5f** (R^1=4-FPh, 5-NO_2) and **5m** (R^1=4-FPh, 5-OMe) at 100 μg/mL ranged from 32.7% to 52.4%, which are better than that of thiadiazole-copper (32.0%). Furthermore, when R^2 was substituted by a 5-OMe group, the obtained compounds exhibited better antibacterial effects against Xoo and Rs. For instance, the anti-Xoo and anti-Rs effects of title compound **5i** (R^2=5-OMe, R^1=4-NO_2) were 26.9% and 25.1%, respectively, which are better than that of title compounds **5b** (R^2=5-NO_2, R^1=4-NO_2, 0.0% and 8.7%) and **5o** (R^2=7-Me, R^1=4-NO_2, 7.3% and 6.2%).

Antiviral activities against TMV in vitro

The antiviral effects of target compounds **5a**–**5o** against TMV *in vivo* were evaluated by a half leaf blight spot method,[36,37] and are shown in Table S2 (Supplemental Materials). The commercial viricide ningnanmycin was tested as a positive control under the same conditions. The results from Table S 2 demonstrate that the curative, protection and inactivation activities ranged 40.1–54.6%, 72.3–79.5% and 82.4–88.3%, respectively. Among them, target compounds **5h**, **5i**, **5j**, **5k**, **5l** and **5n** showed protective activities against tobacco mosaic virus (TMV), with corresponding inhibition rates of 78.3%, 79.5%, 78.3%, 78.3%, 78.9% and 78.5%, respectively, which are superior to ningnanmycin (76.4%). At the same time, the inactivation activities of target compounds **5b**, **5c**, **5f**, **5i**, **5j**, **5k** and **5m** were 87.4%, 87.5%, 87.1%, 88.3%, 88.3%, 87.2% and 87.6%, respectively, which are better than those of ningnanmycin (86.8%).

Structure-activity relationships of antiviral activities

Table S2 (Supplemental Materials) indicated that the anti-TMV activities of target compounds were greatly affected by structural variations of benzothiazole derivatives bearing a 1, 3,4-thiadiazole moiety. First, all title compounds exhibited better inactivation activities than their corresponding curative and protection activities as showed in Table S2 (Supplemental Materials). Second, the 4-NO_2Ph, 2,4-di-ClPh and 4-FPh groups on the R^1 position greatly improved the inactivation activities of title compounds against TMV. For instance, the inactivation activities of target compounds **5b** (R^1=4-NO_2Ph, R^2=5-NO_2) and **5i** (R^1=4-NO_2Ph, R^2=5-OMe), **5c** (R^1=2,4-diClPh, R^2=5-NO_2) and **5j** (R^1=2,4-diClPh, R^2=5-OMe), **5f** (R^1=4-FPh, R^2=5-NO_2) and **5m** (R^1=4-FPh, R^2=5-OMe) were 87.4% and 88.3%, 87.5% and 88.3%, 87.1% and 87.6%, respectively, which are better than that of the other substituent groups. Third, when R^2 was substituted with a 5-OMe group, the corresponding compound **5i** has better inactivation effect against TMV than those compounds bearing a 5-NO_2 (**5b**) or 7-Me (**5o**) group. Finally, when R^1 was substituted by a 2,4-diCl group, the obtained compounds exhibited better protection and inactivation activities against TMV. For instance, the protection and inactivation effects of target compounds **5c** (R^1=2,4-diClPh, R^2=5-NO_2) and **5j** (R^1=2,4-diClPh, R^2=5-OMe) were 77.3% and 87.5%, 78.3% and 88.3%, respectively, which are better than that of ningnanmycin (76.4% and 86.8%).

Experimental

General methods

All reagents and solvents purchased from Chinese Chemical Reagent Company are analytical or chemical pure. Melting points of synthesized compounds were measured by a uncorrected XT-4 Binocular Microscope (Beijing Tech. Instrument, China). Using DMSO-d_6 as the solvent and TMS as an internal standard, a JEOL-ECX 500 NMR spectrometer (JEOL, Japan) were used to record the ^{1}H and 13C NMR spectra of target compounds. The IR spectra were measured by a Bruker VECTOR 22 spectrometer (SHIMADZU, Japan) using a KBr disk. The elemental analyses were measured by an Elementar Vario-III CHN Analyser (Elementar, German). The Supplemental Materials contains sample ^{1}H and 13C NMR spectra and IR spectra of products **5** (Figures S1–S45).

