# Synthesis of 3,5-Dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl Containing 1,2,3-Thiadiazole Derivatives via Ugi Reaction and Their Biological Activities†

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A series of novel 3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl containing 4-methyl-1,2,3-thiadiazole derivatives were designed and synthesized via Ugi reaction. Their structures were confirmed by IR, $^1$H NMR, $^{13}$C NMR and high-resolution mass spectroscopy. The preliminary bioassay results indicated that some title compounds had good fungicide activity at 50 μg/mL; most of the compounds presented a certain degree of direct inhibition activity, good inactivation and curative activity against tobacco mosaic virus at 500 μg/mL and 100 μg/mL; some compounds showed good larvicidal activity against *Plutella xylostella* L. at 200 μg/mL and excellent larvicidal activities against *Culex pipiens pallens* at 2 μg/mL.

**Keywords** 1,2,3-thiadiazole, Ugi reaction, synthesis design, biological activity, multicomponent reactions

## Introduction

1,2,3-Thiadiazoles are a versatile class of compounds which present a wide range of biological activities such as antivirus activity,[1] systemic acquired resistance,[2,3] fungicide activity,[2,4] insecticide activity,[5] antitumor activity,[6] and herbicide activity.[7,8] Moreover, the properties of easy breakdown of the 1,2,3-thiadiazole ring into low molecular weight compounds through releasing of $N_2$ favor the use of its derivatives as environmental friendly pesticide candidates with low toxicity.[9]

Combinatorial chemistry has attracted much attention as an efficient tool for drug discovery. The use of combinatorial chemistry or parallel synthesis for the optimization of highly promising lead compounds arising from the drug-discovery processes around privileged structures and their combinations has been successful in many science and development fields.[10] The Ugi reaction is one of the most prominent multiple component coupling reactions (MCRs) due to its wide applications in organic syntheses and medicinal chemistry.[11] Ugi reaction is an efficient and convenient green method to combine several active moieties into one molecule, and it is convenient to implement structural modification via alternation of diverse starting materials and is applied in combinatorial chemistry.[12,13]

Fluorine and chlorine containing compounds have significant applications in drug and pesticide research and development. Introducing F and Cl into target molecules can be a feasible method to improve its biological activities. Xu *et al.*[14a] has reported that some fluoroalkoxyl containing *S*-methyl benzo-1,2,3-thiadiazole-7-carboxylate derivatives exhibited good systemic acquire resistance. The excellent example for novel pesticide development is the successful discovery of fungicide flumorph, which was designed and synthesized by substituting the Cl of the dimethomorph by the F.[14b] Our group[4c,15] has designed and synthesized series of 1,2,3-thiadiazole derivatives containing 3-chloro-4-methyl-phenyl and 3-fluoro-4-methylphenyl via Ugi four-components condensation reaction (U-4CR). The results indicated that some compounds showed broad-spectrum of activities against several fungi tested and excellent potential antivirus activities. Encouraged by these observations, here we introduced 3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl, the active substructure of a commercial insecticide hexaflu-

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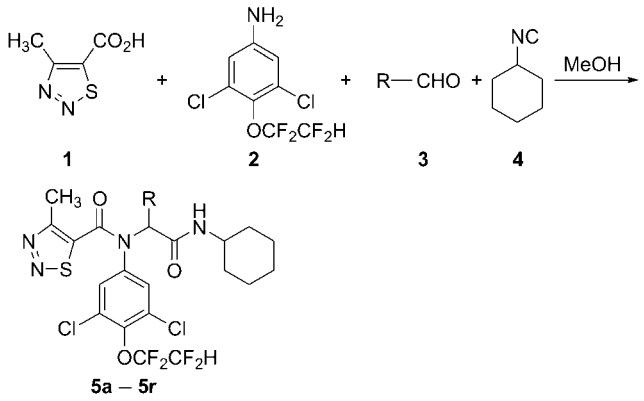
muron, into the 1,2,3-thiadiazoles via Ugi U-4CR. Like our previous work,[4c] 4-methyl-1,2,3-thiadiazole-5-carboxylic acid was chosen as the acid component; substituted benzaldehydes were chosen as the carbonyl components; cyclohexyl isocyanide was chosen as the isocyanide component. This will provide useful information for the study of the structure-activity relationship of these new structures for their insecticide activity. The synthetic route was shown in Scheme 1. The structures of title compounds were confirmed by IR, $^1$H NMR, $^{13}$C NMR and high-resolution mass spectroscopy.

**Scheme 1** General synthetic route of the title compounds **5a**—**5r**




R = phenyl (**5a**); *p*-chlorophenyl (**5b**); *o*-chlorophenyl (**5c**); *m*-chlorophenyl (**5d**); *o*-nitrophenyl (**5e**); *m*-nitrophenyl (**5f**); *p*-nitrophenyl (**5g**); *m*-methylbenzyl (**5h**); *p*-methylbenzyl (**5i**); *o*-fluorophenyl (**5j**); *m*-fluorophenyl (**5k**); *m*-trifluoromethylphenyl (**5l**); *p*-trifluoromethylphenyl (**5m**); *m*-hydroxyphenyl (**5n**); *p*-hydroxyphenyl (**5o**); *o*-methoxyphenyl (**5p**); *m*-methoxyphenyl (**5q**); *p*-methoxyphenyl (**5r**).

## Experimental

### Materials and instruments

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 AVANCE-400 MHz spectrometer, and chemical shift values ($\delta$) were reported with deuteron chloroform ($CDCl_3$) as the solvent and tetramethylsilane (TMS) as the internal standard. High resolution mass spectrometry (HRMS) data were obtained on an FTICR-MS Varian 7.0T FTICR-MS instrument. 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 by using silica gel. 4-Methyl-1,2,3-thiadiazole-5-carboxylic acid (**1**) and cyclohexyl isocyanide (**4**) were synthesized according to Ref. 2 and 4c, respectively.

### General procedure for preparation of the title compounds 5a—5r

3,5-Dichloro-4-(1,1,2,2-tetrafluoroethoxy)benzenamine (0.83 g, 3.0 mmol), 4-methyl-1,2,3-thiadiazole-5-carboxylic acid (0.43 g, 3.0 mmol), and cyclohexyl isocyanide (0.33 g, 3.0 mmol) were added to a solution of benzaldehyde (0.35 g, 3.0 mmol) in 10 mL of methanol in sequence. The color of the mixture grew darker during this procedure. The solution was then stirred for another 1 h at room temperature; afterward, removal of solvent under reduced pressure and purification by flash column chromatography on silica gel using ethyl acetate and petroleum ether (60—90 ℃; 1∶3, *V*∶*V*) as an eluent obtain the products **5a**—**5r**.

