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Synthesis and antiviral activity against tobacco mosaic virus and 3D-QSAR of α-substituted-1,2,3-thiadiazoleacetamides

Wei-Guang Zhao,* Jian-Guo Wang, Zheng-Ming Li and Zhao Yang

National Pesticide Engineering Research Center (Tianjin), State Key Laboratory of Elmento-Organic Chemistry, Nankai University, Tianjin 300071, PR China

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Abstract—A series of α-substituted-1,2,3-thiadiazoleacetamides were prepared and tested in vitro against tobacco mosaic virus. The preliminary bioassays indicated that some of the new compounds are good as compared to the commercial pesticide Virus A at 500 mg/L, and the activity was influenced by the nature of the substituents. 3D-QSAR models were established based on the antiviral activity of the compounds. It has also been found that some of the new compounds also exhibit significant anti-HBV activity in human hepatoblastoma-derived liver Hep-G2 cells.

Virus infections in plants cause a variety of detrimental effects and often leave plants more susceptible to damage by other pests and pathogens. Viruses and viroids are responsible for a wide variety of plant diseases which cause significant and costly crop losses annually. Some viral diseases, for example, rice tungro, African cassava mosaic, and tospoviruses, are estimated to cause annual losses in excess of AUD$1 billion worldwide.[1] The tobacco mosaic virus (TMV) infects plants of commercial importance including tobacco and related plants such as tomato and pepper. While not lethal, TMV affects the growth and productivity of these plants. Most countermeasures, however, were an indirect means of protection and technical methods of virus removal, such as soil disinfection and insecticides.

In the investigation of new agrochemicals, we found 1,2,3-thiadiazole derivatives, which had good biological activities,[2–4] had received only limited attention, but commercial pesticides containing 1,2,3-thiadiazole often possess unique active mechanism. For example, TDZ,[5] a cotton defoliant, had been found to exhibit more significant plant growth regulative activity than 6-BA and zeatin; BTH was the first commercial plant activator;[6] Tiadinil possessed excellent fungicidal activity[7] and could prevent mycelium from invading sideward healthy cell (Fig. 1). We became interested in making 1,2,3-thiadiazoleacetamides, analogues of three commercial pesticides.

Herein, we reported a series of α-substituted 1,2,3-thiadiazoleacetamides that have been found to possess potent antiviral activity against tobacco mosaic virus.

In our previous paper, we reported the synthesis of 2-chloro-*N*-methyl-2-(1,2,3-thiadiazol-4-y)l-acetamide (1).[8] The *N*-acylhydrazone, which was easily prepared from commercially available *N*-methyl-α-chloroacetoacetamide and ethyl carbazate in ethanol, was cyclized with three equivalents of thionyl chloride at room temperature to form α-chloro-*N*-methyl-1,2,3-thiadiazole-4-acetamide (**1**) in accord with the Hurd-Mori reaction conditions. The compound (**1**) reacted with substituted phenols, substituted benzenethiols or mercapto heterocyclic compounds in the presence of inorganic base to yield α-substituted phenoxy(phensulfydryl)-*N*-methyl-1,2,3-thiadiazole-4-acetamide (**2**–**5**,[9] **10**–**13**[10]) as shown

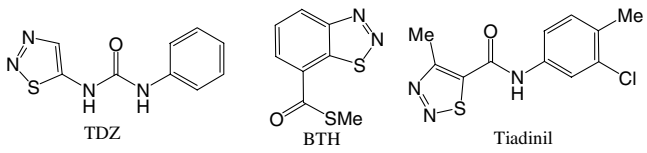

Figure 1.

Keywords: 1,2,3-Thiadiazoleacetamide; Synthesis; TMV; Anti-HBV; 3D-QSAR.
* Corresponding author. Fax: +00862223505948; e-mail: zwg@nankai.edu.cn

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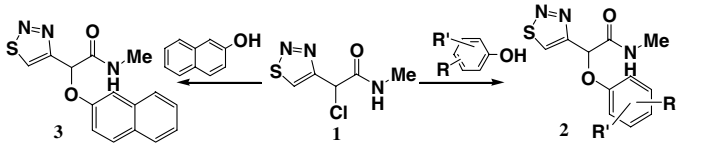
in Schemes 1–3. No by-products are found in the reaction of compounds **1** and phenols, because compound **1** is instable in alkali or heat condition. By controlling reaction temperature, compounds (**4**, **5**) could be easily oxidized by hydrogen peroxide to afford sulfoxide (**6**, **7**[11]) or sulfone (**8**, **9**[12]). And sulfone (**8**, **9**) was readily obtained by the reaction of compound **4** and compound **5** with hydrogen peroxide, respectively.

