Research Article

Synthesis of Novel Thiazolyl Hydrazine Derivatives and Their Antifungal Activity

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A series of novel thiazolyl hydrazine derivatives **3a–3o** were synthesized and evaluated for their *in vitro* antifungal activity against six phytopathogenic strains, namely, *Botryosphaeria dothidea* (B. d.), *Gibberella sanbinetti* (G. s.), *Fusarium oxysporum* (F. o.), *Thanatephorus cucumeris* (T. c.), *Sclerotinia sclerotiorum* (S. s.), and *Verticillium dahliae* (V. d.), by the classical mycelial growth rate method. Biological assessment results showed that most of these target compounds showed good antifungal activity toward tested strains. Especially, compound **3l** showed excellent antifungal activities against B. d. and G. s. with relatively lower EC₅₀ values of 0.59 and 0.69 µg/mL, respectively, which were extremely superior to those of commercial fungicides fluopyram, boscalid, and hymexazol and were comparable to those of carbendazim. Given the excellent bioactivity of designed compounds, this kind of thiazolyl hydrazine framework can provide a suitable point for exploring highly efficient antifungal agents.

1. Introduction

Fungal infection is a serious disease that affects the appearance, yield, and quality of various plants and fruits including wheat, potatoes, rape, maize, soybeans, apple, peppers, and cucumbers, thereby attracting considerable attention in recent years [1–7]. Pesticides that are capable of attacking and annihilating intractable phytopathogenic fungi play an important role in safeguarding our crops [8]. However, due to the frequent and excessive usage of traditional fungicides, drug-resistant pathogens gradually increase year after year [9]. Additionally, plants do not have the same immune system as animals; therefore, it is urgent to develop new eco-friendly pesticides with high bioactivity and selectivity to ensure the quality and yield of agricultural products.

Recently, thiazole derivatives have been strongly highlighted in consideration of their broad-spectrum pharmaceutical and pesticidal activities, such as insecticidal, herbicidal, antiviral, bactericidal, antimalarial, anti-cancer, antioxidant, and anti-tubercular functions [10–16]. Figure 1

illustrates some representative drugs containing the versatile thiazole scaffold including othtilinone, etridiazole (EC₅₀ = 0.006 µg/mL against *Phytophthora nicotianae*), amicarbazol (EC₅₀ = 0.574 µg/mL against *Xanthomonas oryzae* pv. *oryzae*, serving as bactericidal agents), and ethaboxam (EC₅₀ = 0.006 µg/mL against *Phytophthora nicotianae*, serving as a fungicidal agent) [17–20]. On the other hand, molecular structures containing the hydrazide skeleton exhibit various biological activities such as antifungal, insecticidal, and weeding [21–23]. For instance, the correlative insecticides ANS-118 (LC₅₀ = 6.3 µg/mL against beet armyworm) and RH-5849 (EC₅₀ = 0.095 µg/mL against *Daphnia magna*), plant growth regulator daminozide, and bactericide benquinox were commercialized successively [24–27]. Therefore, thiazole and hydrazide scaffolds were considered as important skeletons in the fabrication of active molecules. In our previous works, we found that 1,3,4-oxadiazole hydrazide/sulfone/thioether derivatives showed good biological activity against plant microbial diseases [28–30]. In particular, 1,3,4-oxadiazole hydrazide derivatives performed a relatively high bioactivity against

phytopathogenic oomycetes and fungi [30]. Encouraged by those studies, herein, a series of novel thiazole hydrazide derivatives were synthesized to continue the exploration of superior bioactive substrates. All the target compounds were screened for the *in vitro* activities against phytopathogenic fungi, including *Botryosphaeria dothidea* (B. d.), *Gibberella sanbinetti* (G. s.), *Fusarium oxysporum* (F. o.), *Thanatephorus cucumeris* (T. c.), *Sclerotinia sclerotiorum* (S. s.), and *Verticillium dahliae* (V. d.).

2. Materials and Methods

2.1. Instrument and Chemicals. The NMR spectra of the synthesized compounds were measured by Bruker Biospin-AG-400 apparatus (Bruker Optics, Switzerland). DMSO and TMS were used as the solvent and internal standard, respectively. All chemicals were purchased from Energy Chemical and used without further purification. All solvents meet the standard of analytical purity. The reaction process was detected by TLC.

2.2. General Procedures for Preparing Intermediate 1. Different substituted thiobenzamide (0.01 mol), ethyl 2-chloro-3-oxobutanoate (0.012 mol), and ethanol (50 mL) were added. After reacting for 3–4 h at 100°C, the organic layer was dried, and then 100 mL ethyl acetate was added. The organic layer was washed by water, brine, dried with sodium sulfate, and filtered, followed by the removal of the solvent under vacuum. Intermediate **1** was obtained by using column chromatography with the elution solvent of petroleum ether/ethyl acetate = 30/1.

2.3. General Procedures for Preparing Intermediates 2a–2b. Intermediate **1** (0.01 mol) and sodium hydroxide solution (0.03 mol) were added in methanol (30 mL). After reacting for 2–4 h at 55°C, methanol was removed by distillation under reduced pressure. Then, the concentrated hydrochloric acid was incrementally added until the pH of the system was 2–3. Finally, intermediates **2a–2b** were obtained by filtration and desiccation. 2-(4-Chlorophenyl)-4-methylthiazole-5-carboxylic acid (**2a**): ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.00–7.87 (m, 2H, phenyl-H), 7.57–7.47 (m, 2H, phenyl-H), 2.62 (s, 3H, -CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 167.4, 163.2, 160.1, 136.3, 129.8, 128.6, 123.7, 17.5. 4-Methyl-2-(4-(trifluoromethyl)phenyl)thiazole-5-carboxylic acid (**2b**): ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.17 (d, *J* = 8.1 Hz, 2H, phenyl-H), 7.86 (d, *J* = 8.3 Hz, 2H, phenyl-H), 2.69 (s, 3H, -CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.8, 163.2, 160.2, 136.2, 131.2 (d, ²*J*_{C-F} = 32.1 Hz), 128.3, 126.7 (dd, ³*J*_{C-F} = 7.3, 3.5 Hz), 125.3 (dd, ¹*J*_{C-F} = 289.5, 191.6 Hz), 124.7, 17.5; ¹⁹F NMR (377 MHz, DMSO-*d*₆) δ -61.4.

