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ORIGINAL ARTICLE

Synthesis, crystal structure and antimicrobial activity of 2-((2-(4-(1*H*-1,2,4-triazol-1-yl)phenyl)quinazolin-4-yl)oxy)-*N*-phenylacetamide derivatives against phytopathogens

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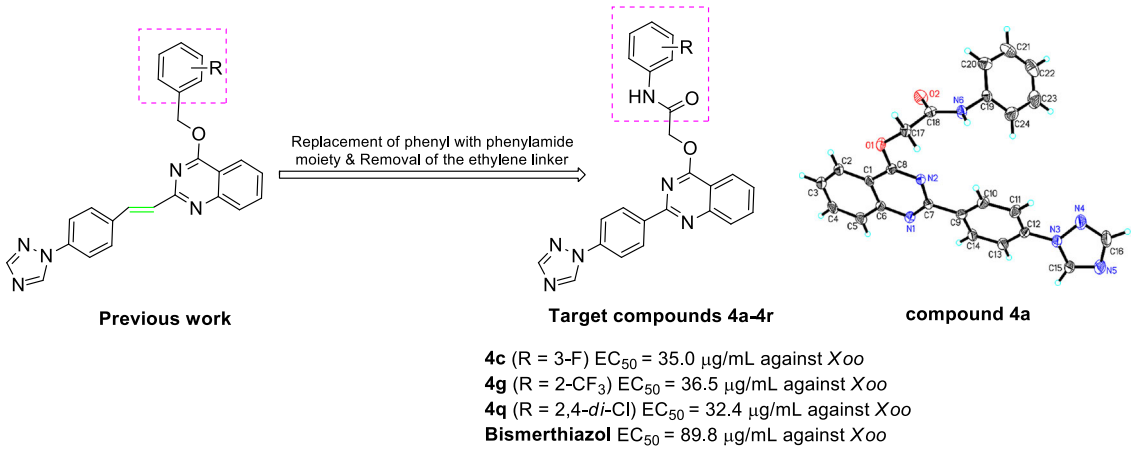
Abstract

A total of eighteen 2-((2-(4-(1*H*-1,2,4-triazol-1-yl)phenyl)quinazolin-4-yl)oxy)-*N*-phenylacetamide derivatives were designed and synthesized, via hybrid pharmacophore approach. Among these compounds, chemical structure of compound **4a** was unambiguously confirmed by means of single-crystal X-ray diffraction analysis. All the compounds were evaluated in vitro for their inhibition activity against several important phytopathogenic bacteria and fungi in agriculture. The obtained results indicated that several compounds demonstrated potent antibacterial activity against *Xanthomonas oryzae* pv. *oryzae* (*Xoo*). For example, compounds **4c**, **4g** and **4q** had EC_{50} values of 35.0, 36.5 and 32.4 μg/mL toward this bacterium, respectively, around 1.5 times more active than commercial bactericide bismerthiazol (EC_{50} = 89.8 μg/mL). Additionally, compounds **4j** and **4p** were found to display comparable antifungal activity against *Gloeosporium fructigenum* at 50 μg/mL, to commercial fungicide hymexazol. Finally, the relationships between antibacterial activities and molecular structures of this class of compounds were discussed in detail.

Graphical abstract



Keywords Quinazoline · 1,2,4-Triazole · Amide · Synthesis · Antimicrobial activity

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Introduction

Natural products have been extensively investigated in the fields of medicinal and pesticide chemistry, due to their unique advantages including extraordinary structural diversity, excellent bioactivities as well as biocompatibility with the natural environment [1]. One of the most important classes of natural products is quinazoline derivatives [2], which exhibit a wide range of biological activities, including antibacterial [3–5], antifungal [6], antiviral [7], antitumor activities [8]. Some quinazoline-containing pharmaceuticals and pesticides have been marketed for years, including anticancer drug Gefitinib, acaricide Fenazaquin and sympatholytic drug Prazosin (Fig. 1).

The pathogenic bacterium of *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) is a rod-shaped, round-ended Gram-negative plant pathogen [9], which is responsible for causing rice bacterial blight via invading the vascular system and entering the xylem tissue from the wounds or natural plant openings [10]. Bacterial blight of rice is one of the most destructive rice diseases around the world, which seriously affects the yield of rice and leads to crop loss up to 50% in some cases [11]. Despite several methods currently available to cope with this disease (biological control, breeding of resistant varieties and cultural practices) [9], the method of chemical control still exhibited distinct advantages over others, including high efficiency, fast acting, low cost as well as convenient application. Chemical control of rice bacterial blight started in the 1950s, by using Bordeaux mixture, some antibiotics along with mercuric–copper compounds [9]. Although a few agrobactericides are currently available on the market for fighting against this bacterial disease, the search for new and more effective bactericides against *Xoo* remains an extremely urgent task facing agricultural chemists, due to some obvious drawbacks of existing antibacterial agents, including low efficiency, environmental hazards, especially increasing bacterial resistance [12].

On the other hand, the electron-rich aromatic framework of 1,2,4-triazole heterocycle allows it to readily bind to relevant receptors and/or enzymes by virtue of multiple non-covalent binding interactions [13], thus exhibiting various bioactivities, such as antibacterial [14–16], antifungal [17] and anticancer [18] activities. Many 1,2,4-triazole-based derivatives have emerged as commercial agents, including therapeutic fungicides Fluconazole and Albaconazole, viricide Ribavirin as well as anticancer drug Letrozole (Fig. 1).