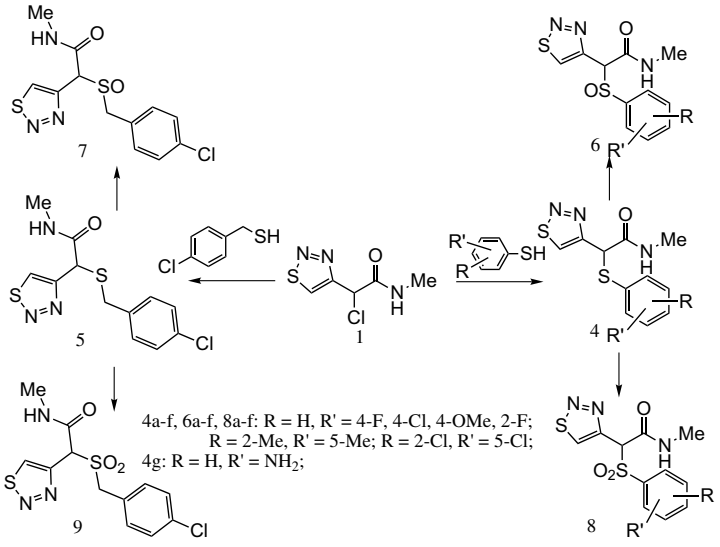
Table 1 summarizes the antiviral screening results of the studied compounds. The results indicated the antiviral activity was different with the substituents of phenyl moiety and oxidation state of sulfur atom.

Having the same linker between 1,2,3-thiadiazole and benzene ring, compounds that were substituted by solely halogen atom at the 2- or 4-position of benzene ring had significant potency against TMV, however if a compound was substituted by two halogen atoms at both 2- and 5-position of benzene ring it had hardly any inhibition. Replacement of halogen with electron-donating group, such as methyl or methoxyl, also abolished



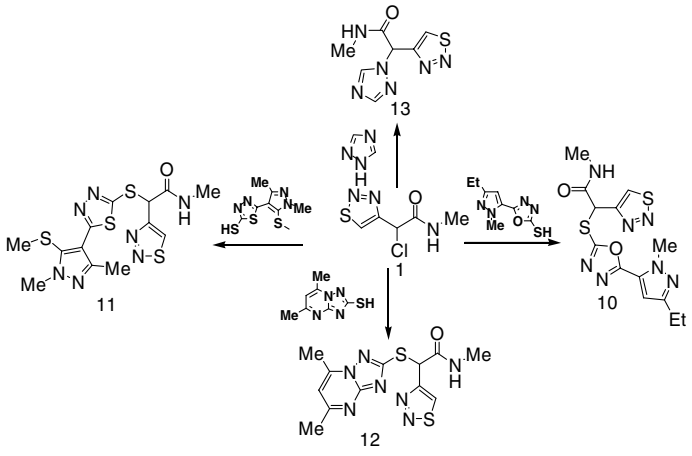
2a-i: R = H, R' = 4-Br, 4-I, 2-Br, H, 4-Me, 3-Me, 2-Cl; R = 2-Cl, R' = 5-Me; R = 3-Me, R' = 4-Me;

Scheme 1.



4a-f, 6a-f, 8a-f: R = H, R' = 4-F, 4-Cl, 4-OMe, 2-F; R = 2-Me, R' = 5-Me; R = 2-Cl, R' = 5-Cl; 4g: R = H, R' = NH_2;

Scheme 2.



Scheme 3.

Table 1. Antiviral activity against TMV at 500 mg/L

Compound	R	R′	Inhibition (%)
2a	H	4-Br	64
2c	H	2-Br	44
2f	H	3-Me	5.5
2g	H	2-Cl	53
2h	2-Cl	5-Me	56
3			44
4a	H	4-F	33
4b	H	4-Cl	42
4d	H	2-F	37
4e	2-Me	5-Me	0
4f	2-Cl	5-Cl	0
4g	H	NH2	15
5			35
Virus A			58
6a	H	4-F	11
6b	H	4-Cl	31
6d	H	2-F	19
6e	2-Me	5-Me	0
7			20
8a	H	4-F	19
8c	H	4-OMe	0
8d	H	2-F	82
8e	2-Me	5-Me	12
9			51
11			35
12			5
13			42

antiviral activity. But if compound **2h** was substituted by *o*-Cl, *m*-Me in ring, it had good antiviral activity.