2.4. General Procedures for Preparing the Target Compounds 3a–3o. Intermediates **2a** or **2b** (0.01 mol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI, 0.02 mol), 1-hydroxybenzotriazole (0.012 mol), and triethylamine (0.012 mol) were added in 10 mL CH₂Cl₂.

After the mixture was completely dissolved, different substituted phenylhydrazines were added. Then, the reaction was stirred for 4–5 h at 25°C. After that, 50 mL CH₂Cl₂ was added into the mixture. And the organic layer was washed by water, brine, dried with sodium sulfate, and filtered, followed by the removal of the solvent under vacuum. Finally, target compounds **3a–3o** were obtained by recrystallization in ethanol. 2-(4-Chlorophenyl)-4-methyl-*N'*-phenylthiazole-5-carbohydrazide (**3a**): a yellow solid, m. p. 185.6–186.7°C, yield 19.7%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.22 (s, 1H, -CONH-), 8.02 (s, 1H, -NH-), 7.98 (d, *J* = 8.6 Hz, 2H, phenyl-H), 7.59 (d, *J* = 8.5 Hz, 2H, phenyl-H), 7.18 (t, *J* = 7.8 Hz, 2H, phenyl-H), 6.79 (d, *J* = 7.9 Hz, 2H, phenyl-H), 6.74 (t, *J* = 7.3 Hz, 1H, phenyl-H), 2.67 (s, 3H, -CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 165.6, 161.8, 156.6, 149.5, 136.1, 131.6, 129.9, 129.3, 128.5, 124.7, 119.3, 112.8, 17.6; HRMS (ESI) [M-H]⁻ calcd for C₁₇H₁₅ON₃ClS: 344.0619, found: 344.0619.

2.5. 2-(4-Chlorophenyl)-*N'*-(2-fluorophenyl)-4-methylthiazole-5-carbohydrazide (3b**).** A yellow solid, m. p. 163.2–164.3°C, yield 25.7%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.29 (s, 1H, -CONH-), 7.98 (d, *J* = 8.6 Hz, 2H, phenyl-H), 7.95 (s, 1H, -NH-), 7.59 (d, *J* = 8.5 Hz, 2H, phenyl-H), 7.11 (d, *J* = 12.0, 8.1, 0.9 Hz, 1H, phenyl-H), 7.03 (t, *J* = 7.7 Hz, 1H, phenyl-H), 6.84 (dd, *J* = 12.2, 4.5 Hz, 1H, phenyl-H), 6.76 (d, *J* = 9.0, 6.4, 1.4 Hz, 1H, phenyl-H), 2.67 (s, 3H, -CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 165.7, 161.9, 156.9, 150.7 (d, ¹*J*_{C-F} = 239.0 Hz), 137.1 (d, ²*J*_{C-F} = 10.6 Hz), 136.1, 131.6, 129.9, 128.5, 125.1 (d, ⁴*J*_{C-F} = 2.8 Hz), 124.5, 119.5 (d, ³*J*_{C-F} = 6.8 Hz), 115.5 (d, ²*J*_{C-F} = 17.9 Hz), 114.2 (d, ³*J*_{C-F} = 3.0 Hz), 17.64; ¹⁹F NMR (377 MHz, DMSO-*d*₆) δ -132.9; HRMS (ESI) [M-H]⁻ calcd for C₁₇H₁₄ON₃ClS: 362.0525, found: 362.0525.

2.6. 2-(4-Chlorophenyl)-*N'*-(3-fluorophenyl)-4-methylthiazole-5-carbohydrazide (3c**).** A yellow solid, m. p. 195.9–196.4°C, yield 40.5%; ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.29 (s, 1H, -CONH-), 8.35 (s, 1H, -NH-), 7.98 (t, *J* = 11.3 Hz, 2H, phenyl-H), 7.58 (dd, *J* = 22.7, 8.6 Hz, 2H, phenyl-H), 7.24–7.15 (m, 1H, phenyl-H), 6.64 (dd, *J* = 15.0, 4.7 Hz, 1H, phenyl-H), 6.62–6.55 (m, 1H, phenyl-H), 6.53 (d, *J* = 6.8 Hz, 1H, phenyl-H), 6.50 (s, 1H, phenyl-H), 2.67 (s, 3H, -CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 165.7, 163.7 (d, ¹*J*_{C-F} = 240.6 Hz), 161.8, 157.0, 151.7 (d, ³*J*_{C-F} = 10.1 Hz), 136.1, 131.6, 131.0 (d, ³*J*_{C-F} = 10.0 Hz), 129.9, 128.6, 124.4, 108.7, 105.4 (d, ²*J*_{C-F} = 21.2 Hz), 99.2 (d, ²*J*_{C-F} = 25.7 Hz), 17.7; ¹⁹F NMR (377 MHz, DMSO-*d*₆) δ -133.0; HRMS (ESI) [M-H]⁻ calcd for C₁₇H₁₂ON₃ClFS: 360.0382, found: 360.0368.

