Research Article

Synthesis and Antifungal and Insecticidal Activities of Novel *N*-Phenylbenzamide Derivatives Bearing a Trifluoromethylpyrimidine Moiety

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Received 27 June 2021; Revised 23 August 2021; Accepted 25 August 2021; Published 16 September 2021

Academic Editor: Yaqiong Su

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Seventeen novel *N*-phenylbenzamide derivatives bearing a trifluoromethylpyrimidine moiety were synthesized via four-step reactions. Their antifungal and insecticidal properties were evaluated. Antifungal test results demonstrated that some of the synthesized compounds showed better in vitro bioactivities against *Phomopsis* sp., *Botryosphaeria dothidea* (*B. dothidea*), and *Botrytis cinerea* (*B. cinerea*) at 50 µg/mL than pyrimethanil. Unfortunately, the synthesized compounds revealed lower insecticidal activities against *Spodoptera frugiperda* (*S. frugiperda*) and *Mythimna separata* (*M. separata*) at 500 µg/mL than chlorantraniliprole.

1. Introduction

Plant fungal diseases and insect pests have drawn widespread attention because of their enormous damage toward agriculture [14]. The traditional commercial fungicides and insecticides used to prevent and control plant diseases could increase the yield, improve the quality of agricultural products, and also not reduced huge loss annually [5, 6]. However, the misuse of traditional fungicides and insecticides had speeded up the resistance of plant diseases, which is rapidly becoming a huge challenge in agriculture [7, 8]. Therefore, it is still an urgent and meaningful task to develop the novel, highly efficient, and promising pesticides.

Pyrimidine is one of best important chemical scaffolds for application in pesticide chemistry, medicinal chemistry, and material chemistry. Many of pyrimidine derivatives play an important role of bioactive compounds, such as antifungal [9, 10], antibacterial [11, 12], acaricidal [13, 14] insecticidal [15, 16], herbicidal [17, 18], and antiviral [19, 20] activities. Meanwhile, *N*-phenylbenzamide, a key active fragment in pesticide chemistry, is usually used as a pesticide active fragment and exhibit extensive biological activities,

such as antiviral, antifungal, antibacterial, herbicidal, and insecticidal activities [21]. Our early work has reported a series of novel benzamide derivatives containing a pyrimidine moiety (Figure 1) with better antiviral, insecticidal, antifungal, and antibacterial activities [26–33].

Herein, to develop new highly bioactivity lead compounds, we replace benzamide to *N*-phenylbenzamide (Figure 2) to design a series of novel *N*-phenylbenzamide derivatives containing a trifluoromethylpyrimidine moiety and then evaluate their antifungal and insecticidal activities.

2. Experimental

2.1. Materials and Methods. The melting points were obtained by using an XT-4 binocular microscope (Beijing Tech. Instrument Co., China). NMR spectral recorded on a Bruker Avance NEO 600 NMR spectrometer (Bruker Corporation, MA, USA) using DMSO-*d*₆ as a solvent. HRMS data were obtained on a Thermo Scientific Q Exactive FOCUS instrument (Thermo Fisher Scientific, CA, USA). Analytical TLC was performed on silica gel GF₂₅₄.

SCHEME 1: Synthetic route for the target compounds **4a–4q**.

FIGURE 1: The structures of the pyrimidine derivatives reported in our previous work.

FIGURE 2: Design route of the target compounds **4a–4q**.

2.2. General Procedure for the Preparation of Intermediates 1 and 2. Trifluoroacetoacetate (0.1 mol) with ethanol (200 mL) was added to a 500 mL round bottom flask. Then, formamidine hydrochloride (0.1 mol) or acetamidine hydrochloride (0.1 mol) and 1,8-diazabicyclo[5.4.0]undecane-7-ene (DBU, 0.15 mol) were added to the mixture and

reacted for 10 h at reflux temperature. After completion, the mixture was cooled to room temperature, acidified with 1 mol/L HCl to pH 7, extracted with ethyl acetate, and evaporated under vacuum to produce intermediate 1. Then, intermediate 1 (0.1 mol), POCl₃ (0.2 mol), and CH₃CN (240 mL) were added to a 500 mL round bottom flask and

reacted for 0.5 h at reflux temperature. After that, diisopropylethylamine (0.12 mol) was added dropwise and continuously reacted for 8 h. After completion, excess POCl₃ and CH₃CN were removed by distillation, and then ice-water mixture (120 mL) was added. Finally, the mixture was alkalinized with 5 mol/L NaOH to pH 9 and extracted using CH₂Cl₂ to give intermediate 2.

2.3. General Procedure for the Preparation of the Key Intermediate 3. To a 100 mL round bottom flask, intermediate 2 (0.012 mol) dissolved in acetone (10 mL), Cs₂CO₃ (0.02 mol), and 4-hydroxybenzoic acid (0.01 mol) were added and reacted for 2–3 h at room temperature. After the completion of reaction, the excess solvent was removed, and the residue was added to distilled water (50 mL) and acidified with concentrated HCl to pH 2–3. The precipitate was filtered and recrystallized from ethanol to give key intermediate 3. The structures of intermediate 3 were confirmed by ¹H NMR and ¹³C NMR. The physical characteristics and ¹H NMR and ¹³C NMR data for intermediate 3 are shown as follows.