The substitution of oxygen for sulfur represents an example of an approach that is commonly known as bioisostere. Exchange of the oxygen linker for sulfur leads to a slight loss in activity. After sulfur was oxidized, the bioassay indicated that the antiviral activity of the thioether was slightly better than sulfoxide, whereas worse than sulfone.

Based on the biological activity of the investigated compounds, 3D-QSAR models were established within SYBYL6.6 (Tripos Associates, St. Louis, MO) software using CoMFA method. Compound **8d** was utilized as a template and conformational search was performed to derive possible biological conformers of all investigated compounds. The activity was expressed in terms of D[13] by the formula

$$D = \lg[a/(100 - a)] - \lg M_w$$

where a is percent inhibition and M_w is the molecular weight of the tested compounds. The crossvalidated q^2, optimal components are 0.517 and 6, respectively. For the steric contour map (Fig. 2a), a steric group in the green region will enhance the activity of the compound and a bulky group in the yellow region will decrease the activity. For the electrostatic contour map (Fig. 2b), a positive charged group in the blue region will increase the activity and a negative charged substituent in the red region will decrease the activity. These results provide useful information for further optimization of the compounds.

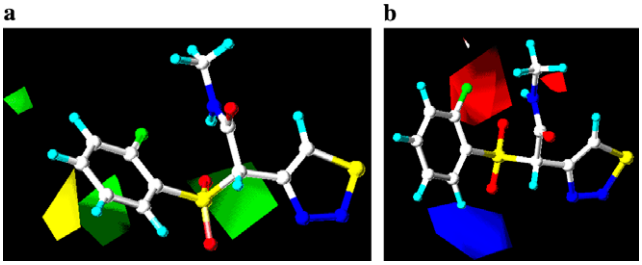


Figure 2.

We had noticed that the active compounds are racemates, the effect of optical activity on biological activity will be studied in future research.

Some compounds have also been found to exhibit significant anti-HBV activity in human hepatoblastoma-derived liver Hep-G2 cells (2.2.15 cells). The inhibition rate of compound **2h** at 0.6 μmol/mL was 88.6% against HBsAg and 15.5% against HBeAg. In contrast, that of purine acyclic acyclovir at 0.4 μmol/mL was 52.9% against HBsAg and 44.2% against HBeAg for comparison of their anti-HBV potency. In addition, it was found that compound **2h** could inhibit viral DNA synthesis activity with an approximate IC_{50} of 400 μM. We postulated the possible mode of anti-viral activity is inhibition of virus replication. Further studies on anti-HBV activities of the title compounds are under investigation and will be reported in due course.

Acknowledgments

The authors are indebted to the National Natural Science Foundation of China (20202003), and National Basic Research Program of China (2003CB114400) for financial support, and the National Center for Drug Screening of China for their technical assistance in performing the biological assays.