***N*-[2-(Cyclohexylamino)-2-oxo-1-phenylethyl]-*N*-[3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide (5a)** White solid, yield 40%, m.p. 178—181 ℃; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.38—7.05 (m, 7H, ph-H), 6.18 (s, 1H, COCH), 6.12—5.85 (m, 1H, $OCF_2CF_2H$), 5.37 (d, $J$=7.6 Hz, 1H, CONH), 3.90—3.82 (m, 1H, cyclohexyl-H), 2.88 (s, 3H, thiadiazolyl-$CH_3$), 2.02—1.04 (m, 10H, cyclohexyl-H); $^{13}$C NMR ($CDCl_3$, 400 MHz) $\delta$: 167.3, 161.1, 142.4, 140.7, 137.7, 132.8, 132.2, 130.8, 130.3, 129.7, 129.1, 65.7, 49.3, 32.8, 25.4, 24.8, 24.7, 14.0; IR (KBr) $v$: 3280, 3080, 2933, 2855, 1647, 1557, 1459, 1353, 1285, 1233, 1142 cm$^{-1}$; HRMS calcd for $C_{26}H_{24}Cl_2F_4N_4O_3S$ $(M+H)^+$ 619.0955, found 619.0959.

***N*-[1-(4-Chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl]-*N*-[3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)-phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide (5b)** White solid, yield 30%, m.p. 187—189 ℃; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.38—7.05 (m, 6H, ph-H), 6.18 (s, 1H, COCH), 6.14—5.87 (m, 1H, $OCF_2CF_2H$), 5.37 (d, $J$ = 7.6 Hz, 1H, CONH), 3.90 — 3.83 (m, 1H, cyclohexyl-H), 2.87 (s, 3H, thiadiazolyl-$CH_3$), 2.01—1.08 (m, 10H, cyclohexyl-H); $^{13}$C NMR ($CDCl_3$, 400 MHz) $\delta$: 167.3, 161.1, 160.8, 149.7, 142.5, 140.8, 137.4, 133.2, 132.1, 131.0, 130.8, 127.4, 125.0, 60.7, 49.6, 32.4, 25.3, 24.8, 24.6, 13.7; IR (KBr) $v$: 3293, 3077, 2937, 2856, 1649, 1552, 1460, 1347, 1287, 1234, 1152 cm$^{-1}$; HRMS calcd for $C_{26}H_{23}C_{l3}F_4N_4O_3S$ $(M+H)^+$ 653.0565, found 653.0573.

***N*-[1-(2-Chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl]-*N*-[3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)-phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide (5c)** White solid, yield 62%, m.p. 163—166 ℃; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.43—7.02 (m, 6H, ph-H), 6.56 (s, 1H, COCH), 6.10—5.84 (m, 1H, $OCF_2CF_2H$), 5.52 (d, $J$ = 6.4 Hz, 1H, CONH), 3.91 — 3.87 (m, 1H, cyclohexyl-H), 2.87 (s, 3H, thiadiazolyl-$CH_3$), 2.06—1.09 (m, 10H, cyclohexyl-H); $^{13}$C NMR ($CDCl_3$, 400 MHz) $\delta$: 167.4, 161.3, 160.9, 149.7, 142.4, 140.7, 137.3, 135.2, 131.3, 131.0, 130.7, 129.8, 127.3, 62.3, 49.5, 32.6, 25.4, 24.8, 24.7, 13.8; IR (KBr) $v$: 3286, 3079, 2934, 2857, 1651, 1561, 1460, 1383, 1341, 1286, 1226, 1159, 1136 cm$^{-1}$; HRMS calcd for $C_{26}H_{23}C_{l3}F_4N_4O_3S$ $(M+H)^+$ 653.0565, found 653.0570.

***N*-[1-(3-Chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl]-*N*-[3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)-phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide (5d)** White solid, yield 40%, m.p. 119—123 ℃; $^1$H NMR

($CDCl_3$, 400 MHz) $\delta$: 7.72—7.00 (m, 6H, ph-H), 6.09 (s, 1H, COCH), 6.13—5.87 (m, 1H, $OCF_2CF_2H$), 5.43 (d, $J$ = 6.4 Hz, 1H, CONH), 3.89 — 3.83 (m, 1H, cyclohexyl-H), 2.88 (s, 3H, thiadiazolyl-$CH_3$), 2.02—1.12 (m, 10H, cyclohexyl-H); $^{13}C$ NMR ($CDCl_3$, 400 MHz) $\delta$: 166.9, 161.9, 161.1, 142.6, 140.4, 137.4, 135.1, 134.7, 132.1, 131.0, 130.5, 130.2, 129.8, 128.3, 65.1, 49.5, 32.7, 25.3, 24.8, 24.7, 14.1; IR (KBr) $v$: 3282, 3075, 2919, 2857, 1654, 1568, 1458, 1380, 1285, 1220, 1151, 1135, 1114 $cm^{-1}$; HRMS calcd for $C_{26}H_{23}C_{l3}F_4N_4O_3S$ $(M+H)^+$ 653.0565, found 653.0570.

***N*-[2-(Cyclohexylamino)-1-(2-nitrophenyl)-2-oxoethyl]-*N*-[3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide (5e)** White solid, yield 25%, m.p. 189—191 ℃; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 7.97—7.28 (m, 6H, ph-H), 6.57 (s, 1H, COCH), 6.10—5.84 (m, 1H, $OCF_2CF_2H$), 5.61 (d, $J$ = 6.4 Hz, 1H, CONH), 3.87 — 3.84 (m, 1H, cyclohexyl-H), 2.88 (s, 3H, thiadiazolyl-$CH_3$), 2.05—1.09 (m, 10H, cyclohexyl-H); $^{13}C$ NMR ($CDCl_3$, 400 MHz) $\delta$: 167.3, 161.1, 160.9, 149.8, 142.5, 140.8, 137.4, 133.2, 132.1, 131.0, 130.8, 127.4, 125.0, 60.6, 49.6, 32.4, 25.3, 24.8, 24.6, 13.7; IR (KBr) $v$: 3302, 3076, 2936, 2857, 1650, 1561, 1527, 1460, 1349, 1286, 1227,1132 $cm^{-1}$; HRMS calcd for $C_{26}H_{23}C_{l2}F_4N_5O_5S$ $(M+H)^+$ 664.0806, found 664.0815.

