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Design, synthesis, and evaluation of new 4(3*H*)-quinazolinone derivatives containing a pyrazole carboxamide moiety

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Abstract

A total of 15 new 4(3*H*)-quinazolinone derivatives containing a pyrazole carboxamide moiety were designed and synthesized in this study. The structures of the target compounds were elucidated using ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis. Then, antifungal activities against *Gibberella zeae* (*G. zeae*), *Fusarium oxysporum* (*F. oxysporum*), *Cytospora mandshurica* (*C. mandshurica*), *Phytophthora infestans* (*P. infestans*), and *Pellicularia sasakii* (*P. sasakii*) as well as antibacterial activities against *Ralstonia solanacearum* (*R. solanacearum*) and *Xanthomomu oryzae* pv. *oryzae* (*Xoo*) were assayed. Bioassay results revealed that the target compounds have certain antifungal and antibacterial activities. Especially, compound 5-chloro-1,3-dimethyl-*N*-(2-(4-*oxo*-2-(*m*-tolylamino)quinazolin-3(4*H*)-yl)ethyl)-1*H*-pyrazole-4-carboxamide (**7g**) exhibited better antibacterial activities against *R. solanacearum* (60%) and *Xoo* (53%) than those of thiodiazole-copper (52% and 38%, respectively) at 200 μg/ml. This study provided a practical tool for guiding the design and synthesis of novel and more promising active small molecules of 4(3*H*)-quinazolinone derivatives containing a pyrazole carboxamide moiety for controlling plant bacterial and fungal diseases.

1 | INTRODUCTION

Plant bacterial and fungal diseases continue to contribute to heavy global crop losses and restrict the sustainable development of agriculture despite the best control efforts of plant pathologists. The preventive and curative use of synthetic chemical pesticides are the most widely accepted approaches in plant bacterial and fungal disease management [1]. However, apart from the sometimes-prohibitive costs and the rapidity with which bacterial and fungal pathogens develop resistance, increased consumer awareness of the detrimental effects of synthetic chemical pesticides threaten their continued use [2]. Therefore, it is necessary to develop novel lead molecules with potent bioactivities against bacterial and fungal diseases.

4(3*H*)-Quinazolinone and its derivatives, a group of high-potential and biologically active pharmacophoric nitrogen-containing heterocyclic molecules, have received

considerable attention in recent years because of their broad spectrum of pesticide properties, including antibacterial [3–7], antifungal [3–6], antiviral [8–10], insecticidal [11–13], and herbicidal [14] activities. Our previous studies have designed and synthesized a series of 4(3*H*)-quinazolinone derivatives containing an imines or isoxazole moiety (Figure 1), bioassay results showed that the target compounds exhibited better antibacterial and antifungal activities [3–5]. Meanwhile, pyrazole carboxamide derivatives are important heterocyclic compounds in the development of chemical pesticides because of their broad spectrum of biological activities like antifungal [15–18], antiviral [19,20], insecticidal [21–23], herbicidal [24,25], and nematocidal [26] activities. Many recent studies have been conducted on the synthesis and biological activity of pyrazole carboxamide derivatives and some pyrazole carboxamide derivatives have been developed and commercialized as fungicides in succession, such as penthiopyrad, furametpyr, penflufen, isopyrazam, and bixafen [15–26].

In view of the facts and to explore the potential lead molecules with potent antifungal and antibacterial activities, a series of 4(3*H*)-quinazolinone derivatives containing a pyrazole carboxamide moiety are designed and synthesized in the current study. Bioassay results revealed that the target compounds have certain antifungal and antibacterial activities. Especially, compound 5-chloro-1,-3-dimethyl-*N*-(2-(4-*oxo*-2-(*m*-tolylamino)quinazolin-3(4*H*)-yl)ethyl)-1*H*-pyrazole-4-carboxamide (**7g**) exhibited good antibacterial activities against *Ralstonia solanacearum* (*R. solanacearum*) and *Xanthomomu oryzae* pv. *oryzae* (*Xoo*) which were even better than those of thiodiazole-copper at 200 μg/ml.

2 | MATERIAL AND METHODS

2.1 | General information

^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL-ECX 500 NMR spectrometer (JEOL Ltd., Japan) operated using DMSO-d_6 as solvent at room temperature. Mass spectral was conducted on an Agilent 5973 mass spectrometer (Agilent Technologies, Santa Clara, CA, USA). Elemental analysis was performed using an Elemental Vario-III CHN analyzer (Elementar, Germany). All solvents were dried by standard methods in advance and distilled before use.

