Design, Synthesis and Bioactivity of Novel Glycosylthiadiazole Derivatives

Guanghui Zong 1,†, Hanqing Zhao 1,2,†, Rui Jiang 1, Jianjun Zhang 1,* , Xiaomei Liang 1, Baoju Li 3, Yanxia Shi 3,* and Daoquan Wang 1

1 Department of Applied Chemistry, China Agricultural University, Beijing 100193, China
2 Department of Fundamental Science, Beijing University of Agriculture, Beijing 102206, China
3 Institute of Vegetables and Flowers, Chinese Academy of Agricultural Sciences, Beijing 100081, China

† The authors contributed equally to this paper.

* Authors to whom correspondence should be addressed; E-Mails: zhangjianjun@cau.edu.cn (J.Z.); shiyanxia@caas.cn (Y.S.); Tel.: +86-10-6273-1115 (J.Z.); Fax: +86-10-6273-2219 (J.Z.).

Received: 21 April 2014; in revised form: 4 June 2014 / Accepted: 5 June 2014 / Published: 11 June 2014

Abstract: A series of novel glycosylthiadiazole derivatives, namely 2-phenylamino-5-glycosyl-1,3,4-thiadiazoles, were designed and synthesized by condensation between sugar aldehydes A/B and substituted thiosemicarbazide C followed by oxidative cyclization by treating with manganese dioxide. The original fungicidal activities results showed that some title compounds exhibited excellent fungicidal activities against Sclerotinia sclerotiorum (Lib.) de Bary and Pyricularia oryzae Cav, especially compounds F-5 and G-8 which displayed better fungicidal activities than the commercial fungicide chlorothalonil. At the same time, the preliminary studies based on the Elson-Morgan method indicated that many compounds exhibited some inhibitory activity toward glucosamine-6-phosphate synthase (GlmS). The structure-activity relationships (SAR) are discussed in terms of the effects of the substituents on both the benzene and the sugar ring.

Keywords: 1,3,4-thiadiazole; carbohydrates; synthesis; fungicidal activity
1. Introduction

Carbohydrates play an important role in the field of pesticide investigation, and many natural carbohydrate products used as pesticides have shown great vitality. Validamycin [1], validoxylamine A [2], trehazolin [3], streptomycin [4] and kasugamycin [5] have already proven excellent activities against pests and fungi, and most of them are considered to be non-toxic for mammals and have no adverse effects on non-target organisms or on the environment. Many natural products containing glycosyl residues in their structures, such as the derivatives of avermecin and spinosad, are well known green pesticides and widely used in the control of many kinds of pests, taking the advantage of excellent bioactivities, good environment compatibility and structure variability [6–9]. Encouraged by the successes of the developed commercial pesticides based on natural carbohydrates, pesticide chemists have paid considerable attention to the design, synthesis and activity evaluation of novel carbohydrate-containing compounds as potential pesticides, finding that heterocyclic compounds modified by carbohydrates exhibit excellent biological activities [10–13].

It is well established that 1,3,4-thiadiazole and their derivatives exhibit a broad spectrum of biological activities not only in research on drugs with anticancer [14], antimicrobial [15], antituberculosis [16], anticonvulsant [17], or anti-inflammatory activities [18,19] but also in pesticide research such as antifungal [20,21], insecticidal [22], herbicidal [23] and also plant growth regulating agents [24]. Consequently, studies on the synthesis and bioassays of 1,3,4-thiadiazole derivatives have attracted increasing attention in the field of pesticide discovery. As pesticides, many of the 1,3,4-thiadiazole derivatives showed high toxicity profiles and were taken off the market. Thus an interest in developing novel bioactive agents with low toxicities and an acceptable impact on the environment is increasing. One way to reach this goal is to modify the parent 1,3,4-thiadiazole structure.

In our previous studies [25–27], numerous 1,3,4-thiadiazole derivatives (I-III, Figure 1) were designed and synthesized. Some of them exhibited good fungicidal activity against *Rhizoctonia solani* Kühn, *Verticillium dahlia* Kleb. and *Pyricularia oryzae* Cav.

**Figure 1.** 1,3,4-Thiadiazole derivatives developed in our laboratory.
Considering the advantages of using carbohydrates in developing novel pesticides, we made some efforts to investigate the antifungal activities of 1,3,4-thiadiazoles modified by carbohydrates, and a series of thiadiazoline derivatives containing glucofuranose were synthesized in our laboratory [28]. The fungicidal activity results obtained showed that compound IV (Figure 1) exhibited excellent fungicidal activities against *Phytophthora parasitica* Dast and *Helminthosporium maydis* Nisik & Miy. Inspired by these promising results, we developed a great interest in searching for potential 1,3,4-thiadiazole derivative pesticides containing furanoses. In the structure of compound IV, the 1,3,4-thiadiazole moiety and the glucofuranose moiety were connected in a spirocyclic manner. In particular the question of the kind of changes in the fungicidal activities that might happen if the two moieties were connected directly to each other (through a single bond) caught our attention. Thus, a series of xylose-based 1,3,4-thiadiazoles, were synthesized and evaluated, as mentioned in one of our former Chinese patents [29]. At the same time, as there is some similarity between the target compounds and the D-fructose-6-P, which is one of the substrates in the first committed step of the hexosamine biosynthesis pathway [30] by glucosamine-6-phosphate synthase (GlmS; EC 2.6.1.16), their enzyme inhibitory activities were evaluated, too. In this paper, we would like to report their synthesis (Schemes 1 and 2) and bioactivities in much greater details, and also their structure-activity relationship studies. Furthermore, to investigate the effects of the protecting groups in the sugar ring on the activities of compounds F and G, the deprotected compounds H, I and J were also synthesized and evaluated. We report herein the preliminary results of the study.

2. Results and Discussion

2.1. Synthesis of the Title Compounds

The synthesis of the target compounds was outlined in Scheme 1. According to the known methods [31–33], two furanosyl aldehydes (A and B) were prepared using D-glucose as the starting material.
The substituted thiosemicarbazides C were synthesized from the corresponding substituted arylamines as previously described [24,31]. The condensation between furanosyl aldehydes A or B and substituted thiosemicarbazides C provided compounds D or E, respectively. Then the target compounds F or G were prepared by treating compounds D or E with MnO₂. Compound H was obtained by deacetylation of compound F-8, and compounds I and J were obtained by deisopropylidenation of the related compounds F-8 and G-7, as shown in Scheme 2.

Scheme 2. Synthesis of the sugar moiety-modified compounds.

All the derivatives were synthesized according to the procedures described in Schemes 1 and 2 in good overall yields of 65%–92%. The synthesized compounds were characterized by ¹H-NMR, MS and HRMS. Most of the ¹H-NMR experiments of compounds F and G were conducted in CDCl₃ as the solvent. Nevertheless, the signal of NH was too weak in some cases, so we had to switch the solvent to DMSO-δ₆. The physical data of the target compounds are given in Table 1.

Table 1. Physical Data of Compounds F/G.

| Compd. | R1   | R2     | Formula               | Status                  | m.p./°C | Yield (%) |
|--------|------|--------|-----------------------|-------------------------|---------|-----------|
| F-1    | Ac   | 4-Br-C₆H₄- | C₁₇H₁₈BrN₃O₅S      | White foamy solid       | 204.1–204.7 | 79        |
| F-2    | Ac   | 4-CH₃-C₆H₄- | C₁₈H₂₁N₃O₅S      | White foamy solid       | 187.9–188.1 | 82        |
| F-3    | Ac   | 4-CH₃O-C₆H₄- | C₁₈H₂₁N₃O₆S   | yellow foamy solid      | 177.7–178.7 | 73        |
| F-4    | Ac   | 2,4-(CH₃)₂-C₆H₄- | C₁₉H₂₃N₃O₅S | White foamy solid       | 133.7–134.3 | 81        |
| F-5    | Ac   | 3,4-Cl₂-C₆H₄- | C₁₇H₁₇Cl₂N₃O₅S | White foamy solid       | 147.7–148.5 | 83        |
| F-6    | Ac   | 2,5-Cl₂-C₆H₄- | C₁₇H₁₇Cl₂N₃O₅S | White foamy solid       | 61.8–62.9  | 85        |
| F-7    | Ac   | 1-Naphthyl- | C₂₁H₂₁N₃O₅S   | White foamy solid       | 57.0–58.1  | 65        |
| F-8    | Ac   | 4-Cl-3-CF₃-C₆H₃- | C₁₈H₁₇ClF₃N₃O₅S | White foamy solid       | 140.0–141.2 | 77        |
| F-9    | Ac   | C₆H₄-  | C₁₇H₁₉N₃O₅S   | White foamy solid       | 195.1–195.5 | 78        |
| F-10   | Ac   | 4-NO₂-C₆H₄- | C₁₉H₂₀N₄O₇S   | yellow foamy solid      | 198.4–198.7 | 73        |
| G-1    | All  | 4-Br-C₆H₄- | C₁₈H₂₀BrN₃O₅S  | White foamy solid       | 204.1–204.7 | 68        |
| G-2    | All  | 4-CH₃-C₆H₄- | C₁₉H₂₃N₃O₅S   | White foamy solid       | 187.9–188.1 | 74        |
| G-3    | All  | 4-CH₃O-C₆H₄- | C₁₉H₂₃N₃O₅S  | White foamy solid       | 177.7–178.7 | 78        |
| G-4    | All  | 2,4-(CH₃)₂-C₆H₄- | C₂₀H₂₅N₃O₅S | White foamy solid       | 133.7–134.3 | 76        |
| G-5    | All  | 3,4-Cl₂-C₆H₄- | C₁₈H₁₉Cl₂N₃O₅S | White foamy solid       | 147.7–148.5 | 81        |
| G-6    | All  | 2,5-Cl₂-C₆H₄- | C₁₈H₁₉Cl₂N₃O₅S | White foamy solid       | 61.8–62.9  | 76        |
| G-7    | All  | 1-Naphthyl- | C₂₂H₂₃N₃O₅S   | yellow foamy solid      | 57.0–58.1  | 68        |
| G-8    | All  | 4-Cl-3-CF₃-C₆H₃- | C₁₉H₁₉ClF₃N₃O₅S | White foamy solid       | 140.0–141.2 | 86        |
| G-9    | All  | C₆H₄-  | C₁₈H₂₀N₃O₅S   | White foamy solid       | 195.1–195.5 | 91        |
| G-10   | All  | 4-NO₂-C₆H₄- | C₁₉H₂₀N₄O₆S   | White foamy solid       | 198.4–198.7 | 71        |
2.2. Fungicidal Activity of Compounds F/G against Six Fungus Species