2.3.1. 4-((6-(Trifluoromethyl)pyrimidine-4-yl)oxy)benzoic acid (3a). White solid; yield: 80.1%; m.p. 147–148°C; ¹H NMR (600 MHz, DMSO-*d*₆, ppm) δ 9.02 (s, 1H, pyrimidine-H), 8.41 (s, 1H, pyrimidine-H), 8.21 (d, 1H, *J* = 8.4 Hz, Ph-H), 7.86 (d, *J* = 8.4 Hz, 1H, Ph-H), 7.70 (t, *J* = 7.2 Hz, 1H, Ph-H), 7.70 (t, *J* = 7.8 Hz, 1H, Ph-H); ¹³C NMR (150 MHz, DMSO-*d*₆, ppm) δ 170.34, 159.75, 156.12 (q, *J* = 36.0 Hz), 143.24, 129.97, 128.63, 126.01, 121.53 (q, *J* = 272.85 Hz), 120.46, 109.99, 105.44.

2.3.2. 4-((2-Methyl-6-(trifluoromethyl)pyrimidine-4-yl)oxy)benzoic acid (3b). White solid; yield: 70.0%; m.p. 145–146°C; ¹H NMR (600 MHz, DMSO-*d*₆, ppm) δ 12.56 (s, 1H, COOH), 7.80 (d, *J* = 8.4 Hz, 2H, Ph-H), 7.48 (s, 1H, pyrimidine-H), 6.83 (d, *J* = 8.4 Hz, 2H, Ph-H), 2.35 (s, 3H, CH₃); ¹³C NMR (150 MHz, DMSO-*d*₆, ppm) δ 167.63, 162.69, 162.06, 151.96 (q, *J* = 35.25 Hz), 131.98, 122.09 (q, *J* = 273.00 Hz), 121.82, 115.56, 111.07, 25.90.

2.4. General Procedure for the Preparation of the Target Compounds (4a–4q). To a 50 mL round bottom flask, the key intermediate 3 (0.024 mol), dichloromethane (20 mL), aromatic amides (0.02 mol), dimethylaminopyridine (DMAP, 0.0004 mol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 0.03 mol) were added, respectively. The reaction was carried out at room temperature for 8–10 h. After the completion of the reaction, the solvent was evaporated under vacuum condition and then the residue was recrystallized from ethanol to give pure target compounds 4a–4q. The physical characteristics, ¹H NMR, ¹³C NMR, and HRMS data for all the target compounds are shown in Supplementary Materials.

2.4.1. N-(4-fluorophenyl)-4-((6-(trifluoromethyl)pyrimidine-4-yl)oxy)benzamide (4a). White solid; yield: 35.0%; m.p. 172–174°C; ¹H NMR (600 MHz, DMSO-*d*₆, ppm) δ 10.37 (s,

1H, CONH), 8.98 (s, 1H, pyrimidine-H), 8.05 (d, *J* = 8.7 Hz, 2H, Ph-H), 7.86 (s, 1H, pyrimidine-H), 7.79 (dd, *J*₁ = 9.1 Hz, *J*₂ = 5.0 Hz, 2H, Ph-H), 7.45 (d, *J* = 8.7 Hz, 2H, Ph-H), 7.20 (t, *J* = 8.9 Hz, 2H, Ph-H); ¹³C NMR (150 MHz, DMSO-*d*₆, ppm) δ 170.38, 165.13, 159.74, 156.24 (q, *J* = 35.60 Hz), 154.57, 135.94, 133.17, 130.07, 122.59, 122.52, 122.17, 121.92, 121.82 (q, *J* = 272.30 Hz), 115.79, 115.57, 107.03; HRMS (ESI) calcd. for C₁₈H₁₂F₄N₃O₂ [M + H]⁺: 378.3061, found: 378.0851.

2.4.2. N-(4-chlorophenyl)-4-((6-(trifluoromethyl)pyrimidine-4-yl)oxy)benzamide (4b). White solid; yield: 42.5%; m.p. 176–179°C; ¹H NMR (600 MHz, DMSO-*d*₆, ppm) δ 10.43 (s, 1H, CONH), 8.98 (s, 1H, pyrimidine-H), 8.05 (d, *J* = 8.5 Hz, 2H, Ph-H), 7.85 (s, 1H, pyrimidine-H), 7.82 (d, *J* = 8.8 Hz, 2H, Ph-H), 7.45 (d, *J* = 8.6 Hz, 2H, Ph-H), 7.41 (d, *J* = 8.8 Hz, 2H, Ph-H); ¹³C NMR (150 MHz, DMSO-*d*₆, ppm) δ 170.26, 162.10, 159.38, 156.24 (q, *J* = 35.60 Hz), 143.29, 137.81, 134.89, 134.83, 134.81, 133.75, 132.50, 126.97, 126.96, 126.92, 122.21 (q, *J* = 273.60 Hz), 106.95; HRMS (ESI) calcd. for C₁₈H₁₂ClF₃N₃O₂ [M + H]⁺: 394.0565, found: 394.0563.