***N*-[2-(Cyclohexylamino)-1-(3-nitrophenyl)-2-oxoethyl]-*N*-[3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide (5f)** White solid, yield 40%, m.p. 214—216 ℃; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 8.19 (d, $J$=7.2 Hz, 1H, ph-H), 8.14 (s, 1H, ph-H), 7.67—7.31 (m, 4H, ph-H), 6.19 (s, 1H, COCH), 5.86—6.18 (m, 1H, $OCF_2CF_2H$), 5.53 (d, $J$=8.4 Hz, 1H, CONH), 3.91—3.86 (m, 1H, cyclohexyl-H), 2.90 (s, 3H, thiadiazolyl-$CH_3$), 2.04—1.05 (m, 10H, cyclohexyl-H); $^{13}C$ NMR ($CDCl_3$, 400 MHz) $\delta$: 166.7, 162.0, 161.1, 148.1, 142.7, 140.3, 137.2, 136.0, 135.1, 132.2, 131.3, 130.0.4, 125.3, 124.2, 64.7, 49.5, 32.6, 25.3, 24.7, 24.6, 14.0; IR (KBr) $v$: 3264, 3079, 2933, 2855, 1649, 1561, 1536, 1457, 1349, 1286, 1253, 1224, 1125 $cm^{-1}$; HRMS calcd for $C_{26}H_{23}C_{l2}F_4N_5O_5S$ $(M+H)^+$ 664.0806, found 664.0812.

***N*-[2-(Cyclohexylamino)-1-(4-nitrophenyl)-2-oxoethyl]-*N*-[3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide (5g)** White solid, yield 34%, m.p. 179—181 ℃; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 8.16 (d, $J$=7.6 Hz, 2H, ph-H), 7.43 (d, $J$=8.0 Hz, 2H, ph-H), 7.35 (s, 1H, ph-H), 7.12 (s, 1H, ph-H), 6.15 (s, 1H, COCH), 6.12—5.86 (m, 1H, $OCF_2CF_2H$), 5.48 (d, $J$=7.6 Hz, 1H, CONH), 3.88—3.83 (m, 1H, cyclohexyl-H), 2.89 (s, 3H, thiadiazolyl-$CH_3$), 2.03—1.05 (m, 10H, cyclohexyl-H); $^{13}C$ NMR ($CDCl_3$, 400 MHz) $\delta$: 166.5, 162.1, 161.1, 148.2, 142.8, 140.1, 140.0, 137.4, 132.0, 131.3, 123.9, 65.0, 49.6, 32.7, 25.3, 24.8, 24.7, 14.1; IR (KBr) $v$: 3325, 3077, 2932, 2857, 1650, 1548, 1459, 1347, 1280, 1214, 1161, 1133 $cm^{-1}$; HRMS calcd for $C_{26}H_{23}C_{l2}F_4N_5O_5S$ $(M+H)^+$ 664.0806, found 664.0818.

***N*-[2-(Cyclohexylamino)-2-oxo-1-*m*-tolylethyl]-*N*-(3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl)-4-methyl-1,2,3-thiadiazole-5-carboxamide (5h)** White solid, yield 24%, m.p. 138—140 ℃; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 7.52—6.88 (m, 6H, ph-H), 6.14 (s, 1H, COCH), 6.12—5.86 (m, 1H, $OCF_2CF_2H$), 5.37 (d, $J$=8.0 Hz, 1H, CONH), 3.88—3.82 (m, 1H, cyclohexyl-H), 2.89 (s, 3H, thiadiazolyl-$CH_3$), 2.25 (s, 3H, ph-$CH_3$), 2.01—1.10 (m, 10H, cyclohexyl-H); $^{13}C$ NMR ($CDCl_3$, 400 MHz) $\delta$: 167.5, 161.5, 161.0, 142.3, 140.8, 139.1, 137.7, 132.6, 132.2, 131.0, 130.6, 130.3, 128.9, 127.4, 65.6, 49.3, 32.8, 25.4, 24.8, 24.7, 14.0; IR (KBr) $v$: 3274, 3078, 2931, 2856, 1651, 1559, 1458, 1385, 1345, 1288, 1225, 1120 $cm^{-1}$; HRMS calcd for $C_{27}H_{26}C_{l2}F_4N_4O_3S$ $(M+H)^+$ 633.1112, found 633.1118.

***N*-[2-(Cyclohexylamino)-2-oxo-1-*p*-tolylethyl]-*N*-(3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl)-4-methyl-1,2,3-thiadiazole-5-carboxamide (5i)** White solid, yield 38%, m.p. 125—127 ℃; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 7.35 (s, 1H, ph-H), 7.12 (s, 1H, ph-H), 7.08 (d, $J$=8.0 Hz, 2H, ph-H), 6.98 (d, $J$=8.0 Hz, 2H, ph-H), 6.13 (s, 1H, COCH), 6.13—5.86 (m, 1H, $OCF_2CF_2H$), 5.36 (d, $J$=8.0 Hz, 1H, CONH), 3.87—3.83 (m, 1H, cyclohexyl-H), 2.88 (s, 3H, thiadiazolyl-$CH_3$), 2.30 (s, 3H, ph-$CH_3$), 2.01 — 1.01 (m, 10H, cyclohexyl-H); $^{13}C$ NMR ($CDCl_3$, 400 MHz) $\delta$: 167.6, 161.5, 161.0, 142.3, 140.9, 139.8, 137.8, 132.2, 130.6, 131.0, 130.2, 129.7, 65.5, 49.3, 32.8, 25.4, 24.8, 24.7, 14.0; IR (KBr) $v$: 3321, 3379, 2938, 2956, 1653, 1562, 1525, 1460, 1392, 1338, 1289, 1235, 1158, 1126 $cm^{-1}$; HRMS calcd for $C_{27}H_{26}C_{l2}F_4N_4O_3S$ $(M+H)^+$ 633.1112, found 633.1118.

***N*-[2-(Cyclohexylamino)-1-(2-fluorophenyl)-2-oxoethyl]-*N*-[3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide (5j)** Light yellow oil, yield 36%; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 7.32—6.98 (m, 4H, ph-H), 6.64 (s, 2H, ph-H), 6.42 (s, 1H, COCH), 6.15—5.85 (m, 1H, $OCF_2CF_2H$), 5.54 (d, $J$=5.2 Hz, 1H, CONH), 3.89—3.84 (m, 1H, cyclohexyl-H), 2.88 (s, 3H, thiadiazolyl-$CH_3$), 2.25 (s, 3H, ph-$CH_3$), 2.04 — 1.06 (m, 10H, cyclohexyl-H); $^{13}C$ NMR ($CDCl_3$, 400 MHz) $\delta$: 167.1, 161.9, 159.5, 146.2, 142.5, 140.7, 137.4, 132.8, 131.9, 131.8, 131.0, 130.8, 130.5, 124.7, 58.9, 49.5, 32.6, 25.3, 24.8, 24.6, 13.8; IR (KBr) $v$: 3292, 3078, 2935, 2858, 1653, 1563, 1460, 1286, 1215, 1166, 1131 $cm^{-1}$; HRMS calcd for $C_{26}H_{23}C_{l2}F_5N_4O_3S$ $(M+H)^+$ 637.0861, found 637.0866.