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9. Preparation of **2a**. The compound **1** (0.69 g, 3.6 mmol) was added to a mixture of sodium hydroxide (0.16 g, 4 mmol), 4-bromophenol (0.69 g, 4 mmol), and methanol (15 mL). The reaction mixture was stirred for 48 h at room temperature. After removal of solvent, the residue was chromatographed on silica gel column eluting with ethyl acetate/petroleum ether (1/3) to give pure **2a**, a white solid; mp: 140–142 °C, yield 46%. ^{1}H NMR ($CDCl_3$): δ 2.91 (d, J = 4.8 Hz, 3H, NCH_3), 6.12 (s, 1H, CH), 6.85–7.39 (q, 4H, Ar-H), 6.93 (br, 1H, NH), 8.63 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{11}H_{10}BrN_3O_2S$: C, 40.26; H, 3.07; N, 12.80; Found: C, 40.41; H, 2.77; N, 12.61. MS (12 eV): *m/z* 329 (M^+, 13, ^{81}Br), 327 (M^+, 13, ^{79}Br), 272 (7), 270 (8), 174 (29), 172 (31), 128 (100). IR (ν, cm^{-1}): 3405, 3145, 1662, 1580, 1486, 1443, 1412, 1297, 1229; **2b**: a white solid; mp: 157–158 °C, yield 23%. ^{1}H NMR ($CDCl_3$): δ 2.91 (d, J = 4.8 Hz, 3H, NCH_3), 6.12 (s, 1H, CH), 6.74–7.57 (m, 4H, Ar-H), 6.92 (br, 1H, NH), 8.62 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{11}H_{10}IN_3O_2S$: C, 35.21; H, 2.69; N, 11.20. Found: C, 35.08; H, 2.55; N, 11.29; **2c**: a white solid; mp: 148–149 °C, yield 39%. ^{1}H NMR ($CDCl_3$): δ 2.95 (d, J = 5.0 Hz, 3H, NCH_3), 6.24 (s, 1H, CH), 6.91–7.58 (m, 4H, Ar-H), 7.28 (br, 1H, NH), 8.63 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{11}H_{10}BrN_3O_2S$: C, 40.26; H, 3.07 N, 12.80. Found: C, 40.29; H, 3.08; N, 12.90; **2d**: a white solid; mp: 140–141 °C, yield 29%. ^{1}H NMR ($CDCl_3$):δ 2.91 (d, J = 5.0 Hz, 3H, NCH_3), 6.16 (s, 1H, CH), 6.95–7.30 (m, 5H, Ar-H), 6.98 (br, 1H, NH), 8.62 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{11}H_{11}N_3O_2S$: C, 53.00; H, 4.45; N, 16.86. Found: C, 53.18; H, 4.46; N, 16.60; **2e**: a white solid; mp: 130–132 °C, yield 15%. ^{1}H NMR ($CDCl_3$): δ 2.26 (s, 3H, CH_3), 2.92 (d, J = 5.0 Hz, 3H, NCH_3), 6.11 (s, 1H, CH), 6.84–7.08 (m, 4H, Ar-H), 6.02 (br, 1H, NH), 8.59 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{12}H_{13}N_3O_2S$: C, 54.74; H, 4.98; N, 15.96. Found: C, 54.46; H, 4.97; N, 15.97; **2f**: a white solid; mp: 127–128 °C, yield 38%. ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H, CH_3), 2.91 (d, J = 5.1 Hz, 3H, NCH_3), 6.15 (s, 1H, CH), 6.80–7.14 (m, 4H, Ar-H), 6.98 (br, 1H, NH), 8.61 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{12}H_{13}N_3O_2S$: C, 5474; H, 4.98; N, 15.96. Found: C, 54.68; H, 4.70; N, 15.95; **2g**: a white solid; mp: 118–119 °C, yield 27%. ^{1}H NMR ($CDCl_3$): δ 2.89 (d, J = 4.6 Hz, 3H, NCH_3), 6.16 (s, 1H, CH), 6.88–7.23 (m, 5H, Ar-H+NH), 8.66 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{11}H_{10}ClN_3O_2S$: C, 46.56; H, 3.55; N, 14.81. Found: C, 46.39; H, 3.30; N, 14.86; **2h**: a white solid; mp: 134–135 °C, yield 25%. ^{1}H NMR ($CDCl_3$):δ 2.89 (s, 3H, CH_3), 2.91 (d, J =5.0 Hz, 3H, NCH_3), 6.11 (s, 1H, CH), 6.74–7.24 (m, 3H, Ar-H), 6.98 (br, 1H, NH), 8.62 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{12}H_{12}ClN_3O_2S$: C, 48.40; H, 4.06; N, 14.11. Found: C, 48.54; H, 3.91; N, 13.90. MS (12 eV): *m/z* 299 (M^+, 12, ^{37}Cl), 297 (M^+, 34, ^{35}Cl), 242 (4), 240 (11), 142 (100), 128 (82). IR (ν, cm^{-1}): 3393, 3088, 1668, 1621, 1559, 1481, 1409, 1306, 1235, 1171; **2i**: a white solid; mp: 116–117 °C, yield 63%. ^{1}H NMR ($CDCl_3$): δ 2.15 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.91 (d, J = 4.6 Hz, 3H, NCH_3), 6.11(s, 1H, CH), 6.71–7.02 (m, 5H, Ar-H+NH), 8.60 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{13}H_{15}N_3O_2S$: C, 56.30; H, 5.45; N, 15.15. Found: C, 56.20; H, 5.54; N, 15.06; **3**: a white solid; mp: 172–173 °C, yield 27%; ^{1}H NMR ($CDCl_3$): 2.94 (d, J = 4.80 Hz, 3H, NCH_3), 6.33 (s, 1H, CH), 7.04 (br, 1H, NH), 7.20–7.79 (m, 7H, naphthalene-H), 8.62 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{15}H_{13}N_3O_2S$: C, 60.18; H, 4.38; N, 14.04. Found: C, 60.07; H, 4.31; N, 13.86. Preparation of **4a**. The 4-fluorobenzenethiol (1.02 g, 8.0 mmol) was added to a mixture of potassium carbonate (1.4 g, 10 mmol), the compound **1** (1.53 g, 4.0 mmol), and acetonitrile (20 mL). The reaction mixture was stirred for 6 h at room temperature. After removal of solvent, the residue was washed with water (10 mL). The precipitate was filtered off and purified by recrystallization from ethanol to afford a white solid, mp: 126–127 °C, yield 62%. ^{1}H NMR ($CDCl_3$): δ 2.82 (d, J = 5.0 Hz, 3H, NCH_3), 5.41 (s, 1H, CH), 6.90–7.34 (m, 5H, Ph+NH), 8.52 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{11}H_{10}FN_3OS_2$: C, 46.63; H, 3.56; N, 14.83. Found: C, 46.77; H, 3.54; N, 14.81. MS (12 eV): *m/z* 283 (M^+, 27), 226 (83), 193 (22), 165 (52), 128 (77), 58 (100). IR (ν, cm^{-1}): 3389, 3138, 2990, 1645, 1617, 1582, 1484, 1394, 1289, 1233, 1190, 1154; **4b**: a white solid; mp: 140–141 °C, yield 52%, ^{1}H NMR ($CDCl_3$): δ 2.84 (d,J = 5.0 Hz, 3H, NCH_3), 5.42 (s, 1H, CH), 6.92 (br, 1H, NH), 7.22–7.40 (m, 4H, Ph), 8.53 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{11}H_{10}ClN_3OS_2$: C, 44.07; H, 3.36; N, 14.02. Found: C, 43.94; H, 3.41; N, 13.88; **4c**: a white solid; mp: 110–111 °C, yield 74%. ^{1}H NMR ($CDCl_3$): δ 2.81 (d, J = 4.5 Hz, 3H, NCH_3), δ 3.73 (s, 3H, CH_3), 5.30 (s, 1H, CH), 6.84 (br, 1H, NH), 6.72–7.23 (m, 4H, Ph), 8.40 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{12}H_{13}N_3O_2S_2$: C, 48.79; H, 4.44; N, 14.23. Found: C, 48.82; H, 4.44; N, 14.18; **4d**: a white solid; mp: 135–137 °C, yield 68%. ^{1}H NMR ($CDCl_3$): δ 2.84 (d, J = 4.2 Hz, 3H, NCH_3), 5.49 (s, 1H, CH), 6.96 (br, 1H, NH), 7.05–7.33 (m, 4H, Ph), 8.57 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{11}H_{10}FN_3OS_2$: C, 46.63; H, 3.56; N, 14.83. Found: C, 46.56; H, 3.55; N, 14.68; **4e:** a white solid; mp: 139–140 °C, yield 68%. ^{1}H NMR ($CDCl_3$): δ 2.24 (s, 3H, CH_3), δ 2.27 (s, 3H, CH_3), δ 2.84 (d, J = 4.7 Hz, 3H, NCH_3), 5.34 (s, 1H, CH), 6.88 (br, 1H, NH), 6.92–7.15 (m, 3H, Ph), 8.46 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{13}H_{15}N_3OS_2$: C, 53.22; H, 5.15; N, 14.32. Found: C, 53.08; H, 4.98; N, 14.14; **4f**: a white solid; mp: 170–172 °C, yield 45%. ^{1}H NMR ($CDCl_3$): δ 2.82 (d, J = 4.4 Hz, 3H, NCH_3), 5.48 (s, 1H, CH), 7.04 (br, 1H, NH), 7.14–7.32 (m, 3H, Ph), 8.58 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{11}H_9Cl_2N_3OS_2$: C, 39.53; H, 2.71; N, 12.57. Found: C, 39.26; H, 2.93; N, 12.78; **4g**: a white solid; mp: 139–141 °C, yield 77%. ^{1}H NMR ($CDCl_3$): δ 2.88 (d, J = 4.8 Hz, 3H, NCH_3), 2.76 (br, 2H, NH_2), 5.30 (s, 1H, CH), 6.92 (br, 1H, NH), 6.55–7.14 (m, 4H, Ph), 8.43 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{11}H_{12}N_4OS_2$: C, 47.12; H, 4.31; N, 19.98. Found: C, 47.25; H, 4.20; N, 19.90; **5**: a white solid; mp: 143–144 °C, yield 64%. ^{1}H NMR ($CDCl_3$): δ 2.80 (d, J = 4.8 Hz, 3H, NCH_3), 3.75, 3.79 (q, AB, 2H, CH_2), 5.30 (s, 1H, CH), 6.84 (br, 1H, NH), 6.72–7.23 (m, 4H, Ph), 8.40 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{11}H_9Cl_2N_3OS_2$: C, 45.93; H, 3.85; N, 13.39. Found: C, 45.71; H, 3.63; N, 13.36.
10. Preparation of **10**: The 5-(5-ethyl-2-methyl-2*H*-pyrazol-3-yl)-1,3,4-oxadiazole-2-thiol (0.66 g, 2.9 mmol) was added to a mixture of potassium carbonate (0.42 g, 2.9 mmol), the compound **1** (0.55 g, 2.9 mmol), and acetonitrile (20 mL). The reaction mixture was stirred for 6 h at room temperature. After removal of solvent, the residue was washed with water (10 mL). The precipitate was filtered off and purified by recrystallization from ethanol to give a white solid, mp: 165–167 °C, yield 15%. ^{1}H NMR ($CDCl_3$): δ 1.23 (t, J = 6.9 Hz, 3H, CH_3), 2.64 (q, J = 7.2 Hz, 2H, CH_2), 2.89 (d, 3H, NCH_3), 4.16 (s, 3H, pyrazole-CH_3), 6.26 (s, 1H, CH), 6.57 (s, 1H, pyrazole-H), 7.14 (br, 1H, NH), 8.96 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{13}H_{15}N_7O_2S_2$: C, 42.73; H, 4.14; N, 26.83. Found: C, 42.63; H, 3.95; N, 26.69; **11**: a white solid; mp: 162–164 °C, yield 40%. ^{1}H NMR (acetone-d_6): δ2.47 (s, 3H, SCH_3), 2.59 (s, 3H, pyrazole-CH_3), 3.31 (s, 3H, NCH_3), 3.83 (s, 3H, pyrazole-CH_3), 6.25 (s, 1H, CH), 9.16 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{13}H_{15}N_7OS_4$: C, 37.75; H, 3.66; N, 23.71. Found: C, 37.89; H, 3.12; N, 23.81. MS (70 eV): 413 (M^+, 14), 258 (39), 185 (40), 58