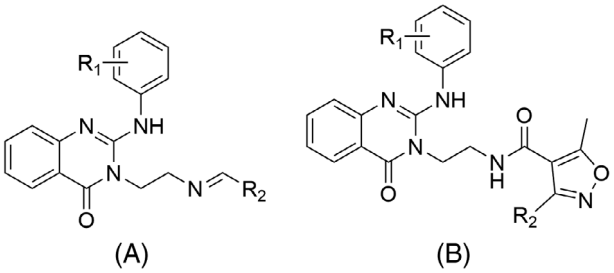


FIGURE 1 Compounds previously reported with good antibacterial and antifungal activities

2.2 | General procedure for the preparation of the key intermediates 6

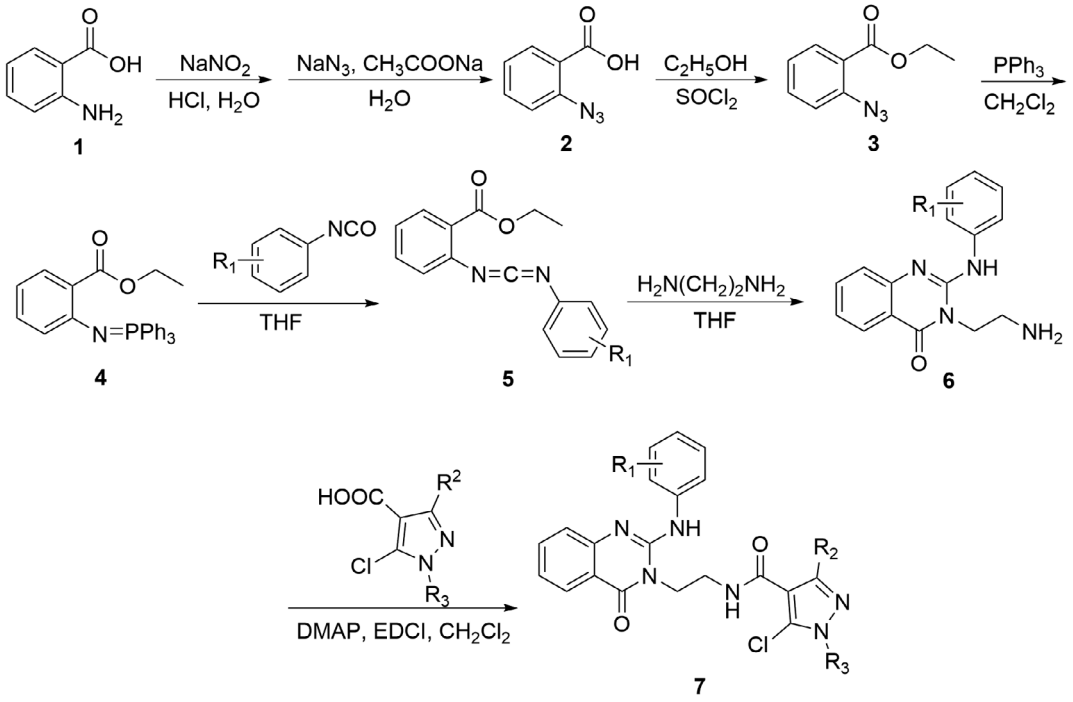
As shown in Scheme 1, intermediates **6** were synthesized by a five-step process following previously reported procedures [4–6].

2.3 | General procedure for the preparation of the target compounds 7a–7o

To a 50 ml three-necked round-bottomed flask, 1,3-substituted 5-chloro-1*H*-pyrazole-4-carboxylic acid (1.2 mmol), dimethylaminopyridine (DMAP, 1.5 mmol), and CH_2Cl_2 (10 ml) were added in order and reacted for 0.5 h at 0°C. After that, intermediates **6** (1.0 mmol), *N*-methylmorpholine (20 μl), and carbodiimide hydrochloride (EDCI, 1.5 mmol) were added to the mixture, and the reactions were reacted at room temperature for 2.5–8.0 h. Upon completion of reaction, the redundant 1,3-substituted 5-chloro-1*H*-pyrazole-4-carboxylic acid was removed by 10% $NaHCO_3$ solution. Finally, the residues were filtrated, dried under vacuum, and recrystallized from CH_2Cl_2/C_2H_5OH (1:15, v/v) to give pure products **7a–7o**.

2.4 | In vitro antifungal activity test

IN this study, the in vitro antifungal activities of the target compounds **7a–7o** against *Gibberella zeae* (*G. zeae*), *Fusarium oxysporum* (*F. oxysporum*), *Cytospora mandshurica* (*C. mandshurica*), *Phytophthora infestans* (*P. infestans*), and *Pellicularia sasakii* (*P. sasakii*) were screened at the concentration of 50 μg/ml by using the mycelium growth rate method [4–6]. All the target compounds, dissolved in 1 ml DMSO, were mixed with 90 ml potato dextrose agar (PDA) medium. Then, approximately 4-mm diameter mycelia dishes, cut from the culture PDA medium, were inoculated in the middle of the PDA plates. After that, the inoculated PDA plates were incubated in biochemical incubator at 28°C for approximately 5 days. DMSO was served as the negative control, whereas hymexazol and epoxiconazole widely used for controlling *G. zeae*,



7a: R_1 = H, R_2 = CH_3, R_3 = Ph
7b: R_1 = H, R_2 = CH_3, R_3 = CH_3
7c: R_1 = H, R_2 = CH_3, R_3 = 4-Cl-Ph
7d: R_1 = 4-CH_3, R_2 = CH_3, R_3 = Ph
7e: R_1 = 4-CH_3, R_2 = CH_3, R_3 = 4-Cl-Ph
7f: R_1 = 3-CH_3, R_2 = CH_3, R_3 = Ph
7g: R_1 = 3-CH_3, R_2 = CH_3, R_3 = CH_3
7h: R_1 = 3-CH_3, R_2 = CH_3, R_3 = 4-Cl-Ph
7i: R_1 = 4-Cl, R_2 = CH_3, R_3 = Ph
7j: R_1 = 4-Cl, R_2 = CH_3, R_3 = CH_3
7k: R_1 = 4-CH_3, R_2 = CF_3, R_3 = Ph
7l: R_1 = 4-OCF_3, R_2 = CF_3, R_3 = Ph
7m: R_1 = 4-Cl, R_2 = CF_3, R_3 = Ph
7n: R_1 = 4-OCF_3, R_2 = Cl, R_3 = 2-pyridyl
7o: R_1 = 4-Cl, R_2 = Cl, R_3 = 2-pyridyl

