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Design, Synthesis and Bioactivity of Novel Glycosylthiadiazole Derivatives

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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.
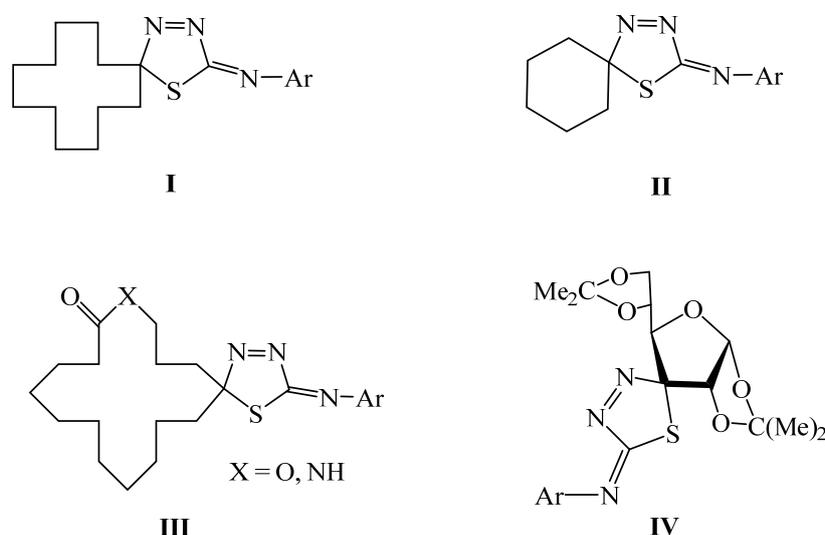
Considering the advantages of using carbohydrates in developing novel pesticides, we made some efforts to investigate the antifungal activities of 1,3,4-thiadiazoles modified by carbohydrates, and a series of thiadiazoline derivatives containing glucofuranose were synthesized in our laboratory [28]. The fungicidal activity results obtained showed that compound **IV** (Figure 1) exhibited excellent fungicidal activities against *Phytophtora 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.

Scheme 1. Synthesis of the target compounds **F/G**.
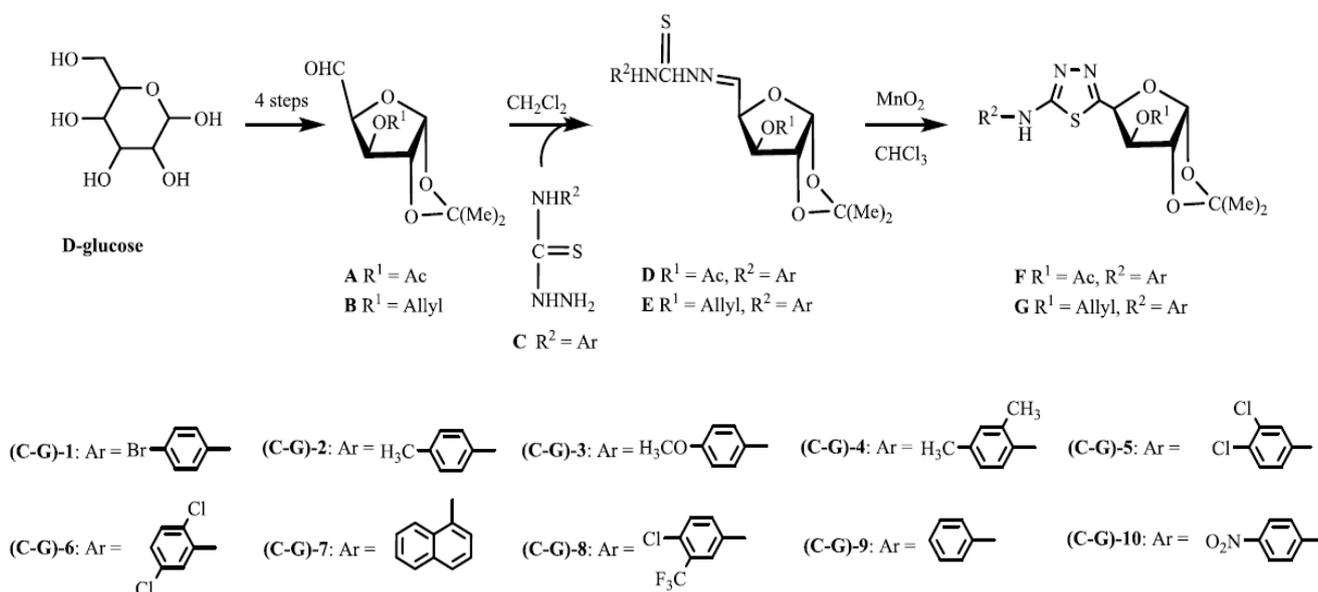
The substituted thiosemicarbazides **C** were synthesized from the corresponding substituted arylamines as previously described [24,31]. The condensation between furanosyl aldehydes **A** or **B** and substituted thiosemicarbazides **C** provided compounds **D** or **E**, respectively. Then the target compounds **F** or **G** were prepared by treating compounds **D** or **E** with MnO_2. 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.