2.7. 2-(4-Chlorophenyl)-*N'*-(4-fluorophenyl)-4-methylthiazole-5-carbohydrazide (3d**).** A yellow solid, m. p. 174.1–175.6°C, yield 29.4%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.24 (s, 1H, -CONH-), 8.00 (s, 1H, -NH-), 7.98 (d, *J* = 8.6 Hz, 2H, phenyl-H), 7.63–7.56 (m, 2H, phenyl-H), 7.02 (t, *J* = 8.8 Hz, 2H, phenyl-H), 6.82–6.77 (m, 2H,

FIGURE 1: Structure of few selected thiazolyl or carbohydrazide-containing drug candidates and the related design strategy for the target molecules.

phenyl-H), 2.66 (s, 3H, -CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 165.6, 161.8, 157.6, 156.5 (d, ¹J_{C-F} = 233.3 Hz), 146.1, 136.1, 131.6, 129.9 (d, ³J_{C-F} = 11.2 Hz), 128.5, 124.6, 115.8 (d, ²J_{C-F} = 22.2 Hz), 114.0 (d, ⁴J_{C-F} = 7.6 Hz), 17.6; ¹⁹F NMR (377 MHz, DMSO-*d*₆) δ -126.2; HRMS (ESI) [M-H]⁺ calcd for C₁₇H₁₂ON₃ClFS: 360.0368, found: 360.0382.

2.8. *N'*-(4-Bromophenyl)-2-(4-chlorophenyl)-4-methylthiazole-5-carbohydrazide (3e). A yellow solid, m. p. 237.7–238.2°C, yield 31.9%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.26 (s, 1H, -CONH-), 8.23 (s, 1H, -NH-), 7.98 (d, *J* = 8.5 Hz, 2H, phenyl-H), 7.59 (d, *J* = 8.5 Hz, 2H, phenyl-H), 7.33 (d, *J* = 8.7 Hz, 2H, phenyl-H), 6.74 (d, *J* = 8.8 Hz, 2H, phenyl-H), 2.66 (s, 3H, -CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 165.7, 161.8, 157.0, 148.9, 136.1, 131.9, 131.6, 129.9, 128.5, 124.4, 114.8, 110.1, 17.7; ¹⁹F NMR (377 MHz, DMSO-*d*₆) δ -61.4; HRMS (ESI) [M-H]⁻ calcd for C₁₇H₁₂ON₃BrClS: 419.9567, found: 419.9587.

2.9. 2-(4-Chlorophenyl)-4-methyl-*N'*-(4-(trifluoromethyl)phenyl)thiazole-5-carbohydrazide (3f). A white solid, m. p. 248.3–249.5°C, yield 28.3%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.37 (s, 1H, -CONH-), 8.67 (s, 1H, -NH-), 8.00 (d, *J* = 8.5 Hz, 2H, phenyl-H), 7.61 (d, *J* = 8.5 Hz, 2H, phenyl-H), 7.52 (d, *J* = 8.5 Hz, 2H, phenyl-H), 6.90 (d, *J* = 8.5 Hz, 2H, phenyl-H), 2.68 (s, 3H, -CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 165.8, 161.8, 157.2, 152.6, 136.2, 131.6, 123.0, 128.6, 126.8 (dd, ³J_{C-F} = 11.9, 2.8 Hz), 125.5 (dd, ¹J_{C-F} = 257.55 Hz), 119.1, 119.0 (dd, ²J_{C-F} = 63.2, 31.7 Hz), 112.1, 17.7; ¹⁹F NMR (377 MHz, DMSO-*d*₆) δ -59.4; HRMS (ESI) [M-H]⁻ calcd for C₁₈H₁₄ON₃ClF₃S: 412.0493, found: 412.0493.

2.10. *N'*-(3-Chlorophenyl)-2-(4-chlorophenyl)-4-methylthiazole-5-carbohydrazide (3g). A white solid, m. p. 197.1–199.3°C, yield 63.7%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.28 (s, 1H, -CONH-), 8.34 (s, 1H, -NH-), 7.98 (d, *J* = 8.5 Hz, 2H, phenyl-H), 7.59 (d, *J* = 8.5 Hz, 2H, phenyl-H), 7.19 (t, *J* = 8.0 Hz, 1H, phenyl-H), 6.77 (s, 1H, phenyl-H), 6.75 (s, 1H, phenyl-H), 6.73 (s, 1H, phenyl-H), 2.67 (s, 3H, -CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 165.7, 161.8, 157.0, 151.1, 136.1, 134.0, 131.6, 131.0, 129.9, 128.6, 124.3, 118.7, 112.0, 111.4, 17.7; HRMS (ESI) [M-H]⁻ calcd for C₁₇H₁₄ON₃Cl₂S: 378.0225, found: 378.0227.

2.11. *N'*-(4-Chlorophenyl)-2-(4-chlorophenyl)-4-methylthiazole-5-carbohydrazide (3h). A yellow solid, m. p. 164.5–165.6°C, yield 13.7%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.26 (s, 1H, -CONH-), 8.21 (s, 1H, -NH-), 7.97 (d, *J* = 8.5 Hz, 2H, phenyl-H), 7.58 (d, *J* = 8.5 Hz, 2H, phenyl-H), 7.21 (d, *J* = 8.7 Hz, 2H, phenyl-H), 6.79 (d, *J* = 8.8 Hz, 2H, phenyl-H), 2.66 (s, 3H, -CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 165.7, 161.8, 156.9, 148.5, 136.1, 131.6, 129.9, 129.1, 128.5, 124.4, 122.6, 114.3, 17.7; HRMS (ESI) [M-H]⁻ calcd for C₁₇H₁₂ON₃Cl₂S: 376.0073, found: 376.0086.