2.4.3. N-(4-bromophenyl)-4-((6-(trifluoromethyl)pyrimidine-4-yl)oxy)benzamide (4c). White solid; yield: 26.8%; m.p. 168–171°C; ¹H NMR (600 MHz, DMSO-*d*₆, ppm) δ 10.42 (s, 1H, CONH), 8.99 (s, 1H, pyrimidine-H), 8.04 (dd, *J*₁ = 8.6, *J*₂ = 6.3 Hz, 2H, Ph-H), 7.84 (s, 1H, pyrimidine-H), 7.76 (d, *J* = 8.9 Hz, 2H, Ph-H), 7.54 (dd, *J*₁ = 8.8, *J*₂ = 1.3 Hz, 2H, Ph-H), 7.45 (d, *J* = 8.7 Hz, 1H, Ph-H), 7.41 (d, *J* = 8.7 Hz, 1H, Ph-H); ¹³C NMR (150 MHz, DMSO-*d*₆, ppm) δ 170.37, 165.36, 164.09, 159.73, 156.25 (q, *J* = 34.6 Hz), 151.28, 139.01, 138.98, 133.07, 132.44, 131.93, 130.15, 122.60, 122.21 (q, *J* = 273.65 Hz), 121.94, 115.85, 107.00; HRMS (ESI) calcd. for C₁₈H₁₁BrF₃N₃O₂ [M + H]⁺: 438.0060, found: 438.0057.

2.4.4. N-(4-methoxyphenyl)-4-((6-(trifluoromethyl)pyrimidine-4-yl)oxy)benzamide (4d). White solid; yield: 62.1%; m.p. 143–145°C; ¹H NMR (600 MHz, DMSO-*d*₆, ppm) δ 10.20 (s, 1H, CONH), 8.99 (s, 1H, pyrimidine-H), 8.06 (d, *J* = 9.0 Hz, 2H, Ph-H), 7.85 (s, 1H, pyrimidine-H), 7.70 (d, *J* = 8.4 Hz, 2H, Ph-H), 7.46 (d, *J* = 8.4 Hz, 2H, Ph-H), 6.95 (d, *J* = 9.0 Hz, 2H, Ph-H), 3.76 (s, 3H, CH₃O); ¹³C NMR (125 MHz, DMSO-*d*₆, ppm) δ 170.41, 169.77, 159.76, 156.20 (q, *J* = 34.95 Hz), 156.06, 154.43, 133.45, 132.65, 129.98, 122.22, 122.09, 121.81 (q, *J* = 272.85 Hz), 114.23, 107.00, 55.65; HRMS (ESI) calcd. for C₁₉H₁₅F₃N₃O₃ [M + H]⁺: 390.1060, found: 390.1060.

2.4.5. N-(4-methylphenyl)-4-((6-(trifluoromethyl)pyrimidine-4-yl)oxy)benzamide (4e). White solid; yield: 62.1%; m.p. 162–164°C; ¹H NMR (600 MHz, DMSO-*d*₆, ppm) δ 10.24 (s, 1H, CONH), 8.99 (s, 1H, pyrimidine-H), 8.18 (d, *J* = 8.4 Hz, 2H, Ph-H), 7.86 (s, 1H, pyrimidine-H), 7.68 (d, *J* = 8.4 Hz, 2H, Ph-H), 7.46 (d, *J* = 8.4 Hz, 2H, Ph-H), 7.18 (d, *J* = 7.8 Hz, 2H, Ph-H), 2.29 (s, 3H, CH₃); ¹³C NMR (150 MHz, DMSO-*d*₆, ppm) δ 170.41, 165.01, 159.76, 156.20 (q, *J* = 35.25 Hz), 154.48, 140.34, 137.07, 133.45, 133.14, 130.05, 129.49, 122.10, 121.81 (q, *J* = 272.85 Hz), 120.80, 106.99, 20.97; HRMS (ESI)

calcd. for $C_{19}H_{15}F_3N_3O_2$ $[M + H]^+$: 374.1113, found: 374.1110.

2.4.6. *N*-(3-chloro-4-fluorophenyl)-4-((6-(trifluoromethyl)pyrimidine-4-yl)oxy)benzamide (**4f**). White solid; yield: 25.6%; m.p. 178–179°C; 1H NMR (600 MHz, DMSO- d_6 , ppm) δ 10.58 (s, 1H, CONH), 9.06 (s, 1H, pyrimidine-H), 8.18–8.12 (m, 3H, Ph-H), 7.93 (s, 1H, pyrimidine-H), 7.82–7.78 (m, 1H, Ph-H), 7.56–7.48 (m, 3H, Ph-H); ^{13}C NMR (150 MHz, DMSO- d_6 , ppm) δ 170.33, 165.34, 159.71, 156.23 (q, J = 35.0 Hz), 155.01, 154.73, 152.60, 136.82, 132.77, 130.12, 121.83 (q, J = 272.85 Hz), 122.23, 121.01, 119.55, 119.37, 117.40, 107.04; HRMS (ESI) calcd. for $C_{18}H_{10}F_4ClN_3O_2$ $[M + Na]^+$: 434.0293, found: 434.0290.