Compounds F/G were evaluated in a series of in vitro fungicidal tests against six fungal species, and compared with the commercial fungicide chlorothalonil. As shown in Table 2, the resulting data revealed that most of the tested compounds displayed a certain degree of fungicidal activity against the six species. Among them, the majority of the compounds showed better fungicidal activity against S. sclerotiorum than the other five fungi. Among the 20 tested compounds, there were seven that displayed an inhibition rate of 90% or more against S. sclerotiorum at a concentration of 50 µg/mL. Therefore, the further activity evaluation of the compounds in our research was performed against S. sclerotiorum.

Table 2. Fungicidal activity of compounds F/G against six fungus species (% control at 50 µg/mL).

| Compds No. | S. sclerotiorum | P. parasitica Dast | B. cinerea | R. solani | P. oryzae Cav. | P. asparagi saecrdo |
|------------|-----------------|--------------------|------------|-----------|----------------|---------------------|
| F-1        | 68              | 11                 | 14         | 60        | 29             | −8                  |
| F-2        | 76              | 40                 | 50         | 65        | 52             | 35                  |
| F-3        | 80              | 22                 | 26         | 70        | 27             | 5                   |
| F-4        | 84              | 35                 | 32         | 69        | 58             | 50                  |
| F-5        | 91              | 21                 | 24         | 67        | 76             | 23                  |
| F-6        | 94              | 97                 | 66         | 77        | 72             | 25                  |
| F-7        | 88              | 67                 | 74         | 62        | 70             | 43                  |
| F-8        | 89              | 37                 | 51         | 53        | 46             | 21                  |
| F-9        | 68              | 27                 | −11        | 63        | 56             | 54                  |
| F-10       | 52              | 12                 | 6          | 59        | 41             | 25                  |
| G-1        | 79              | 30                 | 72         | 58        | 80             | 26                  |
| G-2        | 87              | 32                 | 79         | 77        | 81             | 15                  |
| G-3        | 74              | 65                 | 50         | 80        | 79             | 66                  |
| G-4        | 93              | 61                 | 88         | 62        | 87             | 51                  |
| G-5        | 85              | 74                 | 84         | 56        | 85             | 84                  |
| G-6        | 90              | 63                 | 77         | 63        | 87             | 98                  |
| G-7        | 92              | 42                 | 85         | 68        | 85             | 66                  |
| G-8        | 98              | 64                 | 80         | 59        | 83             | 71                  |
| G-9        | 86              | 40                 | 64         | 55        | 79             | 85                  |
| G-10       | 91              | 43                 | 81         | 55        | 78             | 57                  |
| Chlorothalonil | 93          | 92                | 84         | 100       | 82             | 94                  |

2.3. Precise Fungicidal Activity of Compounds F/G Against S. sclerotiorum

The precise fungicidal activity of compounds F/G against S. sclerotiorum was evaluated, and the data are shown in Table 3. For half of the compounds F/G, i.e., 10 out of the 20 tested compounds, their EC50 values were <3 µg/mL. They thus exhibited good fungicidal activity against S. sclerotiorum. Among them, compounds F-5, F-8, G-5, G-6 and G-8 (the EC50 values of which are 0.29, 1.50, 1.50, 1.62 and 0.46 µg/mL, respectively) exhibited excellent fungicidal activity and they are comparable with the commercial fungicide chlorothalonil (with a EC50 value of 0.59 µg/mL).
Table 3. Fungicidal Activity of Compounds F/G against S. sclerotiorum.

| Compds No. | Regression eq | r   | EC<sub>50</sub> (μg/mL) | EC<sub>90</sub> (μg/mL) |
|------------|---------------|-----|------------------------|------------------------|
| F-1        | Y = 4.93 + 0.57x | 0.9416 | 1.33 | 247.14                |
| F-2        | Y = 3.96 + 1.39x | 0.9880 | 5.64 | 47.03                |
| F-3        | Y = 4.77 + 0.58x | 0.9791 | 2.45 | 382.78              |
| F-4        | Y = 4.11 + 1.04x | 0.9717 | 7.11 | 120.46              |
| F-5        | Y = 5.31 + 0.58x | 0.9349 | 0.29 | 47.38               |
| F-6        | Y = 3.93 + 1.80x | 0.9758 | 3.94 | 20.30               |
| F-7        | Y = 2.04 + 2.18x | 0.9937 | 22.53 | 87.03             |
| F-8        | Y = 4.80 + 1.11x | 0.9543 | 1.50 | 21.6                |
| F-9        | Y = 4.51 + 0.72x | 0.9798 | 4.70 | 276.27              |
| F-10       | Y = 4.13 + 0.56x | 0.9765 | 37.13 | 7558.45           |
| G-1        | Y = 3.84 + 1.29x | 0.9059 | 8.01 | 79.59                |
| G-2        | Y = 3.94 + 1.58x | 0.9993 | 4.70 | 30.32               |
| G-3        | Y = 4.75 + 0.63x | 0.9457 | 2.51 | 273.14              |
| G-4        | Y = 2.48 + 2.52x | 0.9859 | 9.92 | 31.89                |
| G-5        | Y = 4.83 + 0.96x | 0.9880 | 1.50 | 32.10               |
| G-6        | Y = 4.80 + 0.94x | 0.9871 | 1.62 | 37.28                |
| G-7        | Y = 4.68 + 1.06x | 0.9940 | 2.00 | 32.30               |
| G-8        | Y = 5.34 + 0.99x | 0.9961 | 0.46 | 8.91                |
| G-9        | Y = 4.32 + 1.26x | 0.9809 | 3.44 | 35.81               |
| G-10       | Y = 4.69 + 1.00x | 0.9534 | 2.02 | 38.63                |
| Chlorothalonil | 5.19 + 0.84x | 0.9784 | 0.59 | 19.56               |

In general, the following structure-activity relationships (SAR) in compounds F/G were observed: (1) for the two series F and G, on an overall level the latter (R<sup>2</sup> = allyl) displayed a better fungicidal activity than the former (R<sup>2</sup> = Ac), i.e., there were six compounds in series G that exhibited better fungicidal activity than their counterparts in series F; (2) for the F series, the fungicidal activity is increased by improving the electron-withdrawing ability of substituents on the benzene ring, i.e., in compounds F-4 (R<sup>2</sup> = 2,4-(CH<sub>3</sub>)<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>-), F-2 (R<sup>2</sup> = 4-CH<sub>3</sub>-C<sub>6</sub>H<sub>3</sub>-), F-9 (R<sup>2</sup> = C<sub>6</sub>H<sub>3</sub>-), F-3 (R<sup>2</sup> = 4-CH<sub>3</sub>O-C<sub>6</sub>H<sub>3</sub>-) and F-1 (R<sup>2</sup> = 4-Br-C<sub>6</sub>H<sub>3</sub>-) with the EC<sub>50</sub> values of 7.11, 5.64, 4.70, 2.45 and 1.33 μg/mL, respectively; (3) for the G series, the fungicidal activity is increased by improving the electron-withdrawing ability of substituents on the benzene ring, too, i.e., compounds G-4 (R<sup>2</sup> = 2,4-(CH<sub>3</sub>)<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>-), G-2 (R<sup>2</sup> = 4-CH<sub>3</sub>-C<sub>6</sub>H<sub>3</sub>-), G-9 (R<sup>2</sup> = C<sub>6</sub>H<sub>3</sub>-), G-3 (R<sup>2</sup> = 4-CH<sub>3</sub>O-C<sub>6</sub>H<sub>3</sub>-) and G-6 (R<sup>2</sup> = 2,5-Cl<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>-) with the EC<sub>50</sub> values of 9.92, 4.70, 3.44, 2.51 and 1.62 μg/mL, respectively; (4) In both series F and G, the compounds with two electron-withdrawing groups in the benzene ring have the best fungicidal activity in their own series, i.e., compounds F-5 (R<sup>2</sup> = 3,4-Cl<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>-) and G-8 (R<sup>2</sup> = 4-Cl-3-CF<sub>3</sub>-C<sub>6</sub>H<sub>3</sub>-) with the EC<sub>50</sub> values of 0.29 and 0.46 μg/mL, respectively. They were slightly better than the commercial fungicide chlorothalonil (EC<sub>50</sub> value = 0.59 μg/mL). Similarly, compounds F-8 (R<sup>2</sup> = 4-Cl-3-CF<sub>3</sub>-C<sub>6</sub>H<sub>3</sub>-) and G-5 (R<sup>2</sup> = 3,4-Cl<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>-), both with EC<sub>50</sub> values of 1.50 μg/mL, also displayed excellent fungicidal activities. However, the compounds with two electron-donating groups in the benzene ring displayed only moderate fungicidal activity, i.e., compounds F-4 (R<sup>2</sup> = 2,4-Me<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>-) and G-4 (R<sub>2</sub> = 2,4-Me<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>-) with the EC<sub>50</sub> values of 7.11 and 9.92 μg/mL, respectively.
2.4. Effect of Structure Modifications on the Sugar Ring around Compound F/G