It has been widely accepted that the combination of different pharmacophores into a single molecule ("hybrid pharma-

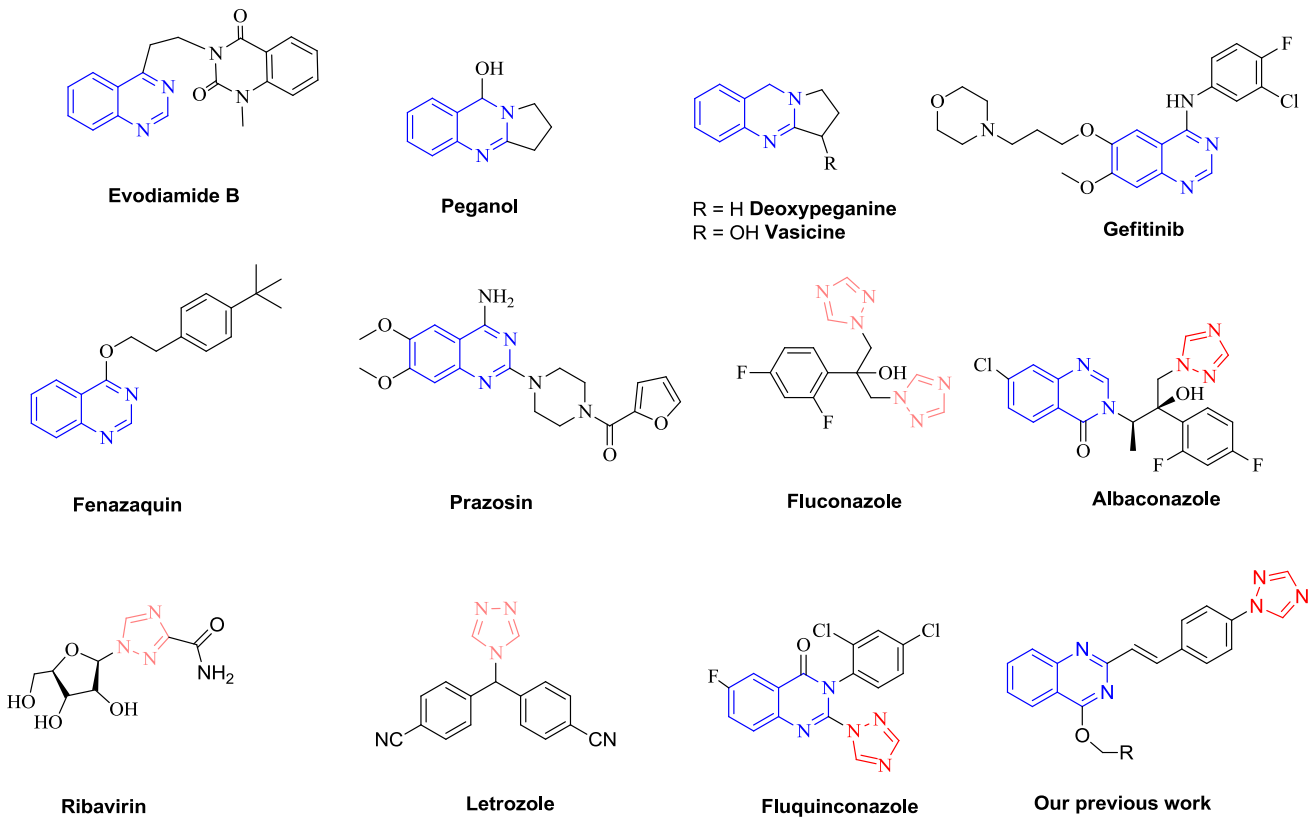


Fig. 1 Chemical structures of some natural compounds, commercial pharmaceutical or pesticide molecules containing either the quinazoline or 1,2,4-triazole ring