2.4.7. *N*-(4-bromo-3-chlorophenyl)-4-((6-(trifluoromethyl)pyrimidine-4-yl)oxy)benzamide (**4g**). White solid; yield: 32.7%; m.p. 187–189°C; 1H NMR (600 MHz, DMSO- d_6 , ppm) δ 10.57 (s, 1H, CONH), 8.99 (s, 1H, pyrimidine-H), 8.18 (d, J = 2.4 Hz, 1H, Ph-H), 8.08 (d, J = 9.0 Hz, 2H, Ph-H), 7.87 (s, 1H, pyrimidine-H), 7.75 (d, J = 9.0 Hz, 1H, Ph-H), 7.73–7.66 (m, 1H, Ph-H), 7.49 (d, J = 9.0 Hz, 2H, Ph-H); ^{13}C NMR (150 MHz, DMSO- d_6 , ppm) δ 170.37, 167.43, 165.56, 159.75, 156.41 (q, J = 34.8 Hz), 154.86, 140.34, 134.27, 133.40, 132.72, 132.17, 131.99, 130.23, 129.13, 122.62, 122.25 (q, J = 272.55 Hz), 120.02, 115.83, 115.36, 110.00, 103.75; HRMS (ESI) calcd. for $C_{18}H_9F_3ClBrN_3O_2$ $[M + Na]^+$: 470.9592, found: 470.9590.

2.4.8. 4-((2-methyl-6-(trifluoromethyl)pyrimidine-4-yl)oxy)-*N*-phenylbenzamide (**4h**). White solid; yield: 30.0%; m.p. 167–169°C; 1H NMR (600 MHz, DMSO- d_6 , ppm) δ 10.32 (s, 1H, CONH), 8.07 (d, J = 8.4 Hz, 2H, Ph-H), 7.79 (d, J = 7.8 Hz, 2H, Ph-H), 7.60 (s, 1H, pyrimidine-H), 7.45 (d, J = 9.0 Hz, 2H, Ph-H), 7.30 (t, J = 7.8 Hz, 2H, Ph-H), 7.12 (t, J = 7.2 Hz, 2H, Ph-H), 2.52 (s, 3H, CH₃); ^{13}C NMR (150 MHz, DMSO- d_6 , ppm) δ 170.30, 169.70, 165.24, 156.39 (q, J = 35.1 Hz), 155.94, 154.64, 139.62, 130.12, 129.11, 124.20, 122.01, 121.83 (q, J = 272.85 Hz), 120.81, 103.80, 25.93; HRMS (ESI) calcd. for $C_{19}H_{14}F_3N_3O_2$ $[M + H]^+$: 372.0964, found: 372.0954.

2.4.9. 4-((2-methyl-6-(trifluoromethyl)pyrimidine-4-yl)oxy)-*N*-(2-methoxyphenyl)benzamide (**4i**). White solid; yield: 21.5%; m.p. 168–170°C; 1H NMR (600 MHz, DMSO- d_6 , ppm) δ 9.96 (s, 1H, CONH), 8.11 (d, J = 8.4 Hz, 2H, Ph-H), 7.59 (s, 1H, pyrimidine-H), 7.45 (d, J = 9.0 Hz, 2H, Ph-H), 7.37 (d, J = 7.2 Hz, 2H, Ph-H), 7.29 (d, J = 7.2 Hz, 2H, Ph-H), 7.23 (t, J = 6.0 Hz, 2H, Ph-H), 7.19 (t, J = 7.2 Hz, 2H, Ph-H), 2.53 (s, 3H, CH₃), 2.26 (s, 3H, CH₃); ^{13}C NMR (150 MHz, DMSO- d_6 , ppm) δ 170.30, 169.71, 164.96, 156.60, 155.41 (q, J = 34.6 Hz), 156.18, 155.94, 154.63, 136.83, 134.22, 132.72, 130.79, 130.07, 127.07, 126.51, 122.21 (q, J = 273.8 Hz), 122.03, 103.76, 25.90, 18.39; HRMS (ESI) calcd. for $C_{20}H_{16}F_3N_3O_2$ $[M + H]^+$: 386.1121, found: 386.1111.

2.4.10. *N*-(4-fluorophenyl)-4-((2-methyl-6-(trifluoromethyl)pyrimidin-4-yl)oxy)benzamide (**4j**). White solid; yield: 38.4%; m.p. 175–178°C; 1H NMR (600 MHz, DMSO- d_6 , ppm) δ 10.38 (s, 1H, CONNH), 8.04 (d, J = 8.7 Hz, 2H, Ph-H), 7.79 (dd, J_1 = 9.1, J_2 = 5.1 Hz, 2H, Ph-H), 7.58 (s, 1H, pyrimidine-H), 7.43 (d, J = 8.7 Hz, 2H, Ph-H), 7.19 (t, J = 8.9 Hz, 2H, Ph-H), 2.51 (s, 3H, CH₃); ^{13}C NMR (150 MHz, DMSO- d_6 , ppm) δ 170.22, 169.66, 165.12, 159.95, 157.54, 156.39 (q, J = 34.8 Hz), 154.62, 135.95, 132.96, 130.06, 122.60, 122.52, 122.24 (q, J = 273.3 Hz), 122.02, 115.77, 115.55, 103.75, 25.88; HRMS (ESI) calcd. for $C_{19}H_{14}F_4N_3O_2$ $[M + H]^+$: 392.1017, found: 392.1014.

