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Synthesis and biological activities of novel *S*- β -D-glucopyranoside derivatives of 1,2,4-triazole

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ABSTRACT

In this study, 14 novel *S*- β -D-glucopyranosides of 1,2,4-triazole derivatives were synthesized and characterized by ¹H NMR, ¹³C NMR, and HRMS. Then their antifungal activities against *Gibberella zeae* (*G. zeae*), *Botryosphaeria dothidea* (*B. dothidea*), *Phomopsis* sp., *Phytophthora infestans* (*P. infestans*), *Thanatephorus cucumeris* (*T. cucumeris*) and antibacterial activities against *Xanthomonas oryzae* pv. *oryzae* (*Xoo*), *Xanthomonas citri* subsp. *citri* (*Xcc*) were evaluated. Bioassay results indicated that most of the title compounds exhibited good antifungal activities. Among them, compounds **4g**, **4k**, **4m**, and **4n** showed better antifungal activities against *P. infestans* with EC₅₀ values of 4.98, 4.09, 3.85, and 4.90 μ g/mL, respectively compared with Dimethomorph (6.06 μ g/mL).

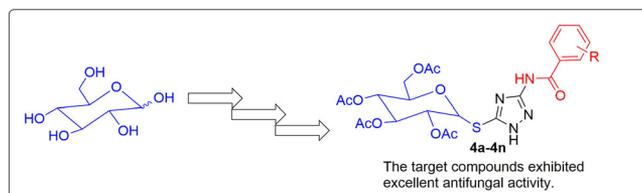
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GRAPHICAL ABSTRACT



Introduction

Plant fungal and bacterial diseases are extremely difficult to manage in agricultural production and are responsible for billions of dollars of economic losses worldwide each year.^[1] To date, a few traditional commercial fungicides and bactericides, such as Carbendazim, Kresoxim-methyl, Thiodiazole copper, Bismethiazol, Zhongshengmycin, and Embamycin, are mainly applied for the control of plant fungal and bacterial diseases. However, long-term use of these traditional pesticides does not only rise to the development of resistance in the target pathogens, but also affects the environment and plant health.^[2,3] Therefore, the discovery and development of new bactericides or fungicides that possess a novel mechanism of action are of great importance in the field of plant protection.

Literature reports revealed that glycosides, the secondary metabolites that widely exist in all organs of plants (such as flowers, fruits, leaves, skins, and roots, etc.), exhibit a wide range of pharmacological activities, such as antiviral,^[4,5] antibacterial,^[6] anticancer,^[7,8] antioxidant,^[9,10] and anti-HIV^[11] activity. Ningnanmycin (Figure 1), an important

biological pesticide glycoside, is mainly used in rice seedling blight, soybean root rot, rice stripe disease, apple spot deciduous leaf disease and cucumber powdery mildew.^[12] Furthermore, it has previously been reported that the 1,2,4-triazole amide group, an important scaffold for synthesis of various active molecules and their derivatives, exhibits a wide range of biological activities including anticancer,^[13] antifungal,^[14,15] and antibacterial^[15] activity.

To aid the development of new, highly active compounds we aimed to introduce the 1,2,4-triazole derivatives into the glycoside structure to design and synthesize a series of novel *S*- β -D-glucopyranoside derivatives of 1,2,4-triazole, and found new bactericides or fungicides with novel mechanism of action.

Results and discussion

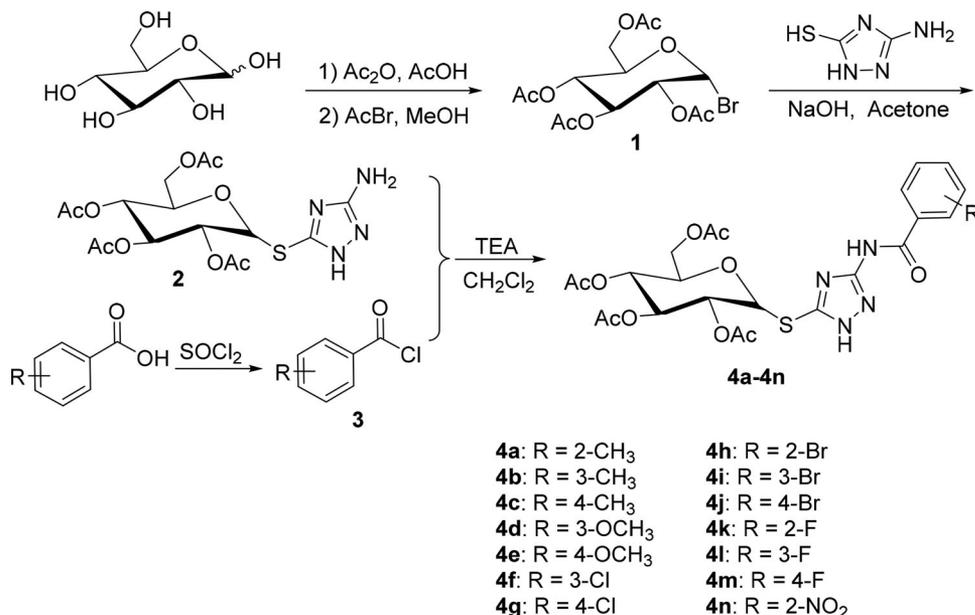
Chemistry

The synthetic route of the target compounds **4a–4n** is depicted in Scheme 1. As shown in Scheme 1, using D-glucose as starting compound, the intermediates **1**, **2**, and **3**