***N*-[2-(Cyclohexylamino)-1-(3-fluorophenyl)-2-oxoethyl]-*N*-[3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide (5k)** White solid, yield 36%, m.p. 162—164 ℃; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 7.30—7.25 (m, 3H, ph-H), 7.06—7.20 (t, $J$=8.0 Hz, 1H, ph-H), 6.94—6.92 (m, 2H, ph-H), 6.10 (s, 1H, COCH), 6.13—5.87 (m, 1H, $OCF_2CF_2H$), 5.42 (d, $J$=8.0 Hz, 1H, CONH), 3.90—3.81 (m, 1H, cyclohexyl-H), 2.89 (s, 3H, thiadiazolyl-$CH_3$), 2.02—1.03 (m, 10H, cyclohexyl-H); $^{13}C$ NMR ($CDCl_3$, 400 MHz) $\delta$: 167.0, 163.9, 161.8, 161.5, 161.0, 142.5, 140.5,

137.5, 135.2, 135.1, 132.1, 130.9, 130.7, 130.6, 126.0, 117.4, 117.2, 116.7, 116.5, 65.1, 49.4, 32.7, 25.3, 24.8, 24.6, 14.0; IR (KBr) *v*: 3303, 3090, 2936, 2854, 1645, 1560, 1460, 1390, 1352, 1288, 1167, 1124 $cm^{-1}$; HRMS calcd for $C_{26}H_{23}Cl_2F_5N_4O_3S$ $(M+H)^+$ 637.0861, found 637.0862.

***N*-{2-(Cyclohexylamino)-2-oxo-1-[3-(trifluoromethyl)phenyl]ethyl}-*N*-[3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide (5l)** White solid, yield 36%, m.p. 164—166 ℃; $^1H$ NMR ($CDCl_3$, 400 MHz) *δ*: 7.60—7.26 (m, 6H, ph-H), 6.20 (s, 1H, COCH), 6.12—5.87 (m, 1H, $OCF_2CF_2H$), 5.46 (d, *J*=8.0 Hz, 1H, CONH), 3.92—3.83 (m, 1H, cyclohexyl-H), 2.90 (s, 3H, thiadiazolyl-$CH_3$), 2.05—1.03 (m, 10H, cyclohexyl-H); $^{13}C$ NMR ($CDCl_3$, 400 MHz) *δ*: 166.9, 162.0, 161.0, 142.6, 140.3, 137.2, 134.0, 133.5, 132.2, 131.7, 131.4, 131.1, 129.6, 127.3, 127.2, 126.2, 124.7, 121.9, 65.0, 49.5, 32.7, 32.6, 25.3, 24.7, 24.6, 14.0; IR (KBr) *v*: 3292, 3081, 2936, 2857, 1651, 1559, 1459, 1332, 1288, 1222, 1171, 1131 $cm^{-1}$; HRMS calcd for $C_{27}H_{23}Cl_2F_7N_4O_3S$ $(M+H)^+$ 687.0829, found 687.0832.

***N*-{2-(Cyclohexylamino)-2-oxo-1-[4-(trifluoromethyl)phenyl]ethyl}-*N*-[3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide (5m)** White solid, yield 60%, m.p. 176—178 ℃; $^1H$ NMR ($CDCl_3$, 400 MHz) *δ*: 7.57—6.96 (m, 6H, ph-H), 6.15 (s, 1H, COCH), 6.12—5.86 (m, 1H, $OCF_2CF_2H$), 5.42 (d, *J*=8.0 Hz, 1H, CONH), 3.91—3.82 (m, 1H, cyclohexyl-H), 2.89 (s, 3H, thiadiazolyl-$CH_3$), 2.03—1.03 (m, 10H, cyclohexyl-H); $^{13}C$ NMR ($CDCl_3$, 400 MHz) *δ*: 166.8, 161.9, 161.1, 142.6, 140.3, 137.4, 136.9, 132.1, 132.0, 131.7, 131.1, 130.7, 125.9, 125.8, 124.7, 122.0, 65.2, 49.5, 32.7, 25.3, 24.8, 24.7, 14.0; IR (KBr) *v*: 3293, 3082, 2939, 2858, 1649, 1553, 1461, 1328, 1232, 1127,1113 $cm^{-1}$; HRMS calcd for $C_{27}H_{23}Cl_2F_7N_4O_3S$ $(M+H)^+$ 687.0829, found 687.0828.

***N*-[2-(Cyclohexylamino)-1-(3-hydroxyphenyl)-2-oxoethyl]-*N*-[3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide (5n)** White solid, yield 39%, m.p. 191—194 ℃; $^1H$ NMR ($CDCl_3$, 400 MHz) *δ*: 7.52—6.65 (m, 6H, ph-H), 6.07 (s, 1H, COCH), 6.13—5.86 (m, 1H, $OCF_2CF_2H$), 5.47 (d, *J*=8.0 Hz, 1H, CONH), 5.31 (s, 1H, OH), 3.88—3.81 (m, 1H, cyclohexyl-H), 2.87 (s, 3H, thiadiazolyl-$CH_3$), 2.05—1.03 (m, 10H, cyclohexyl-H); $^{13}C$ NMR ($CDCl_3$, 400 MHz) *δ*: 166.7, 160.8, 159.8, 142.5, 140.6, 140.2, 138.9, 137.7, 134.3, 132.3, 132.0, 130.9, 130.4, 122.5, 65.8, 49.4, 32.8, 25.4, 24.8, 24.7, 14.0; IR (KBr) *v*: 3278, 3150, 2935, 2857, 1645, 1553, 1459, 1355, 1285, 1231, 136 $cm^{-1}$; HRMS calcd for $C_{26}H_{24}Cl_2F_4N_4O_4S$ $(M+H)^+$ 635.0904, found 635.0906.