2.12. 4-Methyl-*N'*-phenyl-2-(4-(trifluoromethyl)phenyl)thiazole-5-carbohydrazide (3i). A yellow solid, m. p. 182.6–183.3°C, yield 38.8%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.28 (s, 1H, -CONH-), 8.18 (d, *J* = 8.1 Hz, 2H, phenyl-H), 8.03 (s, 1H, -NH-), 7.89 (d, *J* = 8.3 Hz, 2H, phenyl-H), 7.18 (t, *J* = 7.9 Hz, 2H, phenyl-H), 6.80 (d, *J* = 7.8 Hz, 2H, phenyl-H), 6.74 (t, *J* = 7.3 Hz, 1H, phenyl-H), 2.69 (s, 3H, -CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 165.0, 161.7, 156.8, 149.5, 136.3, 129.6, 129.3, 127.6, 126.8 (dd, ²J_{C-F} = 9.8, 5.9 Hz), 125.6, 124.5 (dd, ¹J_{C-F} = 523.4, 251.0 Hz), 119.3, 112.8, 17.6. ¹⁹F NMR (377 MHz, DMSO-*d*₆) δ -61.4; HRMS (ESI) [M-H]⁻ calcd for C₁₈H₁₅ON₃F₃S: 378.0882, found: 378.0875.

2.13. *N'*-(2-Fluorophenyl)-4-methyl-2-(4-(trifluoromethyl)phenyl)thiazole-5-carbohydrazide (**3j**). A white solid, m. p. 148.5–149.6°C, yield 43.0%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.35 (s, 1H, -CONH-), 8.18 (d, *J* = 8.1 Hz, 2H, phenyl-H), 7.97 (s, 1H, -NH-), 7.89 (d, *J* = 8.3 Hz, 2H, phenyl-H), 7.15–7.07 (m, 1H, phenyl-H), 7.03 (t, *J* = 7.7 Hz, 1H, phenyl-H), 6.89–6.83 (m, 1H, phenyl-H), 6.79–6.72 (m, 1H, phenyl-H), 2.69 (s, 3H, -CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 165.1, 161.8, 157.1, 150.7 (d, ¹*J*_{C-F} = 239.2 Hz), 137.0 (d, ²*J*_{C-F} = 10.6 Hz), 136.3, 131.1 (d, ²*J*_{C-F} = 32.1 Hz), 127.7, 126.8 (dd, ³*J*_{C-F} = 10.3, 6.4 Hz), 125.4, 125.1 (d, ⁴*J*_{C-F} = 2.9 Hz), 124.4 (q, ¹*J*_{C-F} = 272.0 Hz), 119.6 (d, ¹*J*_{C-F} = 6.7 Hz), 115.5 (d, ²*J*_{C-F} = 17.7 Hz), 114.2 (d, ³*J*_{C-F} = 3.0 Hz), 17.6; ¹⁹F NMR (377 MHz, DMSO-*d*₆) δ -61.4, -132.9; HRMS (ESI) [M-H]⁺ calcd for C₁₈H₁₂ON₃F₄S: 394.0632, found: 394.0643.

2.14. *N'*-(3-Fluorophenyl)-4-methyl-2-(4-(trifluoromethyl)phenyl)thiazole-5-carbohydrazide (**3k**). A yellow solid, m. p. 167.4–168.7°C, yield 25.4%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.34 (s, 1H, -CONH-), 8.35 (s, 1H, -NH-), 8.18 (d, *J* = 8.1 Hz, 2H, phenyl-H), 7.88 (d, *J* = 8.3 Hz, 2H, phenyl-H), 7.20 (dd, *J* = 15.4, 8.1 Hz, 1H, phenyl-H), 6.65–6.61 (m, 1H, phenyl-H), 6.54 (s, 1H, phenyl-H), 6.52–6.48 (m, 1H, phenyl-H), 2.69 (s, 3H, -CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 165.1, 163.7 (d, ¹*J*_{C-F} = 240.7 Hz), 161.7, 157.2, 151.7 (d, ³*J*_{C-F} = 10.3 Hz), 136.3, 131.3 (d, ³*J*_{C-F} = 10.3 Hz), 131.0 (d, ²*J*_{C-F} = 10.4 Hz), 127.6, 126.8 (dd, ³*J*_{C-F} = 9.0, 5.6 Hz), 125.3, 124.4 (q, ¹*J*_{C-F} = 272.4 Hz), 108.7 (d, ⁴*J*_{C-F} = 0.9 Hz), 105.4 (d, ²*J*_{C-F} = 21.3 Hz), 99.3 (d, ²*J*_{C-F} = 25.7 Hz), 17.6; ¹⁹F NMR (377 MHz, DMSO-*d*₆) δ -61.4, -113.1; HRMS (ESI) [M-H]⁺ calcd for C₁₈H₁₂ON₃F₄S: 394.0632, found: 394.0639.