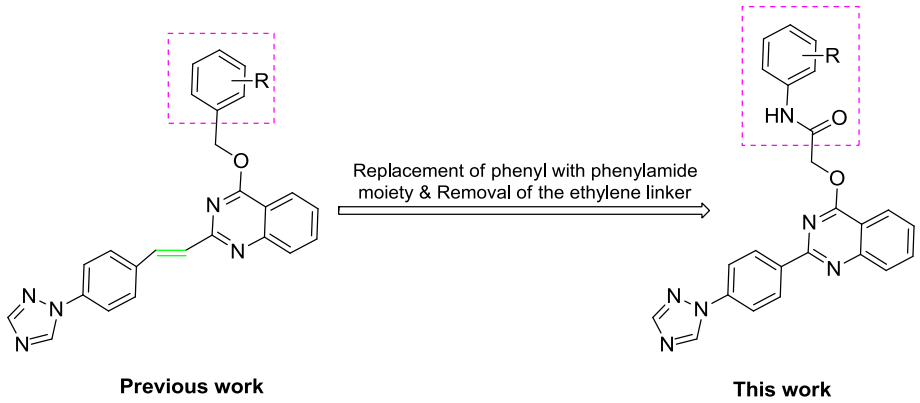


Fig. 2 Design strategy of target compounds in this work

cophore approach") is an effective, practical approach for discovering new bioactive molecules, due to a potential cooperation effect [19, 20]. Fluquinconazole (Schering Agrochem) and Albaconazole (Palau Pharma), widely utilized as antifungal agents in agriculture and medicine, respectively, are two very successful examples of combining quinazolinone and 1,2,4-triazole moieties together. Recently, we synthesized a family of (*E*)-2-(4-(1*H*-1,2,4-triazol-1-yl)styryl)-4-(alkyl/arylmethyleneoxy)quinazoline derivatives, wherein several compounds exhibited much better inhibition activities against the phytopathogenic bacterium *Xanthomonas axonopodis* pv. *citri* (*Xac*), relative to control agent bismerthiazol [21]. However, antibacterial activities of such compounds against tested bacteria were far from satisfactory as a whole. Many previous studies have shown that the presence of an amide group in the antimicrobial molecules is highly favorable, since it can form effective and selective hydrogen-bonding interactions with anionic substrates such as DNA and RNA [22]. Moreover, to the best of our knowledge, quinazoline compounds substituted by a rigid phenyltriazole moiety remain largely unexplored. Based on these considerations and in continuation of our efforts to develop quinazoline-1,2,4-triazole hybrids as antimicrobial agents in agriculture [21, 23–25], herein we introduced various phenylamide groups into the 1,2,4-triazolylphenyl-functionalized quinazoline framework (Fig. 2) and evaluated them for inhibition activities toward some important agricultural phytopathogenic bacteria and fungi.

Experimental

General

All the chemicals were purchased from commercial suppliers and used without further treatment (unless stated otherwise). Melting points were determined and uncorrected on a XT-4 binocular microscope (Beijing Tech Instrument Co., China). ^{1}H and ^{13}C NMR spectra were obtained using a JEOL-ECX 500 NMR spectrometer at room temperature using TMS as an internal standard, and chemical shift (δ) was expressed in parts per million (ppm). The following abbreviations were employed in expressing multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. HRMS-ESI spectra were measured on a Thermo Scientific Q Exactive Hybrid Quadrupole-Orbitrap mass spectrometer. The X-ray crystallographic data were collected using a Bruker Smart Apex CCD area detector diffractometer (Bruker, Germany) with Mo-Kα radiation.

Synthesis

Synthesis of 2-(4-(1H-1,2,4-triazol-1-yl)phenyl)quinazolin-4(3H)-one (2)

Anthranilamide (136 mg, 1.0 mmol) and triazole-substituted benzaldehyde **1** [26] (173 mg, 1.0 mmol) were dissolved in DMSO (10 mL). Next, the reaction mixture was stirred and heated to 120 °C, and the reaction progress was monitored by TLC. After the completion of the reaction, water was added after the reaction mixture was cooled to room temperature. The formed precipitate was collected by filtration and recrystallized from ethanol to give quinazolinone **2**. Yield: 75%; mp > 300 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.65 (s, 1H), 9.46 (s, 1H), 8.39 (d, J = 5.0 Hz, 2H), 8.31 (s, 1H), 8.17 (d, J = 10.0 Hz, 1H), 8.08 (d, J = 5.0 Hz, 2H), 7.87–7.84 (m, 1H), 7.77 (d, J = 10.0 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 162.7, 153.3, 151.7, 149.2, 143.3, 139.2, 135.2, 132.2, 129.9, 128.1, 127.3, 126.4, 121.6, 119.6; ESI-HRMS *m/z*: $[M+H]^+$ calcd for $C_{16}H_{12}N_5O$: 290.1036; found: 290.1037.

General procedure for the synthesis of compounds 4a–4r

A mixture of intermediate **2** (194 mg, 0.67 mmol), K_2CO_3 (185 mg, 1.34 mmol) and the corresponding bromoacetamides **3a**–**3r** [23] (0.67 mmol) was added to DMF (10 mL), which was then stirred and heated to 80 °C for

8 h. Next, the reaction mixture was poured into cold water and the resulted precipitate was filtered, washed with water and recrystallized from ethanol to afford compounds **4a**–**4r** in 43–67% yield.

2-((2-(4-(1H-1,2,4-triazol-1-yl)phenyl)quinazolin-4-yl)oxy)-N-phenylacetamide **(*4a*)** Yield 60%; mp: 260–262 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.48 (s, 1H), 9.39 (s, 1H), 8.60 (d, J = 10.0 Hz, 2H), 8.26 (d, J = 5.0 Hz, 2H), 8.01–7.96 (m, 2H), 7.94 (d, J = 5.0 Hz, 2H), 7.71–7.68 (m, 1H), 7.61 (d, J = 10.0 Hz, 2H), 7.30 (t, J = 7.5 Hz, 2H), 7.04 (t, J = 7.5 Hz, 1H), 5.32 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.5, 166.4, 158.1, 153.2, 151.8, 143.2, 139.1, 139.0, 136.8, 135.2, 130.0, 129.4, 128.2, 128.1, 124.2, 124.1, 120.1, 119.6, 114.9, 66.1. ESI-HRMS *m/z*: $[M+H]^+$ calcd for $C_{24}H_{19}N_6O_2$: 423.1564; found: 423.1574.

2-((2-(4-(1H-1,2,4-triazol-1-yl)phenyl)quinazolin-4-yl)oxy)-N-(2-fluorophenyl)acetamide (4b) Yield 61%; mp: 213–214 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.34 (s, 1H), 9.46 (d, J = 5.0 Hz, 1H), 8.69 (d, J = 10.0 Hz, 2H), 8.33–8.32 (m, 2H), 8.06–8.02 (m, 4H), 7.82 (t, J = 7.5 Hz, 1H), 7.76–7.73 (m, 1H), 7.35–7.31 (m, 1H), 7.22–7.16 (m, 2H), 5.45 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.9, 166.4, 158.1, 154.6 (d, J = 245.5 Hz), 153.2, 151.9, 143.2, 139.0, 136.8, 135.2, 130.0, 128.2, 128.1, 126.4 (d, J = 7.1 Hz), 126.0 (d, J = 11.7 Hz), 125.2, 125.0, 124.1, 119.7, 116.2 (d, J = 19.2 Hz), 114.9, 65.8. ESI-HRMS *m/z*: $[M+H]^+$ calcd for $C_{24}H_{18}FN_6O_2$: 441.1470; found: 441.1486.