Having identified the relatively potent compounds of series F/G, such as F-8, G-8 and G-7, we next focused our attention on investigating the effects of subtle structural changes in the sugar ring of compounds F/G. To this end, compounds H, I and J were prepared and evaluated. The fungicidal results against S. sclerotiorum are provided in Table 4. It is evident from the data (Tables 3 and 4) that, among all the derivatives studied above, compounds with complete OH-protection in the sugar ring, i.e., compounds F-8, G-8 and G-7, displayed the most promising results, with the EC50 values of 1.50, 0.46, 2.00 μg/mL respectively. Meanwhile, compound H without the OH-protection at the 3-position in the sugar ring (and with an EC50 value of 4.61 μg/mL) has shown a slightly decreased fungicidal activity. Compounds I and J without the OH-protection at both 1 and 2-position displayed a significant decrease in their fungicidal activity, with EC50 values of 8.18, 18.91 μg/mL, respectively. The results above demonstrate that appropriate protections of the hydroxyl groups in the sugar ring can make positive contributions to the fungicidal activity against S. Sclerotiorum. Interestingly, however, the enzyme inhibitory activity of compounds H, I and J is superior to that of compound G-8 (Table 5), which may be associated with a better structural similarity between fructose 6-phosphate (Fru-6-P) and compounds H, I and J.

Table 4. Effects of structural modifications in sugar ring of compounds F/G on the activity against S. sclerotiorum.

| Compds No. | Regression eq | r  | EC50  | EC90  |
|------------|---------------|----|-------|-------|
| H          | Y = 4.40 + 0.91x | 0.8678 | 4.61  | 119.37|
| I          | Y = 4.27 + 0.80x | 0.9963 | 8.18  | 321.93|
| J          | Y = 2.80 + 1.72x | 0.9228 | 18.91 | 105.14|

Table 5. Enzyme inhibition Rate of Compounds F and G at 0.35 mm.

| Compd No. | Inhibition Rate (%) | Compd No. | Inhibition Rate (%) |
|-----------|---------------------|-----------|---------------------|
| F-1       | 13.2                | G-1       | 12.0                |
| F-2       | 15.3                | G-2       | 10.8                |
| F-3       | 17.7                | G-3       | 16.1                |
| F-4       | 18.5                | G-4       | 15.2                |
| F-5       | 18.3                | G-5       | 25.8                |
| F-6       | 19.1                | G-6       | 17.4                |
| F-7       | 17.9                | G-7       | 28.1                |
Table 5. Cont.

| Compd No. | Inhibition Rate (%) | Compd No. | Inhibition Rate (%) |
|-----------|---------------------|-----------|---------------------|
| F-8       | 18.1                | G-8       | 26.5                |
| F-9       | 14.7                | G-9       | 20.3                |
| F-10      | 13.3                | G-10      | 24.2                |
| H         | 29.4                | J         | 36.2                |
| I         | 35.8                |           |                     |

2.5. Bioassay of Enzyme Inhibitory Activities [34–37]

Inhibitory activity of all the synthesized compounds towards Candida albicans GlcN-6-P synthase was evaluated using the optimized Elson-Morgan method [38]. The absorption value of the solution was measured at 585 nm, and then the concentration was counted by the specification curve which was determined thanks to the relation between the absorption value and the concentration of glucosamine-6-phosphate. Finally the enzyme inhibition rate was calculated according to Equation (1):

\[
I = \frac{M_0 - \overline{M}}{M_0} \times 100\%
\]

In Equation (1): \(I\) is the inhibition rate, \(\overline{M}_0\) is the average concentration of glucosamine-6-phosphate in the blank test, and \(\overline{M}\) is the average concentration of glucosamine-6-phosphate in the presence of target compounds. The inhibition rates were given in Table 5 at 0.35 mm.

The compounds of series F and G exhibited some enzyme inhibitory activities (Table 5). Compounds G-5, G-7, G-8 and G-10 are more active against glucosamine-6-phosphate synthase than the other compounds. On the whole, the enzyme inhibitory activity of G series of compounds is superior to the F series. The enzyme inhibitory activity of compounds H, I and J is superior to that of compound G-8 (Table 5), which may be associated with a better structural similarity between fructose 6-phosphate (Fru-6-P) and compounds H, I and J.

3. Experimental

3.1. General Methods

All starting materials and reagents were commercially available and used without further purification except as indicated. \(^1\)H-NMR (300 MHz) and \(^13\)C-NMR (75 MHz) spectra was recorded in CDCl\(_3\) or DMSO-\(d_6\) with a Bruker DPX300 spectrometer, using TMS as internal standard; Mass spectra were obtained with Agilent 1100 series LC/MSD mass spectrometer. High-resolution mass spectra (HRMS) was performed by the Peking University. Melting points were measured on a Yanagimoto melting-point apparatus and are uncorrected.

3.2. Chemical Synthesis

General Procedure for the Syntheses of Title Compounds F, G, H, I and J. Substituted aldehydes A and B were prepared from D-glucose as the starting material according to known methods [20–22]. Substituted thiosemicarbazides C were synthesized from amines as previously described [33,39].
General Procedure for the Synthesis of Intermediate Compounds D/E. A solution of aldehyde A/B (5.5 mmol) and thiosemicarbazide C (5 mmol) in CH₂Cl₂ (100 mL) was heated to reflux for 6 h, at the end of which time TLC (eluent: 2:1 petroleum ether-EtOAc) indicated that the reaction was complete. The solvent was evaporated under diminished pressure at 40 °C to give a white solid, and the crude product was used for next step directly without purification.

General Procedure for the Synthesis of Title Compounds F/G. To a stirred solution of compound D/E (5.0 mmol) in CHCl₃ (80 mL) was added MnO₂ (10 g). The mixture was stirred for a further 1 h, at the end of which time TLC (eluent: 2:1 petroleum ether-EtOAc) indicated that the reaction was complete. After filtration, the filtrate was evaporated under reduced pressure to give a crude product, which was purified on silica gel column chromatography with 4:1 petroleum ether-EtOAc as the eluent to give the compounds F/G.

2-(4-Bromophenylamino)-5-(2R,3S-O-isopropylidene-4S-O-acetyl-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazole (F-1). Yield: 79%. White solid, mp 239.1–240.2 °C. ¹H-NMR (DMSO-d₆): δ 10.61 (s, 1H, NH), 7.62 (d, J = 8.9 Hz, 2H, ArH), 7.52 (d, J = 8.9 Hz, 2H, ArH), 6.07 (d, J = 3.7 Hz, 1H, H-1), 5.54 (d, J = 3.0 Hz, 1H, H-3), 5.28 (d, J = 3.0 Hz, 1H, H-4), 4.79 (d, J = 3.7 Hz, 1H, H-2), 2.02 (s, 3H, CH₃CO), 1.52, 1.31 (2s, 6H, Me₂C); ¹³C-NMR (DMSO-d₆) δ 168.82, 165.18, 154.23, 139.71, 131.74, 119.36, 113.27, 111.85, 104.36, 82.63, 76.51, 76.30, 26.33, 25.93, 20.61. ESI-MS m/z calcd. for C¹⁷H¹⁷BrN₃O₅S (M-H) 454.0. Found: 454.0. HRMS for C¹⁷H₁⁹BrN₃O₅S [M+H] + 456.0223. Found: 456.0212.

2-(4-Tolylamino)-5-(2R,3S-O-isopropylidene-4S-O-acetyl-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazole (F-2). Yield: 82%. Pale-yellow solid, mp 227.6–228.0 °C. ¹H-NMR (CDCl₃): δ 10.42 (br, 1H, NH), 7.33-7.27 (m, 2H, ArH), 7.19 (m, 2H, ArH), 6.03 (d, J = 3.6 Hz, 1H, H-1), 5.72 (d, J = 3.1 Hz, 1H, H-3), 5.48 (d, J = 3.1 Hz, 1H, H-4), 4.65 (d, J = 3.7 Hz, 1H, H-2), 2.34 (s, 3H, Ar-CH₃), 2.00 (s, 3H, CH₃CO), 1.59, 1.36 (2s, 6H, Me₂C); ¹³C-NMR (CDCl₃) δ 169.01, 138.05, 133.25, 130.13, 118.45, 112.86, 104.77, 83.30, 77.26, 76.92, 26.75, 26.22, 20.79. ESI-MS m/z calcd. for C₁₈H₂₁N₃NaO₅S (M+Na) 414.1. Found: 414.2. HRMS for C₁₈H₂₂N₃O₅S [M+H]+ 392.1275. Found: 392.1275.

