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Synthesis and Bioactivities of Novel Galactoside Derivatives Containing 1,3,4-Thiadiazole Moiety

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A series of novel galactoside derivatives containing 1,3,4-thiadiazole moiety were synthesized, and the structure of them was verified by spectroscopy of NMR and HRMS, and antifungal and antibacterial activities of them were screened. The results showed that the newly synthesized compounds had good antifungal activities. Among them, Ⅲ16, Ⅲ17, and Ⅲ19 exhibited satisfactory activities against *Phytophthora infestans (P. infestans)*, with EC_{50} values of 5.87, 4.98, and 6.17 μg/ml, respectively, which were similar to those of dimethomorph (5.52 μg/ml). Meanwhile, the title compounds also possessed certain antibacterial activities.

Keywords: galactoside, thiadiazole, aromatic amide, synthesis, bioactivity

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INTRODUCTION

Galactoside and its derivatives are widely found in litchi, laver, seaweed, and snails (Choucry et al., 2021; Kumar, 2020) and had anticancer (Tacke et al., 2017; Oueslati et al., 2020), antiviral (Cai et al., 2006; Abu-Zaied et al., 2021), and antibacterial (Upadhyay et al., 2010) activities. In addition, it was found that novel galactoside derivatives containing a pyrimidine moiety possessed good antifungal activities against *Gibberella zeae* (*G. zeae*), *Botryosphaeria dothidea* (*B. dothidea*), *Phytophthora infestans* (*P. infestans*), *Thanatephorus cucumeris* (*T. cucumeris*), and *Phompsis* sp in the preliminary working of our group (Chen M. H. et al., 2021; Chen et al., 2022). Moreover, it has been reported that glycosylation can improve the properties of active lead compounds, such as solubility, stability, and bioactivity (Wu et al., 2014; Gurung et al., 2017).

It is known that nitrogen-containing heterocyclic compounds have not only a broad spectrum of biological activity and diversity of structure changes but also low toxicity to most warm-blooded animals, birds, fish, and bees (Mermer et al., 2021). 1,3,4-Thiadiazole derivatives, important nitrogen-containing heterocyclic compounds, showed a wide range of bioactivities, such as antifungal (Bhinge et al., 2015; Chudzik et al., 2019), antibacterial (Wu et al., 2021), anticancer (Abas et al., 2021; Avvaru et al., 2021), and antiviral (Yu et al., 2017) activities. In our previous working, 1,3,4-thiadiazole derivatives of glucosides showed good antibacterial and antifungal activities (Chen M. et al., 2021).

In order to find novel structure and effective biological activity of galactoside derivatives, 19 novel galactoside derivatives containing 1,3,4-thiadiazole moiety were synthesized by five reactions and were designed under the guidance of the active substructure splicing method by retaining a part of 1,3,4-thiadiazole and replacing the original glucoside with galactoside on the basis of our previous working (**Figure 1**). Then, the newly synthesized title compounds are tested for antibacterial and antifungal activities.

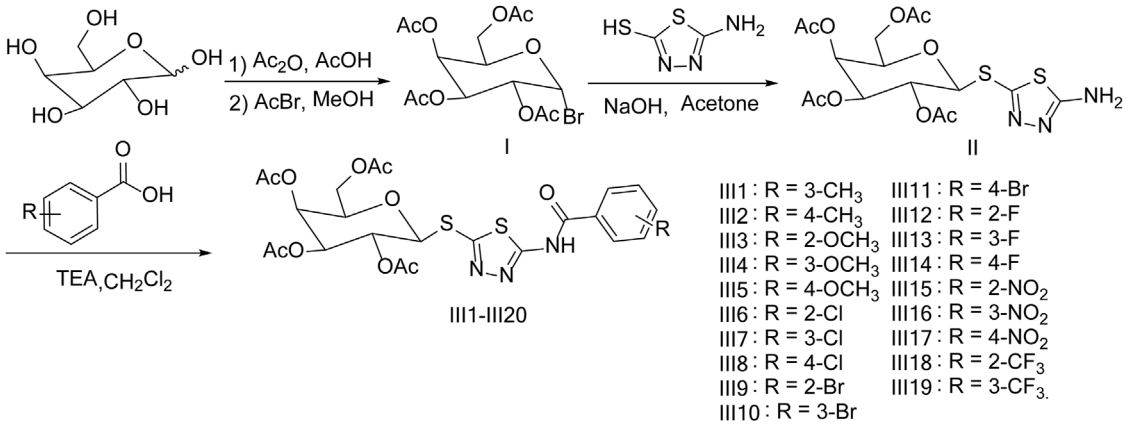

FIGURE 1 | Synthetic route of the target compounds III1–III19.