2.15. *N'*-(4-Fluorophenyl)-4-methyl-2-(4-(trifluoromethyl)phenyl)thiazole-5-carbohydrazide (**3l**). A yellow solid, m. p. 186.3–187.9°C, yield 42.7%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.31 (s, 1H, -CONH-), 8.17 (d, *J* = 8.1 Hz, 2H, phenyl-H), 8.02 (s, 1H, -NH-), 7.88 (d, *J* = 8.3 Hz, 2H, phenyl-H), 7.03 (t, *J* = 8.9 Hz, 2H, phenyl-H), 6.81 (dd, *J* = 9.0, 4.6 Hz, 2H, phenyl-H), 2.68 (s, 3H, -CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 165.0, 161.7, 156.9, 156.5 (d, ¹*J*_{C-F} = 233.7 Hz), 146.0 (d, ⁴*J*_{C-F} = 0.9 Hz), 136.3, 128.4, 127.5 (d, ²*J*_{C-F} = 20.2 Hz), 126.8 (dd, ³*J*_{C-F} = 8.2, 4.9 Hz), 125.5, 124.4 (q, ¹*J*_{C-F} = 272.5 Hz), 115.8 (d, ²*J*_{C-F} = 22.3 Hz), 114.0 (d, ³*J*_{C-F} = 7.6 Hz), 17.6; ¹⁹F NMR (377 MHz, DMSO-*d*₆) δ -61.4, -126.1; HRMS (ESI) [M-H]⁺ calcd for C₁₈H₁₂ON₃F₄S: 394.0632, found: 394.0640.

2.16. *N'*-(4-Bromophenyl)-4-methyl-2-(4-(trifluoromethyl)phenyl)thiazole-5-carbohydrazide (**3m**). A yellow solid, m. p. 214.0–215.2°C, yield 50.3%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.32 (s, 1H, -CONH-), 8.25 (s, 1H, -NH-), 8.18 (d, *J* = 8.1 Hz, 2H, phenyl-H), 7.89 (d, *J* = 8.3 Hz, 2H, phenyl-H), 7.33 (d, *J* = 8.8 Hz, 2H, phenyl-H), 6.75 (d, *J* = 8.8 Hz, 2H, phenyl-H), 2.68 (s, 3H, -CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 165.1, 161.7, 157.1, 148.8, 136.3, 132.3, 131.9, 127.6, 126.7 (dd, ²*J*_{C-F} = 18.9, 7.2 Hz), 125.3, 124.2 (q, ¹*J*_{C-F} = 272.7 Hz), 114.8, 110.1, 17.6; ¹⁹F NMR (377 MHz, DMSO-*d*₆) δ -61.4; HRMS

(ESI) [M-H]⁺ calcd for C₁₈H₁₂ON₃BrF₃S: 453.9846, found: 453.9831.

2.17. 4-Methyl-*N'*,2-bis(4-(trifluoromethyl)phenyl)thiazole-5-carbohydrazide (**3n**). A white solid, m. p. 234.3–235.5°C, yield 68.4%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.43 (s, 1H, -CONH-), 8.67 (s, 1H, -NH-), 8.18 (d, *J* = 8.1 Hz, 2H, phenyl-H), 7.89 (d, *J* = 8.3 Hz, 2H, phenyl-H), 7.51 (d, *J* = 8.5 Hz, 2H, phenyl-H), 6.90 (d, *J* = 8.5 Hz, 2H, phenyl-H), 2.69 (s, 3H, -CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 165.2, 161.7, 157.4, 152.6, 136.2, 131.1 (q, ²*J*_{C-F} = 32.3 Hz), 127.6, 126.8, 126.1 (q, ¹*J*_{C-F} = 271.7 Hz), 125.1, 124.4 (q, ¹*J*_{C-F} = 272.4 Hz), 119.1 (q, ²*J*_{C-F} = 31.6 Hz), 113.2, 112.1, 17.7; ¹⁹F NMR (377 MHz, DMSO-*d*₆) δ -59.4, -61.5; HRMS (ESI) [M-H]⁺ calcd for C₁₉H₁₂ON₃F₉S: 444.0608, found: 444.0600.

2.18. *N'*-(3-Chlorophenyl)-4-methyl-2-(4-(trifluoromethyl)phenyl)thiazole-5-carbohydrazide (**3o**). A white solid, m. p. 201.3–202.6°C, yield 44.6%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.36 (s, 1H, -CONH-), 8.38 (s, 1H, -NH-), 8.20 (d, *J* = 8.1 Hz, 2H, phenyl-H), 7.90 (d, *J* = 8.3 Hz, 2H, phenyl-H), 7.21 (t, *J* = 7.9 Hz, 1H, phenyl-H), 6.86–6.80 (m, 1H, phenyl-H), 6.79 (d, *J* = 5.6 Hz, 1H, phenyl-H), 6.77 (d, *J* = 5.3 Hz, 1H, phenyl-H), 2.71 (s, 3H, -CH₃); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 165.2, 161.7, 157.2, 151.1, 136.3, 134.0, 131.0, 127.6, 127.4, 126.8 (dd, *J* = 9.5, 5.9 Hz), 125.2, 124.4 (dd, *J* = 544.5, 272.3 Hz), 118.8, 112.1, 111.4, 17.6; ¹⁹F NMR (377 MHz, DMSO-*d*₆) δ -61.4; HRMS (ESI) [M-H]⁺ calcd for C₁₈H₁₄ON₃ClF₃S: 412.0490, found: 412.0492.

3. Results and Discussion

3.1. *Synthesis of Target Compounds 3a–3o*. As shown in Scheme 1, the starting material substituted thiobenzamide was subjected by two sequential reactions including cyclization and hydrolysis to provide a crucial intermediate 2-(4-chlorophenyl)-4-methylthiazole-5-carboxylic acid (**2a**) or 4-methyl-2-(4-(trifluoromethyl)phenyl)thiazole-5-carboxylic acid (**2b**). The final target compounds **3a–3o** were obtained through the condensation reaction between **2a** (or **2b**) and different substituted phenylhydrazines in solvent CH₂Cl₂ at 25°C. These chemical structures were determined by using NMR and HRMS analyses (Figures S1–S61, Supplementary Materials).