***N*-[2-(Cyclohexylamino)-1-(4-hydroxyphenyl)-2-oxoethyl]-*N*-[3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide (5o)** White solid, yield 24%, m.p. 123—125 ℃; $^1H$ NMR ($CDCl_3$, 400 MHz) *δ*: 7.52—6.65 (m, 6H, ph-H), 6.13 (s, 1H, COCH), 6.13—5.87 (m, 1H, $OCF_2CF_2H$), 5.63 (s, 1H, OH), 5.44 (d, *J*=8.0 Hz, 1H, CONH), 3.88—3.81 (m, 1H, cyclohexyl-H), 2.87 (s, 3H, thiadiazolyl-$CH_3$), 2.00—1.02 (m, 10H, cyclohexyl-H); $^{13}C$ NMR ($CDCl_3$, 400 MHz) *δ*: 166.6, 162.0, 161.1, 148.1, 142.7, 140.3, 137.3, 136.0, 135.1, 132.2, 131.3, 130.0, 125.3, 124.3, 64.8, 49.5, 32.6, 25.3, 24.7, 24.6, 14.0; IR (KBr) *v*: 3271, 3086, 2933, 2856, 1648, 1560, 1518, 1459, 1384, 1351, 1287, 1216, 1127 $cm^{-1}$; HRMS calcd for $C_{26}H_{24}Cl_2F_4N_4O_4S$ $(M+H)^+$ 635.0904, found 635.0914.

***N*-[2-(Cyclohexylamino)-1-(2-methoxyphenyl)-2-oxoethyl]-*N*-[3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide (5p)** White solid, yield 33%, m.p. 144—145 ℃; $^1H$ NMR ($CDCl_3$, 400 MHz) *δ*: 7.30—6.79 (m, 6H, ph-H), 6.43 (s, 1H, COCH), 6.10—5.84 (m, 1H, $OCF_2CF_2H$), 5.38 (d, *J*=8.0 Hz, 1H, CONH), 3.93—3.88 (m, 1H, cyclohexyl-H), 3.80 (s, 3H, $OCH_3$), 2.88 (s, 3H, thiadiazolyl-$CH_3$), 2.01—1.02 (m, 10H, cyclohexyl-H); $^{13}C$ NMR ($CDCl_3$, 400 MHz) *δ*: 167.8, 157.2, 142.0, 141.2, 137.8, 131.7, 131.3, 131.1, 120.9, 120.8, 110.5, 107.4, 60.3, 55.3, 49.2, 32.8, 25.4, 24.8, 24.7, 13.9; IR (KBr) *v*: 3282, 3074, 2930, 2857, 1654, 1557, 1494, 1461, 1386, 1289, 1253, 1224, 1112 $cm^{-1}$; HRMS calcd for $C_{27}H_{26}Cl_2F_4N_4O_4S$ $(M+H)^+$ 649.1061, found 649.1065.

***N*-[2-(Cyclohexylamino)-1-(3-methoxyphenyl)-2-oxoethyl]-*N*-[3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide (5q)** White solid, yield 27%, m.p. 116—118 ℃; $^1H$ NMR ($CDCl_3$, 400 MHz) *δ*: 7.52—6.61 (m, 6H, ph-H), 6.13 (s, 1H, COCH), 6.19—5.92 (m, 1H, $OCF_2CF_2H$), 5.44 (d, *J*=8.0 Hz, 1H, CONH), 3.89—3.82 (m, 1H, cyclohexyl-H), 3.69 (s, 3H, $OCH_3$), 2.88 (s, 3H, thiadiazolyl-$CH_3$), 2.01—1.03 (m, 10H, cyclohexyl-H); $^{13}C$ NMR ($CDCl_3$, 400 MHz) *δ*: 167.2, 160.0, 142.4, 140.7, 137.7, 134.0, 132.1, 130.8, 130.1, 122.6, 115.8, 115.3, 65.7, 55.3, 49.4, 32.8, 25.4, 24.8, 24.7, 14.0; IR (KBr) *v*: 3281, 3076, 2931, 2855, 1650, 1585, 1561, 1459, 1381, 1355, 1281, 1228, 1156, 1114 $cm^{-1}$; HRMS calcd for $C_{27}H_{26}Cl_2F_4N_4O_4S$ $(M+H)^+$ 649.1061, found 649.1063.

***N*-[2-(Cyclohexylamino)-1-(4-methoxyphenyl)-2-oxoethyl]-*N*-[3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide (5r)** White solid, yield 74%, m.p. 152—155 ℃; $^1H$ NMR ($CDCl_3$, 400 MHz) *δ*: 7.52—6.77 (m, 6H, ph-H), 6.13 (s, 1H, COCH), 6.13—5.87 (m, 1H, $OCF_2CF_2H$), 5.38 (d, *J*=8.0 Hz, 1H, CONH), 3.88—3.3 (m, 1H, cyclohexyl-H), 3.77 (s, 3H, $OCH_3$), 2.88 (s, 3H, thiadiazolyl-$CH_3$), 2.01—1.05 (m, 10H, cyclohexyl-H); $^{13}C$ NMR ($CDCl_3$, 400 MHz) *δ*: 167.7, 161.4, 160.9, 160.4, 142.3, 140.9, 137.8, 134.0, 132.2, 131.7, 130.7, 124.5, 114.3, 107.4, 65.2, 55.3, 49.2, 32.8, 25.4, 24.8, 24.7, 14.0; IR (KBr) *v*: 3290, 3076, 2935, 2856, 1647, 1555, 1512, 1460, 1350, 1257, 1128 $cm^{-1}$; HRMS calcd for $C_{27}H_{26}Cl_2F_4N_4O_4S$ $(M+H)^+$ 649.1061, found 649.1060.

**Biological screening**

**Fungicide screening** Preliminary screening was conducted by fungi growth inhibition method according to the reference using potato dextrose agar (PDA) as cultivation medium.[2] A stock solution of each compound was prepared at 500 μg•mL$^{-1}$ using sterilized water containing 2 drops of *N*,*N*-dimethylformamide (DMF) as a solvent, then 1 mL of the stock solution was transferred into a 10 cm diameter of Petri dish, 9 mL of PDA was then added to prepare the plate containing 50 μg•mL$^{-1}$ of the test compound. Before the plate solidification, the PDA was thoroughly mixed by turning around the Petri dish in the sterilized operation desk 5 times to scatter the compound in PDA evenly. Then, 4 mm of diameter of fungi cake was inoculated on the plate and cultured in the culture tank at 24—26 ℃. The diameter of fungi spread was measured 2 d later. Growth inhibition was then calculated using corresponding control. Azoxystrobin and tricyclazole were used as positive controls. Fungi used in this study included *Alternaria solani* (AS), *Botrytis cinerea* (BC), *Cercospora arachidicola* (CA), *Gibberella zeae* (GZ), *Phytophthora infestans* (Mont) de Bary (PI), *Physalospora piricola* (PP), *Pellicularia sasakii* (PS), *Sclerotinia sclerotiorum* (SS), and *Rhizoctonia cerealis* (RC).