Synthesis of target compounds 5a-5o

According to the reported methods described in the reported literatures,[29,30] the key intermediates **3** (substituted 1,3,4-thiadiazole-2-thiols) was synthesized by three steps including esterification, amidation and cyclization reactions. Intermediates **4** (substituted 2-chloro-*N*-(benzo[*d*]thiazol-2-yl)acetamides) were prepared by a substitution reaction of benzo[*d*]thiazol-2-amine derivatives with chloroacetyl chloride in chloroform.[31,32] A mixture of a intermediate **3** (20 mmol) and potassium hydroxide (20 mmol) in the water (20 mL) was stirred at room temperature for 10 min. Then, substituted 2-chloro-*N*-(benzo[*d*]-thiazol-2-yl) acetamide (20 mmol) was added to the above solution and stirred at 70 °C for 3 h. After the reaction was finished, the solvent was filtered, and the obtained crude

product was purified by recrystallization form a mixture of methanol and dichloromethane (V:V = 1:1) to produce title compounds **5a**–**5o**.

N-*(5-nitrobenzo[d]thiazol-2-yl)-2-((5-(4-(trifluoromethyl)-phenyl)-1,3,4-thiadiazol-2-yl)thio)acetmide (5a)*

Yellow solid, yield: 81%, m.p: 219–222 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.15 (s, 1H, –NH–), 9.01 (d, J = 2.4 Hz, 1H, benzothiazole-4-H), 8.25 (dd, J = 9.0, 2.4 Hz, 1H, benzothiazole-6-H), 8.00–7.96 (m, 2H, benzothiazole-7-H, Ar-2-H), 7.89 (d, J = 9.0 Hz, 1H, Ar-6-H), 7.40–7.36 (m, 2H, Ar-3,5-2H), 4.47 (s, 2H, –SCH_2–); 13C NMR (126 MHz, DMSO-d_6) δ 167.40 (s, benzothiazole-2-C), 167.07 (s, thiadiazole-2-C), 166.28 (s, C = O), 157.35 (s, thiadiazole-5-C), 148.12 (s, benzothiazole-9-C), 133.42 (s, benzothiazole-5-C), 131.65 (s, benzothiazole-8-C), 131.36 (s, Ar-1-C), 130.53 (s, Ar-4-C), 128.86 (s, Ar-2-C), 127.25 (s, Ar-6-C), 126.94 (s, Ar-3-C), 125.41(s, Ar-5-C), 124.25 (s, benzothiazole-7-C), 123.25 (s, benzothiazole -6-C), 119.72 (s, benzothiazole-4-C), 37.49 (s, -CH_2-); IR (KBr, cm^{-1}) v: 3460, 3167, 3003, 1688 (C = O), 1558 (C = N), 1394, 1327, 1259, 1261, 1062, 1029, 831, 942, 750, 704, 663; Anal. calc. for $C_{18}H_{13}F_3N_5O_4S_2$: C, 43.46; H, 2.03; N, 14.03; Found: C, 43.79; H, 2.01; N, 13.97.

N-*(5-nitrobenzo[d]thiazol-2-yl)-2-((5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl)thio)acetamide (5b)*

Red solid, yield: 76%, m.p: >250 °C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 13.16 (s, 1H, –NH–), 9.03 (dd, J = 9.4, 2.4 Hz, 1H, benzothiazole-6-H), 8.37–8.33 (m, 2H, benzothiazole-4,7-2H), 8.25 (dd, J = 8.9, 2.4 Hz, 1H, Ar-3-H), 8.19-8.15 (m, 2H, Ar-5,6-2H), 7.89 (dd, J = 8.9, 4.0 Hz, 1H, Ar-3-H), 4.53 (s, 2H, -SCH_2-); 13C NMR (126 MHz, DMSO-*d6*) δ 168.77 (s, benzothiazole-2-C), 167.71 (s, thiadiazole-2-C), 165.25 (s, C = O), 165.08 (s, thiadiazole-5-C), 163.26 (s, benzothiazole-9-C), 154.34 (s, benzothiazole-5-C), 143.30 (s, Ar-4-C), 132.87 (s, Ar-1-C), 130.47 (d, J = 8.8 Hz, Ar-2-C), 126.39 (s, Ar-6-C), 122.21 (s, Ar-3-C), 120.94 (s, Ar-5-C), 119.40 (s, benzothiazole-7-C, benzothiazole-6-C), 117.22 (s, benzothiazole-6-C), 117.04 (s, benzothiazole-4-C), 38.20 (s, –CH_2–); IR (KBr, cm^{-1}) v: 3300, 3081, 2933, 1693 (C = O), 1574 (C = N), 1518, 1492, 1346, 1288 1149, 1079, 982, 904, 853; Anal. calc. for $C_{17}H_{10}N_6O_5S_3$: C, 43.03; H, 2.12; N, 17.71; Found: C, 43.27; H, 2.11; N, 17.74.