3.2. *Antifungal Activities of Target Compounds 3a–3o and Structure-Activity Relationship (SAR)*. Their antifungal activity against aforementioned six kinds of plant pathogens was evaluated by using the mycelium growth rate approach, while the most applied antimicrobial drugs, namely, fluopyram (FP), boscalid (BS), hymexazol (HM), prochloraz (PC), and carbendazim (CB) were co-assayed for comparison. Table 1 reveals that some of the target compounds were identified with excellent antimicrobial activities at 25.0 μg/mL. For the biological effect against *B. d.* strain, compounds **3a**, **3b**, **3d**, and **3g–3l** gave the inhibition rate within 70.0–88.5%, which were better than positive

SCHEME 1: Synthetic route for target compounds **3a–3o**.TABLE 1: Inhibition rates of compounds **3a–3o** against *B. d.*, *G. s.*, *V. d.*, *T. c.*, *S. s.*, and *F. o.* at 25.0 $\mu\text{g/mL}$.

Compounds	Inhibition rate (%)					
	<i>B. d.</i>	<i>G. s.</i>	<i>V. d.</i>	<i>T. c.</i>	<i>S. s.</i>	<i>F. o.</i>
3a	70.0 $\pm$ 1.7	78.7 $\pm$ 0.7	67.7 $\pm$ 0.9	70.0 $\pm$ 1.5	48.0 $\pm$ 1.7	25.7 $\pm$ 0.5
3b	72.3 $\pm$ 1.2	71.8 $\pm$ 0.8	79.7 $\pm$ 0.6	83.6 $\pm$ 1.2	73.9 $\pm$ 0.5	76.1 $\pm$ 0.5
3c	67.8 $\pm$ 1.3	58.5 $\pm$ 0.9	46.7 $\pm$ 0.6	71.8 $\pm$ 0.4	40.3 $\pm$ 1.0	63.7 $\pm$ 0.6
3d	80.2 $\pm$ 1.7	86.1 $\pm$ 1.0	81.1 $\pm$ 0.6	77.7 $\pm$ 0.6	65.8 $\pm$ 0.8	12.8 $\pm$ 1.7
3e	65.0 $\pm$ 1.0	54.4 $\pm$ 0.5	51.5 $\pm$ 1.5	25.7 $\pm$ 0.6	47.2 $\pm$ 2.1	0
3f	41.0 $\pm$ 1.0	20.4 $\pm$ 1.4	41.1 $\pm$ 0.5	11.3 $\pm$ 0.5	41.2 $\pm$ 0.9	0
3g	76.9 $\pm$ 1.8	64.8 $\pm$ 1.8	34.9 $\pm$ 1.6	49.8 $\pm$ 1.0	0	19.0 $\pm$ 1.0
3h	88.5 $\pm$ 1.0	69.9 $\pm$ 0.5	68.6 $\pm$ 1.6	68.3 $\pm$ 0.6	44.0 $\pm$ 1.2	6.4 $\pm$ 0.9
3i	71.5 $\pm$ 0.8	55.3 $\pm$ 0.4	56.4 $\pm$ 1.0	52.0 $\pm$ 1.7	50.0 $\pm$ 1.8	42.8 $\pm$ 1.3
3j	74.5 $\pm$ 0.9	51.6 $\pm$ 0.1	66.7 $\pm$ 0.7	90.3 $\pm$ 0.6	69.1 $\pm$ 0.1	50.3 $\pm$ 0.9
3k	74.7 $\pm$ 1.0	71.3 $\pm$ 0.5	56.7 $\pm$ 1.0	98.7 $\pm$ 0.6	85.5 $\pm$ 1.5	55.3 $\pm$ 0.1
3l	79.3 $\pm$ 0.8	80.5 $\pm$ 0.5	80.8 $\pm$ 1.0	81.1 $\pm$ 0.6	72.7 $\pm$ 1.7	0
3m	65.0 $\pm$ 1.0	54.4 $\pm$ 0.5	51.5 $\pm$ 1.5	25.7 $\pm$ 0.6	47.2 $\pm$ 2.1	0
3n	8.0 $\pm$ 1.0	17.3 $\pm$ 2.0	44.6 $\pm$ 1.6	19.7 $\pm$ 1.3	33.8 $\pm$ 0.1	0
3o	62.1 $\pm$ 1.1	29.7 $\pm$ 1.3	16.7 $\pm$ 1.4	20.7 $\pm$ 1.8	0	32.0 $\pm$ 1.0
FP	35.3 $\pm$ 0.6	46.9 $\pm$ 1.3	21.3 $\pm$ 1.2	10.1 $\pm$ 1.5	66.1 $\pm$ 1.0	25.7 $\pm$ 1.0
BS	36.5 $\pm$ 1.0	19.8 $\pm$ 1.0	82.7 $\pm$ 2.3	70.6 $\pm$ 1.0	62.8 $\pm$ 1.0	13.4 $\pm$ 1.4
HM	15.4 $\pm$ 1.0	44.6 $\pm$ 1.0	30.0 $\pm$ 1.0	75.2 $\pm$ 0.6	26.9 $\pm$ 1.0	50.6 $\pm$ 0.5
CB	100	100	33.0 $\pm$ 0.5	100	100	100
PC	100	100	75.6 $\pm$ 0.5	37.2 $\pm$ 1.2	100	100

drugs FP (35.3%), BS (36.5%), and HM (15.4%), but lower compared to CB (100%) and PC (100%). For the anti-*G. s.* activity, compounds **3a**, **3b**, **3d**, **3k**, and **3l** afforded the inhibitory effect of 78.7%, 71.8%, 86.1%, 71.3%, and 80.5%, respectively. For the anti-*V. d.* activity, compounds **3b**, **3d**, and **3l** gave the appreciable bioactivity with ratios of 79.7%, 81.1%, and 80.8%, respectively. By contrast, compound **3k** was extremely bioactive against *T. c.* strain with the inhibition ratio of 98.7%. Simultaneously, this compound (**3k**) also displayed the best anti-*S. s.* activity with inhibitory