EXPERIMENTAL

Materials and Instruments

All solvents and reagents were purchased from commercial suppliers and met the standards. ^{1}H NMR and ^{13}C NMR spectra were obtained using Bruker DPX 400 MHz and Bruker DPX 600 MHz spectrometers (Bruker, Germany) in DMSO-*d*6 or CDCl3 solution. High-resolution mass spectrometry (HRMS) of the title compounds was performed using an Agilent Technologies mass spectrometer (Agilent Technologies, United States).

Chemistry

General Synthesis Procedures for Intermediate II

Intermediate I was synthesized by referring to the method of the literature (Kamat et al., 2007; Chen M. et al., 2021). The crude product of intermediate I is used directly for the next step of the reaction. To 2-amino-5-mercapto-1,3,4-thiadiazole (1.33 g, 10.0 mmol), 50 ml acetone and 40% sodium hydroxide solution (10 ml) were added successively into a 100-ml two-necked bottle. Then, a solution of intermediate I (4.11 g, 10.0 mmol) in acetone (5 ml) was added and maintained under stirring for about 30 min (Scattolin et al., 2020; Chen M. et al., 2021). After the reaction was completed, the mixture was concentrated, and 30 ml of water was added and extracted with dichloromethane (3 × 20 ml), and the organic layer was concentrated and recrystallized with ethyl acetate to afford the intermediate II (3.9 g, yield: 84%) as a white solid. ^{1}H NMR (600 MHz, DMSO-*d6*) δ 7.48 (s, 2H, NH_2), 5.33 (s, 1H, H-1′), 5.30–5.21 (m, 2H, H-2′, H-3′), 5.05 (t, *J* = 9.9 Hz, 1H, H-4′), 4.33 (t, *J* = 6.2 Hz, 1H, H-5′), 4.13–4.00 (m, 2H, H-6′, H-6′′), 2.14 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), and 1.93 (s, 3H, CH_3).

General Synthesis Procedures for Title Compounds III1-III19

Substituted benzoic acid (2.4 mmol) was added to 4 ml thionyl chloride in batches with magnetic stirring and refluxed for 2.0 h (monitored by TLC). The solvent was removed under negative pressure; dichloromethane (2 ml) was added into the residue to give a light yellow solution, which was added dropwise into a mixture of the intermediate II (0.93 g, 2.0 mmol), 15 ml dichloromethane, and triethylamine (0.24 g, 2.4 mmol) (Chen M. et al., 2021). After the reaction was completed, 10 ml water was added into the mixture and divided, and the organic layer was concentrated to the crude product. The crude product was recrystallized with isopropanol to afford the title compounds III1–III19. The characterization details of the title compounds III2–III19 are presented in the **Supplemental Material**.

(2*R*,3*S*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-((5-(3-methylbenzamido)-1,3,4-thiadiazol-2-l)thio)tetrahydro-2*H*-pyran-3,4,5-triyltriacetate (III1): white solid, yield 75.0%, m.p. 159–161°C; 1H NMR (400 MHz, $CDCl_3$) *δ* 12.33 (s, 1H, NH), 8.01 (s, 1H, Ar-H), 7.95 (d, *J* = 7.3 Hz, 1H, Ar-H), 7.55–7.37 (m, 2H, Ar-H), 5.48 (d, *J* = 2.9 Hz, 1H, H-3′), 5.38 (t, *J* = 10.0 Hz, 1H, H-1′), 5.11 (dd, *J* = 10.0, 3.3 Hz, 1H, H-2′), 5.03 (d, *J* = 10.1 Hz, 1H, H-4′), 4.20 (d, *J* = 7.6 Hz, 2H, H-5′, H-6′), 3.99 (t, *J* = 6.4 Hz, 1H, H-6′′), 2.48 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.10 (s, 6H, 2×CH_3), and 2.00 (s, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 172.48, 170.58, 170.45, 169.89, 169.80, 154.72, 138.62, 134.24, 131.59, 129.35, 129.11, 126.02, 83.10, 74.70, 71.16, 68.06, 67.32, 62.39, 40.41, 40.27, 40.13, 39.99, 39.85, 39.71, 39.57, 21.35, 20.90, and 20.78; HRMS $[M+H]^+$ calculated for $C_{24}H_{27}N_3O_{10}S_2$: m/z 582.1216, found 582.1210.