N-*(5-nitrobenzo[d]thiazol-2-yl)-2-((5-(2,4-dichlorophenyl)-1,3,4-thiadiazol-2-yl)thio)acetamide (5c)*

Yellow solid, yield: 80%, m.p: 246–247 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.32 -12.91 (m, 1H, –NH–), 8.99 (s, 1H, benzothiazole-4-H), 8.24 (d, J = 8.9 Hz, 1H, benzothiazole-6-H), 8.09 (d, J = 8.5 Hz, 1H, benzothiazole-7-H), 7.86 (d, J = 9.7 Hz, 2H, Ar-3,6-2H), 7.60 (d, J = 8.6 Hz, 1 H, Ar-5-H), 4.51 (s, 2H, –SCH_2–); 13C NMR (126 MHz, DMSO-d_6) δ 167.79 (s, benzothiazole-2-C), 165.23 (s, thiadiazole-2-C), 163.75 (s, C = O), 162.89 (s, thiadiazole-5-C), 156.64 (s, benzothiazole-9-C), 153.93 (s, benzothiazole-5-C), 143.70 (s, benzothiazole-8-C), 133.99 (s, Ar-4-C), 132.77 (s, Ar-2-C), 129.42 (s, Ar-1-C), 122.38 (s, Ar-3-C), 121.37 (s, Ar-5-C), 120.14 (s, Ar-6-C), 119.69 (s, benzothiazole-7-C), 117.60 (s, benzothiazole-6-C), 109.95 (s, benzothiazole-4-C), 36.25 (s, -SCH_2-); IR (KBr, cm^{-1}) v: 3460, 3184, 2963, 1684 (C = O), 1558 (C = N), 1523, 1473, 1398, 1375, 1261, 1153, 1065, 979, 825, 748; Anal. calc. for $C_{17}H_9Cl_2N_5O_3S_3$: C, 40.97; H, 1.82; N, 14.05; Found: C, 40.66; H, 1.83; N, 14.17.

N-*(5-nitrobenzo[d]thiazol-2-yl)-2-((5-(o-tolyl)-1,3,4-thiadiazol-2-yl)thio)acetamide (5d)*

Yellow solid, yield: 81%, m.p: 226–228 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.19 (s, 1H, –NH–), 9.04 (s, 1H, benzothiazole-4-H), 8.26 (d, J = 8.9 Hz, 1H, benzothiazole -6-H), 7.90 (d, J = 8.9 Hz, 1H, benzothiazole-7-H), 7.61 (d, J = 7.6 Hz, 1H, Ar-6-H), 7.46-7.36 (m, 2H, Ar-4,5-2H), 7.31 (t, J = 7.2 Hz, 1H, Ar-3-H), 4.51 (d, J = 21.5 Hz, 2H, –SCH_2–), 2.44 (s, 3H, –CH_3); 13C NMR (126 MHz, DMSO-d_6) δ 167.35 (s, benzothiazole-2-C), 164.65 (s, thiadiazole-2-C), 163.22 (s, C = O), 157.37 (s, thiadiazole-5-C), 154.90 (s, benzothiazole-9-C), 148.12 (s, benzothiazole-5-C), 132.87 (s, benzothiazole-8-C), 131.64 (s, Ar-1-C), 130.51 (s, Ar-2-C), 127.61 (s, Ar-3-C), 127.24 (s, Ar-4-C), 124.22 (s, Ar-5,6-2C), 120.31 (s, benzothiazole-7-C), 119.72 (s, benzothiazole-6-C), 116.88 (s, benzothiazole-4-C), 37.30 (s, –CH_2–), 18.49 (s, –CH_3); IR (KBr, cm^{-1}) v: 3191, 3055, 2917, 1695 (C = O), 1574 (C = N), 1447, 1374, 1297, 1283, 1164, 1085, 977, 905, 834, 797; Anal. calc. for $C_{18}H_{13}N_5O_3S_3$: C, 48.74; H, 2.95; N, 15.79; Found: C, 48.68; H, 2.96; N, 15.73.