2.4.11. *N*-(4-chlorophenyl)-4-((2-methyl-6-(trifluoromethyl)pyrimidine-4-yl)oxy)benzamide (**4k**). White solid; yield: 42.5%; m.p. 172–174°C; 1H NMR (600 MHz, DMSO- d_6 , ppm) δ 10.37 (s, 1H, CONH), 8.05 (d, J = 8.8 Hz, 2H, Ph-H), 7.79 (dd, J_1 = 3.2, J_2 = 6.0 Hz, 2H, Ph-H), 7.60 (s, 1H, pyrimidine-H), 7.45 (d, J = 8.7 Hz, 2H, Ph-H), 7.20 (t, J = 8.9 Hz, 2H, Ph-H), 2.51 (s, 3H, CH₃); ^{13}C NMR (150 MHz, DMSO- d_6 , ppm) δ 170.24, 169.66, 165.32, 156.40 (q, J = 34.6 Hz), 154.71, 138.56, 132.86, 132.47, 130.13, 129.79, 129.02, 127.76, 122.25 (q, J = 273.6 Hz), 122.05, 103.78, 25.90; HRMS (ESI) calcd. for $C_{19}H_{14}ClF_3N_3O_2$ $[M + H]^+$: 408.0721, found: 408.0720.

2.4.12. *N*-(4-bromophenyl)-4-((2-methyl-6-(trifluoromethyl)pyrimidin-4-yl)oxy)benzamide (**4l**). White solid; yield: 42.5%; m.p. 172–174°C; 1H NMR (600 MHz, DMSO- d_6 , ppm) δ 10.44 (s, 1H, CONH), 8.06 (d, J = 8.8 Hz, 2H, Ph-H), 7.78 (d, J = 8.8 Hz, 2H, Ph-H), 7.60 (s, 1H, pyrimidine-H), 7.56 (d, J = 9.2 Hz, 2H, Ph-H), 7.46 (d, J = 8.8 Hz, 2H, Ph-H), 2.52 (s, 3H, CH₃); ^{13}C NMR (150 MHz, DMSO- d_6 , ppm) δ 170.19, 169.64, 165.33, 156.41 (q, J = 34.6 Hz), 155.01, 154.80, 152.59, 136.83, 132.55, 130.11, 122.21 (q, J = 273.0 Hz), 121.03, 119.55, 119.37, 117.18, 103.79, 25.96; HRMS (ESI) calcd. for $C_{18}H_{11}BrF_3N_3O_2$ $[M + H]^+$: 450.0068, found: 450.0065.

2.4.13. *N*-(4-methoxyphenyl)-4-((2-methyl-6-(trifluoromethyl)pyrimidine-4-yl)oxy)benzamide (**4m**). White solid; yield: 56.2%; m.p. 154–155°C; 1H NMR (600 MHz, DMSO- d_6 , ppm) δ 10.21 (s, 1H, –CONH–), 8.04 (d, J = 8.6 Hz, 2H, Ph-H), 7.68 (d, J = 9.0 Hz, 2H, Ph-H), 7.57 (s, 1H, pyrimidine-H), 7.42 (d, J = 8.7 Hz, 2H, Ph-H), 6.92 (d, J = 9.0 Hz, 2H, Ph-H), 3.74 (s, 3H, CH₃O), 2.51 (s, 3H, CH₃); ^{13}C NMR (150 MHz, DMSO- d_6 , ppm) δ 170.26, 169.67, 164.75, 156.39 (q, J = 34.8 Hz), 156.00, 154.46, 133.22, 132.63, 129.95, 122.36, 122.24 (q, J = 273.2 Hz), 121.94, 114.18, 103.74, 55.59, 25.88; HRMS (ESI) calcd. for $C_{20}H_{17}F_3N_3O_2$ $[M + Na]^+$: 425.1195, found: 425.1196.

2.4.14. 4-((2-methyl-6-(trifluoromethyl)pyrimidine-4-yl)oxy)-*N*-(4-methoxyphenyl)benzamide (**4n**). White solid; yield: 39.9%; m.p. 167–168°C; 1H NMR (600 MHz, DMSO- d_6 , ppm) δ 10.24 (s, 1H, CONH), 8.04 (d, J = 8.4 Hz, 2H, Ph-H), 7.65 (d, J = 8.0 Hz, 2H, Ph-H), 7.56 (s, 1H, pyrimidine-H),

7.42 (d, $J = 8.4$ Hz, 2H, Ph-H), 7.15 (d, $J = 7.6$ Hz, 2H, Ph-H), 2.50 (s, 3H, CH₃), 2.26 (s, 3H, CH); ¹³C NMR (150 MHz, DMSO-*d*₆, ppm) δ 170.22, 169.66, 165.01, 156.40 (q, $J = 34.8$ Hz), 154.49, 136.97, 133.16, 130.00, 129.45, 122.23 (q, $J = 273.3$ Hz), 121.94, 120.81, 103.68, 25.86, 20.92; HRMS (ESI) calcd. for C₁₉H₁₄ClF₃N₃O₂ [M + H]⁺: 408.0721, found: 408.0723.