2-((2-(4-(1H-1,2,4-triazol-1-yl)phenyl)quinazolin-4-yl)oxy)-N-(3-fluorophenyl)acetamide (4c) Yield 48%; mp: 260–261 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.75 (s, 1H), 9.44 (s, 1H), 8.64 (d, J = 10.0 Hz, 2H), 8.32 (d, J = 10.0 Hz, 2H), 8.07–8.04 (m, 2H), 7.99 (d, J = 10.0 Hz, 2H), 7.77–7.74 (m, 1H), 7.62 (d, J = 10.0 Hz, 1H), 7.42–7.38 (m, 2H), 6.95–6.91 (m, 1H), 5.38 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.9, 166.3, 162.7 (d, J = 241.7 Hz), 158.1, 153.2, 151.9, 143.1, 140.8 (d, J = 10.9 Hz), 139.0, 136.7, 135.2, 131.1 (d, J = 9.5 Hz), 130.0, 128.2, 128.1, 124.0, 119.6, 115.8, 114.9, 110.7 (d, J = 21.3 Hz), 106.8 (d, J = 26.2 Hz), 66.0. ESI-HRMS *m/z*: $[M+H]^+$ calcd for $C_{24}H_{18}FN_6O_2$: 441.1470; found: 441.1482.

2-((2-(4-(1H-1,2,4-triazol-1-yl)phenyl)quinazolin-4-yl)oxy)-N-(4-fluorophenyl)acetamide (4d) Yield 65%; mp: 231–233 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.56 (s, 1H), 9.43 (s, 1H), 8.64–8.62 (m, 2H), 8.30 (t, J = 5.0 Hz, 2H), 8.05–8.01 (m, 2H), 7.99–7.97 (m, 2H), 7.74–7.72 (m, 1H), 7.66–7.64 (m, 2H), 7.20–7.16 (m, 2H), 5.34 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.5, 166.4, 158.1, 156.8 (d, J = 246.4 Hz), 153.1, 151.9, 143.2, 139.0, 136.7, 135.4, 135.2, 130.0, 128.2, 128.1, 124.1, 121.9 (d, J = 7.8 Hz), 119.7, 116.0 (d, J = 22.3 Hz), 114.9, 66.0. ESI-HRMS *m/z*: $[M+H]^+$ calcd for $C_{24}H_{18}FN_6O_2$: 441.1470; found: 441.1479.

2-((2-(4-(1H-1,2,4-triazol-1-yl)phenyl)quinazolin-4-yl)oxy)-N-(2-chlorophenyl)acetamide (4e) Yield 50%; mp: 229–230 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.23 (s, 1H), 9.43 (s, 1H), 8.67 (d, J = 5.0 Hz, 2H), 8.28 (d, J = 2.0 Hz, 2H), 8.02 (s, 2H), 8.00 (d, J = 1.8 Hz, 1H), 7.99 (s, 1H), 7.96 (d, J = 10.0 Hz, 1H), 7.68 (t, J = 7.1 Hz, 1H), 7.32–7.30 (m, 1H), 7.13 (t, J = 7.5 Hz, 2H), 5.40 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.9, 166.3, 158.1, 153.2, 151.8, 143.2, 139.0, 136.7, 135.2, 134.8, 130.1, 130.0, 128.2, 128.1, 128.0, 127.4, 127.2, 126.8, 124.1, 119.6, 114.9, 65.8. ESI-HRMS *m/z*: $[M+H]^+$ calcd for $C_{24}H_{18}N_6O_2Cl$: 457.1174; found: 457.1193.

2-((2-(4-(1H-1,2,4-triazol-1-yl)phenyl)quinazolin-4-yl)oxy)-N-(4-chlorophenyl)acetamide (4f) Yield 54%; mp: 230–231 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.63 (s, 1H), 9.39 (s, 1H), 8.59 (d, J = 10.0 Hz, 2H), 8.27 (d, J = 5.0 Hz, 2H), 8.01–7.96 (m, 2H), 7.94 (d, J = 10.0 Hz, 2H), 7.71–7.68 (m, 1H), 7.64 (d, J = 10.0 Hz, 2H), 7.36 (d, J = 10.0 Hz, 2H), 5.31 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.7, 166.4, 158.1, 153.2, 151.8, 143.2, 139.0, 138.0, 136.7, 135.3, 130.0, 129.3, 128.2, 128.1, 127.8, 124.1, 121.6, 119.7, 114.9, 66.1. ESI-HRMS *m/z*: $[M+H]^+$ calcd for $C_{24}H_{18}N_6O_2Cl$: 457.1174; found: 457.1177.

2-((2-(4-(1H-1,2,4-triazol-1-yl)phenyl)quinazolin-4-yl)oxy)-N-(2-(trifluoromethyl)phenyl)acetamide (4g) Yield 43%; mp: 221–223 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.07 (s, 1H), 9.46 (s, 1H), 8.71 (d, J = 10.0 Hz, 2H), 8.32 (d, J = 10.0 Hz, 2H), 8.06–8.00 (m, 4H), 7.78–7.71 (m, 2H), 7.66 (t, J = 7.5 Hz, 1H), 7.51 (d, J = 5.0 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 5.43 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.6, 166.3, 158.1, 153.2, 151.9, 143.2, 139.0, 136.8, 135.3, 135.1, 133.6, 130.3, 130.1, 128.2, 128.0, 127.5, 127.3, 126.9, 124.2, 124.1 (q, J = 273.5 Hz), 119.7, 115.0, 65.6. ESI-HRMS *m/z*: $[M+H]^+$ calcd for $C_{25}H_{18}F_3N_6O_2$: 491.1438; found: 491.1448.