SCHEME 1 General synthesis route for the target compounds **7a–7o**

F. oxysporum, *C. mandshurica*, *P. infestans*, and *P. sasakii* [5,27,28] were served as the positive controls. Inhibition rates *I* (%) of the target compounds against the test fungus are calculated by the following formula, where C is the fungi diameter of the untreated PDA medium, and T is the fungi diameter of the treated PDA medium. Each experiment was repeated three times.

$$\text{Inhibition rate } I\,(\%) = (C - T)/(C - 0.4) \times 100.$$

2.5 | In vitro antibacterial activity test

In this study, the in vitro antibacterial activities of the target compounds **7a–7o** against *R. solanacearum* and *Xoo* were screened by the turbidimeter test [4–6]. Approximately 40 μl of solvent nutrient broth (NB) mediums containing *R. solanacearum* and *Xoo*, respectively, were added to the test tubes containing 5 ml solvent NB mediums with the testing compounds or the commercial bactericides concentrations of 200 and 100 μg/ml, respectively. The inoculated test tubes were incubated in a constant temperature shaker at 28°C and 180 rpm for 24–48 h until the optical density at 595 nm (OD_{595}) of the bacteria were cultured to 0.6–0.8. DMSO was served as the negative control, whereas kocide 3000, thiodiazole copper, and bismerthiazol widely used for controlling *R. solanacearum* and *Xoo* [28–30] were served as the positive controls. The OD_{595} values of the cultures were monitored on a Multiskan Sky 1530 spectrophotometer (Thermo Scientific, Poland). Inhibition rates *I* (%) of the target compounds are calculated by the following formula, where C is the corrected turbidity value of the untreated NB medium, T is the corrected turbidity value of the treated NB medium.

$$\text{Inhibition rate } I\,(\%) = (C - T)/C \times 100.$$

3 | RESULTS AND DISCUSSION

3.1 | Chemistry

The synthesis of the target compounds **7a–7o** is outlined in Scheme 1. As shown in Scheme 1, the target compounds **7a–7o** were synthesized with yields of 64%–85%

and determined their structures using ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis. The physical characteristics, ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis data for all synthesized compounds are shown below.

5-chloro-3-methyl-*N*-(2-(4-*oxo*-2-anilinoquinazolin-3(4*H*)-yl)ethyl)-1-phenyl-1*H*-pyrazole-4-carboxamide (**7a**). Off-white solid; yield 85%; ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ: 9.02 (s, 1H, —CONH—), 8.31 (t, 1H, J = 5.00 Hz, —NH—), 7.95 (d, 1H, *J* = 8.50 Hz, Ar—H), 7.78 (d, 2H, J = 8.00 Hz, Ar—H), 7.60–7.47 (m, 6H, Ar—H), 7.34–7.26 (m, 3H, Ar—H), 7.18 (t, 1H, J = 7.50 Hz, Ar—H), 7.05 (t, 1H, J = 7.00 Hz, Ar—H), 4.36 (d, J = 6.50 Hz, 2H, —CH_2—), 3.58 (d, J = 5.5 Hz, 2H, —CH_2—), 2.26 (s, 3H, —CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ: 163.30, 162.51, 149.71, 148.76, 148.31, 140.06, 137.70, 134.83, 129.86, 129.47, 128.89, 126.97, 126.95, 125.90, 125.51, 123.69, 123.44, 122.45, 117.93, 114.44, 40.47, 37.88, 13.98; MS (ESI) m/z: 499.3 ($[M + H]^+$), 521.2 ($[M + Na]^+$); Anal. calcd for $C_{27}H_{23}ClN_6O_2$: C 64.99, H 4.65, N 16.84, found: C 64.63, H 4.87, N 17.09.

5-chloro-1,3-dimethyl-*N*-(2-(4-*oxo*-2-anilinoquinazolin-3(4*H*)-yl)ethyl)-1*H*-pyrazole-4-carboxamide (**7b**). White solid; yield 72%; ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ: 9.16 (s, 1H, —CONH—), 8.16 (s, 1H, —NH—), 8.00 (d, 1H, J = 7.50 Hz, Ar—H), 7.86 (d, 2H, J = 5.50 Hz, Ar—H), 7.75 (s, 1H, Ar—H), 7.40–7.33 (m, 3H, Ar—H), 7.24 (s, 1H, Ar—H), 7.11 (t, J = 7.0 Hz, 1H, Ar—H), 4.37 (t, J = 6.5 Hz, 2H, —CH_2—), 3.74 (s, 3H, —CH_3), 3.60 (d, J = 5.5 Hz, 2H, —CH_2—), 2.25 (s, 3H, —CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ: 163.59, 162.44, 148.76, 148.22, 148.12, 140.08, 134.83, 128.89, 127.07, 126.96, 125.50, 123.60, 123.39, 122.33, 120.00, 117.87, 40.44, 37.85, 36.47, 13.99; MS (ESI) m/z: 437.1 ($[M + H]^+$), 459.2 ($[M + Na]^+$); Anal. calcd for $C_{22}H_{21}ClN_6O_2$: C 60.48, H 4.84, N 19.24, found: C 59.99, H 4.93, N 19.35.