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Scheme 1. Synthetic route of the title compounds **4a–4n**.

were prepared according to previously reported methods.^[16–18] The target compounds **4a–4n** were synthesized via substitution reaction with yields of 58–72%. The structures of the target compounds **4a–4n** were characterized by ¹H NMR, ¹³C NMR spectroscopy, and HRMS. In the ¹H NMR spectra of compound **4n**, the CH₃ protons of acetyl were observed in the range of 2.00–2.05 ppm, the pyran proton appeared in the range of 3.59–5.31 ppm and the signal of the 1,2,4-triazole proton was registered as a singlet at 6.49 ppm. The proton signals of the benzene ring were observed in the range of 7.67–8.23 ppm. In the ¹³C NMR spectra, the signals at 20.59, 20.61, 20.71 ppm, respectively, confirmed the presence of acetyl groups. The signals of the pyran carbon atoms were observed in the range of 61.47–82.54 ppm.

Biological evaluations

The target compounds **4a–4n** were tested for their *in vitro* antifungal activities against *Gibberella zeae* (*G. zeae*), *Botryosphaeria dothidea* (*B. dothidea*), *Phomopsis* sp., *Phytophthora infestans* (*P. infestans*), and *Thanatephorus cucumeris* (*T. cucumeris*) by the poison plate technique.^[19] Dimethomorph was used as reference standard. The results of antifungal activity, as indicated in Table S1 (Supplemental Materials), revealed that the target compounds **4a–4n** showed moderate to good *in vitro* antifungal activities against *G. zeae* (25.3–66.2%), *B. dothidea* (13.0–69.0%), *Phomopsis* sp. (25.4–68.4%), *P. infestans* (21.1–76.6%), and *T. cucumeris* (15.2–67.3%). Expectedly, compounds **4g**, **4k**, **4m**, and **4n** exhibited potent antifungal activity against *P. infestans* at 50 μg/mL, with inhibition rates of 69.3%, 71.2%, 73.1%, and 76.6%, respectively, comparable to that of Dimethomorph (68.3%). Moreover, compounds **4j** and **4m** possessed potential fungicidal activity against *T. cucumeris*, with inhibition rates of 67.3% and 65.9%, respectively, which



Figure 1. The structures of Ningnanmycin.

were superior to that of Dimethomorph (63.0%). Then, the EC₅₀ values of some of the target compounds as well as Dimethomorph against *P. infestans* were also tested and presented in Table S2 (Supplemental Materials). It can be seen from Table S2 that compounds **4g**, **4k**, **4m**, and **4n** displayed promising antifungal activity against *P. infestans*, with EC₅₀ values of 4.98, 4.09, 3.85, and 4.90 μg/mL, respectively, which were even better than that of Dimethomorph (6.06 μg/mL).

The *in vitro* antibacterial activities of the title compounds **4a–4n** against *Xoo* and *Xcc* at 200 and 100 μg/mL were tested by using the turbidimeter test.^[20] For comparison, the antibacterial activities of thiodiazole copper against *Xoo* and *Xcc* were evaluated at the same conditions. The results of the preliminary bioassays, as indicated in Table S3 (Supplemental Materials), revealed that the target compounds **4a–4n** showed moderate to good antibacterial activities against *Xoo* and *Xcc* at 200 and 100 μg/mL. Especially, among the title compounds evaluated compounds **4g**, **4m**, and **4n** exhibited better *in vitro* antibacterial activity against *Xoo* at 200 μg/mL, with inhibition rates of 82.3%, 83.8%, and 83.0%, respectively, compared with Thiodiazole-copper (81.0%) and compound **4n** inhibited better *in vitro* antibacterial activity (55.0%) against *Xoo* at 100 μg/mL compared with Thiodiazole-copper (52.1%). In addition, compounds **4g**, **4i**, and **4n** displayed potent *in vitro* antibacterial activity against *Xoo* at 200 μg/mL, with inhibition rates of 88.5%,

87.8%, and 89.2%, respectively, which were even better or equally to that of Thiodiazole-copper (87.1%).

Material and methods

General information

Melting points were determined on a XT-4 melting apparatus (Beijing Tech Instrument Co., China). The optical rotations were determined on a WXG-4 circular-circling photometer (Shanghai shengguang Co., China). ^1H NMR and ^{13}C NMR spectra were measured on Bruker AVANCE III MD 400 and HD 600 MHz Digital NMR Spectrometers (Bruker Company, Billerica, MA, US.) in CDCl_3 as solvent and recorded in ppm relative to internal standard TMS. HRMS was carried out on an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS using ES (Agilent Technologies, Palo Alto, CA, USA). The course of the reactions was monitored by TLC analysis on silica gel $\text{G}_{\text{F}254}$. All used reagents and solvents met the standards of analytical reagents.