**Systemic acquired resistance screening** Systemic acquired resistance of the target compounds was detected using tobacco against the tobacco mosaic virus (TMV) system as described in Ref. 2. The induction activity was evaluated using the antivirus inhibition ratio, which was calculated by the average number of viral inflammations on the inoculated leaves with corresponding control accordingly. Tiadinil (TDL) and ribavirin were chosen as positive control and negative control, respectively, and all compounds tested were conducted at 100 and 50 μg•mL$^{-1}$, respectively. Before the test of induction activity of systemic acquired resistance, the antivirus activity against TMV was conducted by half leaf juice robbing methods according to reference.[2]

**Protective effects of the target compounds against TMV *in vivo*** Healthy fresh tobacco leaves growing at six-leaf age were selected for the tests. The compound solution was smeared on the whole leaves, and then the leaves were dried in greenhouse. After 12 h, TMV at a concentration of $5.88\times10^{-2}$ μg•mL$^{-1}$ was inoculated on the upper three leaves using the conventional juice-robbing method, and the solvent was smeared on the lower three leaves as a control. The local lesion numbers were then recorded 2—3 d after inoculation. For each compound, three repetitions were conducted. Most compounds tested were conducted at 500 and 100 μg•mL$^{-1}$, respectively.

**Inactivate effect of the target compounds against TMV *in vivo*** Healthy fresh tobacco leaves growing at six-leaf age were selected for the tests. TMV virus at a concentration of $5.88\times10^{-2}$ μg•mL$^{-1}$ was inhibited by mixing with the target compound solution at the same volume for 30 min. Then the mixture was inoculated on the upper three leaves using the conventional juice-robbing method, and the solvent was smeared on the lower three leaves as a control. The local lesion numbers were then recorded 2—3 d after inoculation. For each compound, three repetitions were conducted. All compounds tested were conducted at 500 and 100 μg/mL, respectively.

**Curative effect of target compounds on TMV *in vivo*** Healthy fresh tobacco leaves growing at six-leaf age were selected for the tests. TMV at a concentration of $5.88\times10^{-2}$ μg•mL$^{-1}$ was inoculated on the whole leaves using the conventional juice-robbing method. After the leaves were dried in the greenhouse, the compound solution was smeared on the upper three leaves, and the solvent was smeared on the lower three leaves as control. The local lesion numbers were then recorded 2—3 d after inoculation. For each compound, three repetitions were conducted. All compounds tested were conducted at 500 and 100 μg•mL$^{-1}$, respectively.

The activities of protection, inactivation, and curative effects against TMV were calculated by the average number of viral inflammations on the inoculated leaves with the corresponding control according to the following equation:

$$Y=\frac{\mathrm{CK}-A}{\mathrm{CK}}\times100\%$$

where $Y$ is the antivirus inhibition ratio (protection, inactivation, and curative effects *in vivo*) (%), CK is the average number of viral inflammations on the control leaves *in vivo*, and $A$ is the average number of viral inflammations on the target compound treated leaves *in vivo*.

**Larvicidal activity against *Culex pipiens pallens*.** The larvicidal activity of target compounds **5a**—**5r** was evaluated against mosquito *Culex pipiens pallens* according to the reported procedure.[16] The test solutions were prepared by dissolving 2 mg of the compounds in 10 mL of acetone and adding distilled water respectively to prepare 200 μg•mL$^{-1}$ of mother solution; the 2 μg•mL$^{-1}$ working solution was prepared by diluting 1 mL of mother solution with 89 mL of water and 10 mL of feeding solution into a 100 mL breaker, and 10 forth-instar of *Culex pipiens pallens* larvae were transfered into the beaker. Thereafter, the mosquito larvae in the beakers were cultured in the standard conditioned rooms at 25 ℃ with humidity of 80% for 8 d. The results are expressed as percentage mortality by comparision with the corresponding CK. For comparative purposes, tebufenozide was tested under the same condition.

**Stomach toxicity against *Plutella xylostella* L.** The stomach toxicities of the target compounds **5a**—**5r** against *Plutella xylostella* were tested by the leaf dip method using the reported procedure.[17] A stock solution of each test sample was prepared in dimethylformamide at a concentration of 200 mg•L$^{-1}$ and then diluted to the

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required concentration with water containing TW-20. Leaf disks (6 cm×2 cm) were cut from fresh cabbage leaves and then were dipped into the test solution for 3 s. After air-drying, the treated leaf disks were placed individually into glass tubes. Each dried treated leaf disk was infested with seven third-instar diamondback moth larvae. Percentage mortalities were evaluated 3 d after treatment. Leaves treated with water and dimethylformamide were provided as controls. Each treatment was repeated for three times.

## Results and discussion

### Synthesis

This study used U-4CR as the parallel synthesis method, and the target compounds were proved to be easily synthesized and purified. Following the method developed in our previous study,[4c,15] an amine component and an aldehyde component were first mixed to get an intermediate imine, and then a carbonyl component was added into the mixture for certain time of intervals before the mixing with an isocyanide component. The amount of methanol as solvent added to the reaction mixture was as small as possible, just enough to make the agitation effective. After all components were mixed, products usually precipitated into solvent within 1 h. To obtain high yields, solvent was removed under reduced pressure and then the products were purified by column chromatography on silica gel using ethyl acetate and petroleum ether (60—90 ℃) at 1∶3 (*V*∶*V*) as an eluent.

## Biological activities

### Fungicidal activity

The newly synthesized compounds **5a**—**5r** were tested for their fungicidal activity against following fungi, which represented the pathogen of typical diseases occurring in the Chinese agricultural ecosystem. AS (*Alternaria solani*), BC (*Botrytis cinerea*), CA (*Cercospora arachidicola*), GZ (*Gibberella zeae*), PI (*Phytophthora infestans* (Mont.) de Bary), PP (*Physalospora piricola*), PS (*Pellicularia sasakii*), SS (*Sclerotinia sclerotiorum*) and RC (*Rhizoctonia cerealis*). The results of Table 1 indicated that, most compounds showed lower fungicide activity at 50 μg/mL compared to the two positive controls azoxystrobin and tricyclazole. Some compounds had good fungicide activity, for example, compounds **5b**, **5e** and **5m** exhibited 72.7%, 72.7% and 63.6% of fungicidal activity against SS, respectively; the activity of compounds **5a**, **5d**, **5i** and **5j** against PP were of 64.1%, 71.8%, 61.5% and 71.8%, respectively, which were higher than that of tricyclazole; the inhibition percentages of **5j** to RC and AS were 64.5% and 61.9%, respectively.

