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ARTICLE

Synthesis, Crystal Structure, and Biological Activity of 4-Methyl-1,2,3-thiadiazole-Containing 1,2,4-Triazolo[3,4-*b*][1,3,4]thiadiazoles†

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Heterocyclic compounds play an important role as the main sources of lead molecules of agrochemicals. Synthesis and biological activity of thiadiazole-containing 1,2,4-triazolo[3,4-*b*][1,3,4]-thiadiazoles were seldom reported. To find novel lead compounds with various biological activities, a series of 6-substituted-3-(4-methyl-1,2,3-thiadiazolyl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadizoles were rationally designed and synthesized according to the principle of combinations of bioactive substructures by the condensation of 3-(4-methyl-1,2,3-thiadiazolyl)-4-amino-1,2,4-triazole-5-thione with various carboxylic acids and phosphorus oxychloride. All newly synthesized compounds were identified by proton nuclear magnetic resonance (^{1}H NMR), infrared spectroscopy (IR), electroionization mass spectrometry (EI/MS), and elementary analysis. The crystal structure of 3-(4-methyl-1,2,3-thiadiazolyl)-6-(4-methylphenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadizole was determined by X-ray diffraction crystallography. In this crystal, two intermolecular hydrogen bonds (N2···H−C12 and N3···H−C13), a weak intermolecular interaction (S···S), and the weak pπ−pπ intermolecular interaction were observed. Fungicide screening indicated that all of the target compounds showed certain extent of growth inhibition against fungi tested. 3-(4-Methyl-1,2,3-thiadiazolyl)-6-n-propyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadizole and 3-(4-methyl-1,2,3-thiadiazolyl)-6-trichloromethyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadizole were found to have potential wide spectrum of fungicide activity. The median effective concentrations (EC_{50}) detected for 3-(4-methyl-1,2,3-thiadiazolyl)-6-trichloromethyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadizole to six fungi were from 7.28 μmol/L against *Pellicularia sasakii* (Shirai) to 42.49 μmol/L against *Alternaria solani*. The results indicated that thiadiazole-containing 1,2,4-triazolo[3,4-*b*][1,3,4]-thiadiazoles were potential fungicide lead compounds.

KEYWORDS: 1,2,4-Triazolo[3,4-*b*][1,3,4]thiadiazole; 4-methyl-1,2,3-thiadiazole; fungicide bioassay; systemic acquired resistance

INTRODUCTION

Most heterocyclic compounds extensively studied and reported with pesticide activities are N- or S-containing heterocycles. Among the N- or S-containing five-membered heterocyclic compounds, some triazoles, thiazoles, and thiadiazoles have been commercialized as agrochemicals all over the world (*1*−*4*). However, thiadiazole-containing 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles were seldom reported with biological activity. The chemistry of triazoles and their derivatives has always been the highlight of study in lead compound discovery and biological screening (*5*, *6*). A triazolothiadiazole system may be viewed as a cyclic analogue of two very important components, biguanide and thiosemicarbazide, which often displayed diverse biological activities (*7*). The 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole ring systems have been well studied, and so far a variety of biological activities including antifungal, antibacterial, antitubercular, anticancer, and analgesic activities have been reported (*8*−*12*). The compounds bearing a 1,2,3-thiadiazole group possess versatile biological activities, including anti-inflammatory, antitumor, hypotensive, antibacterial, and antiallergic (*13*−*16*). Especially, some 1,2,3-thiadiazole derivatives could be plant activators (*17*−*20*). Plant activators have little or no direct antimicrobial activity in vitro, but they can induce systemic acquired resistance to the broad spectrum of succeeding pathogens attacking as in the biological, biochemical, and physiological levels. There are two commercialized plant activators containing a 1,2,3-thiadiazole group; they are acibenzolar-*S*-methyl (BTH) (*21*, *22*) and tiadinil (TDL) (*23*). In addition, 1,2,3-thiadiazoles are widely used as synthons in organic synthesis (*24*).

Our group has focused attention on the synthesis and characterization of various 1,2,3-thiadiazole derivatives and their biological activities. We have explored series of thiazole- and oxadiazole-containing thiadiazole derivatives that displayed good systemic acquired resistance to tobacco against TMV and certain degree of fungus growth inhibition in vitro or in vivo (*25*). Prompted by

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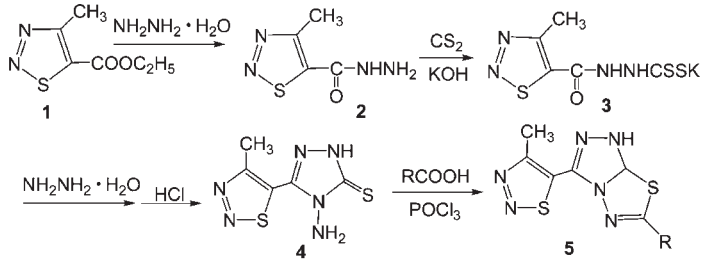
Scheme 1. Synthesis Routine for the Target Compounds



Compd.	R	Compd.	R	Compd.	R
5a	o-$OCH_3C_6H_4$	5i	p-$CF_3C_6H_4$	5q	$C(CH_3)_3$
5b	m-$OCH_3C_6H_4$	5j	m-$NO_2C_6H_4$	5r	2-furyl
5c	p-$OCH_3C_6H_4$	5k	p-$NO_2C_6H_4$	5s	4-pyridyl
5d	o-FC_6H_4	5l	2,6-$2ClC_6H_3$	5t	N-methyl-5-ethyl-3-pyrazolyl
5e	m-FC_6H_4	5m	$CH{=}CHC_6H_5$	5u	4-methyl-1,2,3- thiadiazolyl
5f	p-FC_6H_4	5n	CH_2Cl	5v	5-methyl-1,2,3- thiadiazolyl
5g	o-$CF_3C_6H_4$	5o	CCl_3	5w	3-phenyl-5-methyl-4-isoxazolyl
5h	m-$CF_3C_6H_4$	5p	$CH_2CH_2CH_3$	5x	(2,4-dichlorophenoxy)methyl

these observations, here we designed and synthesized a series of 6-substituted-3-(4-methyl-1,2,3-thiadiazolyl)[1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadizoles **5** according to the principle of combinations of bioactive substructures (**Scheme 1**). The main differences between this study and our former studies existed in the heterocyclic moieties combined with bioactive substructure 4-methyl-1,2,3-thiadiazole: our former studies introduced thiazole- and oxadiazole as monocyclic moieties into the target compounds (*25*); this study introduced the fused heterocyclic moiety 1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadizole into the target compounds. The novel structures synthesized here were confirmed by elemental analysis, IR, ^{1}H NMR, and MS; their biological activities were also detected. Our results also indicate that attachment of the 4-methyl-1,2,3-thiadiazole group to the 3-position of the [1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadizoles can change their biological activities. This kind of molecule was a potential fungicide lead compound.