Antifungal Activity *In Vitro*

The antifungal activity of the title compounds III1–III19 against *G. zeae, B. dothidea, Phompsis* sp., *P. infestans,* and *T. cucumeris in vitro* were tested by a mycelia growth method at 50 μg/ml (Maddila et al., 2016; Chen M. H. et al., 2021; Chen M. et al., 2021; Chen et al., 2022). Dimethomorph was used as a positive control, and DMSO was used as a negative control, and each treatment was operated in three replicates. Subsequently, the title compounds III16, III17, and III19 were further evaluated for their corresponding antifungal EC_{50} values with three replicates and used dimethomorph as the positive controls.

TABLE 1 | Reaction conditions for intermediate II were optimized.

Entry	Catalyst	Solvent	Temperature/°C	Yield[a] (%)
1	$NaHCO_3$	CH_2Cl_2	r.m.	18
2	Na_2CO_3	CH_2Cl_2	r.m.	30
3	NaOH	CH_2Cl_2	r.m.	72
3	Et_3N	CH_2Cl_2	r.m.	55
4	NaOH	THF	r.m.	66
5	NaOH	$CHCl_3$	r.m.	70
6	NaOH	CH_3CN	r.m.	66
7	NaOH	$(CH_3)_2CO$	r.m.	82
8	NaOH	$(CH_3)_2CO$	0°C	72
9	NaOH	$(CH_3)_2CO$	50°C	78
10	NaOH	$(CH_3)_2CO$	Reflux	81

Antibacterial Activity *In Vitro*

The antibacterial activity of the title compounds III1–III19 against *Xcc* and *Xoo in vitro* was tested using the turbidimeter test at 200 and 100 μg/ml (Dalgaard et al., 1994; Yu et al., 2017; Chen M. H. et al., 2021; Chen et al., 2022). Thiodiazole-copper was used as a positive control, and DMF was used as a negative control, and each treatment was operated in three replicates.

RESULT AND DISCUSSION

Synthesis

The method of the synthesis for title compounds was listed as follows: Intermediate I was synthesized by galactose acetylation and bromination, and then intermediate I reacted with 2-amino-5-mercapto-1,3,4-thiadiazole to give intermediate II; substituted benzoic acids were chlorinated by thionyl chloride and reacted with intermediate II to produce the title compounds III1–III19. Moreover, to optimize the reaction conditions of the key intermediate II, the influence of catalyst, temperature, and solvent were tested and are listed in **Table 1**. The results indicated that the catalyst, solvent, and temperature had a pronounced effect on the yield, and a maximum yield of 82% was achieved when sodium hydroxide was used as a catalyst and acetone as a solvent for 0.5 h at room temperature.

TABLE 3 | EC_{50} value of antifungal activity for part of compounds against *P. infestans*.

Compound	Toxic regression equation	*R*	EC_{50} (μg/ml)
III16	y = 0.63x + 4.51	0.96	5.87 ± 1.5
III17	y = 0.61x + 4.57	0.99	4.98 ± 2.1
III19	y = 0.67x + 4.47	0.98	6.17 ± 1.8
Dimethomorph	y = 0.94x + 4.30	0.99	5.52 ± 1.2[a]

[a]*Refer to the previous articles of our group (Chen M. et al., 2021).*

Antifungal Activity *In Vitro*

The antifungal activity of the title compounds III1–III19 against *G. zeae, B. dothidea, P. infestans, Phompsis* sp., and *T. cucumeris* are listed in **Table 2**. **Table 2** indicated that III1–III19 showed good antifungal activities, with the inhibition rates of 21.5%–63.4%, 21.6%–66.0%, 23.6%–80.1%, 32.5%–58.1%, and 33.4–68.4% at 50 μg/ml, respectively. Among them, III16, III17, and III19 exhibited satisfactory *in vitro* antifungal activities against *P. infestans*, with the inhibition rates of 80.1, 79.7, and 79.3%, respectively, which were equal to those of dimethomorph (78.2%). Based on the aforementioned results, the EC_{50} values of III16, III17, and III19 were tested and are shown in **Table 3**. **Table 3** indicated that III16, III17, and III19 showed good

TABLE 2 | Antifungal activity of compounds III1–III19 *in vitro* (50 μg/ml).