(99), 56 (100); **12**: a white solid; mp: 232–234 °C, yield 44%. ^{1}H NMR (acetone-d_6): 2.49 (s, 6H, 2× CH_3), 2.64 (s, 3H, NCH_3), 6.31 (s, 1H, CH), 7.12 (s, 1H, pyrimidne-H), 8.64 (br, 1H, NH), 9.15 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{12}H_{13}N_7OS_2$: C, 42.97; H, 3.91; N, 29.23. Found: C, 42.83; H, 3.70; N, 29.54. Preparation of **13**: The 1,2,4-triazol (0.10 g, 1.4 mmol) was added to a mixture of potassium carbonate (0.20 g, 1.4 mmol), the compound **1** (0.20 g, 1.0 mmol), and acetonitrile (10 mL). The reaction mixture was stirred for 48 h at room temperature. After removal of solvent, the residue was washed with water (10 mL). The precipitate was filtered off and subjected to silica gel column chromatography to give a white solid, mp: 168–170 °C, yield 36%. ^{1}H NMR ($CDCl_3$): 2.90 (d, J = 4.4 Hz, 3H, NCH_3), 6.77 (s, 1H, CH), 6.88 (br, 1H, NH), 8.06 (s, 1H, triazole-H), 8.42 (s, 1H, triazole-H), 8.74 (s, 1H, thiadiazole-H).