EXPERIMENTAL METHODS

Equipment for Structural Characterization. Melting points of all compounds were determined on an X-4 binocular microscope (Gongyi Technical Instrument Co., Henan, China), and the thermometer was not corrected. Proton NMR spectra were obtained using a Bruker AC-P 300 spectrometer, and chemical shift values (δ) were reported as parts per million with deuteruated dimethyl sulfoxide (DMSO-d_6) as the solvent and tetramethylsilane (TMS) as the internal standard. Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. IR was recorded on a Bruker Vector 22 FTIR spectrometer using a KBr pellet press. A Thermo Finnigan HPLC-MS/MS, Surveyor HPLC was equipped with a Diamonsil C_{18}, 4.6 × 250 mm, stainless column and LCQ Advantage MS with ESI. The single-crystal structure for X-ray diffraction was performed with a Bruker Smart 1000 CCD diffractometer. All solvents and liquid reagents were of analytical reagent grade and were dried in advance and distilled before use. Column chromatography purification was carried out using silica gel.

Preparation of 4-Methyl-1,2,3-thiadiazole-5-carboxylic Acid Hydrazide (2). Intermediate 4-methyl-1,2,3-thiadiazole-5-carboxylic acid hydrazide (**2**) was synthesized according to the literature (*26*). A mixture of 4-methyl-1,2,3-thiadiazole-5-carboxylic acid ethyl ester (**1**, 10 mmol) and hydrazine hydrate (12 mmol) in 10 mL of methanol was stirred vigorously for 0.5 h at room temperature, the mixture was filtered, and the solid was washed with cold methanol. After drying, the solid was recrystallized from methanol to give intermediate **2**.

Preparation of 3-(4-Methyl-1,2,3-thiadiazolyl)-4-amino-1,2,4-triazole-5-thione (4). The procedures were improved according to the method in the literature (*27*). 4-Methyl-1,2,3-thiadiazole-5-carboxylic acid hydrazide (**2**, 20 g, 83 mmol) was mixed with a solution of potassium hydroxide (6.4 g, 125 mmol) in methanol (50 mL) at 0−5 °C under stirring. Then, carbon disulfide (9.6 g, 125 mmol) was added dropwise, and the reaction mixture was stirred for 12 h at room temperature. The solid product of potassium dithiocarbazinate (**3**) was collected by filtration and washed with chilled methanol. After drying, it was used for the next reaction directly without purification. The above potassium dithiocarbazinate (**3**) was taken into hydrazine hydrate (200 mmol) and refluxed for 4 h, and the reaction mixture was then diluted with cold water and acidified with concentrated hydrochloric acid. The white precipitate was filtered and collected for washing with cold water and recrystallized from methanol with a yield of 64%: mp 200−201 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 14.34 (1H, s, NH), 6.08 (2H, s, NH_2), 2.95 (3H, s, thiadiazolyl-CH_3).

General Procedures for the Synthesis of 6-Substituted-3-(4-methyl-1,2,3-thiadiazolyl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadizoles (5). The procedures were carried out and revised according to ref *28*. A mixture of 3-(4-methyl-1,2,3-thiadiazolyl)-4-amino-1,2,4-triazole-5-thione (**4**, 1 mmol) and substituted carboxylic acid (1.1 mmol) in $POCl_3$ (5 mL) was refluxed for 5−6 h. The reaction mixture was then slowly poured into crushed ice with vigorous stirring and neutralized with sodium bicarbonate. The solids were filtered and collected for further purification by washing with cold water and recrystallization from DMSO.

Data for ***5a****:* pale yellow crystal; yield, 63%; mp 231−232 °C; IR (KBr) υ (cm^{-1}) 3077, 2931, 1600, 1579, 1506, 1438, 1254, 1013, 956, 762; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.28 (1H, d, $^3J_{HH}$ = 7.8 Hz, benzene−H), 7.70 (1H, t, $^3J_{HH}$ = 7.2 Hz, benzene−H), 7.38 (1H, d, $^3J_{HH}$ = 8.4 Hz, benzene−H), 7.26 (1H, t, $^3J_{HH}$ = 7.8 Hz, benzene−H), 4.09 (3H, s, Ar−OCH_3), 3.11 (3H, s, thiadiazolyl−CH_3); EI-MS (70 eV, *m*/*z*, relative intensity) 330 (M^+, 2), 302 (100), 258 (5), 169 (14), 126 (52), 83 (63), 45 (28), 39 (46). Anal. Calcd for $C_{13}H_{10}N_6OS_2$: C, 47.26; H, 3.05; N, 25.44. Found: C, 47.44; H, 3.19; N, 25.23.

Data for ***5b****:* pale yellow crystal; yield, 89%; mp 232−234 °C; IR (KBr) υ (cm^{-1}) 3088, 2931, 1606, 1579, 1501, 1438, 1249, 1013, 950, 767; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.29(1H, d, $^3J_{HH}$ = 7.8 Hz, benzene−H), 7.71 (1H, t, $^3J_{HH}$ = 7.5 Hz, benzene−H), 7.39 (1H, d, $^3J_{HH}$ = 8.4 Hz,

benzene−H), 7.27(1H, t, $^3J_{HH}$ = 7.8 Hz, benzene−H), 4.09 (3H, s, Ar−OCH_3), 3.11 (3H, s, thiadiazolyl−CH_3); EI-MS (70 eV, *m*/*z*, relative intensity) 330 (M^+, 10), 302 (100), 169 (12), 126 (50), 83 (67), 45 (22), 39 (42). Anal. Calcd for $C_{13}H_{10}N_6OS_2$: C, 47.26; H, 3.05; N, 25.44. Found: C, 47.18; H, 3.20; N, 25.58.