Compound	Inhibition rate (%)				
	G. zeae	*B. dothidea*	*P. infestans*	*Phompsis* sp.	*T. cucumeris*
III1	28.8 ± 1.3	24.5 ± 2.0	23.6 ± 2.8	49.2 ± 2.6	45.2 ± 1.7
III2	34.5 ± 1.6	32.0 ± 1.0	28.1 ± 1.7	36.3 ± 3.4	33.4 ± 1.4
III3	37.6 ± 2.0	31.0 ± 1.8	25.6 ± 2.0	32.5 ± 1.5	56.3 ± 2.1
III4	45.4 ± 2.6	25.8 ± 1.2	24.7 ± 1.5	36.2 ± 1.8	42.6 ± 1.7
III5	40.1 ± 2.1	26.8 ± 2.6	25.3 ± 2.6	47.5 ± 1.9	47.5 ± 1.8
III6	36.2 ± 1.1	21.6 ± 2.8	56.4 ± 1.4	34.2 ± 2.1	43.4 ± 1.5
III7	47.0 ± 1.3	33.2 ± 2.3	56.7 ± 3.2	55.6 ± 1.4	46.3 ± 1.5
III8	34.2 ± 1.6	48.5 ± 2.1	56.1 ± 1.2	35.2 ± 2.4	35.7 ± 2.4
III9	38.6 ± 1.5	54.8 ± 1.7	59.8 ± 2.1	33.5 ± 2.2	45.6 ± 1.8
III10	43.0 ± 1.3	51.6 ± 2.0	57.5 ± 3.0	37.3 ± 2.3	55.4 ± 1.4
III11	45.4 ± 0.8	50.7 ± 1.2	57.6 ± 2.7	45.1 ± 1.9	43.0 ± 1.2
III12	63.4 ± 1.0	50.5 ± 2.3	73.5 ± 2.1	34.5 ± 2.1	59.7 ± 2.2
III13	53.8 ± 1.2	46.4 ± 1.6	73.1 ± 1.6	48.1 ± 1.3	68.3 ± 1.8
III14	52.3 ± 1.8	66.4 ± 1.2	77.5 ± 2.1	42.6 ± 1.2	56.5 ± 2.1
III15	61.0 ± 2.4	65.3 ± 2.6	75.1 ± 2.2	45.2 ± 1.5	56.3 ± 1.3
III16	52.2 ± 2.1	66.0 ± 2.5	80.1 ± 1.3	58.1 ± 1.4	56.5 ± 1.6
III17	45.2 ± 1.6	54.3 ± 2.4	79.7 ± 1.2	43.2 ± 1.5	58.7 ± 1.0
III18	55.4 ± 2.0	55.2 ± 2.0	78.0 ± 2.3	44.5 ± 2.2	65.3 ± 2.0
III19	57.2 ± 1.6	54.7 ± 2.5	79.3 ± 2.1	48.2 ± 1.4	68.4 ± 1.9
Dimethomorph	74.3 ± 2.0[a]	72.3 ± 1.6[a]	78.2 ± 1.1[a]	69.3 ± 1.6[a]	68.3 ± 1.6[a]

[a]*Refer to the previous articles of our group (Chen M. et al., 2021).*

TABLE 4 | Antibacterial activity of compounds (Ⅲ1–Ⅲ19) *in vitro*.