2-(4-Methoxyphenylamino)-5-(2R,3S-O-isopropylidene-4S-O-acetyl-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazoles (F-3). Yield: 73%. Yellow solid, mp 186.7–188.0 °C. ¹H-NMR (DMSO-d₆): δ 10.28 (br, 1H, NH), 7.52 (d, J = 8.9 Hz, 2H, ArH), 6.93 (d, J = 8.9 Hz, 2H, ArH), 6.05 (d, J = 3.8 Hz, 1H, H-1), 5.50 (d, J = 3.0 Hz, 1H, H-3), 5.26 (d, J = 3.1 Hz, 1H, H-4), 4.76 (d, J = 3.8 Hz, 1H, H-2), 3.73 (s, 3H, Ar-CH₃O), 2.02 (s, 3H, CH₃CO), 1.51, 1.30 (2s, 6H, Me₂C); ¹³C-NMR (CDCl₃) δ 169.08, 156.67, 133.90, 121.40, 114.97, 112.97, 104.83, 83.34, 77.29, 77.00, 55.61, 26.81, 26.29, 20.88. ESI-MS m/z calcd. for C₁₈H₂₂N₃O₆S [M+H]+ 408.1. Found: 408.1. HRMS for C₁₈H₂₂N₃O₆S [M+H]+ 408.1224. Found: 408.1218.

2-(2,4-Dimethylphenylamino)-5-(2R,3S-O-isopropylidene-4S-O-acetyl-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazols (F-4). Yield: 81%. White solid, mp 155.9–156.1 °C. ¹H-NMR (CDCl₃): δ 7.79 (br, 1H, NH), 7.29 (d, J = 8.0 Hz, 1H, ArH), 7.10–7.00 (m, 2H, ArH), 5.97 (d, J = 3.6 Hz, 1H, H-1), 5.65 (d, J = 3.1 Hz, 1H, H-3), 5.43 (d, J = 3.1 Hz, 1H, H-4), 4.61 (d, J = 3.7 Hz, 1H, H-2), 2.32 (2s, 6H,
Ar-CH₃), 1.98 (s, 3H, CH₂CO), 1.56, 1.34 (2s, 6H, Me₂C); ¹³C-NMR (CDCl₃) δ 172.26, 168.97, 152.98, 137.24, 136.09, 132.52, 132.10, 127.69, 123.01, 112.83, 104.71, 83.26, 77.28, 76.93, 26.75, 26.25, 20.93, 20.78, 17.89. ESI-MS m/z calcd. for C₁₀H₁₄N₃O₃S [M+H] 406.1. Found: 406.1. HRMS for C₁₉H₂₄N₄O₅S [M+H]+ 406.1431. Found: 406.1422.

2-(3,4-Dichlorophenylamino)-5-(2R,3S-O-isopropylidene-4S-O-acetyl-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazole (F-5). Yield: 83%. White solid, mp 232.6–235.0 °C. ¹H-NMR (DMSO-d₆): δ 10.79 (s, 1H, NH), 8.07 (d, J = 2.5 Hz, 1H, ArH), 7.59 (d, J = 8.8 Hz, 1H, ArH), 7.49 (dd, J = 8.9, 2.5 Hz, 1H, ArH), 6.08 (d, J = 3.7 Hz, 1H, H-1), 5.56 (d, J = 3.1 Hz, 1H, H-3), 5.30 (d, J = 3.1 Hz, 1H, H-4), 4.79 (d, J = 3.8 Hz, 1H, H-2), 2.02 (s, 3H, CH₃CO), 1.52, 1.31 (2s, 6H, Me₂C); ¹³C-NMR (CDCl₃) δ 168.81, 164.87, 154.87, 140.24, 131.30, 130.72, 123.15, 118.55, 117.53, 111.88, 104.40, 82.63, 76.47, 76.29, 26.32, 25.91, 20.59. ESI-MS m/z calcd. for C₁₇H₁₈Cl₂N₃O₅S [M+H]+ 446.0. Found: 446.1. HRMS for C₁₇H₁₈Cl₂N₃O₅S [M+H]+ 446.0339. Found: 446.0330.

2-(2,5-Dichlorophenylamino)-5-(2R,3S-O-isopropylidene-4S-O-acetyl-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazole (F-6). Yield: 85%. White solid, mp 119.6–120.6 °C. ¹H-NMR (CDCl₃): δ 8.22 (d, J = 2.3 Hz, 1H, ArH), 7.69 (s, 1H, NH), 7.33 (d, J = 8.5 Hz, 1H, ArH), 7.00 (dd, J = 8.5, 2.4 Hz, 1H, ArH), 6.05 (d, J = 3.6 Hz, 1H, H-1), 5.73 (d, J = 3.1 Hz, 1H, H-3), 5.50 (d, J = 3.1 Hz, 1H, H-4), 4.68 (d, J = 3.6 Hz, 1H, H-3), 2.04 (s, 3H, CH₃CO), 1.59, 1.36 (2s, 6H, Me₂C); ¹³C-NMR (CDCl₃) δ 169.02, 165.30, 156.89, 137.41, 133.82, 130.28, 123.74, 120.59, 119.02, 113.09, 104.92, 83.30, 77.18, 77.04, 26.80, 26.27, 20.83. ESI-MS m/z calcd. for C₁₇H₁₈Cl₂N₃O₅S [M+H]+ 446.0. Found: 446.1. HRMS for C₁₇H₁₈Cl₂N₃O₅S [M+H]+ 446.0339. Found: 446.0329.

2-(Naphthalen-1-ylamino)-5-(2R,3S-O-isopropylidene-4S-O-acetyl-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazole (F-7). Yield: 65%. Pale-yellow solid, mp 186.1–186.9 °C. ¹H-NMR (DMSO-d₆): δ 8.13 (m, 1H, ArH). 7.95 (m, 1H, ArH), 7.72 (d, J = 8.2 Hz, 1H, ArH), 7.64–7.50 (m, 3H, ArH), 6.06 (d, J = 3.8 Hz, 1H, H-1), 5.54 (d, J = 3.1 Hz, 1H, H-3), 5.29 (d, J = 3.1 Hz, 1H, H-4), 4.78 (d, J = 3.8 Hz, 1H, H-2), 2.01 (s, 3H, CH₃CO), 1.52, 1.30 (2s, 6H, Me₂C); ¹³C-NMR (DMSO-d₆) δ 168.83, 167.94, 153.96, 136.33, 133.93, 128.33, 126.21, 126.01, 125.95, 125.90, 124.06, 121.99, 117.28, 111.79, 104.30, 82.61, 76.59, 76.28, 26.32, 25.92, 20.61. ESI-MS m/z calcd. for C₇₁H₁₈Cl₂N₃O₅S [M+H]+ 428.1. Found: 428.1. HRMS for C₇₁H₁₈Cl₂N₃O₅S [M+H]+ 428.1275. Found: 428.1263.

2-(4-Chloro-3-(trifluoromethyl)phenylamino)-5-(2R,3S-O-isopropylidene-4S-O-acetyl-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazole (F-8). Yield: 77%. Pale-yellow solid, mp 219.8–221.5 °C. ¹H-NMR (DMSO-d₆): δ 9.10 (s, 1H, NH), 8.25 (d, J = 2.5 Hz, 1H, ArH), 7.86 (dd, J = 8.8, 2.5 Hz, 1H, ArH), 7.69 (d, J = 8.8 Hz, 1H, ArH), 6.09 (d, J = 3.7 Hz, 1H, H-1), 5.57 (d, J = 3.1 Hz, 1H, H-3), 5.30 (d, J = 3.1 Hz, 1H, H-4), 4.80 (d, J = 3.7 Hz, 1H, H-2), 2.02 (s, 3H, CH₃CO), 1.52, 1.31 (2s, 6H, Me₂C); ¹³C-NMR (DMSO-d₆) δ 168.84, 164.88, 155.12, 139.63, 132.26, 126.99 (q, J = 30.7 Hz), 124.53, 122.25 (d, J = 1.7 Hz), 122.11, 120.91, 116.03 (q, J = 5.5 Hz), 111.91, 104.43, 82.63, 76.39 (d, J = 11.6 Hz), 26.32, 25.92, 20.57. ESI-MS m/z calcd. for C₁₉H₁₈Cl₂F₃N₃O₅S [M+H]+ 480.1. Found: 480.1. HRMS for C₁₉H₁₈Cl₂F₃N₃O₅S [M+H]+ 480.0602. Found: 480.0588.
2-(Phenylamino)-5-(2R,3S-O-isopropylidene-4S-O-acetyl-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazole (F-9). Yield: 78%. Pale-yellow solid, mp 213.7–214.1 °C. 1H-NMR (DMSO-d6): δ 10.63 (s, 1H, NH), 7.41-7.39 (m, 4H, ArH), 7.11 (m, 1H, ArH), 6.04 (d, J = 3.6 Hz, 1H, H-1), 5.74 (d, J = 3.1 Hz, 1H, H-3), 5.51 (d, J = 3.1 Hz, 1H, H-4), 4.66 (d, J = 3.7 Hz, 1H, H-2), 2.00 (s, 3H, CH3CO), 1.60, 1.36 (2s, 6H, Me2C); 13C-NMR (DMSO-d6) δ 168.84, 165.55, 153.68, 140.43, 129.05, 121.97, 117.43, 111.82, 104.33, 82.62, 76.54, 76.30, 26.32, 25.93, 20.61. ESI-MS m/z calcd. for C17H20N3O5S [M+H]+ 378.1. Found: 378.1. HRMS for C17H20N3O5S [M+H]+ 378.1118. Found: 378.1109.