Data for ***5c****:* pale yellow crystal; yield, 83%; mp 244−246 °C; IR (KBr) υ (cm^{-1}) 3088, 2920, 1616, 1574, 1501, 1448, 1254, 1034, 945, 851; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.02 (2H, d, $^3J_{HH}$ = 8.7 Hz, benzene−H), 7.21(2H, d, $^3J_{HH}$ = 8.7 Hz, benzene−H), 3.90 (3H, s, Ar−OCH_3), 3.10 (3H, s, thiadiazolyl−CH_3); EI-MS (70 eV, *m*/*z*, relative intensity) 330 (M^+, 10), 302 (100), 191 (13), 151 (69), 83 (38), 70 (14), 39 (25). Anal. Calcd for $C_{13}H_{10}N_6OS_2$: C, 47.26; H, 3.05; N, 25.44. Found: C, 47.36; H, 3.14; N, 25.20.

Data for ***5d****:* white needle crystal; yield, 86%; mp 225−227 °C; IR (KBr) υ (cm^{-1}) 3077, 2931, 1611, 1585, 1506, 1448, 1291, 1213, 1102, 956, 762; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.26 (1H, t, $^3J_{HH}$ = 7.5 Hz, benzene−H), 7.77−7.84 (1H, m, benzene−H), 7.62 (1H, d, $^3J_{HH}$ = 8.4 Hz), 7.55 (1H, q, $^3J_{HH}$ = 7.5 Hz, benzene−H), 3.11 (3H, s, thiadiazolyl−CH_3); EI-MS (70 eV, *m*/*z*, relative intensity) 318 (M^+, 6), 290 (100), 246 (5), 139 (50), 83 (31), 39 (16). Anal. Calcd for $C_{12}H_7FN_6S_2$: C, 45.27; H, 2.22; N, 26.40. Found: C, 45.50; H, 2.43; N, 26.21.

Data for ***5e****:* white needle crystal; yield, 92%; mp 242−244 °C; IR (KBr) υ (cm^{-1}) 3088, 2931, 1590, 1558, 1517, 1443, 1275, 1213, 1008, 945, 851, 804; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.92−7.96 (2H, m, benzene−H), 7.73(1H, q, $^3J_{HH}$ = 7.2 Hz, benzene−H), 7.60(1H, s, $^3J_{HH}$ = 7.5 Hz, benzene−H), 3.11 (s, 3H, thiadiazolyl−CH_3); EI-MS (70 eV, *m*/*z*, relative intensity) 318 (M^+, 4), 290 (100), 246 (5), 139 (62), 83 (38), 39 (25). Anal. Calcd for $C_{12}H_7FN_6S_2$: C, 45.27; H, 2.22; N, 26.40. Found: C, 45.20; H, 2.35; N, 26.71.

Data for ***5f****:* white needle crystal; yield, 96%; mp 243−245 °C; IR (KBr) υ (cm^{-1}) 3088, 2931, 1600, 1558, 1522, 1490, 1459, 1244, 1213, 1165, 956, 856, 814; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.14(2H, t, $^3J_{HH}$ = 8.7 Hz, benzene−H), 7.52 (2H, t, $^3J_{HH}$ = 8.7 Hz, benzene−H), 3.10 (3H, s, thiadiazolyl−CH_3); EI-MS (70 eV, *m*/*z*, relative intensity) 318 (M^+, 5), 290 (100), 139 (63), 126 (32), 39 (16). Anal. Calcd for $C_{12}H_7FN_6S_2$: C, 45.27; H, 2.22; N, 26.40. Found: C, 45.15; H, 2.10; N, 26.65.

Data for ***5g****:* white fiber crystal; yield, 92%; mp 241−242 °C; IR (KBr) υ (cm^{-1}) 3077, 2931, 1606, 1558, 1454, 1323, 1223, 1186, 1129, 956, 772; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.94−8.11 (m, 4H, benzene−H), 3.10 (s, 3H, thiadiazolyl−CH_3); EI-MS (70 eV, *m*/*z*, relative intensity) 368 (M^+, 2), 340 (100), 296 (3), 229 (4), 189 (30), 145 (12), 126 (33), 83 (38), 39 (16). Anal. Calcd for $C_{13}H_7F_3N_6S_2$: C, 42.39; H, 1.92; N, 22.81. Found: C, 42.30; H, 2.12; N, 22.75.

Data for ***5h****:* white needle crystal; yield, 91%; mp 273−274 °C; IR (KBr) υ (cm^{-1}) 3067, 2931, 1616, 1558, 1517, 1459, 1422, 1333, 1186, 1076, 977, 819; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.38 (1H, d, $^3J_{HH}$ = 9.0 Hz, benzene−H), 8.31(1H, s, benzene−H), 8.11 (1H, d, $^3J_{HH}$ = 7.8 Hz, benzene−H), 7.92 (1H, t, $^3J_{HH}$ = 7.8 Hz, benzene−H), 3.10 (3H, s, thiadiazolyl−CH_3); EI-MS (70 eV, *m*/*z*, relative intensity) 368 (M^+, 2), 340 (100), 296 (4), 229 (6), 189 (49), 169 (11), 126 (30), 83 (29), 39 (11). Anal. Calcd for $C_{13}H_7F_3N_6S_2$: C, 42.39; H, 1.92; N, 22.81. Found: C, 42.43; H, 2.16; N, 22.90.

Data for ***5i****:* gray needle crystal; yield, 92%; mp 287−289 °C; IR (KBr) υ (cm^{-1}) 3077, 2941, 1616, 1553, 1501, 1454, 1323, 1171, 1123, 1066, 950, 867; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.29 (2H, d, $^3J_{HH}$ = 8.4 Hz, benzene−H), 8.04 (2H, d, $^3J_{HH}$ = 8.4 Hz, benzene−H), 3.11 (3H, s, thiadiazolyl−CH_3); EI-MS (70 eV, *m*/*z*, relative intensity) 368 (M^+, 2), 340 (100), 296 (4), 229 (6), 189 (40), 145 (9), 126 (22), 83 (18), 39 (5). Anal. Calcd for $C_{13}H_7F_3N_6S_2$: C, 42.39; H, 1.92; N, 22.81. Found: C, 42.50; H, 1.98; N, 22.76.