N-*(5-nitrobenzo[d]thiazol-2-yl)-2-((5-(2-methoxyphenyl)-1,3,4-thiadiazol-2-yl)thio) acetamide (5e)*

Yellow solid, yield: 83%, m.p: 204–206 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.44–12.84 (s, 1H, –NH–), 9.03 (t, J = 5.4 Hz, 1H, benzothiazole-4-H), 8.25 (dt, J = 14.2, 7.1 Hz, 1H, benzothiazole-6-H), 8.18 (dd, J = 7.9, 1.7 Hz, 1H, benzothiazole-7-H), 7.91 (t, J = 11.4 Hz, 1H, Ar-6-H), 7.58–7.47 (m, 1H, Ar-4-H), 7.30-7.19 (m, 1H, Ar-5-H), 7.15–7.05 (m, 1H, Ar-3-H), 4.55–4.31 (m, 2H, –SCH_2–), 3.96 (d, J = 18.0 Hz, 3H, –OCH_3); 13C NMR (126 MHz, DMSO-d_6) δ 167.32 (s, benzothiazole-2-C), 165.03 (s, thiadiazole-2-C), 162.43 (s, C = O), 157.39 (s, thiadiazole-5-C), 155.92 (s, benzothiazole -9-C), 148.12 (s, Ar-2-C), 133.25 (s, benzothiazole-5-C), 131.64 (s, benzothiazole-8-C), 130.50 (s, Ar-1-C), 127.74 (s, Ar-4-C), 127.24 (s, Ar-6-C), 124.22 (s, benzothiazole-7-C), 121.79 (s, Ar-5-C), 119.72 (s, benzothiazole-6-C), 118.35 (s, benzothiazole-4-C), 113.01 (s, Ar-3-C), 56.69 (s, –OCH_3), 37.28 (s, -SCH_2-); IR (KBr, cm^{-1}) v: 3420, 3365, 3327, 3930, 1684 (C = O), 1570 (C = N), 1548, 1474, 1435, 1395, 1261, 1166, 1059, 1030, 829; Anal. calc. for $C_{18}H_{13}N_5O_4S_3$: C, 47.05; H, 2.85;N, 15.24; Found: C, 47.17; H, 2.83; N, 15.29.

N-*(5-nitrobenzo[d]thiazol-2-yl)-2-((5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl)thio) acetamide (5f)*

Yellow solid, yield: 84%, m.p: 214–217 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.94 (d, J = 2.3 Hz, 1H, benzothiazole-4-H), 8.22 (dd, J = 2.4 Hz, 1H, benzothiazole-6-H), 7.95–7.89 (m, 2H, benzothiazole-7-H, Ar-2-H), 7.82 (d, J = 9.0 Hz, 1 H, Ar-6-H), 7.38–7.32 (m, 2H, Ar-3,5-2H), 4.47 (s, 2H, –SCH_2–); 13C NMR (126 MHz, DMSO-d_6) δ 168.06 (s, benzothiazole-2-C), 167.20 (s, thiadiazole-2-C), 165.08 (s, C = O), 157.40 (s, thiadiazole-5-C), 148.13 (s, Ar-4-C), 137.04 (s, benzothiazole-9-C), 132.14 (s, benzothiazole-5-C), 131.65 (s, benzothiazole-8-C), 131.21 (s, Ar-1,2-2C), 131.01 (s, Ar-6-C), 130.52 (s, benzothiazole-7-C), 128.86 (s, benzothiazole-6-C), 127.18 (S, benzothiazole-4-C), 124.23 (s, Ar-3-C), 119.72 (s, Ar-5-C), 37.32 (s, -CH_2-); IR (KBr, cm^{-1}) v: 3213, 3094, 2959, 1682 (C = O), 1573 (C = N), 1466, 1338, 1258, 1168, 1164, 1085, 1020, 847, 799; Anal. calc. for $C_{17}H_{10}FN_5O_3S_3$: C, 45.63; H, 2.25; N, 15.65; Found: C, 45.54; H, 2.27; N,15.63.

N-*(5-nitrobenzo[d]thiazol-2-yl)-2-((5-(2-hydroxyphenyl)-1,3,4-thiadiazol-2-yl)thio) acetamide (5g)*