2-(4-Nitrophenylamino)-5-(2R,3S-O-isopropylidene-4S-O-acetyl-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazole (F-10). Yield: 73%. Pale-yellow solid, mp 233.9–235.5 °C. 1H-NMR (DMSO-d6): δ 11.22 (s, 1H, NH), 8.27 (d, J = 8.7 Hz, 2H, ArH), 7.85 (d, J = 8.7 Hz, 2H, ArH), 6.10 (d, J = 3.4 Hz, 1H, H-1), 5.59 (d, J = 2.6 Hz, 1H, H-3), 5.32 (d, J = 2.6 Hz, 1H, H-4), 4.80 (d, J = 3.5 Hz, 1H, H-2), 2.02 (s, 3H, CH3CO), 1.53, 1.31 (2s, 6H, Me2C); 13C-NMR (DMSO-d6) δ 140.67, 140.58, 135.82, 131.70, 129.82, 126.04, 120.62, 114.07, 111.49, 104.28, 82.40, 77.78, 77.07, 26.10, 25.71, 20.36. ESI-MS m/z calcd. for C17H17N4O7S (M-H) 421.1. Found: 421.0. HRMS for C17H16N4O7S [M+H]+ 423.0969. Found: 423.0957.

2-(4-Bromophenylamino)-5-(2R,3S-O-isopropylidene-4S-O-allyl-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazol (G-1). Yield: 68%. Pale-yellow solid, mp 204.1–204.7 °C. 1H-NMR (CDCl3): δ 10.50 (br, 1H, NH), 7.49-7.46 (m, 2H, ArH), 7.36-7.26 m, 2H, ArH), 6.04 (d, J = 3.6 Hz, 1H, H-1), 5.72 (m, 1H, CH2=CHCH2), 5.63 (d, J = 3.1 Hz, 1H, H-3), 5.23-5.14 (m, 2H, CH2=CHCH2), 4.69 (d, J = 3.7 Hz, 1H, H-2), 4.15 (d, J = 3.2 Hz, 1H, H-4), 4.04-3.86 (m, 2H, CH2=CHCH2), 1.58, 1.37 (2s, 6H, Me2C); 13C-NMR (DMSO-d6) δ 168.62, 164.27, 155.82, 145.85, 140.67, 125.20, 116.75, 111.69, 104.22, 82.40, 76.22, 76.07, 26.10, 25.71, 20.36. ESI-MS m/z calcd. for C18H16BrN3O3S (M-H) 452.0. Found: 451.9. HRMS for C18H16BrN3O3S [M+H]+ 454.0431. Found: 454.0415.

2-(4-Tolylamino)-5-(2R,3S-O-isopropylidene-4S-O-allyl-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazole (G-2). Yield: 74%. Pale-yellow solid, mp 187.9–188.1 °C. 1H-NMR (CDCl3): δ 9.39 (br, 1H, NH), 7.29-7.26 (m, 2H, ArH), 7.18-7.16 (m, 2H, ArH), 6.02 (d, J = 3.7 Hz, 1H, H-1), 5.73 (m, 1H, CH2=CHCH2), 5.62 (d, J = 3.1 Hz, 1H, H-3), 5.23-5.13 (m, 2H, CH2=CHCH2), 4.67 (d, J = 3.6 Hz, 1H, H-2), 4.14 (d, J = 3.1 Hz, 1H, H-4), 4.02-3.85 (m, 2H, CH2=CHCH2). 2.33 (s, 3H, Ar-CH3), 1.56, 1.36 (2s, 6H, Me2C); 13C-NMR (DMSO-d6) δ 166.13, 154.21, 138.20, 134.08, 130.77, 129.40, 117.46, 117.11, 111.34, 104.44, 81.82, 71.78, 77.57, 70.44, 26.52, 25.96, 20.28. ESI-MS m/z calcd. for C19H24N3O3S [M+H]+ 390.1. Found: 390.1. HRMS for C19H24N3O3S [M+H]+ 390.1482. Found: 390.1468.

2-(4-Methoxyphenylamino)-5-(2R,3S-O-isopropylidene-4S-O-allyl-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazole (G-3). Yield: 78%. Pale-yellow solid, mp 177.7–178.7 °C. 1H-NMR (CDCl3): δ 9.70 (br, 1H, NH), 7.35–7.26 (m, 2H, ArH), 6.93–6.90 (m, 2H, ArH), 6.01 (d, J = 3.5 Hz, 1H, H-1), 5.72 (m, 1H, CH2=CHCH2), 5.59 (d, J = 3.0 Hz, 1H, H-3), 5.22–5.13 (m, 2H, CH2=CHCH2), 4.66 (d, J = 3.6 Hz, 1H, H-2), 4.13 (d, J = 3.0 Hz, 1H, H-4), 4.01–3.85 (m, 2H, CH2=CHCH2), 3.81 (s, 3H, Ar-CH3O), 1.56, 1.35 (2s, 6H, Me2C); 13C-NMR (DMSO-d6) δ 166.58, 154.53, 153.85, 134.12, 134.08, 119.21, 117.11, 114.26, 111.35, 104.39, 81.83, 77.65, 70.43, 55.19, 26.52, 25.96. ESI-MS m/z calcd. for C19H24N3O3S [M+H]+ 406.1. Found: 406.2. HRMS for C19H24N3O3S [M+H]+ 406.1431. Found: 406.1417.
2-(2,4-Dimethylphenylamino)-5-(2R,3S-O-isopropylidene-4S-O-allyl-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazole (G-4). Yield: 76%. Pale-yellow solid, mp 133.7–134.3 °C. ¹H-NMR (CDCl₃): δ 9.41 (s, 1H, NH), 7.58 (d, J = 9.0 Hz, 1H, ArH), 7.04–6.99 (m, 2H, ArH), 5.96 (d, J = 3.7 Hz, 1H, H-1), 5.82 (m, 1H, CH₂=CHCH₂), 5.53 (d, J = 3.1 Hz, 1H, H-3), 5.22–5.10 (m, 2H, CH₂=CHCH₂), 4.79 (d, J = 3.7 Hz, 1H, H-2), 4.07 (d, J = 3.1 Hz, 1H, H-4), 4.12–3.87 (m, 2H, CH₂=CHCH₂), 2.25, 2.21 (2s, 6H, Ar-CH₃), 1.46,1.29 (2s, 6H, Me₂C); ¹³C-NMR (DMSO-d₆) δ 168.89, 154.03, 136.75, 134.08, 133.48, 131.25, 129.92, 127.02, 122.20, 117.03, 111.29, 104.33, 81.83, 77.67, 70.40, 26.51, 25.95, 20.34, 17.72. ESI-MS m/z calcd. for C₂₀H₂₆N₃O₄S [M+H]⁺ 404.1. Found: 404.1. HRMS for C₂₀H₂₆N₃O₄S [M+H]⁺ 404.1639. Found: 404.1624.

2-(3,4-Dichlorophenylamino)-5-(2R,3S-O-isopropylidene-4S-O-allyl-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazole (G-5). Yield: 81%. Pale-yellow solid, mp 147.7–148.5 °C. ¹H-NMR (CDCl₃): δ 10.77 (s, 1H, NH), 7.59 (s, 1H, ArH), 7.44 (m, 1H, ArH), 7.34 (m, 1H, ArH), 6.06 (d, J = 3.5 Hz, 1H, H-1), 5.74 (m, 1H, CH₂=CHCH₂), 5.65 (s, 1H, H-3), 5.24–5.15 (m, 2H, CH₂=CHCH₂), 4.71 (d, J = 3.5 Hz, 1H, H-2), 4.42–3.82 (m, 3H, H-4, CH₂=CHCH₂), 1.59, 1.38 (2s, 6H, Me₂C); ¹³C-NMR (DMSO-d₆) δ 165.25, 155.74, 140.37, 134.01, 131.25, 130.73, 122.95, 118.44, 117.48, 117.16, 111.41, 104.47, 81.79, 81.75, 77.50, 70.42, 26.51, 25.94. ESI-MS m/z calcd. for C₁₈H₂₀Cl₂N₃O₄S [M+H]⁺ 444.0. Found: 444.0. HRMS for C₁₈H₂₀Cl₂N₃O₄S [M+H]⁺ 444.0546. Found: 444.0526.