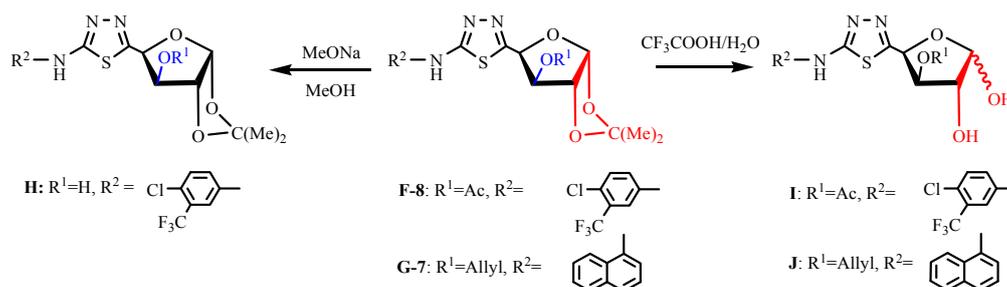
All the derivatives were synthesized according to the procedures described in Schemes 1 and 2 in good overall yields of 65%–92%. The synthesized compounds were characterized by ^{1}H-NMR, MS and HRMS. Most of the ^{1}H-NMR experiments of compounds **F** and **G** were conducted in $CDCl_3$ as the solvent. Nevertheless, the signal of N*H* was too weak in some cases, so we had to switch the solvent to DMSO-d_6. 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-C_6H_4-	$C_{17}H_{18}BrN_3O_5S$	White foamy solid	204.1–204.7	79
F-2	Ac	4-CH_3-C_6H_4-	$C_{18}H_{21}N_3O_5S$	White foamy solid	187.9–188.1	82
F-3	Ac	4-CH_3O-C_6H_4-	$C_{18}H_{21}N_3O_6S$	yellow foamy solid	177.7–178.7	73
F-4	Ac	2,4-$(CH_3)_2$-C_6H_4-	$C_{19}H_{23}N_3O_5S$	White foamy solid	133.7–134.3	81
F-5	Ac	3,4-Cl_2-C_6H_4-	$C_{17}H_{17}Cl_2N_3O_5S$	White foamy solid	147.7–148.5	83
F-6	Ac	2,5-Cl_2-C_6H_4-	$C_{17}H_{17}Cl_2N_3O_5S$	White foamy solid	61.8–62.9	85
F-7	Ac	1-Naphthyl-	$C_{21}H_{21}N_3O_5S$	White foamy solid	57.0–58.1	65
F-8	Ac	4-Cl-3-CF_3-C_6H_3-	$C_{18}H_{17}ClF_3N_3O_5S$	White foamy solid	140.0–141.2	77
F-9	Ac	C_6H_4-	$C_{17}H_{19}N_3O_5S$	White foamy solid	195.1–195.5	78
F-10	Ac	4-NO_2-C_6H_4-	$C_{17}H_{18}N_4O_7S$	yellow foamy solid	198.4–198.7	73
G-1	All	4-Br-C_6H_4-	$C_{18}H_{20}BrN_3O_4S$	White foamy solid	204.1–204.7	68
G-2	All	4-CH_3-C_6H_4-	$C_{19}H_{23}N_3O_4S$	White foamy solid	187.9–188.1	74
G-3	All	4-CH_3O-C_6H_4-	$C_{19}H_{23}N_3O_5S$	White foamy solid	177.7–178.7	78
G-4	All	2,4-$(CH_3)_2$-C_6H_4-	$C_{20}H_{25}N_3O_4S$	White foamy solid	133.7–134.3	76
G-5	All	3,4-Cl_2-C_6H_4-	$C_{18}H_{19}Cl_2N_3O_4S$	White foamy solid	147.7–148.5	81
G-6	All	2,5-Cl_2-C_6H_4-	$C_{18}H_{19}Cl_2N_3O_4S$	White foamy solid	61.8–62.9	76
G-7	All	1-Naphthyl-	$C_{22}H_{23}N_3O_4S$	yellow foamy solid	57.0–58.1	68
G-8	All	4-Cl-3-CF_3-C_6H_3-	$C_{19}H_{19}ClF_3N_3O_4S$	White foamy solid	140.0–141.2	86
G-9	All	C_6H_4-	$C_{18}H_{21}N_3O_4S$	White foamy solid	195.1–195.5	91
G-10	All	4-NO_2-C_6H_4-	$C_{18}H_{20}N_4O_6S$	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 EC_{50} 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 EC_{50} 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 EC_{50} value of 0.59 μg/mL).

Table 3. Fungicidal Activity of Compounds **F/G** against *S. sclerotiorum*.