Data for ***5j****:* golden flake crystal; yield, 84%; mp 251−253 °C; IR (KBr) υ (cm^{-1}) 3074, 2929, 1613, 1534, 1512, 1446, 1346, 1214, 1123, 1008, 950, 820; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.48−8.72 (3H, m, benzene−H), 7.96 (1H, t, $^3J_{HH}$ = 7.8 Hz, benzene−H), 3.11(3H, s, thiadiazolyl−CH_3); EI-MS (70 eV, *m*/*z*, relative intensity) 345 (M^+, 2), 317 (100), 273 (4), 206 (3), 166 (21), 126 (39), 83 (38), 70 (22), 39 (26). Anal. Calcd for $C_{12}H_7N_7O_2S_2$: C, 41.73; H, 2.04; N, 28.39. Found: C, 41.90; H, 2.11; N, 28.56.

Data for ***5k****:* golden flake crystal; yield, 93%; mp 285−287 °C; IR (KBr) υ (cm^{-1}) 3088, 2941, 1606, 1553, 1517, 1454, 1349, 1218, 1108, 1008, 956, 856; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.47 (2H, d, $^3J_{HH}$ = 8.7 Hz, benzene−H), 8.34 (2H, d, $^3J_{HH}$ = 8.7 Hz, benzene−H), 3.11 (3H, s, thiadiazolyl−CH_3); EI-MS (70 eV, *m*/*z*, relative intensity) 345 (M^+, 2), 317 (100), 273 (4), 206 (3), 166 (19), 126 (42), 83 (38), 67 (23), 39 (29). Anal. Calcd for $C_{12}H_7N_7O_2S_2$: C, 41.73; H, 2.04; N, 28.39. Found: C, 41.61; H, 2.20; N, 28.18.

Data for ***5l****:* white fiber crystal; yield, 18%; mp > 280 °C; IR (KBr) υ (cm^{-1}) 3077, 2920, 1637, 1558, 1464, 1427, 1239, 1213, 1029, 956, 819, 783; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.74−7.82 (m, 3H, benzene−H), 3.09 (s, 3H, thiadiazolyl−CH_3); EI-MS (70 eV, *m*/*z*, relative intensity) 368 (M^+, 5), 340 (100), 296 (4), 229 (9), 189 (35), 169 (20), 126 (58), 83 (68), 39 (28). Anal. Calcd for $C_{12}H_6Cl_2N_6S_2$: C, 39.03; H, 1.64; N, 22.76. Found: C, 39.12; H, 1.83; N, 22.90.

Data for ***5m****:* white flake crystal; yield, 96%; mp 225−227 °C; IR (KBr) υ (cm^{-1}) 3035, 2920, 1627, 1553, 1448, 1380, 1213, 1034, 961, 804, 751, 688; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.84−7.87 (t, 3H, benzene−H), 7.64−7.79 (m, 2H, CH=CH), 7.47−7.48 (d, 2H, benzene−H), 3.09 (s, 3H, thiadiazolyl−CH_3); EI-MS (70 eV, *m*/*z*, relative intensity) 326 (M^+, 8), 298 (100), 169 (10), 126 (29), 115 (40), 45 (14), 39 (16). Anal. Calcd for $C_{14}H_{10}N_6S_2$: C, 51.52; H, 3.09; N, 25.75. Found: C, 51.51; H, 2.90; N, 25.55.

Data for ***5n****:* white needle crystal; yield, 74%; mp 212−214 °C; IR (KBr) υ (cm^{-1}) 3025, 2983, 1553, 1522, 1454, 1380, 1275, 1207, 1129, 1029, 956, 804, 730; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 5.32 (s, 2H, CH_2), 3.07 (s, 3H, thiadiazolyl−CH_3); EI-MS (70 eV, *m*/*z*, relative intensity) 272 (M^+, 7), 244 (100), 169 (15), 83 (66), 39 (45). Anal. Calcd for $C_7H_5ClN_6S_2$: C, 30.83; H, 1.85; N, 30.81. Found: C, 30.70; H, 2.06; N, 30.73.

Data for ***5o****:* white flake crystal; yield, 91%; mp 191−193 °C; IR (KBr) υ (cm^{-1}) 2920, 1553, 1511, 1469, 1443, 1380, 1213, 1019, 940, 819, 798, 767; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.07 (s, 3H, thiadiazolyl−CH_3); EI-MS (70 eV, *m*/*z*, relative intensity) 340 (M^+, 20), 314 (68), 277 (25), 169 (40), 126 (100), 83 (92), 70 (98), 39 (84). Anal. Calcd for $C_7H_3Cl_3N_6S_2$: C, 24.61; H, 0.89; N, 24.60. Found: C, 24.43; H, 1.10; N, 24.65.

Data for ***5p****:* white needle crystal; yield, 83%; mp 176−177 °C; IR (KBr) υ (cm^{-1}) 2973, 2931, 1558, 1532, 1438, 1375, 1213, 1160, 1029, 945, 804; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.09−3.14 (2H, m, CH_2), 3.07 (3H, s, thiadiazolyl−CH_3), 1.82 (2H, q, J = 7.5 Hz, CH_2), 1.02 (3H, t, J = 7.2 Hz, CH_3); EI-MS (70 eV, *m*/*z*, relative intensity) 266 (M^+, 8), 238 (100), 194 (9), 169 (12), 126 (39), 83 (41), 39 (28), 27 (15). Anal. Calcd for $C_9H_{10}N_6S_2$: C, 40.58; H, 3.78; N, 31.55. Found: C, 40.50; H, 3.98; N, 31.36.

Data for ***5q****:* white needle crystal; yield, 83%; mp 199−201 °C; IR (KBr) υ (cm^{-1}) 2983, 2931, 1558, 1517, 1438, 1385, 1365, 1207, 1019, 940, 814; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.07 (s, 3H, thiadiazolyl−CH_3), 1.48 (s, 9H, $C(CH_3)_3$); EI-MS (70 eV, *m*/*z*, relative intensity) 280 (M^+, 8), 252 (100), 208 (7), 169 (13), 141 (10), 126 (48), 83 (48), 57 (50), 41 (79), 27 (24). Anal. Calcd for $C_{10}H_{12}N_6S_2$: C, 42.84; H, 4.31; N, 29.97. Found: C, 42.63; H, 4.23; N, 29.75.

Data for ***5r****:* gray needle crystal; yield, 91%; mp 236−238 °C; IR (KBr) υ (cm^{-1}) 3109, 2941, 1590, 1506, 1438, 1396, 1213, 1040, 987, 825, 767; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.91 (1H, s, furyl−H), 7.65 (1H, s, furyl−H), 8.19 (1H, s, furyl−H), 3.09 (3H, s, thiadiazolyl−CH_3); EI-MS (70 eV, *m*/*z*, relative intensity) 290 (M^+, 9), 262 (100), 169 (11), 111 (58), 83 (34), 39 (39). Anal. Calcd for $C_{10}H_6N_6OS_2$: C, 41.37; H, 2.08; N, 28.95. Found: C, 41.15; H, 2.12; N, 28.79.