α -Acetobromoglucose (**1**) was synthesized by following the procedures described in the literature.^[16]

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-[(5-amino-1,3,4-thiadiazol-2-yl)thio]tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**2**) was prepared as described in the literature.^[17]

Preparation of the title compounds 4a–4n

The aromatic acid (1.2 mmol) was dissolved in SOCl_2 (4 mL) and refluxed for about 2 h. SOCl_2 was distilled off in vacuo to obtain the intermediates **3a–3n**.^[18] A solution of **3a–3n** in CH_2Cl_2 (5 mL) was added dropwise to a mixture of **2** (1.0 mmol) and triethyl amine (1.0 mmol) in CH_2Cl_2 (15 mL). After the reaction was completed (monitored by TLC), the mixture was diluted with water, the organic layer was dried over anhydrous sodium sulfate, filtered, distilled off in vacuo, and petroleum ether was added to residue. The crude products were recrystallized with isopropanol to afford the target compounds **4a–4n**. The Supplemental Materials contains sample ^1H and ^{13}C NMR and high resolution mass spectra of the products **4** (Supplementary material Figures S1–S46).

(2*R*,3*R*,4*S*,5*R*)-2-(Acetoxymethyl)-6-[(3-(2-methylbenzamide)-1*H*-1,2,4-triazol-5-yl)thio]tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**4a**). White solid, yield 70%, m.p. 180–182 °C, $[\alpha]_{\text{D}}^{20} = 12^\circ$ ($c = 1$, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ : 7.58 (d, $J = 7.8$ Hz, 1H, ArH), 7.45 (t, $J = 9.0$ Hz, 1H, ArH), 7.31–7.28 (m, 2H, ArH), 6.43 (s, 2H), 5.28–5.20 (m, 3H), 5.11–5.06 (m, 1H), 4.21 (dd, $J_{6a,6b} = 12.5$, $J_{5,6b} = 4.2$ Hz, 1H), 3.99 (dd, $J_{6a,6b} = 12.5$, $J_{5,6a} = 2.2$ Hz, 1H), 3.60–3.55 (m, 1H, H5'), 2.41 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.01 (s, 3H, CH_3); ^{13}C NMR (150 MHz, CDCl_3) δ : 170.68, 170.19, 169.47, 169.36, 169.29, 158.64, 158.60, 157.96, 157.92, 137.29, 132.07, 131.57, 130.76, 129.19, 125.03, 86.10, 82.52, 76.02, 73.90, 69.29, 67.88, 61.63, 20.74, 20.61, 20.60, 20.02; HRMS $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{24}\text{H}_{28}\text{N}_4\text{O}_{10}\text{S}$: m/z 565.1589, found 565.1600.

(2*R*,3*R*,4*S*,5*R*)-2-(acetoxymethyl)-6-[(3-(3-methylbenzamide)-1*H*-1,2,4-triazol-5-yl)thio]tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**4b**). White solid, yield 72%, m.p. 182–184 °C; ^1H NMR (600 MHz, CDCl_3) δ : 7.58 (d, $J = 7.8$ Hz, 1H), 7.50–7.39 (m, 1H), 7.29 (dd, $J = 7.5$, 3.3 Hz, 2H), 6.43 (s, 2H), 5.32–5.15 (m, 3H), 5.15–5.03 (m, 1H), 4.21 (dd, $J = 12.5$, 4.2 Hz, 1H), 3.99 (dd, $J = 12.5$, 2.2 Hz, 1H), 3.58–3.55 (m, 1H), 2.41 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ : 170.67, 170.17, 169.40, 169.35, 167.90, 158.55, 158.46, 138.07, 134.36, 131.47, 131.29, 128.50, 127.86, 82.60, 76.20, 73.91, 69.45, 68.02, 61.83, 21.40, 20.69, 20.64, 20.62; HRMS $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{24}\text{H}_{28}\text{N}_4\text{O}_{10}\text{S}$: m/z 565.1589, found 565.1598.

(2*R*,3*R*,4*S*,5*R*)-2-(acetoxymethyl)-6-[(3-(4-methylbenzamide)-1*H*-1,2,4-triazol-5-yl)thio]tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**4c**). White solid, yield 64%, m.p. 183–185 °C; ^1H NMR (600 MHz, CDCl_3) δ : 7.58 (d, $J = 7.8$ Hz, 1H), 7.50–7.39 (m, 1H), 7.29 (dd, $J = 7.5$, 3.3 Hz, 2H), 6.43 (s, 2H), 5.32–5.15 (m, 3H), 5.15–5.03 (m, 1H), 4.21 (dd, $J = 12.5$, 4.2 Hz, 1H), 3.99 (dd, $J = 12.5$, 2.2 Hz, 1H), 3.60–3.55 (m, 1H), 2.41 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ : 170.67, 170.17, 169.40, 169.35, 167.90, 158.55, 158.46, 138.07, 134.36, 131.47, 131.29, 128.50, 127.86, 82.60, 76.20, 73.91, 69.45, 68.02, 61.83, 21.40, 20.69, 20.64, 20.62; HRMS $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{24}\text{H}_{28}\text{N}_4\text{O}_{10}\text{S}$: m/z 565.1589, found 565.1603.