Yellow solid, yield: 81%, m.p: >250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.12 (s, 1H, –NH–), 11.22 (s, 1H, –OH), 9.04 (dd, J = 9.8, 2.4 Hz, 1H, benzothiazole-4-H), 8.28–8.17 (m, 1H, benzothiazole-6-H), 8.10 (dd, J = 7.9, 1.4 Hz, 1H, benzothiazole -7-H), 7.90 (dd, J = 8.9, 4.1 Hz, 1H, Ar-6-H), 7.37 (ddd, J = 15.5, 4.6 Hz, 1H, Ar-4-H), 7.07–6.91 (m, 2 H, Ar-3,5-2H), 4.50 (d, J = 15.9 Hz, 2H, –SCH_2); 13C NMR (126 MHz, DMSO-d_6) δ 169.04 (s, benzothiazole-2-C), 167.67 (s, thiadiazole-2-C), 165.59 (s, C = O), 165.24 (s, thiadiazole-5-C), 163.26 (s, Ar-5-C), 154.51 (s, benzothiazole-9-C), 143.17 (s, benzothiazole-5-C), 132.92 (s, benzothiazole-8-C), 130.48 (d, J = 8.7 Hz, Ar-4,6-2C), 126.41 (s, Ar-1-C), 122.17 (s, Ar-3,5-2C), 120.80 (s, benzothiazole-7-C), 119.32 (s, benzothiazole-6-C), 117.14 (d, J = 22.2 Hz, benzothiazole-4-C), 38.43 (s, -CH_2-); IR (KBr, cm^{-1}) v: 3186, 3089, 2998, 1682 (C = O), 1551 (C = N), 1434, 1393, 1314, 1282, 1168, 1030, 982, 823; Anal. calc. for $C_{17}H_{11}N_5O_4S_3$: C, 45.83; H, 2.49; N, 15.72; Found: C, 45.84; H, 2.47; N, 15.76.

N-*(5-methoxybenzo[d]thiazol-2-yl)-2-((5-(4-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)thio)acetamide (5h)*

White solid, yield: 81%, m.p: >250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.61 (s, 1H, –NH–), 8.08 (s, 2H, benzothiazole-4,7-2H), 7.87 (s, 2H, Ar-3,5-2H), 7.71–7.44 (m, 2H, Ar-2,6-2H), 7.12–6.90 (m, 1H, benzothiazole-6-H), 4.49 (s, 2H, –SCH_2–), 3.77 (s, 3H, –OCH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.24 (s, benzothiazole-2-C), 167.19 (s, thiadiazole-2-C), 166.35 (s, C = O), 165.13 (s, thiadiazole-5-C), 157.20 (s, benzothiazole-5-C), 148.08 (s, benzothiazole-9-C), 136.81 (s, Ar-1-C), 132.42 (s, Ar-4-C), 131.67 (s, Ar-2-C), 131.34 (d, J = 11.9 Hz, Ar-6-C), 130.55 (s, Ar-3-C), 129.27 (s, Ar-5-C), 127.27 (s, benzothiazole-7-C), 124.28 (d, J = 11.6 Hz, benzothiazole-6-C), 119.74 (d, J = 7.8 Hz, benzothiazole-4-C), 43.02 (s, –OCH_3), 37.32 (s, -CH_2-); IR (KBr, cm^{-1}) v: 3196, 3184, 3086, 1682 (C = O), 1610 (C = N), 1470, 1332, 1319, 1275, 1199, 1172, 1097, 1026, 819, 810; Anal. calc. for $C_{19}H_{13}F_3N_4O_2S_3$: C, 47.29; H, 2.72; N, 11.61; Found: C, 47.18; H, 2.71; N, 11.53.

N-*(5-methoxybenzo[d]thiazol-2-yl)-2-((5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl)thio)acetamide (5i)*

Yellow solid, yield: 77%, m.p: >250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.65 (s, 1H, –NH–), 8.33 (d, J = 8.7 Hz, 2 H, Ar-3,5-2H), 8.14 (d, J = 8.7 Hz, 2 H, Ar-2,6-2H), 7.59 (dd, J = 48.0, 5.5 Hz, 2H, benzothiazole-4,7-2H), 7.01 (dd, J = 8.7, 2.4 Hz, 1H, benzothiazole-6-H), 4.49 (d, J = 15.6 Hz, 2H, –OCH_3), 3.77 (s, 3H, –SCH_2–); 13C NMR (126 MHz, DMSO-d_6) δ 166.69 (s, benzothiazole-2-C), 166.03 (s, thiadiazole -2-C), 163.14 (s, C = O), 156.83 (s, thiadiazole-5-C), 156.07 (s, benzothiazole-9-C), 143.14 (s, benzothiazole-5-C), 138.03 (s, Ar-4-C), 133.35 (s, Ar-1-C), 132.26 (s, Ar-2-C), 132.08 (s, Ar-6-C), 129.17 (s, Ar-3-C), 126.97 (s, Ar-5-C), 122.62 (s, benzothiazole-8-C), 121.89 (s, benzothiazole-7-C), 115.64 (s, benzothiazole-6-C), 105.32 (s, benzothiazole-4-C), 56.19 (s, -OCH_3), 36.09 (s, -CH_2-); IR (KBr, cm^{-1}) v: 3481, 3196, 3080, 2995, 1690 (C = O), 1558 (C = N), 1464, 1437, 1406, 1368, 1258, 1173, 1065; Anal. calc. for $C_{18}H_{13}N_5O_4S_3$: C, 47.05; H, 2.85; N, 15.21; Found: C, 47.09; H, 2.84; N, 15.18.