Compds No.	Regression eq	r	EC$_{50}$ (μg/mL)	EC$_{90}$ (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^2 = allyl) displayed a better fungicidal activity than the former (R^2 = 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^2 = 2,4-(CH$_3$)$_2$-C$_6$H$_3$-), **F-2** (R^2 = 4-CH$_3$-C$_6$H$_3$-), **F-9** (R^2 = C$_6$H$_3$-), **F-3** (R^2 = 4-CH$_3$O-C$_6$H$_3$-) and **F-1** (R^2 = 4-Br-C$_6$H$_3$-) with the EC$_{50}$ 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^2 = 2,4-(CH$_3$)$_2$-C$_6$H$_3$-), **G-2** (R^2 = 4-CH$_3$-C$_6$H$_3$-), **G-9** (R^2 = C$_6$H$_3$-), **G-3** (R^2 = 4-CH$_3$O-C$_6$H$_3$-) and **G-6** (R^2 = 2,5-Cl$_2$-C$_6$H$_3$-) with the EC$_{50}$ 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^2 = 3,4-Cl$_2$-C$_6$H$_3$-) and **G-8** (R^2 = 4-Cl-3-CF$_3$-C$_6$H$_3$-) with the EC$_{50}$ values of 0.29 and 0.46 μg/mL, respectively. They were slightly better than the commercial fungicide chlorothalonil (EC$_{50}$ value = 0.59 μg/mL). Similarly, compounds **F-8** (R^2 = 4-Cl-3-CF$_3$-C$_6$H$_3$-) and **G-5** (R^2 = 3,4-Cl$_2$-C$_6$H$_3$-), both with EC$_{50}$ 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^2 = 2,4-Me$_2$-C$_6$H$_3$-) and **G-4** (R_2 = 2,4-Me$_2$-C$_6$H$_3$-) with the EC$_{50}$ 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 EC_{50} 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 EC_{50} 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 EC_{50} 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	EC$_{50}$	EC$_{90}$
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):

$$I = \frac{\overline{M}_0 - \overline{M}}{\overline{M}_0} \times 100\% \tag{1}$$

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 CH_2Cl_2 (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 $CHCl_3$ (80 mL) was added MnO_2 (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. ^{1}H-NMR (DMSO-d_6): δ 10.61 (s, 1H, N*H*), 7.62 (d, *J* = 8.9 Hz, 2H, Ar*H*), 7.52 (d, *J* = 8.9 Hz, 2H, Ar*H*), 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, C*H*₃CO), 1.52, 1.31 (2s, 6H, *Me*₂C); ^{13}C-NMR (DMSO-d_6) 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 $C_{17}H_{17}BrN_3O_5S$ (M-H) 454.0. Found: 454.0. HRMS for $C_{17}H_{19}BrN_3O_5S$ [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. ^{1}H-NMR (CDCl₃): δ 10.42 (br, 1H, N*H*), 7.33-7.27 (m, 2H, Ar*H*), 7.19 (m, 2H, Ar*H*), 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-C*H*₃), 2.00 (s, 3H, C*H*₃CO), 1.59, 1.36 (2s, 6H, *Me*₂C); ^{13}C-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 $C_{18}H_{21}N_3NaO_5S$ (M+Na) 414.1. Found: 414.2. HRMS for $C_{18}H_{22}N_3O_5S$ [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-thiadiazols (**F-3**). Yield: 