(2*R*,3*R*,4*S*,5*R*)-2-(acetoxymethyl)-6-[(3-(3-methoxybenzamide)-1*H*-1,2,4-triazol-5-yl)thio]tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**4d**). White solid, yield 71%, m.p. 187–189 °C; ^1H NMR (600 MHz, CDCl_3) δ : 7.81 (d, $J = 7.8$ Hz, 1H), 7.76 (d, $J = 2.3$ Hz, 1H), 7.43 (t, $J = 8.0$ Hz, 1H), 7.17 (dd, $J = 8.1$, 2.3 Hz, 1H), 6.52 (s, 1H), 5.44 (d, $J = 10.0$ Hz, 1H), 5.37–5.03 (m, 3H), 4.35–4.08 (m, 2H), 3.87 (s, 3H), 3.87–3.74 (m, 1H), 2.04 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ : 170.73, 170.20, 169.41, 169.34, 167.26, 158.47, 132.36, 129.17, 123.70, 118.85, 117.44, 114.90, 82.61, 76.17, 73.94, 69.38, 68.00, 61.76, 55.52, 20.72, 20.63, 20.61; HRMS $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{24}\text{H}_{28}\text{N}_4\text{O}_{11}\text{S}$: m/z 581.1560, found 581.1551.

(2*R*,3*R*,4*S*,5*R*)-2-(acetoxymethyl)-6-[(3-(4-methoxybenzamide)-1*H*-1,2,4-triazol-5-yl)thio]tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**4e**). White solid, yield 60%, m.p. 186–188 °C; ^1H NMR (600 MHz, CDCl_3) δ : 7.81 (d, $J = 7.8$ Hz, 1H), 7.76 (d, $J = 2.3$ Hz, 1H), 7.43 (t, $J = 8.0$ Hz, 1H), 7.17 (dd, $J = 8.1$, 2.3 Hz, 1H), 6.52 (s, 1H), 5.44 (d, $J = 10.0$ Hz, 1H), 5.37–5.03 (m, 3H), 4.35–4.08 (m, 2H), 3.87 (s, 3H), 3.83–3.63 (m, 1H), 2.04 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ : 170.79, 170.24, 169.46, 169.45, 166.63, 163.93, 158.79, 157.93, 133.97, 123.35, 113.47, 82.51, 77.28, 77.07, 76.85, 76.11, 73.88, 69.44, 68.11, 64.28, 61.97, 55.58, 25.26, 20.64, 20.57; HRMS $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{24}\text{H}_{28}\text{N}_4\text{O}_{10}\text{S}$: m/z 581.1560, found 581.1548.

(2*R*,3*R*,4*S*,5*R*)-2-(acetoxymethyl)-6-[(3-(3-chlorobenzamide)-1*H*-1,2,4-triazol-5-yl)thio]tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**4f**). White solid, yield 66%, m.p. 197–199 °C; ^1H NMR (600 MHz, CDCl_3) δ : 8.25 (s, 1H), 8.10 (d,

$J = 7.9$ Hz, 1H), 7.62 (d, $J = 9.9$ Hz, 1H), 7.47 (t, $J = 8.0$ Hz, 1H), 6.63 (s, 1H), 4.28 (dd, $J = 12.5, 4.4$ Hz, 1H), 4.12 (dd, $J = 12.5, 2.1$ Hz, 1H), 3.85–3.82 (m, 1H), 2.04 (s, 6H), 2.02 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ : 170.69, 170.19, 169.43, 169.39, 166.06, 159.30, 158.52, 134.11, 133.57, 132.90, 131.20, 129.54, 129.48, 82.48, 76.19, 73.87, 69.35, 67.90, 61.81, 20.73, 20.66, 20.65, 20.63; HRMS $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{23}\text{H}_{25}\text{ClN}_4\text{O}_{10}\text{S}$: m/z 585.1048, found 585.1055.

(2*R*,3*R*,4*S*,5*R*)-2-(acetoxymethyl)-6-[(3-(4-chlorobenzamido)-1*H*-1,2,4-triazol-5-yl)thio]tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**4g**). White solid, yield 71%, m.p. 193–195 °C; ^1H NMR (600 MHz, CDCl_3) δ : 8.25 (s, 1H), 8.10 (d, $J = 7.9$ Hz, 1H), 7.62 (d, $J = 9.9$ Hz, 1H), 7.47 (t, $J = 8.0$ Hz, 1H), 6.63 (s, 1H), 4.28 (dd, $J = 12.5, 4.4$ Hz, 1H), 4.12 (dd, $J = 12.5, 2.1$ Hz, 1H), 3.86–3.83 (m, 1H), 2.04 (s, 6H), 2.02 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ : 170.62, 170.18, 169.38, 169.36, 166.43, 159.00, 158.40, 140.27, 132.83, 129.59, 128.54, 82.52, 76.18, 73.85, 69.40, 68.08, 61.97, 20.71, 20.64, 20.62; HRMS $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{23}\text{H}_{25}\text{ClN}_4\text{O}_{10}\text{S}$: m/z 585.1048, found 585.1053.