N-*(5-methoxybenzo[d]thiazol-2-yl)-2-((5-(2,4-dichlorophenyl)-1,3,4-thiadiazol-2-yl)thio) acetamide (5j)*

White solid, yield: 80%, m.p: 202–204 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.76 – 12.46 (m, 1H, –NH–), 8.16-8.02 (m, 1H, benzothiazole-4-H), 7.93-7.79 (m, 1H, benzothiazole -7-H), 7.72-7.45 (m, 3H, Ar-3,5,6-3H), 7.01 (dd, J = 8.9, 2.5 Hz, 1H, benzothiazole-6-H), 4.44 (d, J = 42.2 Hz, 2H, –OCH_3), 3.79 (d, J = 15.3 Hz, 3H, –SCH_2); 13C NMR (126 MHz, DMSO-d_6) δ 166.88 (s, benzothiazole-2-C), 164.62(s, thiadiazole-2-C), 163.23 (s, C = O), 157.82 (s, thiadiazole-5-C), 157.30(s, benzothiazole-9-C), 148.12(s, benzothiazole-5-C), 134.20(s, Ar-1-C), 131.64(s, Ar-4-C), 130.58 (s, Ar-2-C), 127.26 (s, Ar-3-C), 124.28 (s, Ar-6-C), 121.24 (s, Ar-5-C), 119.74 (s, benzothiazole-8-C), 113.17 (d, benzothiazole-6,7-2C), 112.31(s, benzothiazole-4-C), 56.48 (s, -OCH_3), 36.03 (s, -CH_2-); IR (KBr, cm^{-1}) v: 3443, 3183, 2992, 1682 (C = O), 1558 (C = N), 1472, 1383, 1348, 1253, 1157, 1054, 1036, 806; Anal. calc. for $C_{18}H_{12}Cl_2N_4O_3S_3$: C, 44.72; H, 2.50; N, 11.59; Found: C, 44.48; H, 2.51; N, 11.55.

N-*(5-methoxybenzo[d]thiazol-2-yl)-2-((5-(o-tolyl)-1,3,4-thiadiazol-2-yl)thio)acetamide (5k)*

White solid, yield: 82%, m.p: 199–201 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.68 (d, J = 37.5 Hz, 1H, –NH–), 7.67–7.59 (m, 2H, benzothiazole-4,7-2H), 7.54 (t, J = 4.4 Hz, 1H, Ar-6-H), 7.41 (ddd, J = 15.2, 10.7, 4.1 Hz, 2H, Ar-4,5-2H), 7.31 (dd, J = 14.2, 6.7 Hz, 1H, Ar-3-H), 7.00 (dt, J = 9.5, 4.7 Hz, 1H, benzothiazole-6-H), 4.49 (d, J = 14.8 Hz, 2H, -SCH_2-), 3.77 (s, 3H, –OCH_3); 13C NMR (126 MHz, DMSO-d_6) δ 167.32 (s, benzothiazole-2-C), 165.03 (s, thiadiazole-2-C), 162.44 (s, C = O), 157.40 (s, thiadiazole-5-C),

155.94 (s, benzothiazole-5-C), 148.13 (s, benzothiazole-9-C), 133.25 (s, Ar-1-C), 131.65 (s, Ar-2-C), 130.51 (s, Ar-3-C), 127.75 (s, Ar-4-C), 127.24 (s, Ar-6-C), 124.22 (s, Ar-5-C), 121.80 (s, benzothiazole-8-C), 119.72 (s, benzothiazole-7-C), 118.36 (s, benzothiazole-6-C), 113.02 (s, benzothiazole-4-C), 56.69 (s, $-OCH_3$), 37.29 (s, $-CH_2-$); IR (KBr, cm^{-1}) *v*: 3461, 3061, 2959, 1703 (C = O), 1576 (C = N), 1449, 1348, 1298, 1271, 1246, 1151, 984, 888, 773, 747; Anal. calc. For $C_{19}H_{16}N_4O_2S_3$: C, 53.35; H, 3.76; N, 13.27; Found: C, 53.32; H, 3.74; N, 13.29.