73%. Yellow solid, mp 186.7–188.0 °C. ^{1}H-NMR (DMSO-d_6): δ 10.28 (br, 1H, N*H*), 7.52 (d, *J* = 8.9 Hz, 2H, Ar*H*), 6.93 (d, *J* = 8.9 Hz, 2H, Ar*H*), 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-C*H*₃O), 2.02 (s, 3H, C*H*₃CO), 1.51, 1.30 (2s, 6H, *Me*₂C); ^{13}C-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 $C_{18}H_{22}N_3O_6S$ [M+H] 408.1. Found: 408.1. HRMS for $C_{18}H_{22}N_3O_6S$ [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. ^{1}H-NMR (CDCl₃): δ 7.79 (br, 1H, N*H*), 7.29 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.10–7.00 (m, 2H, Ar*H*), 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-CH_3), 1.98 (s, 3H, CH_3CO), 1.56, 1.34 (2s, 6H, Me_2C); ^{13}C-NMR (CDCl$_3$) 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 C$_{19}$H$_{24}$N$_3$O$_5$S [M+H] 406.1. Found: 406.1. HRMS for C$_{19}$H$_{24}$N$_3$O$_5$S [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. ^{1}H-NMR (DMSO-d_6): 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, CH_3CO), 1.52, 1.31 (2s, 6H, Me_2C); ^{13}C-NMR (DMSO-d_6) 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 C$_{17}$H$_{18}$Cl$_2$N$_3$O$_5$S [M+H] 446.0. Found: 446.1. HRMS for C$_{17}$H$_{18}$Cl$_2$N$_3$O$_5$S [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. ^{1}H-NMR (CDCl$_3$): 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, CH_3CO), 1.59, 1.36 (2s, 6H, Me_2C); ^{13}C-NMR (CDCl$_3$) 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 C$_{17}$H$_{18}$Cl$_2$N$_3$O$_5$S [M+H] 446.0. Found: 446.1. HRMS for C$_{17}$H$_{18}$Cl$_2$N$_3$O$_5$S [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. ^{1}H-NMR (DMSO-d_6): δ 10.36 (s, 1H, NH), 8.25 (m, 1H, ArH), 8.13 (d, *J* = 7.5 Hz, 1H, ArH), 7.96 (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, CH_3CO), 1.52, 1.30 (2s, 6H, Me_2C); ^{13}C-NMR (75 MHz, DMSO-d_6) 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 C$_{21}$H$_{22}$N$_3$O$_5$S [M+H] 428.1. Found: 428.1. HRMS for C$_{21}$H$_{22}$N$_3$O$_5$S [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. ^{1}H-NMR (DMSO-d_6): δ 10.95 (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, CH_3CO), 1.52, 1.31 (2s, 6H, Me_2C); ^{13}C-NMR (DMSO-d_6) 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 C$_{18}$H$_{18}$ClF$_3$N$_3$O$_5$S [M+H] 480.1. Found: 480.1. HRMS for C$_{18}$H$_{18}$ClF$_3$N$_3$O$_5$S [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. ^{1}H-NMR (DMSO-d_6): δ 10.63 (s, 1H, N*H*), 7.41-7.39 (m, 4H, Ar*H*), 7.11 (m, 1H, Ar*H*), 