2.4.15. 4-((2-methyl-6-(trifluoromethyl)pyrimidine-4-yl)oxy)-*N*-(4-(trifluoromethoxy)phenyl) benzamide (**4o**). White solid; yield: 26.2%; m.p. 164–167°C; ¹H NMR (600 MHz, DMSO-*d*₆, ppm) δ 10.51 (s, 1H, CONH), 8.07 (d, $J = 8.4$ Hz, 2H, Ph-H), 7.92 (d, $J = 8.4$ Hz, 2H, Ph-H), 7.61 (s, 1H, pyrimidine-H), 7.46 (d, $J = 8.4$ Hz, 2H, Ph-H), 7.38 (d, $J = 8.4$ Hz, 2H, Ph-H), 2.53 (s, 3H, CH₃); ¹³C NMR (150 MHz, DMSO-*d*₆, ppm) δ 170.25, 169.69, 165.38, 156.65, 156.41 (q, $J = 35.25$ Hz), 154.77, 144.37, 138.83, 132.82, 130.17, 122.09, 122.05, 121.96, 121.82 (q, $J = 272.85$ Hz), 121.48 (q, $J = 254.25$ Hz), 103.76, 25.80; HRMS (ESI) calcd. for C₂₀H₁₃F₆N₃O₃ [M + Na]⁺: 480.0756, found: 480.0753.

2.4.16. *N*-(4-bromo-3-chlorophenyl)-4-((2-methyl-6-(trifluoromethyl)pyrimidine-4-yl)oxy)benzamide (**4p**). White solid; yield: 48.0%; m.p. 166–169°C; ¹H NMR (600 MHz, DMSO-*d*₆, ppm) δ 10.57 (s, 1H, CONH), 8.18 (d, $J = 2.4$ Hz, 1H, Ph-H), 8.07 (d, $J = 9.0$ Hz, 2H, Ph-H), 7.76 (d, $J = 9.0$ Hz, 1H, Ph-H), 7.73–7.66 (m, 1H, Ph-H), 7.61 (s, 1H, pyrimidine-H), 7.47 (d, $J = 9.0$ Hz, 2H, Ph-H), 2.51 (s, 3H, CH₃); ¹³C NMR (150 MHz, DMSO-*d*₆, ppm) δ 170.23, 169.68, 167.43, 165.54, 156.42 (q, $J = 34.9$ Hz), 155.01, 154.93, 140.35, 134.25, 133.40, 132.50, 132.17, 131.98, 130.22, 129.13, 122.12, 122.24 (q, $J = 273.3$ Hz), 122.08, 121.03, 119.55, 117.40, 117.18, 103.79, 25.88. HRMS (ESI) calcd. for C₁₉H₁₂BrClF₃N₃O₂ [M + H]⁺: 485.9826, found: 485.9825.

2.4.17. *N*-(3-chloro-4-(trifluoromethoxy)phenyl)-4-((2-methyl-6-(trifluoromethyl)pyrimidine-4-yl)oxy)benzamide (**4q**). White solid; yield: 29.0%; m.p. 176–178°C; ¹H NMR (600 MHz, DMSO-*d*₆, ppm) δ 10.66 (s, 1H, CONH), 8.20 (d, $J = 2.4$ Hz, 1H, Ph-H), 8.08 (d, 2H, $J = 8.4$ Hz, Ph-H), 7.86 (dd, $J_1 = 2.4$ Hz, $J_2 = 6.6$ Hz, 1H, Ph-H), 7.59–7.57 (m, 2H, Ph-H and pyrimidine-H), 7.47 (d, $J = 9.0$ Hz, 2H, Ph-H), 2.53 (s, 3H, CH₃); ¹³C NMR (150 MHz, DMSO-*d*₆, ppm) δ 170.21, 169.69, 165.59, 156.42 (q, $J = 34.8$ Hz), 154.95, 139.92, 132.42, 130.24, 126.44, 123.99, 122.11, 121.99, 121.81 (q, $J = 273.3$ Hz), 121.41 (q, $J = 256.35$ Hz), 120.53, 103.78, 25.88. HRMS (ESI) calcd. for C₂₀H₁₃F₆ClN₃O₃ [M + H]⁺: 492.0551, found: 492.0544.