(2*R*,3*R*,4*S*,5*R*)-2-(acetoxymethyl)-6-[(3-(2-bromobenzamido)-1*H*-1,2,4-triazol-5-yl)thio]tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**4h**). White solid, yield 66%, m.p. 206–208 °C; ^1H NMR (600 MHz, CDCl_3) δ : 7.68 (d, $J = 7.4$ Hz, 1H), 7.58–7.31 (m, 3H), 6.63 (s, 2H), 5.31–4.91 (m, 4H), 4.20 (dd, $J = 12.5, 4.0$ Hz, 1H), 3.95 (dd, $J = 12.6, 2.0$ Hz, 1H), 3.54–3.50 (m, 1H), 2.05 (s, 3H), 2.02 (s, 6H), 2.01 (s, 3H); ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ : 170.69, 170.21, 169.37, 169.28, 167.31, 159.36, 157.49, 134.72, 133.00, 132.33, 129.57, 126.96, 120.04, 82.60, 76.01, 73.91, 69.27, 67.83, 61.55, 20.76, 20.63, 20.62, 20.59; HRMS $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{23}\text{H}_{25}\text{BrN}_4\text{O}_{10}\text{S}$: m/z 629.0550, found 629.0552.

(2*R*,3*R*,4*S*,5*R*)-2-(acetoxymethyl)-6-[(3-(3-bromobenzamido)-1*H*-1,2,4-triazol-5-yl)thio]tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**4i**). White solid, yield 58%, m.p. 207–209 °C; ^1H NMR (600 MHz, CDCl_3) δ : 8.25 (s, 1H), 8.10 (d, $J = 7.9$ Hz, 1H), 7.62 (d, $J = 9.9$ Hz, 1H), 7.47 (t, $J = 8.0$ Hz, 1H), 6.63 (s, 1H), 4.28 (dd, $J = 12.5, 4.4$ Hz, 1H), 4.12 (dd, $J = 12.5, 2.1$ Hz, 1H), 3.84–3.82 (m, 1H), 2.04 (s, 6H), 2.02 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ : 170.68, 170.16, 169.52, 169.43, 169.39, 136.62, 136.53, 134.02, 133.13, 130.07, 129.92, 129.81, 128.68, 82.34, 76.24, 73.85, 69.42, 67.87, 61.83, 20.75, 20.71, 20.64, 20.61; HRMS $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{23}\text{H}_{25}\text{BrN}_4\text{O}_{10}\text{S}$: m/z 629.0550, found 629.0546.

(2*R*,3*R*,4*S*,5*R*)-2-(acetoxymethyl)-6-[(3-(4-bromobenzamido)-1*H*-1,2,4-triazol-5-yl)thio]tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**4j**). White solid, yield 60%, m.p. 204–205 °C; ^1H NMR (600 MHz, CDCl_3) δ : 8.25 (s, 1H), 8.10 (d, $J = 7.9$ Hz, 1H), 7.62 (d, $J = 9.9$ Hz, 1H), 7.47 (t, $J = 8.0$ Hz, 1H), 6.63 (s, 1H), 4.28 (dd, $J = 12.5, 4.4$ Hz, 1H), 4.12 (dd, $J = 12.5, 2.1$ Hz, 1H), 3.86–3.82 (m, 1H), 2.04 (s, 6H), 2.02 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ : 170.68, 170.16, 169.52, 169.43, 169.39, 136.62, 136.53, 134.02, 133.13, 130.07, 129.92, 129.81, 128.68, 82.34, 76.24, 73.85, 69.42, 67.87, 61.83, 20.75, 20.71, 20.64, 20.61; HRMS

$[\text{M} + \text{H}]^+$ calculated for $\text{C}_{23}\text{H}_{25}\text{BrN}_4\text{O}_{10}\text{S}$: m/z 629.0550, found 629.0552.

(2*R*,3*R*,4*S*,5*R*)-2-(acetoxymethyl)-6-[(3-(2-fluorobenzamido)-1*H*-1,2,4-triazol-5-yl)thio]tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**4k**). White solid, yield 70%, 183–185 °C; ^1H NMR (600 MHz, CDCl_3) δ : 8.25 (s, 1H), 8.10 (d, $J = 7.9$ Hz, 1H), 7.62 (d, $J = 9.9$ Hz, 1H), 7.47 (t, $J = 8.0$ Hz, 1H), 6.63 (s, 1H), 4.28 (dd, $J = 12.5, 4.4$ Hz, 1H), 4.12 (dd, $J = 12.5, 2.1$ Hz, 1H), 3.86–3.82 (m, 1H), 2.04 (s, 6H), 2.02 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ : 170.71, 170.20, 169.37, 169.32, 165.20, 159.06, 157.61, 134.28, 130.81, 123.85, 116.27, 116.13, 82.56, 76.10, 73.91, 69.32, 67.92, 61.64, 20.73, 20.61; HRMS $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{23}\text{H}_{25}\text{FN}_4\text{O}_{10}\text{S}$: m/z 569.1352, found 569.1349.