2-((2-(4-(1H-1,2,4-triazol-1-yl)phenyl)quinazolin-4-yl)oxy)-N-(4-(trifluoromethyl)phenyl)acetamide (4h) Yield 52%; mp: 245–246 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.07 (s, 1H), 9.46 (s, 1H), 8.71 (d, J = 10.0 Hz, 2H), 8.32 (d, J = 10.0 Hz, 2H), 8.06–8.0 (m, 4H), 7.76–7.71 (m, 2H), 7.66 (t, J = 7.5 Hz, 1H), 7.51 (d, J = 5.0 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 5.43 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.2, 166.3, 158.0, 153.2, 151.9, 143.2, 142.7, 139.0, 136.7, 135.3, 129.9, 128.2, 128.1, 126.8, 124.8 (q, J = 271.4 Hz), 124.3, 124.0, 119.9, 119.7, 114.9, 66.0. ESI-HRMS *m/z*: $[M+H]^+$ calcd for $C_{25}H_{18}F_3N_6O_2$: 491.1438; found: 491.1455.

2-((2-(4-(1H-1,2,4-triazol-1-yl)phenyl)quinazolin-4-yl)oxy)-N-(2-nitrophenyl)acetamide (4i) Yield 61%; mp: 203–205 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.86 (s, 1H), 9.42 (s, 1H), 8.66–8.64 (m, 2H), 8.31 (d, J = 10.0 Hz, 1H), 8.28 (s, 1H), 8.02–7.99 (m, 4H), 7.98–7.96 (m, 1H), 7.86–7.85 (m, 1H), 7.73–7.70 (m, 2H), 7.36–7.33 (m, 1H), 5.38 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.0, 166.1, 158.1, 153.2, 151.9, 143.2, 142.2, 139.0, 136.7, 135.3, 135.0, 131.6, 130.1, 128.2, 128.1, 126.0, 125.7, 125.5, 124.0, 119.7, 114.9, 65.8. ESI-HRMS m/z: $[M+H]^+$ calcd for $C_{24}H_{18}N_7O_4$: 468.1415; found: 468.1413.

2-((2-(4-(1H-1,2,4-triazol-1-yl)phenyl)quinazolin-4-yl)oxy)-N-(3-nitrophenyl)acetamide (4j) Yield 62%; mp: 229–231 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.37 (d, J = 2.6 Hz, 1H), 8.61 (d, J = 2.1 Hz, 1H), 8.59 (d, J = 2.3 Hz, 1H), 8.54 (d, J = 2.4 Hz, 1H), 8.27 (d, J = 5.0 Hz, 1H), 8.25 (d, J = 5.0 Hz, 1H), 8.00 (s, 2H), 7.97–7.94 (m, 2H), 7.92 (d, J = 10.0 Hz, 1H), 7.89 (d, J = 10.0 Hz, 2H), 7.72–7.69 (m, 1H), 7.63–7.59 (m, 1H), 5.36 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.4, 166.4, 158.0, 153.2, 151.9, 148.5, 143.2, 140.5, 139.0, 136.7, 135.3, 130.9, 129.9, 128.2, 128.1, 126.1, 124.1, 119.7, 118.6, 114.9, 114.2, 66.1. ESI-HRMS m/z: $[M+H]^+$ calcd for $C_{24}H_{18}N_7O_4$: 468.1415; found: 468.1411.

2-((2-(4-(1H-1,2,4-triazol-1-yl)phenyl)quinazolin-4-yl)oxy)-N-(m-tolyl)acetamide (4k) Yield 67%; mp: 200–202 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.43 (s, 1H), 9.39 (s, 1H), 8.60 (d, J = 10.0 Hz, 2H), 8.27–8.26 (m, 2H), 8.02–7.98 (m, 2H), 7.97–7.93 (m, 2H), 7.71–7.68 (m, 1H), 7.44 (s, 1H), 7.38 (d, J = 10.0 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 6.85 (d, J = 10.0 Hz, 1H), 5.30 (s, 2H), 2.23 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.4, 158.1, 153.2, 151.8, 146.6, 143.1, 142.1, 139.0, 138.6, 136.7, 135.2, 130.0, 129.2, 128.2, 128.1, 124.9, 124.1, 120.6, 119.6, 117.3, 114.9, 65.9, 21.5. ESI-HRMS m/z: $[M+H]^+$ calcd for $C_{25}H_{21}N_6O_2$: 437.1721; found: 437.1721.

2-((2-(4-(1H-1,2,4-triazol-1-yl)phenyl)quinazolin-4-yl)oxy)-N-(p-tolyl)acetamide (4l) Yield 49%; mp: 257–258 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.40 (s, 1H), 9.42 (s, 1H), 8.62 (d, J = 5.0 Hz, 2H), 8.29 (d, J = 5.0 Hz, 2H), 8.03–8.00 (m, 2H), 7.98 (s, 1H), 7.96 (s, 1H), 7.73–7.70 (m, 1H), 7.50 (d, J = 10.0 Hz, 2H), 7.11 (d, J = 10.0 Hz, 2H), 5.32 (s, 2H), 2.23 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.4, 166.2, 158.1, 153.2, 151.8, 143.2, 139.0, 136.8, 136.5, 135.2, 133.1, 130.0, 129.8, 128.2, 128.1, 124.1, 120.1, 119.7, 114.9, 66.1, 21.0. ESI-HRMS m/z: $[M+H]^+$ calcd for $C_{25}H_{21}N_6O_2$: 437.1721; found: 437.1721.