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, C*H*$_3$CO), 1.60, 1.36 (2s, 6H, *Me*$_2$C); ^{13}C-NMR (DMSO-d_6) 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 $C_{17}H_{20}N_3O_5S$ [M+H] 378.1. Found: 378.1. HRMS for $C_{17}H_{20}N_3O_5S$ [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. ^{1}H-NMR (DMSO-d_6): δ 11.22 (s, 1H, N*H*), 8.27 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.85 (d, *J* = 8.7 Hz, 2H, Ar*H*), 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, C*H*$_3$CO), 1.53, 1.31 (2s, 6H, *Me*$_2$C); ^{13}C-NMR (DMSO-d_6) 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 $C_{17}H_{17}N_4O_7S$ (M-H) 421.1. Found: 421.0. HRMS for $C_{17}H_{19}N_4O_7S$ [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. ^{1}H-NMR (CDCl$_3$): δ 10.50 (br, 1H, N*H*), 7.49-7.46 (m, 2H, Ar*H*), 7.36-7.26 m, 2H, Ar*H*), 6.04 (d, *J* = 3.6 Hz, 1H, H-1), 5.72 (m, 1H, CH$_2$=C*H*CH$_2$), 5.63 (d, *J* = 3.1 Hz, 1H, H-3), 5.23-5.14 (m, 2H, C*H*$_2$=CHCH$_2$), 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, CH$_2$=CHC*H*$_2$), 1.58, 1.37 (2s, 6H, *Me*$_2$C); ^{13}C-NMR (DMSO-d_6) δ 165.56, 155.14, 139.84, 134.03, 131.70, 119.28, 117.15, 113.08, 111.47, 111.39, 104.44, 81.82, 81.78, 77.57, 70.44, 26.52, 25.96. ESI-MS *m/z* calcd. for $C_{18}H_{19}BrN_3O_4S$ (M-H) 452.0. Found: 451.9. HRMS for $C_{18}H_{21}BrN_3O_4S$ [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. ^{1}H-NMR (CDCl$_3$): δ 9.39 (br, 1H, N*H*), 7.29–7.26 (m, 2H, Ar*H*), 7.18-7.16 (m, 2H, Ar*H*), 6.02 (d, *J* = 3.7 Hz, 1H, H-1), 5.73 (m, 1H, CH$_2$=C*H*CH$_2$), 5.62 (d, *J* = 3.1 Hz, 1H, H-3), 5.23-5.13 (m, 2H, C*H*$_2$=CHCH$_2$), 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, CH$_2$=CHC*H*$_2$), 2.33 (s, 3H, Ar-C*H*$_3$), 1.56, 1.36 (2s, 6H, *Me*$_2$C); ^{13}C-NMR (DMSO-d_6) δ 166.13, 154.21, 138.20, 134.08, 130.77, 129.40, 117.46, 117.11, 111.34, 104.40, 81.81, 77.62, 70.42, 26.53, 25.96, 20.28. ESI-MS *m/z* calcd. for $C_{19}H_{24}N_3O_4S$ [M+H] 390.1. Found: 390.1. HRMS for $C_{19}H_{24}N_3O_4S$ [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. ^{1}H-NMR (CDCl$_3$): δ 9.70 (br, 1H, N*H*), 7.35–7.26 (m, 2H, Ar*H*), 6.93–6.90 (m, 2H, Ar*H*), 6.01 (d, *J* = 3.5 Hz, 1H, H-1), 5.72 (m, 1H, CH$_2$=C*H*CH$_2$), 5.59 (d, *J* = 3.0 Hz, 1H, H-3), 5.22–5.13 (m, 2H, C*H*$_2$=CHCH$_2$), 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, CH$_2$=CHC*H*$_2$), 3.81 (s, 3H, Ar-C*H*$_3$O), 1.56, 1.35 (2s, 6H, *Me*$_2$C); ^{13}C-NMR (DMSO-d_6) 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 $C_{19}H_{24}N_3O_5S$ [M+H] 406.1. Found: 406.2. HRMS for $C_{19}H_{24}N_3O_5S$ [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. ^{1}H-NMR (CDCl$_3$): δ 9.41 (s, 1H, N*H*), 7.58 (d, *J* = 9.0 Hz, 1H, Ar*H*), 7.04–6.99 (m, 2H, Ar*H*), 5.96 (d, *J* = 3.7 Hz, 1H, H-1), 5.82 (m, 1H, CH$_2$=C*H*CH$_2$), 5.53 (d, *J* = 3.1 Hz, 1H, H-3), 5.22–5.10 (m, 2H, C*H*$_2$=CHCH$_2$), 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, CH$_2$=CHC*H*$_2$), 2.25, 2.21 (2s, 6H, Ar-C*H*$_3$), 1.46,1.29 (2s, 6H, *Me*$_2$C); ^{13}C-NMR (DMSO-*d*$_6$) 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 C$_{20}$H$_{26}$N$_3$O$_4$S [M+H] 404.1. Found: 404.1. HRMS for C$_{20}$H$_{26}$N$_3$O$_4$S [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. ^{1}H-NMR (CDCl$_3$): δ 10.77 (s, 1H, N*H*), 7.59 (s, 1H, Ar*H*), 7.44 (m, 1H, Ar*H*), 7.34 (m, 1H, Ar*H*), 6.06 (d, *J* = 3.5 Hz, 1H, H-1), 5.74 (m, 1H, CH$_2$=C*H*CH$_2$), 5.65 (s, 1H, H-3), 5.24–5.15 (m, 2H, C*H*$_2$=CHCH$_2$), 4.71 (d, *J* = 3.5 Hz, 1H, H-2), 4.42–3.82 (m, 3H, H-4, CH$_2$=CHC*H*$_2$), 1.59, 1.38 (2s, 6H, *Me*$_2$C); ^{13}C-NMR (DMSO-*d*$_6$) 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 C$_{18}$H$_{20}$C$_{12}$N$_3$O$_4$S [M+H] 444.0. Found: 444.0. HRMS for C$_{18}$H$_{20}$C$_{12}$N$_3$O$_4$S [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. ^{1}H-NMR (CDCl$_3$): δ 8.21 (m, 1H, Ar*H*), 7.73 (br, 1H, N*H*), 7.30 (m, 1H, Ar*H*), 6.98 (m, 1H, Ar*H*), 6.05 (d, *J* = 3.6 Hz, 1H, H-1), 5.74 (m, 1H, CH$_2$=C*H*CH$_2$), 5.63 (d, *J* = 3.2 Hz, 1H, H-3), 5.25–5.16 (m, 2H, C*H*$_2$=CHCH$_2$), 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, CH$_2$=CHC*H*$_2$), 1.57, 1.37 (2s, 6H, *Me*$_2$C); ^{13}C-NMR (DMSO-*d*$_6$) 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 C$_{18}$H$_{20}$C$_{12}$N$_3$O$_4$S [M+H] 444.0. Found: 444.0. HRMS for C$_{18}$H$_{20}$C$_{12}$N$_3$O$_4$S [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. ^{1}H-NMR (CDCl$_3$): δ 10.28 (br, 1H, N*H*), 8.23 (m, 1H, Ar*H*), 8.12 (m, 1H, Ar*H*), 7.95 (m, 1H, Ar*H*), 7.00 (m, 1H, Ar*H*), 7.58-7.49 (m, 3H, Ar*H*), 5.98 (d, *J* = 3.6 Hz, 1H, H-1), 5.78 (m, 1H, CH$_2$=C*H*CH$_2$), 5.37 (d, *J* = 3.1 Hz, 1H, H-3), 5.22–5.10 (m, 2H, C*H*$_2$=CHCH$_2$), 4.81 (d, *J* = 3.7 Hz, 1H, H-2), 4.14–3.64 (m, 3H, H-4, CH$_2$=CHC*H*$_2$), 1.48, 1.30 (2s, 6H, *Me*$_2$C); ^{13}C-NMR (DMSO-*d*$_6$) 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 C$_{22}$H$_{24}$N$_3$O$_4$S [M+H] 426.1. Found: 426.1. HRMS for C$_{22}$H$_{24}$N$_3$O$_4$S [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. ^{1}H-NMR (CDCl$_3$): δ 10.54 (s, 1H, N*H*), 7.81 (m, 1H, Ar*H*), 7.63-7.48 (m, 2H, Ar*H*), 6.05 (d, *J* = 3.5 Hz, 1H, H-1), 5.74 (m, 1H, CH$_2$=C*H*CH$_2$), 5.64 (d, *J* = 3.1 Hz, 1H, H-3), 5.24–5.15 (m, 2H, C*H*$_2$=CHCH$_2$), 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, CH$_2$=CHC*H*$_2$), 1.59, 1.38 (2s,