5-chloro-1-(4-chlorophenyl)-3-methyl-*N*-(2-(4-*oxo*-2-anilinoquinazolin-3(4*H*)-yl)ethyl)-1*H*-pyrazole-4-carboxamide (**7c**). White solid; yield 82%; ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ: 9.07 (s, 1H, —CONH—), 8.38 (t, 1H, J = 5.5 Hz, —NH—), 8.02 (d, J = 6.5 Hz, 1H, Ar—H), 7.84 (d, J = 8.0 Hz, 2H, Ar—H), 7.68–7.59 (m, 5H, Ar—H), 7.39 (t, J = 8.0 Hz, 2H, Ar—H), 7.34 (d, J = 8.0 Hz, 1H, Ar—H), 7.26 (t, J = 7.5 Hz, 1H, Ar—H), 7.12 (t, J = 7.5 Hz, 1H, Ar—H), 4.44 (t, J = 6.0 Hz, 2H, —CH_2—), 3.66 (t, J = 6.5 Hz, 2H, —CH_2—), 2.32 (s, 3H, —CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ: 163.13, 162.52, 150.00, 148.76, 148.32, 140.05, 136.49, 134.83, 133.93, 129.91, 128.88, 127.58, 127.12, 126.97, 125.51, 123.69, 123.44, 122.45, 117.93, 114.74, 40.47, 37.89, 13.96; MS (ESI) m/z: 533.2 ($[M + H]^+$), 555.2 ($[M + Na]^+$); Anal. calcd for $C_{27}H_{22}Cl_2N_6O_2$: C 60.80, H 4.16, N 15.76, found: C 60.55, H 4.64, N 15.66.

5-chloro-3-methyl-*N*-(2-(4-*oxo*-2-(*p*-tolylamino)quinazolin-3(4*H*)-yl)ethyl)-1-phenyl-1*H*-pyrazole-4-carboxamide (**7d**). Off-white solid; yield 80%; ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ: 9.10 (s, 1H, CONH), 8.33 (s, 1H, —NH—), 7.97 (d, 1H, *J* = 7.50 Hz, Ar—H), 7.63–7.50 (m, 8H, Ar—H), 7.30 (d, J = 8.0 Hz, 1H, Ar—H), 7.20–7.10 (m, 3H, Ar—H), 4.40 (s, 2H, —CH_2—), 3.63 (d, 2H, *J* = 6.0 Hz, —CH_2—), 2.30 (s, 3H, —CH_3), 2.29 (s, 3H, —CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ: 163.15, 162.34, 149.68, 149.65, 137.72, 134.86, 129.84, 129.51, 129.47, 129.44, 127.06, 126.90, 125.87, 123.02, 122.98, 122.97, 114.51, 107.46, 40.46, 37.77, 21.03, 13.98; MS (ESI) m/z: 513.3 ($[M + H]^+$); Anal. calcd for $C_{28}H_{25}ClN_6O_2$: C 65.56, H 4.91, N 16.38, found: C 65.21, H 5.02, N 16.25.

5-chloro-1-(4-chlorophenyl)-3-methyl-*N*-(2-(4-*oxo*-2-(*p*-tolylamino)quinazolin-3(4*H*)-yl)ethyl)-1*H*-pyrazole-4-carboxamide (**7e**). White solid; yield 83%; ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ: 8.94 (s, 1H, —CONH—), 8.32 (t, *J* = 6.0 Hz, 1H, —NH—), 7.97 (dd, *J*1 = 1.0 Hz, *J*2 = 8.0 Hz, 1H, Ar—H), 7.65–7.55 (m, 8H, Ar—H), 7.27 (d, *J* = 6.5 Hz, 1H, Ar—H), 7.21–7.15 (m, 2H, Ar—H), 4.39 (t, 2H, *J* = 6.5 Hz, —CH_2—), 3.62 (t, 2H, *J* = 6.0 Hz, —CH_2—), 2.29 (s, 3H, —CH_3), 2.28 (s, 3H, —CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ: 163.09, 162.52, 150.00, 148.91, 148.50, 137.37, 136.50, 134.79, 133.92, 132.80, 129.90, 129.30, 127.57, 127.10, 126.96, 125.42, 123.22, 122.80, 117.77, 114.76, 37.87, 37.83, 21.01, 13.96; MS (ESI) m/z: 547.2 ($[M + H]^+$); Anal. calcd for $C_{28}H_{24}Cl_2N_6O_2$: C 61.43, H 4.42, N 15.35, found: C 61.24, H 4.65, N 15.71.