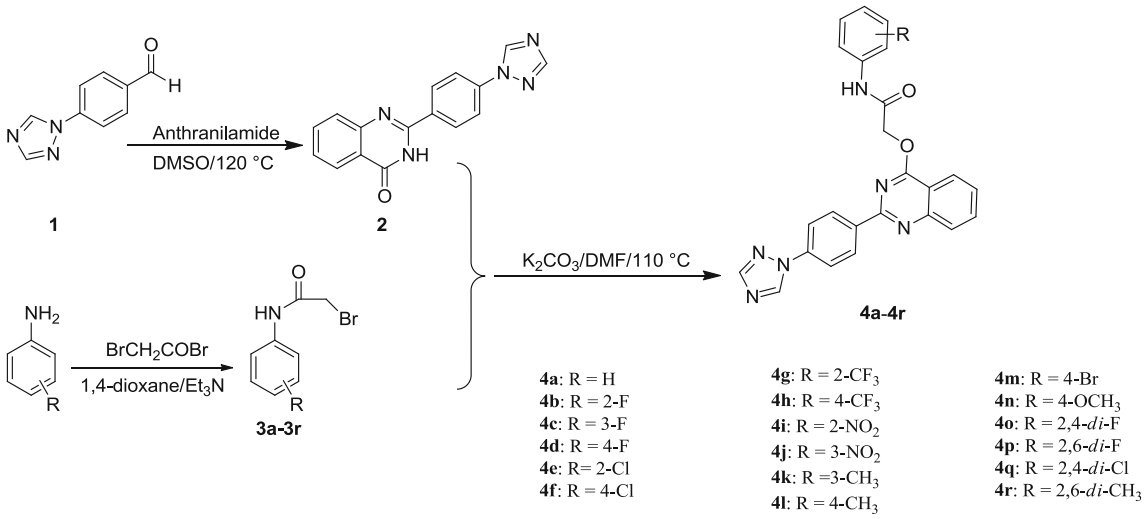
2-((2-(4-(1H-1,2,4-triazol-1-yl)phenyl)quinazolin-4-yl)oxy)-N-(4-bromophenyl)acetamide (4m) Yield 52%; mp: 249–250 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.62 (s, 1H), 9.39 (d, J = 5.0 Hz, 1H), 8.58 (d, J = 10.0 Hz, 2H), 8.26 (d, J = 0.9 Hz, 1H), 8.24 (d, J = 0.6 Hz, 1H), 8.00–7.96 (m, 2H), 7.95–7.94 (m, 1H), 7.92 (s, 1H), 7.69–7.66 (m, 1H), 7.59 (d, J = 10.0 Hz, 2H), 7.48 (d, J = 10.0 Hz, 2H), 5.31 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.7, 166.3, 158.1, 153.2, 151.8, 143.2, 139.0, 138.4, 136.7, 135.2, 132.2, 130.0, 128.2, 128.1, 124.1, 122.0, 119.6, 115.8, 114.9, 66.1. ESI-HRMS m/z: $[M+H]^+$ calcd for $C_{24}H_{18}N_6O_2Br$: 501.0669; found: 501.0672.

2-((2-(4-(1H-1,2,4-triazol-1-yl)phenyl)quinazolin-4-yl)oxy)-N-(4-methoxyphenyl)acetamide (4n) Yield 66%; mp: 236–237 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.33 (s, 1H), 9.43 (s, 1H), 8.64 (d, J = 10.0 Hz, 2H), 8.30 (d, J = 10.0 Hz, 2H), 8.02 (t, J = 7.5 Hz, 2H), 7.99 (d, J = 5.0 Hz, 2H), 7.74–7.71 (m, 1H), 7.53 (d, J = 10.0 Hz, 2H), 6.90 (d, J = 5.0 Hz, 2H), 5.31 (s, 2H), 3.70 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.4, 166.0, 158.1, 156.0, 153.2, 151.9, 143.2, 139.0, 136.8, 135.2, 132.1, 130.0, 128.2, 128.1, 124.1, 121.8, 119.7, 115.0, 114.5, 66.1, 55.7. ESI-HRMS m/z: $[M+H]^+$ calcd for $C_{25}H_{21}N_6O_3$: 453.1670; found: 453.1690.

2-((2-(4-(1H-1,2,4-triazol-1-yl)phenyl)quinazolin-4-yl)oxy)-N-(2,4-difluorophenyl)acetamide (4o) Yield 51%; mp: 225–227 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.35 (s, 1H), 9.46 (s, 1H), 8.69–8.66 (m, 2H), 8.33–8.31 (m, 2H), 8.04–8.02 (m, 4H), 7.76–7.71 (m, 2H), 7.41–7.39 (m, 1H), 7.10–7.06 (m, 1H), 5.43 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.0, 166.3, 158.1, 157.0 (d, J = 243.7 Hz), 155.0 (d, J = 249.6 Hz), 153.2, 151.8, 143.2, 139.0, 136.8, 135.2, 130.0, 128.1 (t, J = 15.2 Hz), 126.8 (d, J = 9.7 Hz), 124.1, 122.5, 122.4, 119.6, 114.92, 111.8 (d, J = 24.9 Hz), 104.9 (t, J = 23.7 Hz), 65.5. ESI-HRMS m/z: $[M+H]^+$ calcd for $C_{24}H_{17}F_2N_6O_2$: 459.1376; found: 459.1369.