2.5. In Vitro Antifungal Activity Test. The in vitro antifungal activities against *Phomopsis* sp., *B. dothidea*, and *B. cinerea* of the target compounds **4a–4q** at 50 μ g/mL were evaluated by the mycelium growth rate technique [32]. Each compound was dissolved in 1 mL DMSO and 9 mL 0.1% Twain aqueous solution, and then the mixture solution was added to 90 mL potato dextrose agar (PDA) medium to obtain 100 mL mixed PDA medium with the test compound concentration

of 50 μ g/mL. The mixed PDA mediums were poured into 6 dishes and cooled to room temperature to prepare PDA plates. Then, approximately 0.4 cm diameter mycelia dishes were cut from culture medium and transferred to the middle of PDA plates with a germfree inoculation needle. After that, the inoculated PDA plates were fostered at 27 $\pm$ 1°C for 3–4 days. Three replicates were conducted for each treatment. The following formula (1) was used to calculate the inhibition rates *I* (%), where *C* (cm) represents the diameter of fungi growth on untreated PDA and *T* (cm) represents the diameter of fungi on treated PDA:

$$I(\%) = \left[\frac{(C - T)}{(C - 0.4)} \right] \times 100. \quad (1)$$

2.6. Insecticidal Activity Test. The insecticidal activities against *S. frugiperda* and *M. separata* of the target compounds **4a–4q** at 500 μ g/mL were performed according to the reported methods [33]. Each compound was added to 0.1 mg/L NP-10 solvent to prepare the test compound solution with 500 μ g/mL concentration. Then, approximately 5 cm length maize leaves and 3 cm diameter sweet corn leaves were soaked into the mixed solutions for 10 s and then dried at room temperature and placed in the Petri dish. After that, 30 larvae of second-instar *S. frugiperda* and *M. separata* were transferred into the Petri dish and cultivated in the incubator at 27 $\pm$ 1°C for 48 h. Three replicates were performed for each treatment. The mortality rates were determined using Abbott's formula.

3. Results and Discussion

3.1. Chemistry. The synthetic route for the target compounds is summarized in Scheme 1. Firstly, using ethyl trifluoroacetoacetate, formamidine hydrochloride, and acetamidine hydrochloride as raw materials, 2-substituted-4-chloro-6-(trifluoromethyl)pyrimidine (**2**) was synthesized including cyclization and chlorination reactions. Next, the key intermediate 2-substituted-4-((6-(trifluoromethyl)pyrimidin-4-yl)oxy)benzoic acid (**3**) was synthesized from 2-substituted-4-chloro-6-(trifluoromethyl)pyrimidine (**2**) reacting with 4-hydroxybenzoic acid and cesium carbonate in acetone under reflux conditions. Finally, the target compounds **4a–4q** were obtained from 2-substituted-4-((6-(trifluoromethyl)pyrimidin-4-yl)oxy)benzoic acid (**3**) and aromatic amines by amidation reaction.

3.2. Antifungal Activity Test in Vitro. Table 1 showed that compounds **4a**, **4j**, **4o**, and **4q** exhibited higher antifungal activity against *B. dothidea*, with the inhibition rates of 89.8%, 85.9%, 93.1%, and 98.5%, respectively, which were even better than pyrimethanil (84.4%). Meanwhile, compounds **4o** and **4q** exhibited higher antifungal activity against *Phomopsis* sp., with the inhibition rates of 89.0% and 92.0%, respectively, which were even better than pyrimethanil (85.1%). Furthermore, compounds **4a**, **4f**, **4g**, **4o**, **4p**, and **4q** revealed excellent antifungal activity against

TABLE 1: The *in vitro* antifungal activities against *Phomopsis* sp., *B. dothidea*, and *B. cinerea* of the target compounds **4a–4q** at 50 $\mu\text{g/mL}$.

Compounds	Inhibition rate (%)		
	<i>B. dothidea</i>	<i>Phomopsis</i> sp.	<i>B. cinerea</i>
4a	90.8 $\pm$ 1.1	63.4 $\pm$ 2.1	93.3 $\pm$ 1.2
4b	79.2 $\pm$ 1.2	57.0 $\pm$ 1.3	83.6 $\pm$ 1.4
4c	67.5 $\pm$ 1.1	50.5 $\pm$ 1.8	72.0 $\pm$ 1.0
4d	64.5 $\pm$ 1.9	60.2 $\pm$ 2.1	66.6 $\pm$ 1.2
4e	24.6 $\pm$ 1.5	46.0 $\pm$ 1.4	56.8 $\pm$ 1.4
4f	94.3 $\pm$ 1.4	80.6 $\pm$ 2.0	91.7 $\pm$ 2.3
4g	76.8 $\pm$ 1.1	79.1 $\pm$ 1.2	86.8 $\pm$ 1.7
4h	46.5 $\pm$ 2.3	56.1 $\pm$ 2.1	55.2 $\pm$ 2.6
4i	32.1 $\pm$ 2.4	34.4 $\pm$ 1.1	39.6 $\pm$ 1.1
4j	85.9 $\pm$ 1.9	61.0 $\pm$ 2.1	81.3 $\pm$ 3.2
4k	70.9 $\pm$ 1.2	51.2 $\pm$ 1.8	75.2 $\pm$ 1.8
4l	62.9 $\pm$ 2.5	45.1 $\pm$ 2.2	66.8 $\pm$ 2.3
4m	53.5 $\pm$ 1.5	56.2 $\pm$ 1.1	56.0 $\pm$ 1.8
4n	43.4 $\pm$ 1.8	46.1 $\pm$ 2.1	53.8 $\pm$ 1.2
4o	93.5 $\pm$ 1.3	89.0 $\pm$ 1.0	96.7 $\pm$ 2.2
4p	70.8 $\pm$ 1.1	72.1 $\pm$ 1.2	83.8 $\pm$ 1.0
4q	98.5 $\pm$ 1.3	92.0 $\pm$ 1.0	97.6 $\pm$ 2.2
Pyrimethanil	84.4 $\pm$ 2.1	85.1 $\pm$ 1.4	82.8 $\pm$ 1.4