5-chloro-3-methyl-*N*-(2-(4-*oxo*-2-(*m*-tolylamino)quinazolin-3(4*H*)-yl)ethyl)-1-phenyl-1*H*-pyrazole-4-carboxamide (**7f**). White solid; yield 79%; ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ: 9.01 (s, 1H, —CONH—), 8.34 (t, J = 5.5 Hz, 1H, —NH—), 7.99 (d, *J* = 8.0 Hz, 1H, Ar—H), 7.71 (d, J = 8.0 Hz, 1H, Ar—H), 7.64–7.52 (m, 8H, Ar—H), 7.32 (d, J = 8.0 Hz, 1H, Ar—H), 7.26–7.20 (m, 2H, Ar—H), 6.90 (d, J = 7.5 Hz, 1H, Ar—H), 4.38 (t, J = 6.0 Hz, 2H, —CH_2—), 3.62 (dd, J1 = 6.5 Hz, J2 = 12.0 Hz, 2H, —CH_2—), 2.32 (s, 3H, —CH_3), 2.31 (s, 3H, —CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ: 163.32, 162.50, 149.84, 148.80, 148.28, 139.99, 137.98, 137.70, 134.81, 129.88, 129.81, 129.47, 128.73, 126.99, 126.96, 125.89, 125.73, 125.52, 124.35, 123.39, 122.93, 120.00, 119.52, 117.87, 114.29, 40.47, 37.95, 21.73, 14.05; MS (ESI) m/z: 513.3 ($[M + H]^+$); Anal. calcd for $C_{28}H_{25}ClN_6O_2$: C 65.56, H 4.91, N 16.38, found: C 65.86, H 5.11, N 16.42.

5-chloro-1,3-dimethyl-*N*-(2-(4-*oxo*-2-(*m*-tolylamino)quinazolin-3(4*H*)-yl)ethyl)-1*H*-pyrazole-4-carboxamide (**7g**). White solid; yield 75%; ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ: 9.10 (s, 1H, —CONH—), 8.16 (t, J = 5.0 Hz, 1H, —NH—), 8.01 (d, 1H, J = 7.0 Hz, Ar—H), 7.75 (d, 1H, J = 8.0 Hz, Ar—H), 7.69–7.65 (m, 1H, Ar—H), 7.62 (s, 1H, Ar—H), 7.35 (d, 1H, J = 8.0 Hz, Ar—H), 7.27 (dd, 2H, J1 = 8.0 Hz, J2 = 16.5 Hz, Ar—H), 6.94 (d, 1H, J = 7.5 Hz, Ar—H), 4.37 (t, 2H, J = 7.0 Hz, —CH_2—), 3.76 (s, 3H, —CH_3), 3.60 (t, 2H, J = 7.0 Hz, —CH_2—), 2.35 (s, 3H, —CH_3), 2.27 (s, 3H, Ar—CH_3); ^{13}C

NMR (125 MHz, DMSO-d_6, ppm) δ: 163.58, 162.46, 148.78, 148.25, 148.21, 139.98, 137.98, 134.85, 128.74, 127.12, 126.94, 125.52, 124.32, 122.83, 119.42, 112.18, 55.46, 37.90, 36.51, 21.72, 14.04; MS (ESI) m/z: 451.3 ($[M + H]^+$), 473.2 ($[M + Na]^+$); Anal. calcd for $C_{23}H_{23}ClN_6O_2$: C 61.26, H 5.14, N 18.64, found: C 60.84, H 5.33, N 18.85.

5-chloro-1-(4-chlorophenyl)-3-methyl-*N*-(2-(4-*oxo*-2-(*m*-tolylamino)quinazolin-3(4*H*)-yl)ethyl)-1*H*-pyrazole-4-carboxamide (**7h**). White solid; yield 85%; ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ: 9.01 (s, 1H, —CONH—), 8.36 (t, J = 6.0 Hz, 1H, —NH—), 7.94 (dd, J1 = 1.0 Hz, J2 = 8.0 Hz, 1H, Ar—H), 7.69–7.65 (m, 3H, Ar—H), 7.61–7.59 (m, 3H, Ar—H), 7.34 (d, 1H, J = 8.0 Hz, Ar—H), 7.29–7.24 (m, 2H, Ar—H), 6.94 (d, J = 7.5 Hz, 1H, Ar—H), 4.42 (t, J = 7.0 Hz, 2H, —CH_2—), 3.65 (t, J = 6.0 Hz, 2H, —CH_2—), 2.34 (s, 3H, —CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ: 163.13, 162.51, 150.10, 148.79, 148.30, 139.97, 137.97, 136.49, 134.82, 133.94, 129.91, 128.74, 127.57, 127.15, 126.96, 125.52, 124.37, 123.40, 122.95, 119.55, 117.88, 114.62, 37.93, 37.92, 21.72, 14.00; MS (ESI) m/z: 547.2 ($[M + H]^+$); Anal. calcd for $C_{28}H_{24}Cl_2N_6O_2$: C 61.43, H 4.42, N 15.35, found: C 61.48, H 4.72, N 15.35.

5-chloro-*N*-(2-(2-(4-chloroanilino)-4-oxoquinazolin-3(4*H*)-yl)ethyl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxamide (**7i**). White solid; yield 80%; ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ: 9.17 (s, 1H, —CONH—), 8.33 (t, J = 6.0 Hz, 1H, —NH—), 7.99 (d, 1H, J = 6.5 Hz, Ar—H), 7.85 (d, J = 6.0 Hz, 2H, Ar—H), 7.65 (t, J = 8.5 Hz, 1H, Ar—H), 7.59–7.50 (m, 6H, Ar—H), 7.41 (d, J = 8.5 Hz, 2H, Ar—H), 7.32 (d, J = 8.5 Hz, 1H, Ar—H), 7.25–7.22 (m, 1H, Ar—H), 4.40 (t, J = 6.0 Hz, 2H, —CH_2—), 36.2 (t, J = 5.5 Hz, 2H, —CH_2—), 2.29 (s, 3H, —CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ: 163.30, 162.46, 149.69, 148.52, 148.13, 139.15, 137.69, 134.88, 129.85, 129.48, 128.73, 127.22, 126.99, 125.55, 119.99, 118.05, 114.37, 40.46, 37.88, 14.00; MS (ESI) m/z: 533.2 ($[M + H]^+$); Anal. calcd for $C_{27}H_{22}Cl_2N_6O_2$: C 60.80, H 4.16, N 15.76, found: C 60.74, H 4.22, N 15.75.