Data for ***5s****:* pale yellow needle crystal; yield, 90%; mp 239−241 °C; IR (KBr) υ (cm^{-1}) 3088, 3046, 2931, 1600, 1558, 1464, 1412, 1213, 971, 987, 950, 846; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.90 (2H, d, $^3J_{HH}$ = 4.8 Hz, pyridyl−H), 8.03 (2H, d, $^3J_{HH}$ = 4.8 Hz, pyridyl−H), 3.11 (3H, s, thiadiazolyl−CH_3); EI-MS (70 eV, *m*/*z*, relative intensity) 301 (M^+, 5), 273 (100), 229 (5), 169 (8), 126 (28), 122 (31), 67 (15), 39 (12). Anal. Calcd for $C_{11}H_7N_7S_2$: C, 43.84; H, 2.34; N, 32.54. Found: C, 43.80; H, 2.38; N, 32.67.

Data for ***5t****:* white needle crystal; yield, 86%; mp 232−234 °C; IR (KBr) υ (cm^{-1}) 2983, 2931, 1564, 1532, 1454, 1412, 1380, 1291, 1218, 1186, 1024, 956, 924, 804; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.85 (1H, s, pyrazolyl−CH), 3.88 (3H, s, N−CH_3), 3.09 (3H, s, thiadiazolyl−CH_3), 2.96−2.77 (2H, q, $^3J_{HH}$ = 7.5 Hz, CH_2), 1.27 (3H, t, $^3J_{HH}$ = 7.5 Hz, CH_3); EI-MS (70 eV, *m*/*z*, relative intensity) 332 (M^+, 10), 304 (100), 246 (6), 153 (48), 83 (45), 39 (22). Anal. Calcd for $C_{12}H_{12}N_8S_2$: C, 43.36; H, 3.64; N, 33.71. Found: C, 43.52; H, 3.58; N, 33.60.

Data for ***5u****:* green needle crystal; yield, 96%; mp 211−213 °C; IR (KBr) υ (cm^{-1}) 2920, 1558, 1443, 1375, 1218, 1034, 950, 908, 825, 762;

Table 1. Selected Bond Lengths and Bond Angles for Compound **5c**

bond	length (Å)	bond	length (Å)	bond	length (Å)
S(1)−N(2)	1.6694(14)	S(1)−C(3)	1.7125(16)	N(1)−N(2)	1.2930(2)
S(2)−C(5)	1.7359(15)	S(2)−C(6)	1.7756(15)	N(1)−C(2)	1.3680(2)
N(3)−C(4)	1.3239(19)	N(3)−N(4)	1.4013(16)	N(4)−C(5)	1.3189(19)
N(5)−C(5)	1.3569(18)	N(5)−C(4)	1.3635(18)	N(5)−N(6)	1.3641(17)
N(6)−C(6)	1.3065(18)	O(1)−C(10)	1.3611(18)	O(1)−C(13)	1.4261(19)
C(2)−C(3)	1.377(2)	C(3)−C(4)	1.4520(19)	C(7)−C(8)	1.3900(2)
angle	**deg**	**angle**	**deg**	**angle**	**deg**
N(2)−S(1)−C(3)	92.52(7)	N(6)−C(6)−C(7)	120.48(13)	N(1)−C(2)−C(3)−S(1)	0.77(16)
N(2)−N(1)−C(2)	114.50(13)	C(10)−O(1)−C(13)	117.21(12)	N(2)−S(1)−C(3)−C(4)	178.04(12)
C(5)−N(4)−N(3)	105.62(11)	C(4)−N(3)−N(4)	108.57(12)	N(4)−N(3)−C(4)−N(5)	0.23(15)
C(2)−C(3)−S(1)	107.91(11)	C(5)−N(5)−N(6)	120.15(12)	N(6)−N(5)−C(4)−N(3)	−179.07(14)
N(5)−C(4)−C(3)	121.93(13)	N(3)−C(4)−C(3)	129.53(13)	N(6)−N(5)−C(4)−C(3)	1.30(2)
C(4)−N(5)−N(6)	133.46(12)	N(4)−C(5)−S(2)	140.90(11)	S(1)−C(3)−C(4)−N(5)	−0.21(19)
N(5)−C(5)−S(2)	108.20(11)	N(3)−C(4)−N(5)	108.54(12)	N(3)−N(4)−C(5)−N(5)	−0.15(15)
C(5)−S(2)−C(6)	88.04(7)	N(6)−C(6)−S(2)	116.07(11)	N(3)−N(4)−C(5)−S(2)	179.06(14)
N(1)−N(2)−S(1)	112.07(11)	C(2)−N(1)−N(2)−S(1)	−0.48(17)	N(6)−N(5)−C(5)−N(4)	179.24(12)
C(5)−N(5)−C(4)	106.38(12)	C(4)−N(3)−N(4)−C(5)	−0.05(15)	N(6)−N(5)−C(5)−N(4)	179.24(12)
C(4)−C(3)−S(1)	122.67(11)	C(4)−N(5)−N(6)−C(6)	178.89(14)	C(6)−S(2)−C(5)−N(4)	−179.14(18)
N(4)−C(5)−N(5)	110.89(12)	N(2)−N(1)−C(2)−C(3)	−0.22(19)	C(7)−C(8)−C(9)−C(10)	0
C(6)−N(6)−N(5)	107.54(12)	N(1)−C(2)−C(3)−C(4)	−178.04(14)	C(8)−C(9)−C(10)−O(1)	−179.25(13)

^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.03 (s, 3H, thiadiazolyl−CH_3), 3.10 (s, 3H, thiadiazolyl−CH_3); EI-MS (70 eV, m/z, relative intensity) 322 (M^+, 6), 294 (99), 266 (40), 141 (14), 126 (84), 83 (100), 39 (79). Anal. Calcd for $C_9H_6N_8S_3$: C, 33.53; H, 1.88; N, 34.76. Found: C, 33.43; H, 2.03; N, 34.85.