**Table 1** The antifungal activities of title compounds *in vitro* at 50 μg•mL$^{-1}$

| Compound | GZ | SS | PI | PP | BC | RC | PS | AS | CA |
|---|---|---|---|---|---|---|---|---|---|
| **5a** | 0 | 45.5 | 0 | 64.1 | 18.2 | 41.9 | 14.1 | 33.3 | 14.3 |
| **5b** | 0 | 72.7 | 23.8 | 46.2 | 18.2 | 41.9 | 14.1 | 4.8 | 21.4 |
| **5c** | 0 | 54.6 | 0 | 33.3 | 0 | 32.3 | 14.1 | 9.5 | 0 |
| **5d** | 0 | 36.4 | 14.3 | 71.8 | 27.3 | 48.4 | 14.1 | 33.3 | 0 |
| **5e** | 0 | 72.7 | 0 | 20.5 | 4.6 | 0 | 42.3 | 4.8 | 0 |
| **5f** | 0 | 54.6 | 0 | 20.5 | 36.4 | 22.6 | 42.3 | 33.3 | 0 |
| **5g** | 0 | 45.5 | 0 | 38.5 | 27.3 | 32.3 | 4.2 | 33.3 | 14.3 |
| **5h** | 0 | 36.4 | 19.1 | 38.5 | 0 | 22.6 | 42.3 | 0 | 14.3 |
| **5i** | 23.8 | 45.5 | 23.8 | 61.5 | 0 | 9.7 | 14.1 | 47.6 | 21.4 |
| **5j** | 0 | 0 | 23.8 | 71.8 | 27.3 | 64.5 | 21.1 | 61.9 | 42.9 |
| **5k** | 0 | 45.5 | 9.5 | 28.2 | 27.3 | 41.9 | 0 | 47.6 | 0 |
| **5l** | 0 | 36.4 | 0 | 53.9 | 4.6 | 29.0 | 14.1 | 14.3 | 0 |
| **5m** | 0 | 63.6 | 0 | 33.3 | 4.6 | 32.3 | 42.3 | 33.3 | 0 |
| **5n** | 0 | 27.3 | 0 | 7.7 | 4.6 | 16.1 | 14.1 | 0 | 0 |
| **5o** | 0 | 18.2 | 0 | 33.3 | 0 | 48.4 | 7.0 | 14.3 | 0 |
| **5p** | 0 | 54.6 | 0 | 59.0 | 4.6 | 0 | 42.3 | 42.9 | 21.4 |
| **5q** | 0 | 27.3 | 23.8 | 28.2 | 13.6 | 16.1 | 0 | 23.8 | 0 |
| **5r** | 0 | 27.3 | 0 | 33.3 | 0 | 22.6 | 0 | 33.3 | 0 |
| Azoxystrobin | 40.0 | 100 | 88.9 | 85.0 | 21.2 | 100 | 69.74 | 63.1 | 80.0 |
| Tricyclazole | 24.0 | 100 | 29.6 | 25.0 | 36.8 | 65.9 | 29.0 | 5.3 | 13.3 |

### Antivirus activity

Tiadinil, ribavirin and ninamycin were used as positive controls. The results of activity screening by half-leaf juice-robbing method against TMV indicated that (Table 2) most compounds showed certain degree of direct inhibition activities against TMV *in vitro* with results no more than 50% except **5j**. However, compounds **5d**, **5k**, **5m** and **5o**, **5j** had direct inhibition activities of 45%, 46%, 43% and 45%, 53% at 100 μg•mL$^{-1}$, respectively. These were as twice as that of ribavirin. However, the activities at 500 μg•mL$^{-1}$ were lower. Only compound **5j** had high activity at both 500 and 100 μg•mL$^{-1}$ with inhibition above 50%, and they are significantly higher than those of the positive control agents ribavirin and tiadinil.

The antivirus activity of all title compounds including protective, inactivate and curative effect, and the inductive activities were also evaluated. The results listed in Table 2 indicated that, most of the compounds had good inactivation and curative activity against tobacco mosaic virus. Among these, compounds **5a**—**5d** and **5o** had inactivation activities of 66%, 87%, 73%, 70% and 71% at 500 μg•mL$^{-1}$, respectively, and 49%, 59%, 51%, 48% and 52% at 100 μg•mL$^{-1}$, respectively. These were better than that of the positive control agent ribavirin; compounds **5g**, **5h**, **5j**, **5m** and **5o** had good curative activities of 65%, 59%, 59%, 72% and 72% at 500 μg•mL$^{-1}$, respectively, and 43%, 52%, 47%, 56%

  

**Table 2** Antivirus activity of the title compounds **5a**—**5r** against TMV

| Compound | Concentration/ ($\mu g \cdot mL^{-1}$) | (Half leaf activity±SD)/% | (Protective activity±SD)/% | (Inactivate activity±SD)/% | (Curative activity±SD)/% | (Inductive activity±SD)/% |
|---|---|---|---|---|---|---|
| **5a** | 500 | 36±4 | 45±7 | 66±5 | 55±7 | 65±1[a] |
| | 100 | 36±5 | 22±7 | 49±8 | 39±3 | 57±7[b] |
| **5b** | 500 | 31±6 | 48±3 | 87±3 | 50±8 | 38±6[a] |
| | 100 | 26±5 | 16±7 | 59±4 | 50±3 | 7±8[b] |
| **5c** | 500 | 24±5 | 22±3 | 73±8 | 59±1 | 30±5[a] |
| | 100 | 27±6 | 13±6 | 51±3 | 41±9 | 64±3[b] |
| **5d** | 500 | 45±2 | 55±8 | 70±8 | 47±6 | 61±4[a] |
| | 100 | 45±3 | 42±8 | 48±4 | 14±5 | 22±3[b] |
| **5e** | 500 | 28±5 | 34±4 | 58±5 | 48±8 | 36±6[a] |
| | 100 | 22±2 | 16±7 | 48±4 | 41±9 | 25±6[b] |
| **5f** | 500 | 38±3 | 36±5 | 49±7 | 11±4 | 38±5[a] |
| | 100 | 37±3 | 29±7 | 23±6 | 7±3 | 5±4[b] |
| **5g** | 500 | 34±5 | 56±7 | 55±8 | 65±9 | 12±8[a] |
| | 100 | 35±3 | 27±0 | 36±7 | 43±7 | 6±3[b] |
| **5h** | 500 | 37±3 | 49±2 | 43±4 | 59±7 | 64±3[a] |
| | 100 | 33±3 | 9±9 | 11±8 | 52±6 | 49±8[b] |
| **5i** | 500 | 35±5 | 58±5 | 24±6 | 38±4 | 57±1[a] |
| | 100 | 33±3 | 45±5 | 13±2 | 21±7 | 56±4[b] |
| **5j** | 500 | 51±9 | 60±4 | 9±7 | 59±3 | 54±10[a] |
| | 100 | 53±6 | 33±8 | 14±5 | 47±9 | 60±3[b] |
| **5k** | 500 | 37±5 | 51±2 | 43±9 | 30±5 | 28±4[a] |
| | 100 | 46±1 | 35±7 | 12±1 | 10.37±3 | 72±4[b] |
| **5l** | 500 | 27±1 | 76±2 | 15±8 | 61±5 | 41±3[a] |
| | 100 | 34±3 | 59±6 | 14±5 | 37±9 | 45±2[b] |
| **5m** | 500 | 20±3 | 58±5 | 47±7 | 72±1 | 75±5[a] |
| | 100 | 43±3 | 51±3 | 11±7 | 56±3 | 75±3[b] |
| **5n** | 500 | 37±3 | 41±1 | 50±6 | 47±7 | 59±1[a] |
| | 100 | 33±3 | 337±2 | 10±8 | 13±5 | 67±4[b] |
| **5o** | 500 | 37±6 | 57±3 | 71±3 | 72±3 | 30±4[a] |
| | 100 | 45±3 | 46±10 | 52±3 | 43±8 | 15±7[b] |
| **5p** | 500 | 43±1 | 34±6 | 34±6 | 37±9 | 65±5[a] |
| | 100 | 34±8 | 22±7 | 11±3 | 30±3 | 14±6[b] |
| **5q** | 500 | 16±1 | 72±4 | 62±7 | 34±6 | 15±2[a] |
| | 100 | 29±10 | 48±5 | 12±7 | 16±3 | 45±8[b] |
| **5r** | 500 | 26±8 | 69±5 | 13±6 | 49±2 | 83±4[a] |
| | 100 | 25±2 | 59±3 | 8±5 | 33±8 | 67±3[b] |
| Ribavirin | 500 | 32±1 | 65±3 | 48±4 | 52±7 | 20±5[a] |
| | 100 | 20±2 | 50±8 | 26±4 | 30±4 | 65±8[b] |
| Ninamycin | 500 | 49±4 | 73±5 | 63±9 | 55±8 | 46±5[a] |
| | 100 | 39±6 | 56±3 | 43±9 | 41±8 | 63±5[b] |
| Tiadinil | 500 | 32±3 | 66±3 | 56±7 | 50±9 | 57±2[a] |
| | 100 | 36±4 | 55±4 | 47±9 | 36±6 | 65±4[b] |