5-chloro-*N*-(2-(2-(4-chloroanilino)-4-oxoquinazolin-3(4*H*)-yl)ethyl)-1,3-dimethyl-1*H*-pyrazole-4-carboxamide (**7j**). White solid; yield 83%; ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ: 9.26 (s, 1H, —CONH—), 8.13 (t, J = 5.5 Hz, 1H, —NH—), 8.00 (dd, J1 = 1.0 Hz, J2 = 8.0 Hz, 1H, Ar—H), 7.89 (s, 1H, Ar—H), 7.87 (d, J = 2.5 Hz, 1H, Ar—H), 7.68–7.65 (m, 1H, Ar—H), 7.42 (d, J = 8.5 Hz, 2H, Ar—H), 7.34 (d, J = 7.5 Hz, 1H, Ar—H), 7.25 (t, J = 7.5 Hz, 1H, Ar—H), 4.35 (t, 2H, J = 6.5 Hz, —CH_2—), 3.73 (s, 3H, —CH_3), 3.58 (t, 2H, J = 6.5 Hz, —CH_2—), 2.22 (s, 3H, —CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ: 163.60, 162.40, 148.50, 148.11, 148.06, 139.14, 134.88, 128.72, 127.16, 127.12, 126.96, 123.61, 118.00, 112.19, 40.36, 37.85, 36.47, 14.02; MS (ESI) m/z: 471.2 ($[M + H]^+$), 493.2 ($[M + Na]^+$); Anal. calcd for $C_{22}H_{20}Cl_2N_6O_2$: C 56.06, H 4.28, N 17.83, found: C 56.17, H 4.37, N 17.94.

5-chloro-*N*-(2-(4-*oxo*-2-(*p*-tolylamino)quinazolin-3(4*H*)-yl)ethyl)-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide (**7k**). White solid; yield 72%; ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ: 8.90 (t, J = 5.5 Hz, 1H, —NH—), 8.87 (s, 1H, —CONH—), 8.00 (d, J = 7.0 Hz, 1H, Ar—H), 7.68–7.62 (m, 8H, Ar—H), 7.30 (d, J = 8.0 Hz, 1H, Ar—H), 7.24–7.20 (m, 2H, Ar—H), 4.43 (t, J = 6.0 Hz, 2H, —CH_2—), 3.68 (t, J = 6.5 Hz, 2H, —CH_2—), 2.34 (s, 3H, —CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ: 162.49, 160.67, 148.86, 148.41, 137.36, 136.87, 134.80, 132.87, 130.77, 130.19, 129.32, 129.02, 126.99, 126.36, 125.45, 123.28, 122.85, 120.00, 117.82, 115.63, 40.63, 37.90, 21.00; MS (ESI) m/z: 567.3 ($[M + H]^+$), 589.3 ($[M + Na]^+$); Anal. calcd for $C_{28}H_{22}ClF_3N_6O_2$: C 59.32, H 3.91, N 14.82, found: C 59.02, H 4.10, N 14.71.

5-chloro-*N*-(2-(4-*oxo*-2-(4-trifluoromethoxyanilino)quinazolin-3(4*H*)-yl)ethyl)-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide (**7l**). White solid; yield 83%; ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ: 9.08 (s, 1H, —CONH—), 8.90 (t, J = 5.5 Hz, 1H, —NH—), 8.01 (d, J = 8.0 Hz, 1H, Ar—H), 7.91 (d, J = 9.5 Hz, 2H, Ar—H), 7.64 (d, J = 5.5 Hz, 4H, Ar—H), 7.61–7.59 (m, 2H, Ar—H), 7.39 (d, J = 9.0 Hz, 2H, Ar—H), 7.35 (d, J = 8.0 Hz, 1H, Ar—H), 7.26 (t, J = 8.0 Hz, 1H, Ar—H), 4.44 (t, J = 6.5 Hz, 2H, —CH_2—), 3.66 (t, J = 6.5 Hz, 2H, —CH_2—); ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ: 162.42, 160.67, 148.42, 148.07, 144.08, 139.37, 136.83, 134.90, 130.77, 130.19, 128.95, 127.02, 126.33, 125.57, 124.13, 123.78, 123.56, 122.68, 121.73, 118.15, 115.62, 40.54, 37.85; MS (ESI) m/z: 637.3 ($[M + H]^+$), 659.3 ($[M + Na]^+$); Anal. calcd for $C_{28}H_{19}ClF_6N_6O_3$: C 52.80, H 3.01, N 13.19, found: C 52.49, H 2.97, N 13.25.