(2*R*,3*R*,4*S*,5*R*)-2-(acetoxymethyl)-6-[(3-(3-fluorobenzamido)-1*H*-1,2,4-triazol-5-yl)thio]tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**4l**). White solid, yield 68%, m.p. 184–185 °C; ^1H NMR (600 MHz, CDCl_3) δ : 8.25 (s, 1H), 8.10 (d, $J = 7.9$ Hz, 1H), 7.62 (d, $J = 9.9$ Hz, 1H), 7.47 (t, $J = 8.0$ Hz, 1H), 6.63 (s, 1H), 4.28 (dd, $J = 12.5, 4.4$ Hz, 1H), 4.12 (dd, $J = 12.5, 2.1$ Hz, 1H), 3.83–3.79 (m, 1H), 2.04 (s, 6H), 2.02 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ : 170.69, 170.20, 169.43, 169.39, 159.12, 158.55, 129.92, 129.87, 127.16, 127.14, 120.77, 120.63, 118.54, 118.37, 82.50, 76.20, 73.86, 69.36, 67.96, 61.83, 20.69, 20.62, 20.60; HRMS $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{23}\text{H}_{25}\text{FN}_4\text{O}_{10}\text{S}$: m/z 569.1352, found 569.1349.

(2*R*,3*R*,4*S*,5*R*)-2-(acetoxymethyl)-6-[(3-(4-fluorobenzamido)-1*H*-1,2,4-triazol-5-yl)thio]tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**4m**). White solid, yield 60%, m.p. 180–182 °C; ^1H NMR (600 MHz, CDCl_3) δ : 8.32 (d, $J = 9.0$ Hz, 2H), 7.20 (d, $J = 17.3$ Hz, 2H), 6.57 (s, 1H), 5.46 (d, $J = 10.3$ Hz, 2H), 5.38 (t, $J = 10.0$ Hz, 1H), 5.13 (dd, $J = 9.7, 3.4$ Hz, 1H), 4.23–3.97 (m, 3H), 2.15 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ : 170.33, 170.23, 170.04, 170.02, 169.60, 166.25, 159.10, 158.54, 156.49, 134.37, 134.31, 115.54, 115.40, 83.15, 74.74, 71.84, 67.13, 66.84, 61.35, 20.74, 20.68, 20.66, 20.59; HRMS $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{23}\text{H}_{25}\text{FN}_4\text{O}_{10}\text{S}$: m/z 569.1352, found 569.1349.

(2*R*,3*R*,4*S*,5*R*)-2-(acetoxymethyl)-6-[(3-(2-nitrobenzamido)-1*H*-1,2,4-triazol-5-yl)thio]tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (**4n**). Yellow solid, yield 63%, m.p. 211–213 °C; ^1H NMR (600 MHz, CDCl_3) δ : 8.32 (d, $J = 9.0$ Hz, 2H), 7.20 (d, $J = 17.3$ Hz, 2H), 6.57 (s, 1H), 5.46 (d, $J = 10.3$ Hz, 2H), 5.38 (t, $J = 10.0$ Hz, 1H), 5.13 (dd, $J = 9.7, 3.4$ Hz, 1H), 4.23–3.97 (m, 3H), 2.15 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ : 170.74, 170.18, 169.38, 169.32, 165.97, 156.95, 147.02, 134.18, 132.07, 129.62, 129.07, 128.77, 123.87, 82.54, 75.91, 73.87, 69.34, 67.78, 61.47, 20.74, 20.61, 20.59; HRMS $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{23}\text{H}_{25}\text{N}_5\text{O}_{12}\text{S}$: m/z 596.1288, found 596.1290.

Antifungal activity test in vitro

Antifungal activities of the target compounds against *Gibberella zeae* (*G. zeae*), *Botryosphaeria dothidea* (*B. dothidea*), *Phomopsis* sp., *Phytophthora infestans* (*P. infestans*), and

Thanatephorus cucumeris (*T. cucumeris*) were evaluated by the poison plate technique. The compounds **4a–4n** were dissolved in 1 mL DMSO before mixing with 90 mL potato dextrose agar (PDA) to prepare concentration of 50 µg/mL. Then, mycelia dishes of approximately 4 mm diameter were cut from the culture medium. A mycelium is obtained using a germ-free inoculation needle and inoculated in the middle of the PDA plate aseptically. The inoculated plates are incubated at 27 ± 1 °C for 5 d. DMSO in sterile distilled water served as the negative control and Dimethomorph served as the positive control. Each treatment condition consisted of three replicates.^[19] The relative inhibition rates *I* (%) were calculated as follows where *C* is the diameter of fungal growth on untreated PDA, *T* is the diameter of fungi on treated PDA.

$$I(\%) = [(C - T)/(C - 0.4)] \times 100\%$$

Based on the previous bioassays, the results of antifungal activity (expressed by EC₅₀) of some of the target compounds against *P. infestans* were also evaluated and calculated with SPSS 17.0 software. The experiments were repeated three times for each compound.