11. Preparation of **6a**. To a solution of the compound **4a** (4.8 g, 1.7 mmol) in glacial acetic acid (10 mL) was added dropwise 30% hydrogen peroxide (0.4 g, 3.5 mmol). The mixture was stirred for 24 h at room temperature and poured into water (20 mL). The precipitate was filtered off and purified by recrystallization from ethanol to give a white solid, mp: 157.5–159 °C, yield 51%. ^{1}H NMR ($CDCl_3$): δ 2.86 (d, J = 5.0 Hz, 3H, NCH_3), 5.44 (s, 1H, CH), 6.96 (br, 1H, NH), 7.05–7.34 (m, 4H, Ph), 8.65 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{11}H_{10}FN_3O_2S_2$: C, 44.14; H, 3.37; N, 14.04. Found: C, 44.16; H, 3.17; N, 13.85. ; **6b**: a white solid; mp: 126–129 °C, yield 62%. ^{1}H NMR (acetone-d_6): δ 3.30 (s, 3H, NCH_3), 5.69 (s, 1H, CH), 6.92 (br, 1H, NH), 7.31–7.52 (m, 4H, Ph), 9.15 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{11}H_{10}ClN_3O_2S_2$: C, 41.84; H, 3.19; N, 13.31. Found: C, 41.54; H, 3.04; N, 13.09. IR (v, cm^{-1}): 3391, 3163, 2929, 1689, 1556, 1472, 1399, 1279, 1046; **6c**: a white solid; mp: 163–165 °C, yield 38%. ^{1}H NMR ($CDCl_3$): δ 2.90 (s, J = 4.5 Hz, 3H, NCH_3), δ 3.81 (s, 3H, CH_3), 5.46 (s, 1H, CH), 6.84–7.21 (m, 5H, Ph+NH), 8.56 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{12}H_{13}N_3O_3S_2$: C, 46.29; H, 4.21; N, 13.49. Found: C, 46.16; H, 4.16; N, 13.42; **6d**: a white solid; mp: 170–172 °C, yield 72%. ^{1}H NMR ($CDCl_3$): δ 2.94 (d, J = 4.5 Hz, 3H, NCH_3), 5.62 (s, 1H, CH), 6.80 (br, 1H, NH), 7.07–7.44 (m, 4H, Ph), 8.69 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{11}H_{10}FN_3O_2S_2$: C, 44.14; H, 3.37; N, 14.04. Found: C, 44.00; H, 3.38; N, 13.85. MS (70 eV): m/z 299 (M+, 0.35), 156 (6.0), 144 (57), 143 (24), 128 (67), 58 (100); **6e**: a white solid; mp: 160–161.5 yield 94%. ^{1}H NMR ($CDCl_3$): δ 2.24 (s, 3H, CH_3), δ 2.27 (s, 3H, CH_3), δ 2.84 (d, J = 4.7 Hz, 3H, NCH_3), 5.44 (s, 1H, CH), 6.88 (br, 1H, NH), 6.92–7.15 (m, 3H, Ph), 8.46 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{13}H_{15}N_3O_2S_2$: C, 50.46; H, 4.89; N, 13.58. Found: C, 50.38; H, 4.90; N, 13.46; **6f**: a white solid; mp: 170–172 °C, yield 57%. ^{1}H NMR ($CDCl_3$): δ 2.85 (d, J = 4.6 Hz, 3H, NCH_3), 5.38 (s, 1H, CH), 6.95 (br, 1H, NH), 7.07–7.37(m, 3H, Ph), 8.75 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{11}H_9Cl_2N_3O_2S_2$: C, 37.72; H, 2.59; N, 12.00. Found: C, 37.52; H, 2.81; N, 12.29;**7**: a white solid; mp: 126–129 °C, yield 53%. ^{1}H NMR ($CDCl_3$): δ 2.88 (d, J = 4.2 Hz, 3H, NCH_3), 3.88, 3.92 (q, AB, 2H, CH_2), 5.23 (s, 1H, CH), 6.96 (br, 1H, NH), 7.15–7.36 (m, 4H, Ph), 8.79 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{11}H_9Cl_2N_3O_2S_2$: C, 43.70; H, 3.67; N, 12.74. Found: C, 43.66; H, 3.39; N, 12.50. IR (v, cm^{-1}): 3301, 3130, 2961, 1664, 1559, 1489, 1406, 1286, 1231, 1032.