N-*(5-methoxybenzo[d]thiazol-2-yl)-2-((5-(2-methoxyphenyl)-1,3,4-thiadiazol-2-yl)thio)acetamide (5l)*

White solid, yield: 84%, m.p: >250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.69 (s, 1H, –NH–), 8.27 (dd, *J* = 7.9, 1.6 Hz, 1H, benzothiazole-4-H), 7.70 (t, *J* = 6.9 Hz, 1H, benzothiazole-7-H), 7.63-7.57 (m, 2H, Ar-4,6-2H), 7.32 (d, *J* = 8.3 Hz, 1H, Ar-5-H), 7.18 (t, *J* = 7.8 Hz, 1H, Ar-3-H), 7.08 (dd, *J* = 8.8, 2.6 Hz, 1H, benzothiazole-6-H), 4.53 (d, *J* = 17.5 Hz, 2H, $-CH_2-$), 4.02 (s, 3H, $-OCH_3$), 3.84 (s, 3H, $-OCH_3$); 13C NMR (126 MHz, DMSO-d_6) δ 167.49 (s, benzothiazole-2-C), 165.45 (s, thiadiazole-2-C), 159.55 (s, C = O), 158.74 (s, thiadiazole-5-C), 156.25 (s, benzothiazole-5-C), 152.38 (s, Ar-2-C), 150.68 (s, benzothiazole-9-C), 145.73 (s, Ar-4-C), 137.22 (s, Ar-6-C), 129.52 (s, benzothiazole-8-C), 129.08 (s, Ar-1-C), 128.11 (s, benzothiazole-7-C), 118.38 (s, Ar-5-C), 107.62 (s, Ar-3-C), 101.46 (d, benzothiazole-4,6-2C), 56.76 (s, $-OCH_3$), 56.55 (s, $-OCH_3$), 38.05 (s, $-CH_2-$); IR (KBr, cm^{-1}) *v*: 3480, 3169, 2988, 1676 (C = O), 1558 (C = N), 1393, 1304, 1219, 1161, 1065, 1047, 980, 818; Anal. calc. for $C_{19}H_{16}N_4O_3S_3$: C, 51.33; H, 3.63; N, 12.60; Found: C, 51.42; H, 3.64; N, 12.71.

N-*(5-methoxybenzo[d]thiazol-2-yl)-2-((5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl)thio) acetamide (5m)*

Yellow solid, yield: 84%, m.p: 238–240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ12.60 (s, 1H, –NH–), 7.95–7.90 (m, 2H, benzothiazole-4,7-2H), 7.63 (d, *J* = 8.8 Hz, 1H, Ar-2-H), 7.53 (d, *J* = 2.6 Hz, 1H, Ar-6-H), 7.35 (ddd, *J* = 9.8, 2.6 Hz, 2H, Ar-3,5-2H), 7.03-6.98 (m, 1H, benzothiazole-6-H), 4.46 (s, 2H, $-SCH_2-$), 3.77 (s, 3H, $-OCH_3$); 13C NMR (126 MHz, DMSO-d_6) δ 167.34 (s, benzothiazole-4-C), 162.44 (s, thiadiazole-2-C), 157.45 (s, C = O), 155.94 (s, thiadiazole-5-C), 148.14(s, Ar-4-C), 133.25 (s, benzothiazole-9-C), 131.66 (s, benzothiazole-5-C), 130.49 (d, Ar-1,2-2C), 127.75 (s, Ar-6-C), 127.22 (s, benzothiazole-8-C), 124.20 (s, benzothiazole-7-C), 121.80 (s, benzothiazole-6-C), 119.71 (s, Ar-3-C), 118.38 (s, Ar-5-C), 113.03 (s, benzothiazole-4-C), 56.70 (s, $-OCH_3$), 37.33 (s, $-SCH_2-$); IR (KBr, cm^{-1}) *v*: 3452, 3187, 3077, 1681 (C = O), 1559 (C = N), 1465, 1371, 1309, 1255, 1237, 1121, 1070, 983, 836, 814; Anal. calc. for $C_{18}H_{13}FN_4O_2S_3$: C, 49.89; H, 3.03; N, 12.75; Found: C, 49.76; H, 3.04; N, 12.74.