Antibacterial activity test in vitro

The *in vitro* antibacterial activities of **4a–4n** against *Xanthomonas oryzae* pv. *oryzae* (*Xoo*), *Xanthomonas citri* subsp. *citri* (*Xcc*) were evaluated by using the turbidimeter test, commercial agricultural antibacterial Thiodiazole-copper was used as positive control. The test compounds were dissolved in 150 µL of DMF and diluted with 0.1% (v/v) Tween-20 to prepare two concentrations of 200 and 100 µg/mL. One milliliter of the liquid sample was added to the 40 mL nontoxic nutrient broth medium (NB: 1.5 g of beef extract, 2.5 g of peptone, 0.5 g of yeast powder, 5.0 g of glucose, and 500 mL of distilled water, pH 7.0–7.2). Then, 40 µL of NB medium containing *Xoo* or *Xcc* was added to 5 mL of solvent NB containing the test compounds or Thiodiazole-copper. The inoculated test tubes were incubated at 30 ± 1 °C under continuous shaking at 180 rpm for 48 h. The culture growth was monitored spectrophotometrically by measuring the optical density at 600 nm (OD₆₀₀) and expressed as corrected turbidity.^[20] The relative inhibition rates *I* (%) were calculated as follows, where *C*_{tur} is the corrected turbidity value of bacterial growth on untreated NB, *T*_{tur} is the corrected turbidity value of bacterial growth on treated NB.

$$I(\%) = (C_{tur} - T_{tur})/C_{tur} \times 100\%$$

Conclusion

A series of novel *S*-β-*D*-glucopyranoside of 1,2,4-triazole derivatives were synthesized and evaluated for their *in vitro* antifungal and antibacterial activities. Results indicated that the title compounds exhibited moderate to good antifungal and antibacterial activities. Especially, compounds **4g**, **4k**, **4m**, and **4n** showed better antifungal activity against *P.*

infestans than that of Dimethomorph. To the best of our knowledge, this is the first report on the antifungal and antibacterial activities of this series of novel *S*-β-*D*-glucopyranoside derivatives containing a 1,2,4-triazole amide moiety.

Conflicts of interest

The authors declare no conflict of interest.

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References

- [1] Zhan, J.; Thrall, P. H.; Papa, J.; Xie, L.; Burdon, J. J. Playing on a Pathogen's Weakness: Using Evolution to Guide Sustainable Plant Disease Control Strategies. *Annu. Rev. Phytopathol.* **2015**, *53*, 19–43. DOI: 10.1146/annurev-phyto-080614-120040.
- [2] Aktar, W.; Sengupta, D.; Chowdhury, A. Impact of Pesticides Use in Agriculture: Their Benefits and Hazards. *Interdiscip. Toxicol.* **2009**, *2*, 1–12. DOI: 10.2478/v10102-009-0001-7.
- [3] Lin, Y.; He, Z.; Rosskopf, E. N.; Conn, K. L.; Powell, C. A.; Lazarovits, G. A Nylon Membrane Bag Assay for Determination of the Effect of Chemicals on Soilborne Plant Pathogens in Soil. *Plant Dis.* **2010**, *94*, 201–206. DOI: 10.1094/PDIS-94-2-0201.
- [4] Khodair, A. I.; Attia, A. M.; Gendy, E. A.; Elshair, Y. A. M. M.; Mohammed, A.; El-Magd, M. A. Discovery of New *S*-Glycosides and *N*-Glycosides of Pyridine-Biphenyl System with Antiviral Activity and Induction of Apoptosis in MCF7 Cells. *J. Heterocyclic Chem.* **2019**, *56*, 1733–1746. 2019, DOI: 10.1002/jhet.3527.
- [5] Chen, W.; Zhang, H.; Wang, J.; Hu, X. Flavonoid Glycosides from the Bulbs of *Lilium Speciosum* Var. *Gloriosoides* and Their Potential Antiviral Activity against RSV. *Chem. Nat. Compd.* **2019**, *55*, 461–464. DOI: 10.1007/s10600-019-02714-7.
- [6] Mohammed, H. S.; Abdel-Aziz, M. M.; Abu-Baker, M. S.; Saad, A. M.; Mohamed, M. A.; Ghareeb, M. A. Antibacterial and Potential Antidiabetic Activities of Flavone C-glycosides Isolated from *Beta vulgaris* Subspecies *Cicla* L. var. *Flavescens* (Amaranthaceae) Cultivated in Egypt. *Curr. Pharm. Biotechnol.* **2019**, *20*, 595–604. DOI: 10.2174/1389201020666190613161212.
- [7] Rahim, A.; Mostofa, M. G.; Sadik, M. G.; Rahman, M. A. A.; Alam, A. K. The Anticancer Activity of Two Glycosides from the Leaves of *Leea aequata* L. *Nat. Prod. Res.* **2020**, 1–5. DOI: 10.1080/14786419.2020.1798661.
- [8] Gurung, R. B.; Gong, S. Y.; Dhakal, D.; Le, T. T.; Jung, N. R.; Jung, H. J.; Oh, T.-J.; Sohng, J. K. Synthesis of Curcumin Glycosides with Enhanced Anticancer Properties Using One-Pot Multienzyme Glycosylation Technique. *J. Microbiol. Biotechnol.* **2018**, *27*, 1639–1648. DOI: 10.4014/jmb.1701.01054.
- [9] Hawas, U. W.; El-Kassem, L. T. A.; Shaher, F.; Al-Farawati, R. In Vitro Inhibition of Hepatitis c Virus Protease and Antioxidant by Flavonoid Glycosides from the Saudi Coastal Plant *Sarcocornia fruticosa*. *Nat. Prod. Res.* **2019**, *33*, 3364–3371. DOI: 10.1080/14786419.2018.1477153.