Data for ***5v****:* gray needle crystal; yield, 62%; mp 252−254 °C; IR (KBr) v (cm^{-1}) 2931, 1553, 1443, 1375, 1265, 1213, 1024, 950, 893, 830; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.10 (s, 3H, thiadiazolyl−CH_3), 3.13 (s, 3H, thiadiazolyl−CH_3); EI-MS (70 eV, m/z, relative intensity) 322 (M^+, 10), 294 (100), 234 (18), 141 (7), 126 (62), 39 (45). Anal. Calcd for $C_9H_6N_8S_3$: C, 33.53; H, 1.88; N, 34.76. Found: C, 33.51; H, 2.00; N, 34.90.

Data for ***5w****:* pale yellow fiber crystal; yield, 73%; mp 233−234 °C; IR (KBr) v (cm^{-1}) 3067, 2920, 1590, 1564, 1454, 1375, 1291, 1213, 1029, 945, 893, 777, 694; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.57−7.72 (m, 5H, benzene−H), 3.06 (s, 3H, thiadiazolyl−CH_3), 2.86 (s, 3H, isoxazolyl−CH_3); EI-MS (70 eV, m/z, relative intensity) 381 (M^+, 3), 353 (100), 216 (5), 142 (21), 77 (41), 43 (78). Anal. Calcd for $C_{16}H_{11}N_7OS_2$: C, 50.38; H, 2.91; N, 25.70. Found: C, 50.42; H, 3.02; N, 25.55.

Data for ***5x****:* pale yellow fiber crystal; yield, 87%; mp 250−251 °C; IR (KBr) v (cm^{-1}) 3098, 2931, 1532, 1490, 1454, 1375, 1296, 1207, 1066, 961, 798, 762; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.40−7.70 (m, 3H, benzene−H), 5.78 (s, 2H, CH_2), 3.07 (s, 3H, thiadiazolyl−CH_3); EI-MS (70 eV, m/z, relative intensity) 398 (M^+, 1), 370 (52), 314 (10), 209 (86), 133 (30), 84 (100), 57 (58). Anal. Calcd for $C_{13}H_8Cl_2N_6OS_2$: C, 39.11; H, 2.02; N, 21.05. Found: C, 39.06; H, 2.18; N, 21.15.

Crystal Structure Determination for Compound (5c). The crystal of compound **5c** was cultured from DMSO. X-ray intensity data were recorded on a Bruker SMART 1000 CCD diffraction meter using graphite monochromated Mo Kα radiation (λ = 0.71073 Å). A total of 9505 reflections were measured, of which 3274 were unique (R_{int} = 0.0384) in the range of 2.14° ≤ θ ≤ 27.88° (h, −8 to 14; k, −6 to 6; l, −31 to 31), and 2802 observed reflections with $I > 2\sigma(I)$ were used in the refinement on F^2. The structure was solved by direct methods with the SHELXS-97 program. All of the non-H atoms were refined anisotropically by full-matrix least-squares to give the final R = 0.0329 and wR = 0.0866 ($w = 1/[\sigma^2(F_0^2) + (0.0490P)^2 + 0.30P]$), where $P = (F_0^2 + 2F_c^2)/3$) with $(\Delta/\sigma)_{max}$ = 0.001 and S = 1.082 by using the SHELXL program. The hydrogen atoms were located from a difference Fourier map and refined isotropically.

Biological Screening. Biological activities of the target compounds were evaluated systematically including fungicide and systemic acquired resistance according to the standard operation practice (SOP) as follows.

Fungicide Screening. Preliminary screening was conducted by fungus growth inhibition method according to ref *25*. Fungi used in this studies included *Alternaria solani*(AS), *Botrytis cinerea* (BC), *Cercospora arachidicola* (CA), *Cercospora beticola* (CB), *Colletotrichum lagenarium* (CL), *Fusarium oxysporum* (FO), *Gibberella zeae* (GZ), *Macrophoma kuwatsukai* (MK), *Phytophthora infestans* (Mont) de Bary (PI), *Physalospora piricola* (PP), *Pellicularia sasakii* (Shirai) (PS), *Puccinia triticina* Eriks (PT), and *Rhizoctonia solani* Kuhn (RS). Precision toxicity studies were conducted according to the above methods by determination of growth inhibition of specific fungi using the same compound by five to seven different concentrations; the median effective concentration (EC_{50}) was calculated by the linear regression of logarithm of the concentration with probability of the corresponding growth inhibition by Excel (*29*).

Systemic Acquired Resistance Screening. Using tobacco against the tobacco mosaic virus (TMV) system described in ref *25*, the induction activity was evaluated using the antivirus inhibition ratio, which was calculated by the average number of the viral inflammations on the inoculated leaves with the corresponding control. TDL was chosen as positive control; all compounds tested was conducted at 100 μg/mL of concentration.

RESULTS AND DISCUSSION

Preparation of the Novel 6-Substituted-3-(4-Methyl-1,2,3-thiadiazolyl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadizole Derivatives. The reaction sequence employed for the synthesis of the title compounds is shown in **Scheme 1**. The starting material 4-methyl-1,2,3-thiadiazole-5-carboxylic acid ethyl ester was prepared according to the literature (*25*). 4-Methyl-1,2,3-thiadiazole-5-carboxylic acid hydrazide **2**, which was obtained by reaction of 4-methyl-1,2,3-thiadiazole-5-carboxylic acid ethyl ester with hydrazine hydrate (*26*), reacted with carbon disulfide in methanolic potassium hydroxide to give dithiocarbazinate **3** in good yield and was directly used for the next reaction without further purification. The key intermediate **4** was synthesized by refluxing dithiocarbazinate **3** with hydrazine hydrate without the step of iodomethylation as described in the literature (*27*). Condensation of **4** with various substituted carboxylic acids in the presence of phosphorus oxychloride under refluxing gave the title compounds 6-substituted-3-(4-methyl-1,2,3-thiadiazolyl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadizoles **5** in good yield (*28*).