Compound	*Xoo*		*Xcc*	
	200 μg/ml	100 μg/ml	200 μg/ml	100 μg/ml
Ⅲ1	47.6 ± 2.5	29.1 ± 1.6	45.4 ± 1.4	28.5 ± 1.2
Ⅲ2	43.5 ± 1.2	23.1 ± 1.3	42.2 ± 2.3	29.2 ± 1.5
Ⅲ3	46.7 ± 1.2	25.4 ± 2.0	44.3 ± 2.1	24.1 ± 1.3
Ⅲ4	45.5 ± 1.1	23.1 ± 1.2	48.0 ± 2.3	29.2 ± 1.4
Ⅲ5	35.3 ± 2.0	18.3 ± 2.4	42.1 ± 1.5	24.7 ± 2.1
Ⅲ6	41.5 ± 2.3	21.5 ± 3.1	45.1 ± 2.1	24.8 ± 1.4
Ⅲ7	36.2 ± 2.8	19.2 ± 3.0	57.7 ± 1.3	36.1 ± 1.7
Ⅲ8	45.4 ± 2.3	26.5 ± 2.1	53.5 ± 2.1	34.8 ± 2.5
Ⅲ9	37.3 ± 1.8	19.1 ± 1.0	55.0 ± 1.8	27.0 ± 1.4
Ⅲ10	43.4 ± 2.6	24.3 ± 1.2	53.1 ± 1.4	26.2 ± 1.2
Ⅲ11	44.2 ± 1.5	27.5 ± 2.7	40.0 ± 1.7	19.8 ± 2.0
Ⅲ12	52.6 ± 2.4	26.8 ± 1.8	41.2 ± 1.0	20.4 ± 1.4
Ⅲ13	56.2 ± 1.1	26.5 ± 3.1	48.1 ± 2.5	25.7 ± 2.5
Ⅲ14	57.6 ± 2.0	29.0 ± 1.0	45.2 ± 1.1	21.2 ± 1.6
Ⅲ15	64.2 ± 1.2	30.3 ± 1.4	54.1 ± 2.9	26.0 ± 1.7
Ⅲ16	58.6 ± 1.2	23.2 ± 2.1	55.1 ± 1.8	27.8 ± 1.1
Ⅲ17	62.8 ± 1.1	34.5 ± 0.9	57.0 ± 2.2	28.9 ± 2.0
Ⅲ18	54.2 ± 1.2	33.0 ± 1.3	49.0 ± 1.0	29.4 ± 2.7
Ⅲ19	53.0 ± 1.4	36.2 ± 2.2	45.4 ± 2.6	23.8 ± 2.5
Thiodiazole-copper	70.1 ± 2.3[a]	43.6 ± 1.5[a]	80.2 ± 1.5[a]	46.1 ± 1.3[a]

[a]*Refer to the previous articles of our group (Chen et al., 2022).*

antifungal activities against *P. infestans,* with EC_{50} values of 5.87, 4.98, and 6.17 μg/ml, respectively, which were similar to those of dimethomorph (5.52 μg/ml) (Chen et al., 2022), and which were comparable to those of the previously found inhibitory activity of glucosides derivatives containing 4-fluorobenzamido-1,3,4-thiadiazole against *P. infestans* (3.43 μg/ml) (Chen M. et al., 2021).

Antibacterial Activity *In Vivo*

Moreover, the antibacterial activities of the title compounds against *Xcc* and *Xoo* were tested at 200 and 100 μg/ml and are listed in **Table 4**. **Table 4** indicated that the title compounds Ⅲ1–Ⅲ19 exhibited certain antibacterial activities against *Xoo* and *Xcc* at 200 and 100 μg/ml, with the inhibition rates of 31.5%–64.2% and 40.8%–57.7% and 18.3%–36.2% and 19.8%–36.1%, respectively, which were lower than those of thiodiazole-copper (70.1, 43.6, and 46.1%), and which were comparable to that of the previously found novel glucoside derivatives containing 1,3,4-thiadiazole moiety with antibacterial activity (Chen M. et al., 2021). Based on the aforementioned results, it was demonstrated that the antifungal and antibacterial activities of compounds replacing the original glucoside with galactoside did not show any improvement, that is, the configuration of the third on the six-member sugar ring has little influence on the antifungal and antibacterial activities.

CONCLUSION

A total of 19 novel galactoside derivatives containing 1,3,4-thiadiazole moiety were designed under the guidance of the active substructure splicing method and synthesized by five reactions. The bioactivity results indicated that the title compounds exhibited good antibacterial and antifungal activities, while some of them showed excellent antifungal activities. Therefore, it was demonstrated that the galactoside derivatives containing 1,3,4-thiadiazole moiety can be used to develop potential agrochemicals in the future.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

YS and MC performed the synthesis and bioactivity of all compounds. DL and HL contributed to the original manuscript. ZZ, AL, and JL analyzed the results. JHY, XH, and JQY drafted the version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2022.910710/full#supplementary-material

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