rate of 85.5%. For the anti-*F. o.* activity, compound **3b** yielded the best bioactivity with the rate of 76.1%. Among all the target molecules, compounds **3b**, **3j**, and **3k** displayed the comprehensive bioactivity against all the tested fungal strains (*B. d.*, *G. s.*, *V. d.*, *T. c.*, *S. s.*, and *F. o.*) with the corresponding inhibitory rates of 72.3%, 71.8%, 79.7%, 83.6%, 73.9%, and 76.1% (for compound **3b**), 74.5%, 51.6%, 66.7%, 90.3%, 69.1%, and 50.3% (for compound **3j**), and 74.7%, 71.3%, 56.7%, 98.7%, 85.5%, and 55.3% (for compound **3k**). After careful observation, it was found that the

TABLE 2: EC₅₀ values of compounds **3a–3o** against tested fungi *in vitro*.

Comp.	Pathogens	Regression equation	EC ₅₀ (μg/mL)	Comp.	Pathogens	Regression equation	EC ₅₀ (μg/mL)
3a	<i>B. d.</i>	$y = 0.493x + 4.987$	1.05 ± 0.17	3h	<i>V. d.</i>	$y = 0.541x + 4.696$	3.63 ± 0.18
	<i>G. s.</i>	$y = 1.104x + 4.220$	5.08 ± 0.20		<i>T. c.</i>	$y = 1.186x + 3.626$	14.4 ± 0.33
	<i>S. s.</i>	$y = 1.491x + 3.361$	12.6 ± 0.6	3i	<i>B. d.</i>	$y = 1.028x + 4.992$	1.01 ± 0.09
	<i>T. c.</i>	$y = 0.759x + 4.110$	14.9 ± 1.3		<i>B. d.</i>	$y = 0.562x + 4.483$	1.75 ± 0.16
	<i>B. d.</i>	$y = 0.460x + 4.937$	1.36 ± 0.53	3j	<i>S. s.</i>	$y = 0.508x + 4.547$	7.77 ± 0.70
3b	<i>G. s.</i>	$y = 0.476x + 4.977$	1.11 ± 0.13		<i>V. d.</i>	$y = 0.672x + 4.543$	4.78 ± 0.32
	<i>S. s.</i>	$y = 1.545x + 3.651$	7.45 ± 0.29		<i>T. c.</i>	$y = 1.726x + 4.269$	2.64 ± 0.06
	<i>V. d.</i>	$y = 0.677x + 4.939$	1.22 ± 0.25	3k	<i>B. d.</i>	$y = 0.476x + 5.030$	0.86 ± 0.12
	<i>T. c.</i>	$y = 0.905x + 4.444$	4.10 ± 0.27		<i>G. s.</i>	$y = 0.596x + 4.772$	2.41 ± 0.15
	<i>F. o.</i>	$y = 1.162x + 3.984$	7.47 ± 0.21		<i>S. s.</i>	$y = 1.352x + 3.559$	11.6 ± 0.38
3c	<i>B. d.</i>	$y = 0.351x + 4.939$	1.48 ± 0.22	3l	<i>T. c.</i>	$y = 1.578x + 4.636$	1.70 ± 0.02
	<i>G. s.</i>	$y = 0.281x + 4.806$	4.89 ± 0.52		<i>B. d.</i>	$y = 0.547x + 5.123$	0.59 ± 0.04
	<i>T. c.</i>	$y = 0.827x + 4.219$	8.77 ± 0.85		<i>G. s.</i>	$y = 1.163x + 5.186$	0.69 ± 0.04
	<i>F. o.</i>	$y = 0.528x + 4.318$	19.6 ± 3.5	3m	<i>S. s.</i>	$y = 1.352x + 3.559$	5.57 ± 0.30
	<i>B. d.</i>	$y = 0.585x + 4.883$	1.58 ± 0.06		<i>V. d.</i>	$y = 1.208x + 4.820$	1.40 ± 0.06
3d	<i>G. s.</i>	$y = 1.048x + 4.721$	1.84 ± 0.12		<i>T. c.</i>	$y = 1.150x + 4.330$	3.82 ± 0.17
	<i>S. s.</i>	$y = 2.100x + 2.913$	9.48 ± 0.24	3o	<i>B. d.</i>	$y = 0.695x + 4.373$	7.97 ± 0.91
	<i>V. d.</i>	$y = 1.171x + 4.346$	3.61 ± 0.15		<i>B. d.</i>	$y = 0.690x + 4.392$	7.60 ± 0.51
	<i>T. c.</i>	$y = 0.967x + 4.478$	3.46 ± 0.23		<i>B. d.</i>	$y = 1.131x + 5.996$	0.13 ± 0.01
3e	<i>B. d.</i>	$y = 0.695x + 4.373$	7.97 ± 0.91	CB	<i>G. s.</i>	$y = 4.016x + 5.629$	0.70 ± 0.01
	<i>B. d.</i>	$y = 0.507x + 5.015$	0.93 ± 0.03		<i>S. s.</i>	$y = 3.322x + 7.326$	0.20 ± 0.01
3f	<i>G. s.</i>	$y = 0.524x + 4.682$	4.05 ± 0.12		<i>T. c.</i>	$y = 2.322x + 4.772$	1.25 ± 0.05
	<i>B. d.</i>	$y = 0.520x + 5.133$	0.55 ± 0.02		<i>F. o.</i>	$y = 4.116x + 6.058$	0.55 ± 0.01
3g	<i>G. s.</i>	$y = 0.558x + 4.815$	2.14 ± 0.21				