The structures of all newly synthesized compounds were characterized by elemental analysis, IR, ^{1}H NMR, and MS studies. Intermediate **4** existed both in thione and in thiol tautomeric forms (*1*) and showed two characteristic broad signals at δ 6.08 and 14.34. Due to the reaction of NH_2 and SH with acid,

their ^{1}H NMR signals disappeared in the title products **5**. As a result of the overall inductive effect and magnetic anisotropic effect of the triazolothiadiazole ring, the chemical shift of the CH_3 group in the thiadiazole moiety in the target compounds appears downfield at δ 2.98−3.15. The EI-MS spectra of **5** showed each of their molecular ion peaks M^+ at a relative intensity of 1−20%. All of the fragmentation ions were consistent with their structures and could be clearly assigned. In addition, the results of X-ray single-crystal diffraction of **5c** were further validated the structure of the title compounds because there existed many N and limited C and H in this molecule, which gave limited information in ^{1}H NMR chromatography. Bond lengths and angles within the heterocyclic system (**Table 1**) agreed well with the standard values for compound **5c**. The bond lengths indicated some degree of delocalization around the ring system, with the three C═N bonds averaging 1.3148 (3) Å and the N—N bonds ranging from 1.3641 (17) to 1.4013 (16) Å. Compound **5c** (**Figure 1**) consists of a fused triazolothiadiazole system, one 1,2,3-thiadiazole ring, and one phenyl ring. The four rings are almost coplanar, with average deviations from planarity of 0.0011(2), 0.0008(2), 0.0041(3), and 0.0018(3) Å for the triazole ring, 1,3,4-thiadiazole ring, 1,2,3-thiadiazole ring, and phenyl ring, respectively. As expected, the 1,2,4-triazole and 1,3,4-thiadiazole rings are planar; the dihedral angle between rings is 0.7°, which can be attributed to a wide range of electron delocalization. The 1,2,4-triazole ring is almost coplanar with the 1,2,3-thiadiazole ring with a dihedral angle of 1.7(3)°, whereas the phenyl ring is rotated by 5.6(2)° as compared with the 1,3,4-thiadiazole ring. In the crystal lattice, there exist two intermolecular hydrogen bonds, N2···H−C12 and N3···H−C13, and one weak intermolecular interaction (S···S) as shown in **Figure 2**. In addition, the weak pπ−pπ intermolecular interaction was observed, too. The planes of the 1,2,3-triazole ring, phenyl ring, and fused 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole ring system are parallel to each other for each molecule. Another compound, **5u**, was also synthesized, and its crystal structure was cultured and determined; the results also validated the structure of this kind of derivative (*30*).

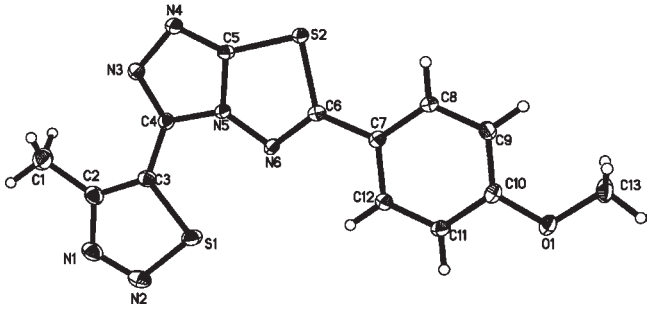


Figure 1. X-ray structure of compound **5c**.

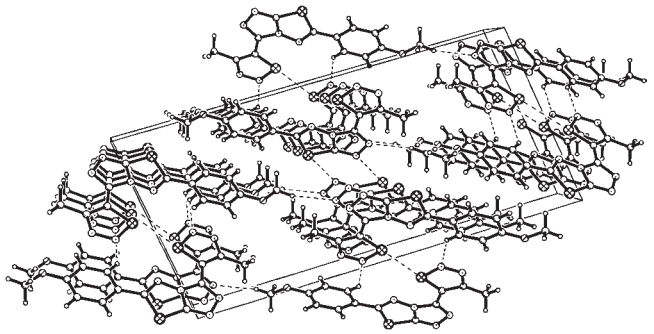


Figure 2. Packing diagram in a unit cell of compound **5c**.

Biological Activity. Fungicide activities against the representative typical fungi often occurring in the Chinese agro-ecosystem such as AS, BC, CA, CB, CL, FO, GZ, PI, PP, PS, PT, and RS were detected at 50 μg/mL. The results indicated that some compounds had good fungicide activity (**Table 2**). All compounds have good growth inhibition to BC, compounds **5b**, **5d**, and **5g** inhibited > 50% of the growth to PS, PS, and FO, respectively;

Table 2. Fungicide Activity of the Title Compounds (Percent)[a]

compd	AS	BC	CA	CB	CL	FO	GZ	PI	PP	PS	PT	RS
5a	30.0	50.0	25.0	30.0	27.3	17.2	18.2	11.1	24.4	32.84	nd	nd
5b	23.3	nd	18.2	14.3	0	19.4	nd	17.3	45.2	60.8	31.6	nd
5c	0	nd	7.7	0	18.2	44.4	nd	4.8	7.7	46.4	10.0	11.1
5d	40.0	nd	18.2	23.8	11.8	19.4	nd	20.0	24.2	58.8	21.1	nd
5e	37.1	75.0	23.5	27.3	0	10.0	40.5	0	54.1	32.8	nd	nd
5f	26.3	53.3	33.1	7.1	10.3	9.3	14.3	15.6	18.6	11.3	nd	nd
5g	4.8	nd	7.7	0	45.5	86.0	nd	0	15.4	35.7	0	5.6
5h	23.7	68.9	23.1	35.7	13.8	18.6	4.8	17.8	25.6	35.2	nd	nd
5i	9.5	nd	15.4	0	18.2	44.4	nd	4.8	17.9	30.4	70.0	11.1
5j	9.5	nd	7.7	0	0	47.2	nd	54.8	12.8	25.0	10.0	11.1
5k	26.7	60.0	30.8	14.3	13.8	20.9	11.9	22.2	34.9	32.4	nd	nd
5l	23.7	64.4	23.1	28.6	20.7	13.9	14.3	20.0	37.2	42.3	nd	nd
5m	31.3	81.8	27.6	13.3	26.9	9.1	17.5	18.2	40.5	33.3	nd	nd
5n	23.8	65.2	34.8	21.4	4.3	25.0	33.3	11.4	33.3	38.4	nd	nd
5o	66.7	nd	63.6	71.4	64.7	75.0	nd	70.7	83.9	84.8	78.9	83.3
5p	34.4	84.9	62.1	33.3	50.0	93.0	75.0	75.8	40.5	77.8	nd	nd
5q	16.7	nd	36.4	23.8	5.88	13.9	nd	14.7	17.7	56.7	26.3	nd
5r	43.3	nd	36.4	42.9	0	22.2	nd	14.7	29.0	45.1	21.0	nd
5s	9.5	nd	23.1	0	27.3	44.4	nd	0	7.7	44.6	10.0	5.7
5t	9.5	nd	7.7	0	0	47.2	nd	4.8	12.8	30.4	10.0	19.4
5u	30.3	67.5	48.5	24.9	30.8	18.6	21.5	37.6	20.5	45.3	nd	nd
5v	31.3	81.8	34.5	20.0	19.2	9.1	30.0	18.2	23.8	44.4	nd	nd
5w	33.3	46.2	30.0	10.0	13.6	13.8	27.3	7.4	8.9	25.4	nd	nd
5x	31.3	nd	31.0	20.0	19.2	3.0	12.5	12.1	23.8	33.3	nd	nd