12. Preparation of **8a**. To a solution of the compound **4a** (4.8 g, 1.7 mmol) in glacial acetic acid (10 mL) was added dropwise 30% hydrogen peroxide (0.4 g, 3.5 mmol). The mixture was stirred for 6 h at 80 °C and poured over water (20 mL). The precipitate was filtered off and purified by recrystallization from ethanol to give a white solid, mp: 156–158 °C, yield 92%. ^{1}H NMR ($CDCl_3$): δ 2.91 (d, J = 4.8 Hz, 3H, NCH_3), 5.99 (s, 1H, CH), 7.13–7.66 (m, 5H, Ph+NH), 8.92 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{11}H_{10}FN_3O_3S_2$: C, 41.90; H, 3.20; N, 13.33. Found: C, 41.66; H, 3.14; N, 13.17. MS (12 eV): 251 (10), 194 (11), 128 (100), 58 (83). IR (v, cm^{-1}): 3384, 3181, 2931, 1683, 1585, 1509, 1410, 1318, 1233, 1146; **8b**: a white solid; mp: 196–198 °C, yield 87%. ^{1}H NMR (acetone-d_6): δ 2.93 (d, J = 4.8 Hz, 3H, NCH_3), 5.88 (s, 1H, CH), 7.07 (br, 1H, NH), 7.28–7.60 (m, 4H, Ph), 8.90 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{11}H_{10}ClN_3O_3S_2$: C, 39.82; H, 3.04; N, 12.66. Found: C, 39.63; H, 3.10; N, 12.44. MS (12 eV): 267 (5.8), 210 (8.4), 128 (48), 58 (100); **8c**: a white solid; mp: 178–179 °C, yield 94%. ^{1}H NMR ($CDCl_3$): δ 2.93 (s, 3H, NCH_3), δ 3.83 (s, 3H, CH_3), 5.94 (s, 1H, CH), 7.17 (br, 1H, NH), 6.86–7.51 (m, 4H, Ph), 8.90 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{12}H_{13}N_3O_4S_2$: C, 44.02; H, 4.00; N, 12.84. Found: C, 44.04; H, 3.91; N, 12.86; **8d**: a white solid; mp: 147–148.5 °C, yield 76%. ^{1}H NMR ($CDCl_3$): δ 2.93 (d, J = 4.4 Hz, 3H, NCH_3), 6.15 (s, 1H, CH), 7.11-7.63 (m, 5H, Ph+NH), 8.69 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{11}H_{10}FN_3O_3S_2$: C, 41.90; H, 3.20; N, 13.33. Found: C, 41.66; H, 3.03; N, 13.28; **8e**: a white solid; mp: 176–178 °C, yield 63%. ^{1}H NMR ($CDCl_3$): δ 2.21 (s, 3H, CH_3), δ 2.55 (s, 3H, CH_3), δ 2.94 (d, J = 4.7 Hz, 3H, NCH_3), 5.91 (s, 1H, CH), 7.12–7.29 (m, 4H, Ph+NH), 8.89 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{13}H_{15}N_3O_3S_2$: C, 47.98; H, 4.65; N, 12.91. Found: C, 47.74; H, 4.40; N, 12.91; **8f**: a white solid; mp: 172–174 °C, yield 53%. ^{1}H NMR ($CDCl_3$): δ 2.95 (d, J = 4.2 Hz, 3H, NCH_3), 6.42 (s, 1H, CH), 7.06 (br, 1H, NH), 7.10–7.62(m, 3H, Ph), 9.07 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{11}H_9Cl_2N_3O_3S_2$: C, 36.07; H, 2.48; N, 11.47. Found: C, 36.14; H, 2.48; N, 11.44; **9**: a white solid; mp: 161–163 °C, yield 66%. ^{1}H NMR ($CDCl_3$): δ 2.87 (d, J = 4.2 Hz, 3H, NCH_3), 4.28, 4.40 (q, AB, 2H, CH_2), 5.63 (s, 1H, CH), 7.12 (br, 1H, NH), 7.21–7.42 (m, 4H, Ph), 8.79 (s, 1H, thiadiazole-H). Anal. Calcd for $C_{11}H_9Cl_2N_3O_3S_2$: C, 41.68; H, 3.50; N, 12.15. Found: C, 41.40; H, 3.75; N, 12.39. IR (v, cm_{-1}): 3352, 3124, 1664, 1590, 1527, 1488, 1420, 1332, 1131.

13. Zou, X. J.; Jin, G. Y.; Zhang, Z. X. *J. Food Agric. Chem.* **2002**, *50*, 1451.