5-chloro-*N*-(2-(2-(4-chloroanilino)-4-oxoquinazolin-3(4*H*)-yl)ethyl)-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide (**7m**). White solid; yield 75%; ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ: 8.97 (s, 1H, —CONH—), 8.83 (t, J = 5.5 Hz, 1H, —NH—), 7.95 (d, J = 7.0 Hz, 1H, Ar—H), 7.78 (d, J = 8.5 Hz, 2H, Ar—H), 7.59 (d, J = 2.0 Hz, 4H, Ar—H), 7.55 (dd, J1 = 2.0 Hz, J2 = 7.0 Hz, 2H, Ar—H), 7.37 (d, J = 9.5 Hz, 2H, Ar—H), 7.28 (d, J = 9.0 Hz, 1H, Ar—H), 7.20 (t, J = 8.0 Hz, 1H, Ar—H), 4.37 (t, J = 6.5 Hz, 2H, —CH_2—), 3.61 (t, J = 6.0 Hz, 2H, —CH_2—); ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ: 162.42, 160.67, 148.47, 148.07, 139.10, 136.84, 134.89, 130.77, 130.20, 128.98, 128.73, 127.33, 127.02, 126.36, 125.56, 123.91, 118.09, 115.59, 40.38, 37.88; MS (ESI) m/z: 587.3 ($[M + H]^+$), 609.2 ($[M + Na]^+$); Anal. calcd for $C_{27}H_{19}Cl_2F_3N_6O_2$: C 55.21, H 3.26, N 14.31, found: C 55.46, H 3.16, N 14.44.

3-chloro-*N*-(2-(4-*oxo*-2-(4-trifluoromethoxyanilino) quinazolin-3(4*H*)-yl)ethyl)-1-(pyridin-2-yl)-1*H*-pyrazole-5-carboxamide (**7n**). White solid; yield 64%; ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ: 9.33 (s, 1H, —CONH—), 8.92 (s, 1H, —NH—), 8.52 (d, J = 3.5 Hz, 1H, Ar—H), 8.23 (d, J = 7.0 Hz, 1H, Ar—H), 8.00 (d, J = 2.0 Hz, 1H, Ar—H), 7.69–7.64 (m, 4H, Ar—H), 7.36–7.25 (m, 4H, Ar—H), 7.04 (s, 1H, Ar—H), 4.30 (d, J = 7.0 Hz, 2H, —CH_2—), 3.50 (d, J = 5.5 Hz, 2H, —CH_2—); ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ: 162.36, 158.60, 149.09, 148.38, 147.84, 147.65, 143.86, 139.99, 139.75, 139.24, 134.95, 128.65, 127.18, 126.93, 125.61, 123.86, 122.99, 121.65, 119.74, 118.05, 107.35, 40.53, 37.60; MS (ESI) m/z: 604.3 ($[M + H]^+$), 626.2 ($[M + Na]^+$); Anal. calcd for $C_{26}H_{18}Cl_2F_3N_7O_3$: C 54.79, H 3.36, N 17.02, found: C 54.38, H 3.38, N 16.99.

3-chloro-*N*-(2-(2-(4-chloroanilino)-4-oxoquinazolin-3 (4*H*)-yl)ethyl)-1-(pyridin-2-yl)-1*H*-pyrazole-5-carboxamide (**7o**). White solid; yield 83%; ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ: 9.33 (s, 1H, —CONH—), 8.85 (s, 1H, —NH—), 8.51 (s, 1H, Ar—H), 8.22 (s, 1H, Ar—H), 7.96 (d, J = 13.0 Hz, 1H, Ar—H), 7.66 (s, 2H, Ar—H), 7.55 (d, J = 8.5 Hz, 1H, Ar—H), 7.32 (d, J = 9.5 Hz, 3H, Ar—H), 7.24 (d, J = 5.5 Hz, 1H, Ar—H), 7.03 (s, 1H, Ar—H); ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ: 158.62, 149.09, 148.39, 147.65, 139.97, 139.76, 134.95, 134.95, 131.62, 129.37, 128.63, 128.12, 127.21, 126.93, 125.57, 123.77, 123.27, 117.97, 115.79, 107.33, 107.23, 40.91, 37.61; MS (ESI) m/z: 556.2 ($[M + H]^+$); Anal. calcd for $C_{25}H_{18}Cl_3N_7O_2$: C 57.70, H 3.68, N 18.84, found: C 57.54, H 3.52, N 18.96.

3.2 | Biological evaluations

The preliminary in vitro antifungal and antibacterial activities of the target compounds **7a–7o** were determined and the results are listed in Tables 1 and 2. As suggested in Table 1, most of the target compounds exhibited antifungal activities against *G. zeae*, *F. oxysporum*, *C. mandshurica*, *P. infestans*, and *P. sasakii* to some extent at 50 μg/ml, unfortunately, lower than those of hymexazol and epoxiconazole. Meanwhile, Table 2 showed that most of the target compounds exhibited certain antibacterial activities against *R. solanacearum* and *Xoo* at 200 and 100 μg/ml. It was interesting that compound 5-chloro-1,3-dimethyl-*N*-(2-(4-*oxo*-2-(*m*-tolylamino)quinazolin-3(4*H*)-yl)ethyl)-1*H*-pyrazole-4-carboxamide (**7g**) showed better antibacterial activities against *R. solanacearum* (60%) and *Xoo* (53%) at 200 μg/ml than those of thiodiazole-copper, to the contrary, lower than those of kocide 3000 and bismerthiazol.