[a] 50 $\mu g \cdot mL^{-1}$ of concentration; [b] 100 $\mu g \cdot mL^{-1}$ of concentration.

  

and 43% at 100 μg/mL, respectively. These were also better than the positive control agent ribavirin. As for the protection effect and induction activities, most of them had lower activities as compared with the positive control. However, some compounds stood out, compounds **5l**, **5q** and **5r** had good protection activities of 76%, 72% and 69% at 500 μg•mL$^{-1}$, respectively, and 58%, 47% and 59% at 100 μg•mL$^{-1}$, respectively. Compounds **5m**, **5n** and **5r** had good induction activities of 75%, 59% and 83% at 500 μg•mL$^{-1}$, respectively, and 75%, 67% and 67% at 100 μg•mL$^{-1}$, respectively. These were approximately equal to or higher than that of the positive controls. We observed no phytotoxicity to tobacco during the course of experiments. No significant structure-activity relationship was observed from these studies. This indicated that the whole molecular structure played an important role in these activities rather than one moiety in the molecule.

### Larvicidal activity

Table 3 showed the larvicidal activities of compounds **5a** — **5r** and positive control tebufenozide against *Plutella xylostella* L. and *Culex pipiens pallens*. The results indicate that most of the compounds exhibited different larvicidal activities against *Plutella xylostella* L. and *Culex pipiens pallens*. On the whole, the larvicidal activities of the *meta*-substituted and *para*-substituted benzoyl against *Plutella xylostella* L. were better than those of *ortho*-substituted and non-substituted compounds. For example, compounds **5b**, **5d**, **5f**, **5g**, **5n**, **5o** and **5r** displayed higher larvicidal activities against *Plutella xylostella* L. than compounds **5a**, **5c**, **5e**, **5j** and **5p** at 200 μg•mL$^{-1}$. Compounds **5b**, **5f**, **5g**, **5n**, **5o** and **5r** had good larvicidal activity against *Plutella xylostella* L., which were approximately equal to that of the commercialized product tebufenozide at 200 μg•mL$^{-1}$. Compounds **5o** and **5q** also exhibited excellent larvicidal activities against *Culex pipiens pallen* among the test compounds, which had 100% mortality at 2 μg•mL$^{-1}$.

## Conclusion

In summary, a series of new 4-methyl-1,2,3-thiadiazole derivatives containing active substructure of 3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl were conveniently synthesized and easily purified via 4 component Ugi reaction. Bioassay results indicated that all of these title compounds showed a certain degree of fungicidal activity at 50 μg•mL$^{-1}$. The larvicidal activities of the benzoyl *meta*-substituted or *para*-substituted compounds against *Plutella xylostella* L. were better than those of benzoyl *ortho*-substituted or non-substituted compounds. Compounds **5o** and **5q** exhibited excellent larvicidal activities against *Culex pipiens pallens* with 100% mortality at 2 μg•mL$^{-1}$. Most of the compounds presented different extent of anti-TMV activity with different mode of action.

**Table 3** Insecticidal activities of of the title compounds **5a**—**5r**

| Compound | *Plutella xylostella* L. | | *Culex pipiens pallens* | |
|---|---|---|---|---|
| | Concentration/(μg•mL$^{-1}$) | Larvicidal activity/% | Concentration/(μg•mL$^{-1}$) | Larvicidal activity/% |
| **5a** | 200 | 7.89 | 2 | 20 |
| **5b** | 200 | 22.86 | 2 | 20 |
| **5c** | 200 | 7.69 | 2 | 40 |
| **5d** | 200 | 17.50 | 2 | 20 |
| **5e** | 200 | 5.41 | 2 | 0 |
| **5f** | 200 | 21.05 | 2 | 10 |
| **5g** | 200 | 23.68 | 2 | 0 |
| **5h** | 200 | 5.26 | 2 | 10 |
| **5i** | 200 | 7.89 | 2 | 0 |
| **5j** | 200 | 15.00 | 2 | 20 |
| **5k** | 200 | nd[a] | 2 | 30 |
| **5l** | 200 | 2.63 | 2 | 20 |
| **5m** | 200 | 15.79 | 2 | 20 |
| **5n** | 200 | 22.92 | 2 | 40 |
| **5o** | 200 | 21.62 | 2 | 100 |
| **5p** | 200 | 10.81 | 2 | nd |
| **5q** | 200 | 7.90 | 2 | 100 |
| **5r** | 200 | 20.00 | 2 | 20 |
| Tebufenozide | 200 | 26.30 | 2 | 100 |

[a] nd: not detected.

  

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