2-((2-(4-(1H-1,2,4-triazol-1-yl)phenyl)quinazolin-4-yl)oxy)-N-(2,6-difluorophenyl)acetamide (4p) Yield 47%; mp: 270–271 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.25 (s, 1H), 9.48 (s, 1H), 8.71 (d, J = 10.0 Hz, 2H), 8.33 (d, J = 10.0 Hz, 2H), 8.05 (d, J = 5.0 Hz, 2H), 8.04–8.02 (m, 2H), 7.73 (t, J = 7.5 Hz, 1H), 7.39–7.33 (m, 1H), 7.18 (t, J = 10.0 Hz, 2H), 5.44 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.1, 166.3, 158.3 (d, J = 249.1 Hz), 158.2, 153.2, 151.8, 143.2, 139.0, 136.7, 135.2, 130.1, 128.8 (t, J = 10.0 Hz), 128.2, 128.0, 124.2, 119.6, 115.0, 114.4 (t, J = 16.9 Hz), 112.5 (d, J = 22.9 Hz), 65.6. ESI-HRMS m/z: $[M+H]^+$ calcd for $C_{24}H_{17}F_2N_6O_2$: 459.1376; found: 459.1377.

2-((2-(4-(1H-1,2,4-triazol-1-yl)phenyl)quinazolin-4-yl)oxy)-N-(2,4-dichlorophenyl)acetamide (4q) Yield 58%; mp: 254–255 °C; ^{1}H NMR (500 MHz, DMSO-d_6):



Scheme 1 Synthetic route of target compounds **4a**–**4r**

δ 10.18 (s, 1H), 9.44 (s, 1H), 8.67 (d, J = 10.0 Hz, 2H), 8.30 (s, 2H), 8.02 (d, J = 10.0 Hz, 4H), 7.73–7.68 (m, 3H), 7.40 (d, J = 10.0 Hz, 1H), 5.44 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.1, 166.3, 160.4, 158.1, 153.2, 151.8, 143.2, 139.0, 136.7, 135.3, 134.0, 130.3, 130.0, 129.6, 128.2, 128.1, 127.9, 124.1, 120.0, 119.7, 114.9, 65.8. ESI-HRMS m/z: $[M+H]^+$ calcd for $C_{24}H_{17}N_6O_2Cl_2$: 491.0785; found: 491.0783.

2-((2-(4-(1H-1,2,4-triazol-1-yl)phenyl)quinazolin-4-yl)oxy)-N-(2,6-dimethylphenyl)acetamide ***(4r)*** Yield 61%; mp: 285–286 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.70 (s, 1H), 9.47 (s, 1H), 8.72 (d, J = 10.0 Hz, 2H), 8.36 (d, J = 5.0 Hz, 1H), 8.32 (s, 1H), 8.07 (d, J = 10.0 Hz, 2H), 8.03 (s, 2H), 7.73 (d, J = 5.0 Hz, 1H), 7.03 (s, 3H), 5.44 (s, 2H), 2.09 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.6, 166.3, 158.2, 153.2, 151.8, 143.2, 139.0, 136.7, 135.9, 135.2, 134.9, 130.5, 130.1, 128.2, 127.9, 127.2, 124.5, 119.6, 115.1, 65.7, 18.3. ESI-HRMS m/z: $[M+H]^+$ calcd for $C_{26}H_{23}N_6O_2$: 451.1877; found: 451.1867.

Antimicrobial assay

Antibacterial assay

Antibacterial activities of target compounds were determined against three pathogenic bacteria (*Xac*, *Xoo* and *Rs/Ralstonia solanacearum*), using the turbidimetric method [23, 27]. The tested compounds were prepared at two concentrations of 200 and 100 μg/mL. Pure DMSO in sterile distilled water was utilized as blank control, and commercial agrobactericides bismerthiazol (BMT) and thiodiazole-copper (TDC) were used as positive control agents. About 40 μL of solvent NB (3 g of beef extract, 5 g of peptone, 1 g of yeast

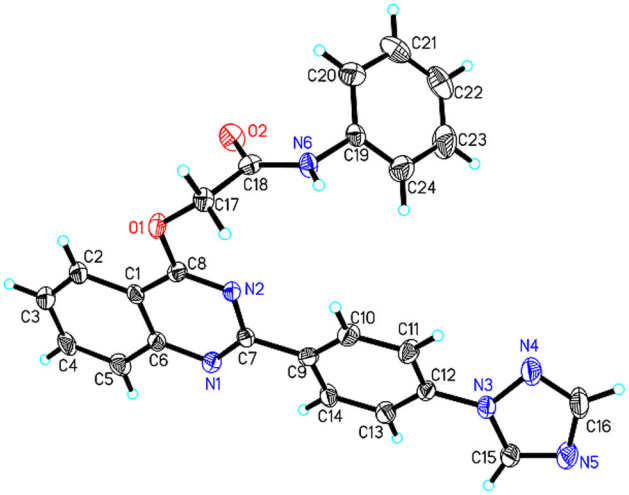


Fig. 3 Crystal structure of compound **4a**

powder, 10 g of glucose, 1 L of distilled water, pH = 7.0 – 7.2) containing the bacterium *Xoo*/*Xac*/*Rs* was added to the mixed solvent system including 4 mL of solvent NB and 1 mL of 0.1% Tween-20 aqueous solution containing tested compound or BMT. The above test tube was incubated at 30 ± 1 °C and continuously shaken at 180 rpm for 1–3 days. The bacterial growth was monitored by measuring the optical density at 600 nm (OD_{600}), given by $\text{turbidity}_{\text{corrected values}} = OD_{\text{bacterium}} - OD_{\text{no bacterium}}$, $I = (C_{\text{tur}} - T_{\text{tur}})/C_{\text{tur}} \times 100\%$. The C_{tur} represents the corrected turbidity value of bacterial growth of untreated NB (blank control), and T_{tur} represents the corrected turbidity value of bacterial growth of compound-treated NB. The I represents the inhibition rate of test compound against the bacterium.