final bioactivity of target compounds could be significantly affected by a number of factors, such as the kind and electronic property of substitutional group, the type of halogen, and the location of halogen on the benzene ring. The detailed SAR is summarized as follows. (1) As $R_1 = 4\text{-Cl}$, introducing 2-F (**3b**) and 4-F (**3d**) on the benzene ring could improve the bioactivity against *B. d.*, *G. s.*, *V. d.*, *T. c.*, and *S. s.* strains compared to **3a** ($R_2 = \text{H}$), while $R_2 = 3\text{-F}$ and 4-Br normally gave a reduced tendency on the bioactivity. (2) A strong electron-withdrawing group ($R_2 = 4\text{-CF}_3$, **3f**) significantly decreased the antifungal activity. (3) The halogen atom at the para-position showed better bioactivity than that of meta-position, illustrated by compounds **3d** (4-F, 80.2%, 86.1%, 81.1%, 77.7%, and 65.8% against *B. d.*, *G. s.*, *V. d.*, *T. c.*, and *S. s.*, respectively) and **3c** (3-F, 67.8%, 58.5%, 46.7%, 71.8%, and 40.3% against *B. d.*, *G. s.*, *V. d.*, *T. c.*, and *S. s.*, respectively), and **3h** (4-Cl, 88.5%, 69.9%, 68.6%, 68.3%, and 44.0% against *B. d.*, *G. s.*, *V. d.*, *T. c.*, and *S. s.*, respectively) and **3g** (3-Cl, 76.9%, 64.8%, 34.9%, 49.8%, and 0 against *B. d.*, *G. s.*, *V. d.*, *T. c.*, and *S. s.*, respectively). (4) As $R_1 = 4\text{-CF}_3$, introducing 2-F, 3-F, or 4-F could distinctly enhance the anti-*T. c.* activity from 52.0% (-H, **3i**) to 90.3% (2-F, **3j**), 98.7% (3-F, **3k**), and 81.1% (4-F, **3l**), respectively. (5) Similarly, the strong electron-withdrawing group ($R_2 = 4\text{-CF}_3$, **3n**) significantly reduced the antifungal activity. (6) The bioactivity comparison of **3a–3g** ($R_1 = 4\text{-Cl}$) and **3i–3o** ($R_1 = 4\text{-CF}_3$) revealed that the former series compound normally gave a relatively ameliorative antifungal activity.

Further bioactivity screening results are shown in Table 2 and expressed by EC₅₀ values. Clearly, compounds **3g**, **3h**, **3k**, and **3l** provided excellent biological actions against *B. d.*, with the corresponding values of 0.93, 0.55, 0.86, and 0.59 μg/mL.

The EC₅₀ values of these compounds were close to CB (0.13 μg/mL). Compounds **3b**, **3d**, **3h**, **3k**, and **3l** showed good anti-*G. s.* activity with EC₅₀ values of 1.11, 1.84, 2.14, 2.41, and 0.69 μg/mL, respectively. Distinctly, compound **3l** exerted the comparative inhibitory effect than that of CB (0.70 μg/mL). Compounds **3b**, **3d**, **3h**, **3j**, and **3l** were bioactive against *V. d.* with the corresponding EC₅₀ values of 1.22, 3.61, 3.63, 4.78, and 1.40 μg/mL. By contrast, compounds **3a**, **3b**, **3d**, **3j**, and **3k** provided moderate anti-*S. s.* activity with EC₅₀ values of 12.6, 7.45, 9.48, 7.77, and 11.6 μg/mL, respectively. For the anti-*T. c.* activity, compounds **3b**, **3d**, **3j**, **3k**, and **3l** showed good inhibitory effect with EC₅₀ values of 4.10, 3.46, 2.64, 1.70, and 3.82 μg/mL, respectively. By contrast, only compounds **3b** and **3c** had good EC₅₀ values against *V. d.* (7.47 and 19.6 μg/mL, respectively). The above result indicated that the rational design of thiazolyl hydrazine derivatives can help in acquiring high bioactive substrates.

4. Conclusions

In summary, novel simple thiazolyl hydrazide derivatives were prepared and assessed for their antifungal activities. The result indicated that most of these designed compounds gave good antifungal activity against the tested six fungi. Compounds **3a**, **3b**, **3c**, **3d**, and **3g–3o** displayed strong bioactivity against *B. d.*, providing EC₅₀ values ranging from 0.59 to 1.75 μg/mL, which were better than controlled drugs of fluopyram (>25 μg/mL), hymexazol (>25 μg/mL), and boscalid (>25 μg/mL) and slightly weaker than carbendazim (0.13 μg/mL). Compounds **3b**, **3d**, and **3l** displayed excellent bioactivity against *G. s.* with EC₅₀ values of 1.11, 1.84, and 0.69 μg/mL, respectively. Given these excellent bioactivities,

this novel thiazolyl hydrazide framework can provide a good starting point for designing more potent antifungal agents.

Data Availability

The data supporting these results are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Jianjun Zhu was responsible for investigation, data curation, formal analysis, methodology, and original draft preparation. Yazhen Chen and Fen Su were responsible for data curation, formal analysis, and methodology. Peiyi Wang was responsible for data curation, supervision, formal analysis, and review and editing.

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Supplementary Materials

The supplementary data contain the related NMR and HRMS spectra for the intermediates **2a-2b** and target compounds **3a-3o** (Figures S1–S61). (*Supplementary Materials*)

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