[a] AS, *Alternaria solani*; BC, *Botrytis cinerea*; CA, *Cercospora arachidicola*; CB, *Cercospora beticola*; CL, *Colletotrichum lagenarium*; FO, *Fusarium oxysporum*; GZ, *Gibberella zeae*; MK, *Macrophoma kuwatsukai*; PI, *Phytophthora infestans* (Mont) de Bary; PP, *Physalospora piricola*; PS, *Pellicularia sasakii* (Shirai); PT, *Puccinia triticina* Eriks; RS, *Rhizoctonia solani* Kuhn; nd, not detected.

Table 3. EC_{50} Determination of Compound **5o** against Six Fungi

fungus	regression equation	R^2	EC_{50} (μg/mL)	EC_{50} (μmol/L)
Alternaria solani	$y = 0.8577x + 3.9950$	0.9879	14.6	42.49
Fusarium oxysporum f. *cucumerinum*	$y = 0.7959x + 4.1643$	0.9154	11.2	32.59
Macrophoma kuwatsukai	$y = 0.9710x + 4.2185$	0.9549	6.4	18.62
Phytophthora infestans (Mont.) de Bary	$y = 0.8570x + 4.0613$	0.9509	12.5	36.38
Pellicularia sasakii (Shirai)	$y = 1.1611x + 4.5416$	0.9148	2.5	7.28
Rhizoctonia solani	$y = 1.2018x + 4.2649$	0.9262	4.1	11.93

Table 4. Antivirus Activities of the Title Compounds (Percent)[a]

compd	500 μg/mL	100 μg/mL	50 μg/mL
5a	nd	nd	40
5b	nd	nd	0
5c	nd	nd	17.86
5d	53.57	9.50	nd
5e	30.71	24.24	nd
5f	nd	nd	0
5g	nd	nd	25
5h	37.50	30.00	nd
5i	nd	nd	10.15
5j	44.44	44.44	nd
5k	52.94	16.67	nd
5l	nd	nd	12.5
5m	27.78	16.67	nd
5n	nd	nd	29.17
5o	27.78	33.33	nd
5p	nd	nd	0
5q	nd	nd	7.89
5r	23.53	20	nd
5s	nd	nd	27.03
5t	nd	nd	34.78
5u	nd	nd	11.76
5v	30.77	26.67	nd
5w	nd	nd	14.63
5x	nd	nd	0
ribavirin	37.93	21.62	16.7
tiadinil	nd	36.59	nd

[a] nd, not detected.

compound **5o** was a broad-spectrum of fungicide against all of the fungi tested with growth inhibition from 60 to 85%; compound **5p** also exhibited broad spectrum of fungicidal activity against PS, PI, GZ, FO, and CA with growth inhibition of 77.8, 75.8, 75.0, 93.0, and 62.1%, respectively. Precision toxicity of compound **5o** was studied further, and EC_{50} values were detected from 7.28 μmol/L against *Pellicularia sasakii* (Shirai) to 42.49 μmol/L against *Alternaria solani* to six fungi tested as listed in **Table 3**. This indicated that compound **5o** was a fungicide lead and deserved further modification. Aliphatic or halogen-substituted aliphatic derivatives such as chlorinated aliphatic derivatives had better fungicide activity than aromatic derivatives; diverse derivatives need to be synthesized and screened for further studies.

The antivirus activity of the novel compounds synthesized was evaluated systemically. The results in **Table 4** indicated that ribavirin exhibited certain degree of anti-TMV activity at 500 μg/mL, but had almost no activity at 50 μg/mL, and compounds **5d** and **5k** had good anti-TMV activity at 500 μg/mL; however, they had almost no antivirus activity when the concentration was lowered to 100 μg/mL. Compounds **5a**, **5n**, and **5t** had good anti-TMV activity with inhibition of about 30% even at 50 μg/mL. To get clear structure−activity relationship results of antivirus study, more derivatives of heterocyclic acid need to be synthesized and tested. Induction screening of systemic acquired resistance for tobacco against TMV at 100 μg/mL indicated that ribavirin exhibited no induction activity, whereas TDL had 48.92% induction activity. All compounds synthesized had certain degree of phototoxicity to tobacco during the course of screening for induction activity; the leaves curved, rotted, or dried severely after treatment with these compounds. All of the biological screenings indicated that 6-substituted-3-(4-methyl-1,2,3-thiadiazolyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadizoles exhibited various biological activities: they were the fungicide lead compounds.

ABBREVIATIONS USED

AS, *Alternaria solani*; BC, *Botrytis cinerea*; BTH, acibenzolar-*S*-methyl; CA, *Cercospora arachidicola*; CB, *Cercospora beticola*; CL, *Colletotrichum lagenarium*; DMSO-d_6, deutero-, dimethyl sulfoxide; EC_{50}, median effective concentration; EI/MS, electroionization mass spectrometry; FO, *Fusarium oxysporum*; GZ, *Gibberella zeae*; ^{1}H NMR, proton nuclear magnetic resonance; HRMS, high-resolution mass spectrometry; IR, infrared spectroscopy; MK, *Macrophoma kuwatsukai*; nd, not detected; PDA, potato dextrose agar; PI, *Phytophthora infestans* (Mont) de Bary; PP, *Physalospora piricola*; PS, *Pellicularia sasakii* (Shirai); PT, *Puccinia triticina* Eriks; RS, *Rhizoctonia solani* Kuhn; SOP, standard operation practice; TDL, Tiadinil; TMS, tetramethylsilane; TMV, tobacco mosaic virus.

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There was an error in the page numbers of reference 30 in the version of this paper published ASAP December 16, 2009; the corrected version published ASAP February 3, 2010.

Supporting Information Available: Crystal data of compound **5c**: r80811a.cif. This information is available free of charge via the Internet at http://pubs.acs.org.

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