2-(2,5-Dichlorophenylamino)-5-(2R,3S-O-isopropylidene-4S-O-allyl-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazole (G-6). Yield: 76%. Pale-yellow solid, mp 61.8–62.9 °C. ¹H-NMR (CDCl₃): δ 8.21 (m, 1H, ArH), 7.73 (br, 1H, NH), 7.30 (m, 1H, ArH), 6.98 (m, 1H, ArH), 6.05 (d, J = 3.6 Hz, 1H, H-1), 5.74 (m, 1H, CH₂=CHCH₂), 5.63 (d, J = 3.2 Hz, 1H, H-3), 5.25–5.16 (m, 2H, CH₂=CHCH₂), 4.70 (d, J = 3.6 Hz, 1H, H-2), 4.18 (d, J = 3.2 Hz, 1H, H-4), 4.05–3.87 (m, 2H, CH₂=CHCH₂), 1.57, 1.37 (2s, 6H, Me₂C); ¹³C-NMR (DMSO-d₆) δ 165.69, 157.21, 138.18, 134.05, 132.07, 130.79, 122.92, 120.35, 119.94, 117.16, 111.42, 104.50, 81.83, 77.66, 70.45, 26.52, 25.96. ESI-MS m/z calcd. for C₁₈H₂₀Cl₂N₃O₄S [M+H]⁺ 444.0. Found: 444.0. HRMS for C₁₈H₂₀Cl₂N₃O₄S [M+H]⁺ 444.0546. Found: 444.0527.

2-(Naphthalen-1-ylamino)-5-(2R,3S-O-isopropylidene-4S-O-allyl-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazole (G-7). Yield: 68%. Pale-yellow solid, mp 57.0–58.1 °C. ¹H-NMR (CDCl₃): δ 10.28 (br, 1H, NH), 8.23 (m, 1H, ArH), 8.12 (m, 1H, ArH), 7.95 (m, 1H, ArH), 7.00 (m, 1H, ArH), 7.58–7.49 (m, 3H, ArH), 5.98 (d, J = 3.6 Hz, 1H, H-1), 5.78 (m, 1H, CH₂=CHCH₂), 5.37 (d, J = 3.1 Hz, 1H, H-3), 5.22–5.10 (m, 2H, CH₂=CHCH₂), 4.81 (d, J = 3.7 Hz, 1H, H-2), 4.14–3.64 (m, 3H, H-4, CH₂=CHCH₂), 1.48, 1.30 (2s, 6H, Me₂C); ¹³C-NMR (DMSO-d₆) δ 168.27, 154.99, 136.47, 134.05, 133.94, 128.30, 126.18, 126.03, 125.93, 125.83, 123.88, 122.04, 117.10, 111.36, 104.42, 81.85, 77.71, 70.44, 26.53, 25.97. ESI-MS m/z calcd. for C₂₂H₂₄N₃O₄S [M+H]⁺ 426.1. Found: 426.1. HRMS for C₂₂H₂₄N₃O₄S [M+H]⁺ 426.1482. Found: 426.1462.

2-(4-Chloro-3-(trifluoromethyl)phenylamino)-5-(2R,3S-O-isopropylidene-4S-O-allyl-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazole (G-8). Yield: 86%. Pale-yellow solid, mp 140.0–141.2 °C. ¹H-NMR (CDCl₃): δ 10.54 (s, 1H, NH), 7.81 (m, 1H, ArH), 7.63–7.48 (m, 2H, ArH), 6.05 (d, J = 3.5 Hz, 1H, H-1), 5.74 (m, 1H, CH₂=CHCH₂), 5.64 (d, J = 3.1 Hz, 1H, H-3), 5.24–5.15 (m, 2H, CH₂=CHCH₂), 4.71 (d, J = 3.5 Hz, 1H, H-2), 4.17 (d, J = 3.0 Hz, 1H, H-4), 4.07–3.87 (m, 2H, CH₂=CHCH₂), 1.59, 1.38 (2s,
6H, Me₂C); ¹³C-NMR (DMSO-d₆) δ 165.26, 155.95, 139.76, 134.01, 132.21, 126.96 (q, J = 30.6 Hz), 124.53, 122.06 (d, J = 1.9 Hz), 122.01, 120.91, 117.13, 115.94 (q, J = 5.6 Hz), 111.44, 104.51, 81.81 (d, J = 2.1 Hz), 77.53, 70.45, 26.50, 25.93. ESI-MS m/z calcd. for C₁₉H₂₀ClF₃N₃O₄S [M+H] 478.1. Found: 478.2. HRMS for C₁₉H₂₀ClF₃N₃O₄S [M+H]+ 478.0810. Found: 478.0802.

2-(Phenylamino)-5-(2R,3S-O-isopropylidene-4S-O-allyl-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazole (G-9). Yield: 91%. Pale-yellow solid, mp 195.1–195.5 °C. ¹H-NMR (CDCl₃): δ 10.66 (s, 1H, NH), 7.46–7.35 (m, 4H, ArH), 7.09 (m, 1H, ArH), 6.04 (d, J = 3.6 Hz, 1H, H-1), 5.73 (m, 1H, CH₂=CHCH₂), 5.65 (d, J = 3.1 Hz, 1H, H-3), 5.23–5.13 (m, 2H, CΗ₂=CHCH₂), 4.69 (d, J = 3.6 Hz, 1H, H-2), 4.16 (d, J = 3.1 Hz, 1H, H-4), 4.13–3.86 (m, 2H, CH₂=CHCΗ₂), 1.58, 1.37 (2s, 6H, Me₂C); ¹³C-NMR (DMSO-d₆) δ 165.96, 154.62, 140.58, 134.06, 129.01, 117.35, 117.11, 111.37, 104.43, 81.82, 77.62, 70.43, 26.52, 25.97. ESI-MS m/z calcd. for C₁₈H₂₁N₃O₄SNa (M+Na) 398.1. Found: 398.1. HRMS for C₁₈H₂₂N₃O₄S [M+H]+ 376.1326. Found: 376.1323.

2-(4-Nitrophenylamino)-5-(2R,3S-O-isopropylidene-4S-O-allyl-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazole (G-10). Yield: 71%. Pale-yellow solid, mp 198.4–198.7 °C. ¹H-NMR (CDCl₃): δ 11.75 (s, 1H, NH), 8.33–8.28 (m, 2H, ArH), 7.62–7.57 (m, 2H, ArH), 6.08 (d, J = 3.6 Hz, 1H, H-1), 5.80–5.69 (m, 2H, CH₂=CHCH₂, H-3), 5.25–5.15 (m, 2H, CΗ₂=CHCH₂), 4.74 (d, J = 3.7 Hz, 1H, H-2), 4.21 (d, J = 3.2 Hz, 1H, H-4), 4.16-3.89 (m, 2H, CH₂=CHCΗ₂), 1.62, 1.40 (2s, 6H, Me₂C); ¹³C-NMR (DMSO-d₆) δ 164.86, 156.82, 146.19, 140.78, 134.00, 125.32, 117.16, 116.84, 111.48, 104.55, 81.85, 81.79, 77.54, 70.49, 26.49, 25.91. ESI-MS m/z calcd. for C₁₈H₂₁N₄O₆S [M+H] 421.1. Found: 421.1. HRMS for C₁₈H₂₁N₄O₆S [M+H]+ 421.1176. Found: 421.1173.

2-(4-Chloro-3-(trifluoromethyl)phenylamino)-5-(2R,3S-O-isopropylidene-4S-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazole (H). To a solution of F-8 (0.48 g, 1.0 mmol) in MeOH (20 mL) was added MeONa (0.05 g). The reaction mixture was stirred at rt for 0.5 h, at the end of which time TLC (1:2 petroleum ether–EtOAc) indicated that the reaction was complete. Neutralization of the reaction mixture with acidic ion exchange resin (Amberlite IR-120 (H +), Alfa Aesar, Tianjin, China) was conducted, and the organic phase was concentrated under reduced pressure to give a crude product, which could be purified by recrystallization from a mixture solvents of petroleum ether (10 mL) and EtOAc (2 mL). Yield: 92%. White solid, mp 249.8–250.3 °C. ¹H-NMR (DMSO-d₆): δ 10.84 (s, 1H, NH), 8.26 (d, J = 2.5 Hz, 1H, ArH), 7.86 (dd, J = 2.5, 8.8 Hz, 2H, ArH), 7.68 (d, J = 8.8 Hz, 1H, ArH), 6.01 (d, 1H, J = 3.6 Hz, 1H, H-1), 5.98 (d, J = 5.2 Hz, 1H, OH), 5.33 (d, J = 2.7 Hz, 1H, H-4), 4.60 (d, J = 3.6 Hz, 1H, H-2), 4.68 (dd, J = 3.6 Hz, 5.2 Hz, 1H, H-3), 1.48, 1.29 (2s, 6H, Me₂C); ¹³C-NMR (DMSO-d₆) δ 165.13, 156.93, 139.88, 132.26, 127.00 (q, J = 30.7 Hz), 124.58, 121.97, 120.96, 115.93 (q, J = 5.6 Hz), 111.33, 104.52, 84.86, 78.49, 74.58, 26.66, 26.01. ESI-MS m/z calcd. for C₁₆H₁₆ClF₃N₃O₄S [M+H]+ 438.0. Found: 438.0. HRMS for C₁₆H₁₆ClF₃N₃O₄S[M+H]+ 438.0497. Found: 438.0478.