TABLE 1 Antifungal activities of the target compounds **7a-7o** against *Gibberella zeae*, *Fusarium oxysporum*, *Cytospora mandshurica*, *Phytophthora infestans*, and *Pellicularia sasakii* at 50 μg/ml

	Inhibition rate (%)				
Compounds	***G. zeae***	***F. oxysporum***	***C. mandshurica***	***P. infestans***	***P. sasakii***
7a	4.45 ± 0.77	5.33 ± 0.90	1.20 ± 0.84	16.51 ± 0.59	0
7b	7.12 ± 1.39	6.33 ± 1.00	0	26.91 ± 1.29	0
7c	2.08 ± 0.67	8.00 ± 1.18	0.00 ± 0.52	11.93 ± 0.62	0
7d	9.50 ± 1.09	6.67 ± 1.34	8.98 ± 0.54	10.70 ± 1.51	0
7e	6.53 ± 0.65	7.33 ± 0.91	1.80 ± 0.52	9.79 ± 0.50	0
7f	18.10 ± 1.55	6.67 ± 1.03	0.60 ± 0.52	8.26 ± 0.40	0
7g	13.95 ± 0.93	4.33 ± 0.99	0.30 ± 0.53	4.89 ± 0.49	0
7h	8.31 ± 0.80	8.00 ± 1.18	11.08 ± 0.56	6.73 ± 0.67	0
7i	7.12 ± 0.60	5.33 ± 1.13	2.10 ± 0.54	25.08 ± 2.00	3.56 ± 0.87
7j	8.90 ± 0.99	11.33 ± 1.46	0.90 ± 0.77	26.91 ± 1.18	12.62 ± 1.97
7k	0	0	0.60 ± 0.52	8.26 ± 0.76	0
7l	1.19 ± 0.64	4.67 ± 0.89	5.69 ± 0.55	3.98 ± 1.05	0
7m	1.78 ± 0.59	3.00 ± 1.02	1.20 ± 0.72	4.59 ± 0.87	0
7n	4.45 ± 0.63	3.67 ± 0.85	3.59 ± 0.38	16.51 ± 1.01	10.03 ± 0.56
7o	2.67 ± 0.63	3.33 ± 1.01	0.90 ± 0.33	21.41 ± 0.89	19.09 ± 0.74
Hymexazol	55.54 ± 3.90	56.12 ± 4.10	49.61 ± 7.84	51.21 ± 5.96	68.22 ± 2.41
Epoxiconazole	100.00 ± 4.90	100.00 ± 2.89	100.00 ± 3.96	96.07 ± 4.76	87.62 ± 3.06

TABLE 2 Antibacterial activities of the target compounds **7a–7o** against *Ralstonia solanacearum* and *Xanthomomu oryzae pv. oryzae* at 200 and 100 μg/ml

	Inhibition rate (%)			
	R. solanacearum		*Xoo*	
Compounds	**200 μg/ml**	**100 μg/ml**	**200 μg/ml**	**100 μg/ml**
7a	25 ± 4.50	15 ± 4.12	14 ± 2.11	10 ± 2.1
7b	29 ± 3.05	18 ± 3.08	38 ± 1.11	8 ± 1.32
7c	9 ± 2.01	7 ± 1.49	0	0
7d	25 ± 4.12	10 ± 2.02	36 ± 1.56	12 ± 2.18
7e	25 ± 3.16	18 ± 2.30	28 ± 3.12	25 ± 2.01
7f	51 ± 1.55	39 ± 3.11	55 ± 2.00	35 ± 1.59
7g	60 ± 2.34	40 ± 2.50	53 ± 1.48	32 ± 2.07
7h	47 ± 3.14	11 ± 3.15	0	0
7i	7 ± 0.83	5 ± 1.14	0	0
7j	32 ± 2.13	26 ± 3.12	18 ± 2.04	0
7k	24 ± 2.37	10 ± 3.16	35 ± 1.17	20 ± 1.57
7l	45 ± 2.85	20 ± 2.39	48 ± 1.95	33 ± 1.99
7m	20 ± 2.41	4 ± 2.95	64 ± 3.00	34 ± 2.24
7n	25 ± 2.15	5 ± 2.72	11 ± 3.58	0
7o	43 ± 1.50	23 ± 2.09	25 ± 3.55	0
Kocide 3000	100 ± 1.25	68 ± 3.13	0	0
Thiodiazole copper	52 ± 1.18	31 ± 3.21	38 ± 3.45	32 ± 2.51
Bismerthiazol	/	/	73 ± 0.68	52 ± 1.61

4 | CONCLUSION

In conclusion, a total of 15 new 4(3*H*)-quinazolinone derivatives containing a pyrazole carboxamide moiety were synthesized and investigated for their in vitro antifungal and antibacterial activities. The preliminary bioassay results showed that the target compounds exhibited certain inhibitory activity against the test bacteria and fungus. Especially, compound **7g** exhibited good antibacterial activities against *R. solanacearum* and *Xoo*, which were even better than those of thiodiazole-copper at 200 μg/ml. To the best of our knowledge, this is the first report on the antifungal and antibacterial activities of this series of new 4(3*H*)-quinazolinone derivatives containing a pyrazole carboxamide moiety.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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