- [10] Jiang, X. L.; Wang, L.; Wang, E. J.; Zhang, G. L.; Chen, B.; Wang, M. K.; Li, F. Flavonoid Glycosides and Alkaloids from the Embryos of *Nelumbo Nucifera* Seeds and Their Antioxidant Activity. *Fitoterapia* **2018**, *125*, 184–190. DOI: [10.1016/j.fitote.2018.01.009](https://doi.org/10.1016/j.fitote.2018.01.009).
- [11] He, X.; Wang, Y.; Luo, R.-H.; Yang, L.-M.; Wang, L.; Guo, D.; Yang, J.; Deng, Y.; Zheng, Y.-T.; Huang, S.-X. Dimeric Pyranonaphthoquinone Glycosides with Anti-HIV and Cytotoxic Activities from a Soil-Derived *Streptomyces*. *J. Nat. Prod.* **2019**, *82*, 1813–1819. DOI: [10.1021/acs.jnatprod.9b00022](https://doi.org/10.1021/acs.jnatprod.9b00022).
- [12] Xiang, G.; Hu, H.; Chen, J.; Chen, W.; Wu, L. A New Agricultural Antibiotic-Ningnanmycin. *Acta Microbiol. Sin.* **1995**, *35*, 368–374. (Chinese)
- [13] Pragathi, Y. J.; Sreenivasulu, R.; Veronica, D.; Raju, R. R. Design, Synthesis, and Biological Evaluation of 1,2,4-Thiadiazole-1,2,4-Triazole Derivatives Bearing Amide Functionality as Anticancer Agents. *Arab. J. Sci. Eng.* **2021**, *46*, 225–232. DOI: [10.1007/s13369-020-04626-z](https://doi.org/10.1007/s13369-020-04626-z).
- [14] Wu, W. N.; Jiang, Y. M.; Fei, Q.; Du, H. T.; Yang, M. F. Synthesis and Antifungal Activity of Novel 1,2,4-Triazole Derivatives Containing an Amide Moiety. *J. Heterocyclic Chem.* **2020**, *57*, 1379–1386. DOI: [10.1002/jhet.3874](https://doi.org/10.1002/jhet.3874).
- [15] Mohamed, N. G.; Sheha, M. M.; Hassan, H. Y.; Abdel-Hafez, L. J. M.; Omar, F. A. Synthesis, Antimicrobial Activity and Molecular Modeling Study of 3-(5-Amino-(2H)-1,2,4-triazol-3-yl)-Naphthyridinones as Potential DNA-Gyrase Inhibitors. *Bioorg. Chem.* **2018**, *81*, 599–611. DOI: [10.1016/j.bioorg.2018.08.031](https://doi.org/10.1016/j.bioorg.2018.08.031).
- [16] Koto, S.; Yoshida, T.; Takenaka, K.; Zen, S. A through-Process for the Preparation of Methyl per-O-Acetyl 1-Thio-Glycosides from Aldoses. *BCSJ* **1982**, *55*, 3667–3668. DOI: [10.1246/bcsj.55.3667](https://doi.org/10.1246/bcsj.55.3667).
- [17] Elgemeie, G. H.; Abu-Zaied, M. A.; Nawwar, G. A. First Novel Synthesis of Triazole Thioglycosides as Ribavirin Analogues. *Nucleosides Nucleotides Nucleic Acids.* **2018**, *37*, 112–123. DOI: [10.1080/15257770.2017.1423079](https://doi.org/10.1080/15257770.2017.1423079)
- [18] Chiasson, A. I.; Robichaud, S.; Ndongou Moutombi, F. J.; Hébert, M. P. A.; Mbarik, M.; Surette, M. E.; Touaibia, M. New Zileuton-Hydroxycinnamic Acid Hybrids: Synthesis and Structure-Activity Relationship towards 5-Lipoxygenase Inhibition. *Molecules* **2020**, *25*, 4686–4704. DOI: [10.3390/molecules25204686](https://doi.org/10.3390/molecules25204686).
- [19] Tarun, K. C.; Prem, D. J. Antifungal Activity of 4-Methyl-6-Alkyl-2H-Pyran-2-Ones. *J. Agric. Food Chem.* **2006**, *54*, 2129–2133. DOI: [10.1021/jf052792s](https://doi.org/10.1021/jf052792s).
- [20] Dalgaard, P.; Ross, T.; Kamperman, L.; Neumeier, K.; McMeekin, T. A. Estimation of Bacterial Growth Rates from Turbidimetric and Viable Count Data. *Int. J. Food Microbiol.* **1994**, *23*, 391–404. DOI: [10.1016/0168-1605\(94\)90165-1](https://doi.org/10.1016/0168-1605(94)90165-1)