TABLE 2: The insecticidal activities against *S. frugiperda* and *M. separata* of the target compounds **4a–4q** at 500 $\mu\text{g/mL}$.

Compounds	Mortality rate (%)	
	<i>S. frugiperda</i>	<i>M. separata</i>
4a	20.0 $\pm$ 1.6	13.3 $\pm$ 1.0
4b	30.0 $\pm$ 1.0	26.7 $\pm$ 1.2
4c	33.3 $\pm$ 1.5	36.7 $\pm$ 2.2
4d	23.3 $\pm$ 2.0	16.7 $\pm$ 2.0
4e	10.0 $\pm$ 1.5	13.3 $\pm$ 1.3
4f	53.3 $\pm$ 2.8	56.7 $\pm$ 1.2
4g	46.7 $\pm$ 2.0	50.0 $\pm$ 1.0
4h	73.3 $\pm$ 2.2	90.0 $\pm$ 1.5
4i	30.0 $\pm$ 1.2	53.3 $\pm$ 1.2
4j	26.7 $\pm$ 1.5	20.0 $\pm$ 1.8
4k	40.0 $\pm$ 2.4	33.3 $\pm$ 2.0
4l	43.3 $\pm$ 1.5	36.7 $\pm$ 2.2
4m	26.7 $\pm$ 2.0	20.0 $\pm$ 2.4
4n	16.7 $\pm$ 1.2	23.3 $\pm$ 1.8
4o	83.3 $\pm$ 1.6	60.0 $\pm$ 2.3
4p	40.0 $\pm$ 1.3	63.3 $\pm$ 1.5
4q	86.7 $\pm$ 1.8	80.0 $\pm$ 2.4
Chlorantraniliprole	100	100

B. cinerea, with the inhibition rates of 90.3%, 91.7%, 86.8%, 96.7%, 83.8%, and 98.5%, respectively, which were even better than pyrimethanil (82.8%). Especially, compound **4q** revealed the best antifungal activity against *B. dothidea* (98.5%), *Phomopsis* sp. (92.0%), and *B. cinerea* (98.5%) than those of pyrimethanil and the other target compounds.

According to the antifungal activity data, the difference of R_1 and R_2 substituent groups was related to the antifungal activity of the target compounds. When the R_2 was the same group, with the presence of -H at R_1 , the target compound

revealed higher antifungal activity than compound with the R_1 was -CH₃. When R_1 was H, compounds with the presence of -F and -OCF₃ at R_2 represented higher antifungal activity compared with the other target compounds.

3.3. Insecticidal Activity Test. Table 2 shows that the target compounds **4a–4p** indicated lower insecticidal activities against *S. frugiperda* (10.0–86.7%) and *M. separata* (13.3–90.0%) at 500 $\mu\text{g/mL}$ than those of chlorantraniliprole. Especially, compound **4h** demonstrated an excellent mortality rate of 90.0% against *M. separata* as well as compounds **4o** and **4q** revealed moderate insecticidal activity against *S. frugiperda* with the mortality rates of 83.3% and 86.7%, respectively.

4. Conclusion

In summary, 17 novel *N*-phenylbenzamide derivatives containing a trifluoromethylpyrimidine moiety were prepared, and their structures were confirmed by ¹H NMR, ¹³C NMR, and HRMS. Biological activity results indicated that most of the target compounds exhibited moderate to good antifungal and insecticidal activities. Among them, compound **4q** revealed the best antifungal activities against *Phomopsis* sp., *B. dothidea*, and *B. cinerea* than those of pyrimethanil and the other target compounds. This study provided hope for discovery, development, design, and synthesis of novel *N*-phenylbenzamide derivatives containing a trifluoromethylpyrimidine.

Data Availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

All authors state that there are no conflicts of interest.

Acknowledgments

The authors acknowledge funds from the Science and Technology Fund Project of Guizhou (nos. [2020]1Z023, [2019]1454, and [2019]1015), National Natural Science Foundation of China (nos. 31701821 and 21762037), Young Sci-Tech Talents Growth Program from the Department of Education of Guizhou Province (nos. QJHKYZ[2018]297 and QJHKYZ[2018]303), Guiyang Science and Technology Bureau and Guiyang University (no. GYU-KY-[2021]), and Undergraduate Innovation and Entrepreneurship Training Program (nos. 2018520773 and 2018520841).

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