N-*(5-methoxybenzo[d]thiazol-2-yl)-2-((5-(2-hydroxyphenyl)-1,3,4-thiadiazol-2-yl)thio) acetamide (5n)*

White solid, yield: 82%, m.p: 234–236 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.58 (s, 1H, –NH–), 11.23 (s, 1H, –OH), 8.16-8.06 (m, 1H, benzothiazole-4-H), 7.63 (d, *J* = 8.8 Hz, 1H, benzothiazole-7-H), 7.53 (d, *J* = 2.5 Hz, 1H, Ar-6-H), 7.38-7.32 (m, 1 H, Ar-4-H), 7.04–6.98 (m, 2H, Ar-3,5-2H), 6.98-6.92 (m, 1 H, benzothiazole-6-H), 4.42 (d, *J* = 12.2 Hz, 2H, $-SCH_2-$), 3.77 (d, *J* = 4.8 Hz, 3H, $-OCH_3$); 13C NMR (126 MHz, DMSO-d_6) δ 167.32 (s, benzothiazole-2-C), 165.03 (s, thiadiazole-2-C), 162.43 (s, C = O), 157.39 (s, thiadiazole-5-C), 155.92 (s, benzothiazole-5-C), 148.12 (s, Ar-2-C), 133.25 (s, benzothiazole-9-C), 131.64 (s, Ar-4-C), 130.50 (s, Ar-6-C), 127.74 (s, Ar-1-C), 127.24 (s, benzothiazole-8-C), 124.22 (s, Ar-5-C), 121.79 (s, benzothiazole -7-C), 119.72 (s, Ar-3-C), 118.35 (s, benzothiazole-6-C), 113.01 (s, benzothiazole -4-C), 56.69 (s, $-OCH_3$), 37.28 (s, $-CH_2-$); IR (KBr, cm^{-1}) *v*: 3480, 3184, 3078, 1684 (C = O), 1558 (C = N), 1474, 1458, 1398, 1261, 1153, 1065, 826; Anal. calc. for $C_{17}H_{11}N_5O_4S_3$: C, 50.22; H, 3.28; N, 13.01; Found: C, 50.18; H, 3.27; N, 13.05.

N-*(7-methylbenzo[d]thiazol-2-yl)-2-((5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl)thio)acetamide (5o)*

White solid, yield: 84%, m.p: 204–206 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.88 (s, 1H, –NH–), 8.00-7.94 (m, 2H, Ar-3,5-2H), 7.76 (d, *J* = 7.7 Hz, 1H, benzothiazole -4-H), 7.40–7.33 (m, 2H, Ar-2,6-2H), 7.25-7.16 (m, 2H, benzothiazole-5,6-2H), 4.42 (s, 2H, $-SCH_2-$), 2.54 (s, 3H, $-CH_3$); 13C NMR (126 MHz, DMSO-d_6) δ 166.88 (s, benzothiazole-2-C), 165.17 (s, thiadiazole-2-C), 162.97 (s, C = O), 157.29 (s, thiadiazole-5-C), 156.63 (s, benzothiazole-9-C), 148.11 (s, Ar-4-C), 133.99 (s, Ar-1-C), 131.65 (s, benzothiazole-7-C), 130.55 (s, Ar-2-C), 129.45 (s, Ar-6-C), 127.26 (s, Ar-3-C), 124.28 (s, Ar-5-C), 120.12 (s, benzothiazole-8-C), 119.74 (s, benzothiazole-6-C), 117.58 (s, benzothiazole-5-C), 109.96 (s, benzothiazole-4-C), 36.08 (s, $-SCH_2-$), 18.48 (s, $-CH_3$); IR (KBr, cm^{-1}) *v*: 3460, 3196, 3086, 1670 (C = O), 1557 (C = N), 1522, 1472, 1458, 1396, 1362, 1348, 1265, 1163, 1062,860, 808, 707; Anal. calc. for $C_{18}H_{12}C_{l2}N_4OS_3$: C, 46.25; H, 2.59; N, 11.99; Found: C, 46.42; H, 2.58; N, 12.02.

Conclusion

A series of benzothiazole derivatives bearing a 1,3,4-thiadiazole moiety were designed, synthesized, and structures of all title compounds were identified by ^{1}H NMR, 13C NMR, IR and elemental analyses. At the same time, the results of biological assays indicated that most of target compounds showed good antiviral activities against TMV and antibacterial activities against Xoo and Rs. Especially, the anti-Xoo effects of title compounds **5d**, **5e**, **5f**, **5k**, **5l** and **5m** reached 38.7–52.4% at 100 *μ*g/mL, and the anti-Rs effects of title compounds **5a**, **5f**, **5h** and **5m** ranged 64.7–71.6% at 100 *μ*g/mL, which are superior to that of bismerthiazol (32.0% and 52.3%). In addition, the protective and inactivation activities of title compound **5i** against TMV was 79.5% and 88.3%, respectively, which are better than those that of

ningnanmycin (76.4% and 86.8%). Further studies on the antiviral and antibacterial mechanism are currently underway.

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