2-(4-Chloro-3-(trifluoromethyl)phenylamino)-5-(3S,4S-O-acetyl-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazole (I). A solution of F-8 (0.48 g, 1.0 mmol) and CF₃COOH (9 mL) and H₂O (1 mL) was stirred at rt for 12 h, at the end of which time TLC (1:2 petroleum ether-EtOAc) indicated that the reaction was complete. The reaction mixture was neutralized with solid NaHCO₃, and filtered through
Celite. The filtrate was evaporated under reduced pressure to give a crude product, which was purified on silica gel column chromatography with 1:1 petroleum ether-EtOAc as the eluent to give the compound. Yield: 79%. Pale-yellow solid, mp 115.6–116.5 °C. \(^1\)H-NMR (DMSO-\(d_6\)): \(\delta\) 10.87 (d, \(J = 12.2\) Hz, 1H, NH), 8.26 (d, \(J = 2.6\) Hz, 1H, ArH), 7.83 (dd, \(J = 2.6, 8.8\) Hz, 2H, ArH), 7.68 (d, \(J = 8.8\) Hz, 1H, ArH), 7.05 (br, 1H, OH), 5.89 (br, 1H, OH), 5.55–5.52 (m, 1H, H-1), 5.40–5.26 (m, 1H, H-3), 5.19–5.17 (m, 1H, H-4), 4.13–4.00 (m, 1H, H-2), 1.92 (s, 3H, OCH\(_3\)). ESI-MS \(m/z\) calcd. for C\(_{15}\)H\(_{12}\)ClF\(_3\)N\(_3\)O\(_5\)S (M-H) 438.0. Found: 438.0. HRMS for C\(_{15}\)H\(_{14}\)ClF\(_3\)N\(_3\)O\(_5\)S \([M+H]^{+}\) 440.0289. Found: 440.0272.

2-(Naphthalen-1-ylamino)-5-(3S,4S-O-acetyl-tetrahydrofuro-2,3,4-triol-5S)-1,3,4-thiadiazole (J). Deisopropylidenation of G-7 (0.52 g, 1.2 mmol) was accomplished by following the same procedure employed for the preparation of compound J. Yield: 73%. Yellow solid, mp 57.2–59.7 °C. \(^1\)H-NMR (DMSO-\(d_6\)): \(\delta\) 10.19 (s, 1H, NH), 8.24–8.22 (m, 1H, ArH), 8.09 (d, \(J = 7.4\) Hz, 1H, ArH), 7.97–7.94 (m, 1H, ArH), 7.70 (d, \(J = 8.1\) Hz, 1H, ArH), 7.58–7.49 (m, 3H, ArH), 5.77–5.70 (m, 1H, CH\(_2\)=CHCH\(_2\)), 5.57 (d, \(J = 4.3\) Hz, 0.5H), 5.43–5.28 (m, 2H), 5.20–5.05 (m, 2.5H), 4.01–3.87 (m, 4H). ESI-MS \(m/z\) calcd. for C\(_{19}\)H\(_{20}\)N\(_3\)O\(_4\)S \([M+H]^{+}\) 386.1. Found: 386.0. HRMS for C\(_{19}\)H\(_{20}\)N\(_3\)O\(_4\)S \([M+H]^{+}\) 386.1169. Found: 386.1169.

### 3.3. Fungicidal Assays

Each of the test compounds was dissolved in DMSO (10 mL). Fungicidal activities of compounds F, G, H, I and J against Sclerotinia sclerotiorum (Lib.) de Bary, Phytophthora parasitica Dast, Botrytis cinerea Pers., Rhizoctonia solani Kühn., Pyricularia oryzae Cav. and Phoma asparagi Saecrdo were evaluated using the mycelium growth rate test as previously reported [40].

Inhibition rates of compounds F and G against S. sclerotiorum, P. Parasitica Dast, B. cinerea, R solani, P. oryzae Cav and P. asparagi Saecrdo at 50 μg/mL were determined first and the results are given in Table 2. The inhibition rate of compounds F, G, H, I and J against S. sclerotiorum were further determined at the concentrations of 50, 20, 10, 5 and 2 μg/mL, respectively. Then EC\(_{50}\) and EC\(_{90}\) values were estimated using logit analysis [41]. The commercial fungicide chlorothalonil was used as a control in the above bioassay.

### 3.4. Enzyme Inhibitory Activities Bioassay

Inhibitory activities of all the synthesized compounds towards Candida albicans GlcN-6-P synthase were evaluated using the mycelium growth rate test as previously reported [38]. Three replicates were performed. Absorbance at \(\lambda = 585\) nm was measured and GlcN-6-P concentration in the sample was read from the standard curve (solutions of glucosamine-HCl (0.1–1 mM) were assayed simultaneously, to obtain a standard line from the plot of extinction against concentration of glucosamine). In each experiment, two control samples, one without enzyme and one without substrates, were assayed in the same way.
4. Conclusions

In summary, a series of novel glycosylthiadiazole derivatives were synthesized, and their bioactivities were evaluated. The bioassays showed that they had the inhibitory activities against glucosamine-6-phosphate synthase, and at the same time, the results from the Chinese Academy of Agricultural Science have shown that most of the tested compounds have good fungicidal activities against *S. sclerotiorum*. Among all the novel compounds tested, compounds F-5 and G-8 displayed better fungicidal activities than the commercial fungicide chlorothalonil. The SAR of the designed compounds was studied: compounds with two electron-withdrawing substituents in the benzene ring have better fungicidal activities than those with two electron-donating substituents. The compounds with the protecting groups in the sugar ring have less inhibitory activities against Glms than those without protecting groups, but displayed better fungicidal activities against *S. sclerotiorum*, and the advantage depends on the number and type of the protection groups. Further studies are in progress.

Supplementary Materials

Supplementary materials can be accessed at: http://www.mdpi.com/1420-3049/19/6/7832/s1.

Acknowledgments

We acknowledge financial support of this investigation by NSFC of China (21172257), the National High Technology Research and Development Programme of China (2011AA10A206), the National Basic Research Program of China (2010CB126105, 2011BAE06B02-01, 2012BAK25B03-01) and Key laboratory of Horticultural Crops Genetic Improvement, Ministry of Agriculture in China.

Author Contributions

Main text paragraph Guanghui Zong was in charge of the synthesis experiments, Hanqing Zhao was in charge of bioassay, they wrote the manuscript together; Rui Jiang provided help in the synthesis experiments and bioassay experiments; $^1$H and $^{13}$C-NMR spectra were tested by Xiaomei Liang; Jianjun Zhang provided guidance and suggestions for all the experiments and he also provided proper suggestions when wrote and revised the manuscript; Daoquan Wang provided guidance and suggestions in the synthesis experiments. Yanxia Shi and Baoju Li provided guidance and suggestions in the bioassay experiments.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Horii, S.; Kameda, Y.; Kawahara, K. Studies on validamycins, new antibiotics. VIII. Validamycins C, D, E and F. *J. Antibi ot*. 1972, 25, 48–53.
2. Asano, N.; Takeuchi, M.; Kameda, Y.; Matsui, K.; Kono, Y. Trehalase inhibitors, validoxylamine A and related compounds as insecticides. *J. Antibi ot*. 1990, 43, 722–726.
3. Kyosseva, S.V.; Kyossev, Z.N.; Elbein, A.D. Elbein, Inhibitors of pig kidney trehalase. *Arch. Biochem. Biophys.* **1995**, *316*, 821–826.

4. Schatz, A.; Bugie, E.; Waksman, S.A. Streptomycin, a substance exhibiting antibiotic activity against Gram-positive and Gram-negative bacteria. *Proc. Soc. Exp. Biol. Med.* **1944**, *55*, 66–69.

5. Hamada, M.; Hashimoto, T.; Takahashi, T.; Yokoyama, S.; Miyake, M.; Takeuchi, T.; Okami, Y.; Umezawa, H.A. Antimicrobial activity of kasugamycin. *J. Antibiot. Ser. A* **1965**, *18*, 104–106.

6. Geoffrey, H.; Davis, I. Avermectins and milbemycins Part I. *Chem. Soc. Rev.* **1991**, *20*, 211–260.

7. Chabala, J.C.; Fisher, M.H. Selective Hydrogenation Products of C-076 Compounds and Derivatives Thereof. U.S. Patent 4,199,569, 22 April 1980.

8. Mrozik, H.; Eskola, P.; Linn, B.O.; Lusi, A.; Shih, T.L.; Tischler, M.; Waksman, F.S.; Wyvratt, M.J.; Hilton, N.J. Discovery of novel avermectins with unprecedented insecticidal activity. *Experientia* **1989**, *45*, 315–316.

9. Gary, D.; Thomapson, R.D.; Thomas, C.S. Spinosad-a case study: An example from a natural products discovery programme. *Pest. Manag. Sci.* **2000**, *56*, 696–702.

10. Da Rocha, D.R.; Santos, W.C.; Lima, E.S.; Ferreira, V.F. Synthesis of 1,2,3-triazole glycoconjugates as inhibitors of α-glucosidases. *Carbohydr. Res.* **2012**, *350*, 14–19.