6H, *Me*₂C); ¹³C-NMR (DMSO-*d*₆) 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, N*H*), 7.46–7.35 (m, 4H, Ar*H*), 7.09 (m, 1H, Ar*H*), 6.04 (d, *J* = 3.6 Hz, 1H, H-1), 5.73 (m, 1H, CH₂=C*H*CH₂), 5.65 (d, *J* = 3.1 Hz, 1H, H-3), 5.23–5.13 (m, 2H, C*H*₂=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=CHC*H*₂), 1.58, 1.37 (2s, 6H, *Me*₂C); ¹³C-NMR (DMSO-*d*₆) δ 165.96, 154.62, 140.58, 134.06, 129.01, 121.80, 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, N*H*), 8.33–8.28 (m, 2H, Ar*H*), 7.62–7.57 (m, 2H, Ar*H*), 6.08 (d, *J* = 3.6 Hz, 1H, H-1), 5.80–5.69 (m, 2H, CH₂=C*H*CH₂, H-3), 5.25–5.15 (m, 2H, C*H*₂=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=CHC*H*₂), 1.62, 1.40 (2s, 6H, *Me*₂C); ¹³C-NMR (DMSO-*d*₆) 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-*d*₆): δ 10.84 (s, 1H, N*H*), 8.26 (d, *J* = 2.5 Hz, 1H, Ar*H*), 7.86 (dd, *J* = 2.5, 8.8 Hz, 2H, Ar*H*), 7.68 (d, *J* = 8.8 Hz, 1H, Ar*H*), 6.01 (d, 1H, *J* = 3.6 Hz, H-1), 5.98 (d, *J* = 5.2 Hz, 1H, O*H*), 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, *Me*₂C); ¹³C-NMR (DMSO-*d*₆) 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): δ 10.87 (d, *J* = 12.2 Hz, 1H, N*H*), 8.26 (d, *J* = 2.6 Hz, 1H, Ar*H*), 7.83 (dd, *J* = 2.6, 8.8 Hz, 2H, Ar*H*), 7.68 (d, *J* = 8.8 Hz, 1H, Ar*H*), 7.05 (br, 1H, O*H*), 5.89 (br, 1H, O*H*), 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, OC*H*$_3$). ESI-MS *m/z* calcd. for $C_{15}H_{12}ClF_3N_3O_5S$ (M-H) 438.0. Found: 438.0. HRMS for $C_{15}H_{14}ClF_3N_3O_5S$ [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): δ 10.19 (s, 1H, N*H*), 8.24–8.22 (m, 1H, Ar*H*), 8.09 (d, *J* = 7.4 Hz, 1H, Ar*H*), 7.97–7.94 (m, 1H, Ar*H*), 7.70 (d, *J* = 8.1 Hz, 1H, Ar*H*), 7.58–7.49 (m, 3H, Ar*H*), 6.62 (d, *J* = 5.5 Hz, 0.5H), 6.51 (d, *J* = 7.3 Hz, 0.5H), 5.77–5.70 (m, 1H, CH$_2$=C*H*CH$_2$), 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 $C_{19}H_{20}N_3O_4S$ [M+H] 386.1. Found: 386.0. HRMS for $C_{19}H_{20}N_3O_4S$ [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 λ = 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

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.

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