11. Zhang, P.; Wei, C.; Wang, E.; Wang, W.; Liu, M.; Yin, Q.; Chen, H.; Wang, K.; Li, X.; Zhang, J. Synthesis and biological activities of novel isoxazoline-linked pseudo-disaccharide derivatives. *Carbohydr. Res.* **2012**, *351*, 7–16.

12. Chen, H.; Jiao, L.; Guo, Z.; Li, X.; Ba, C.; Zhang, J. Synthesis and biological activity of novel thiazolidin-4-ones with a carbohydrate moiety. *Carbohydr. Res.* **2008**, *343*, 3015–3020.

13. Bokor, E.; Docsa, T.; Gergely, P.; Somsak, L. Synthesis of 1-(glucopyranosyl)-1,2,3-triazoles and their evaluation as glycogen phosphorylase inhibitors. *Bioorg. Med. Chem.* **2010**, *18*, 1171–1180.

14. Noolvi, M.; Patel, H.; Singh, N.; Gadad, A.; Cameotra, S.; Badiger, A. Synthesis and anticancer evaluation of novel 2-cyclopropylimidazo[2,1-b] [1,3,4]-thiadiazole derivatives. *Eur. J. Med. Chem.* **2010**, *46*, 4411–4418.

15. Shen, X.; Zhong, H.; Zheng, H.; Zhang, H.; Zhao, G.; Wu, Q.; Mao, H.; Wang, E.; Zhu, Y. Crystal structure, thermal decomposition kinetics and antimicrobial activities of [Zn(eatz)$_2$(OAc)$_2$] (eatz=5-ethyl-2-amino-1,3,4-thiadiazole). *Polyhedron* **2004**, *23*, 1851–1857.

16. Oruc, E.; Rollas, S.; Kandemirli, F.; Shvets, N.; Dimoglo, A. 1,3,4-Thiadiazole derivatives. Synthesis, structure elucidation, and structure-antituberculosis activity relationship investigation. *J. Med. Chem.* **2004**, *47*, 6760–6767.

17. Pattanayak, P.; Sharma, R. 2-Amino-5-sulphanyl-1,3,4-thiadiazole derivatives as anticonvulsant agents: Synthesis and evaluation. *Indian J. Chem. B.* **2011**, *49B*, 1531–1534.

18. Kadi, A.; Al-Abdullah, E.; Shehata, I.; Habib, E.; Ibrahim, T.; El-Emam, A. Synthesis, antimicrobial and anti-inflammatory activities of novel 5-(1-adamantyl)-1,3,4-thiadiazole derivatives. *Eur. J. Med. Chem.* **2010**, *45*, 5006–5011.

19. Schenone, S.; Brullo, C.; Bruno, O.; Bondavalli, F.; Ranise, A.; Filippelli, W.; Rinaldi, B.; Capuano, A.; Falcone, G. New 1,3,4-thiadiazole derivatives endowed with analgesic and anti-inflammatory activities. *Bioorg. Med. Chem.* **2006**, *14*, 1698–1705.
20. Chen, C.; Song, B.; Yang, S.; Xu, G.; Bhadury P.S.; Jin, L.; Hu, D.; Li, Q.; Liu, F.; Xue, W.; et al. Synthesis and antifungal activities of 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-thiadiazole and 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-oxadiazole derivatives. *Bioorg. Med. Chem.* 2007, 15, 3981–3989.
21. Niewiadomy, A.; Matysiak, J. Fungicidal evaluation of substituted 4-(1,3,4-thiadiazol-2-yl) benzene-1,3-diols. *Pestycydy* 2011, 1–4, 5–14.
22. Wan, R.; Zhang, J.; Han, F.; Wang, P.; Yu, P.; He, Q. Synthesis and insecticidal activities of novel 1,3,4-thiadiazole 5-fluorouracil acetamides derivatives: An RNA interference insecticide. *Nucleos. Nucleot. Nucleic Acids* 2011, 30, 280–292.
23. Wang, T.; Miao, W.; Wu, S.; Bing, G.; Zhang, X.; Qin, Z.; Yu, H.; Qin, X.; Fang, J. Synthesis, crystal structure, and herbicidal activities of 2-cyanoacrylates containing 1,3,4-thiadiazole moieties. *Chin. J. Chem.* 2011, 29, 959–967.
24. Chen, C.; Zhang, Z.; Du, M.; Wang, S.; Wang, Y. Synthesis of N-[(5-mercapto-1,3,4-thiadiazol-2-yl)amino]carbonyl[benzamide and 2-(phenoxy)-N-[(5-mercapto-1,3,4-thiadiazol-2-yl)amino]carbonyl]acetamide derivatives and determination of their activity as plant growth regulators. *Chin. J. Org. Chem.* 2007, 27, 1444–1447.
25. Chen, L.; Wang, D.; Jin, S. Synthesis and fungicidal activity of 2-(1,11-undecylidene)-5-substituted imino-Δ²⁻¹,3,4-thiadiazolines. *Chin. J. Appl. Chem.* 2002, 19, 212–215.
26. Yang, X.; Jin, S.; Yang, C.; Wang, D. Synthesis and fungicidal activity of 2-(1,5-pentamethylene)-5-substituted imino-Δ²⁻¹,3,4-thiadiazolines. *Chin. J. Pest. Sci.* 2004, 6, 22–25.
27. Li, J.; Liang, X.; Jin, S.; Zhang, J.; Yuan, H.; Qi, S.; Chen, F.; Wang, D. Synthesis, fungicidal activity, and structure-activity relationship of spiro-compounds containing macro lactam (macrolactone) and thiadiazoline rings. *J. Agric. Food Chem.* 2010, 58, 2659–2663.
28. Zhang, J.; Wang, D.; Yan, S.; Liang, X.; Wu, J. Preparation of Thiadiazoline and Furan Ring-Containing Spirocyclic Compounds as Fungicides. CN 101624396, 13 January 2010.
29. Zhang, J.; Zong, G.; Liang, X.; Wang, D. Preparation of Furanosyl-Modified 1,3,4-thiadiazole Derivatives as Agricultural Bactericides. CN 102153602, 24 February 2011.
30. Durand, P.; Golinelli-Pimpaneau, B.; Mouilleron, S.; Badet, B.; Badet-Denisot, M.A. Highlights of glucosamine-6P synthase catalysis. *Arch. Biochem. Biophys.* 2008, 474, 302–317.
31. Zou, X.J.; Lai, L.H.; Jin, G.Y.; Zhang, Z.X. Synthesis, fungicidal activity, and 3D-QSAR of pyridazinone-substituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles. *J. Agric. Food Chem.* 2002, 50, 3757–3760.
32. Kalidhar, U.; Kaur, A. 1,3,4-Thiadiazole derivatives and their biological activities: A review. *Res. J. Pharm. Biol. Chem. Sci.* 2011, 2, 1091–1106.
33. Han, M.J.; Yoo, K.S.; Kim, Y.H.; Chang, J.Y. Polymeric enzyme mimics: Catalytic activity of ribose-containing polymers for a phosphate substrate. *Org. Biomol. Chem.* 2003, 1, 2276–2282.
34. Olchowy, J.; Kur, K.; Sachadyn, P. Construction, purification, and functional characterization of his-tagged candida albicans glucosamine-6-phosphate synthase expressed in escherichia coli. *Protein Expr. Purif.* 2006, 46, 309–315.
35. Chittur, S.V.; Griffith, R.K. Multisubstrate analogue inhibitors of glucosamine-6-phosphate synthase from candida albicans. *Bioorg. Med. Chem. Lett.* 2002, 12, 2639–2642.
36. Bearne, S.L. Active site-directed inactivation of escherichia coli glucosamine-6-phosphate synthase. *J. Biol. Chem.* **1996**, *271*, 3052–3057.

37. Dias, D.F.; Roux, C.; Durand, P.; Iorga, B.; Badet-Denisot, M.A.; Badet, B.; Alves, R.J. Design, synthesis and *In Vitro* evaluation on glucosamine-6P synthase of aromatic analogs of 2-aminoheptitols-6P. *J. Braz. Chem. Soc.* **2010**, *21*, 680–685.

38. Zhao, H.Q.; Zhou, M.J.; Duan, L.F.; Wang, W.; Zhang, J.J.; Wang, D.Q.; Liang, X.M. Efficient Synthesis and Anti-Fungal Activity of Oleanolic Acid Oxime Esters. *Molecules* **2013**, *18*, 3615–3629.

39. Kaliappan, K.P.; Kumar, N. Efficient metathesis route to the B-ring of eleutherobin and other medium-sized cyclic ethers. *Tetrahedron* **2005**, *61*, 7461–7469.

40. Tisler, M. Syntheses in the 4-substituted thiosemicarbazide series. *Croat. Chem. Acta* **1956**, *28*, 147–154.

41. Li, X.H.; Yang, X.L.; Ling, Y.; Fan, Z.J.; Liang, X.M.; Wang, D.Q.; Chen, F.H.; Li, Z.M. Synthesis and fungicidal activity of novel 2-oxocycloalkylsulfonylureas. *J. Agric. Food Chem.* **2005**, *53*, 2202–2206.

*Sample Availability:* Samples of the compounds C-5, C-6, C-8, F-8 and G-8 are available from the authors.

© 2014 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0/).