Next, antibacterial activities of target compounds were further assessed against *Xoo* under five different concentra-

Table 1 Antibacterial activities of compounds **4a**–**4r** against pathogenic phytobacteria *Xoo*, *Xac* and *Rs*

Compd.	Inhibition rate (%)[a]					
	Xoo		*Xac*		*Rs*	
	200 μg/mL	100 μg/mL	200 μg/mL	100 μg/mL	200 μg/mL	100 μg/mL
4a	73.5 ± 1.9	67.2 ± 1.1	40.8 ± 3.2	21.4 ± 1.4	42.6 ± 3.8	17.4 ± 2.2
4b	67.3 ± 2.0	48.8 ± 1.2	32.9 ± 5.4	16.6 ± 3.3	19.3 ± 4.6	2.8 ± 1.3
4c	94.1 ± 1.9	83.4 ± 0.5	41.2 ± 0.5	29.9 ± 2.2	29.1 ± 2.7	11.3 ± 2.1
4d	79.1 ± 1.0	68.7 ± 0.8	32.3 ± 2.9	24.0 ± 1.8	15.7 ± 1.6	13.4 ± 2.0
4e	68.0 ± 3.9	44.6 ± 1.0	19.6 ± 1.6	6.5 ± 3.4	21.3 ± 1.5	14.2 ± 1.7
4f	61.9 ± 1.1	41.4 ± 1.6	34.6 ± 0.9	29.5 ± 1.8	21.5 ± 0.7	9.7 ± 1.4
4g	81.5 ± 4.2	76.5 ± 0.3	40.2 ± 4.0	8.7 ± 0.5	22.0 ± 1.3	19.8 ± 1.9
4h	67.6 ± 2.8	54.1 ± 0.4	52.7 ± 4.7	41.9 ± 3.1	16.4 ± 1.1	11.5 ± 2.3
4i	82.0 ± 4.7	62.4 ± 2.6	56.8 ± 2.4	39.2 ± 1.6	38.1 ± 2.4	21.7 ± 1.5
4j	58.5 ± 1.1	49.7 ± 2.9	59.6 ± 1.1	47.6 ± 3.1	40.2 ± 2.3	25.6 ± 3.4
4k	53.6 ± 5.1	41.9 ± 2.1	19.2 ± 1.6	6.5 ± 1.3	13.4 ± 1.2	4.6 ± 2.1
4l	62.2 ± 3.7	34.1 ± 3.9	36.5 ± 3.4	12.0 ± 1.2	23.7 ± 1.7	11.3 ± 2.3
4m	69.2 ± 3.5	44.6 ± 1.0	33.5 ± 1.4	25.4 ± 1.9	5.8 ± 0.9	2.5 ± 1.0
4n	71.0 ± 4.2	62.6 ± 3.3	51.3 ± 4.9	32.6 ± 3.7	30.1 ± 0.8	20.9 ± 1.8
4o	69.2 ± 2.8	61.0 ± 0.5	40.5 ± 0.6	32.0 ± 1.7	28.3 ± 2.3	24.7 ± 1.3
4p	66.9 ± 5.7	43.6 ± 3.2	36.7 ± 0.9	19.2 ± 2.4	19.4 ± 1.6	3.0 ± 1.1
4q	96.3 ± 2.2	84.6 ± 3.4	45.1 ± 6.5	32.8 ± 2.2	27.0 ± 0.5	3.3 ± 1.8
4r	45.2 ± 1.7	24.5 ± 3.0	37.0 ± 1.2	20.0 ± 2.1	26.1 ± 0.3	3.5 ± 1.7
TDC[b]	NT	NT	NT	NT	52.3 ± 4.8	21.2 ± 3.5
BMT[b]	79.0 ± 1.7	57.1 ± 3.7	83.6 ± 1.2	62.4 ± 4.5	NT	NT

NT = not tested

[a]The average of three trials

[b]Commercial agrobactericides bismerthiazol (BMT) and thiodiazole-copper (TDC) were used as positive control agents

tions (200, 100, 50, 25 and 12.5 μg/mL) to obtain their EC_{50} values, which were statistically determined by Probit analysis using the software package SPSS 17.0.

Antifungal assay

Mycelial growth rate method [28] was utilized to evaluate antifungal activities of target compounds against six phytopathogenic fungi. DMSO solution of the tested compound was added into sterilized Petri dishes, which contained about 10 mL molten potato dextrose agar (PDA). Subsequently, a 4-mm-diameter mycelial plug was cut from the fungal colony and placed at the center of PDA plate at 28 ± 1 °C for 4 days. Antifungal assays were conducted in triplicate for each compound. Additionally, pure DMSO and commercial fungicide (Hymexazol) were utilized as negative and positive controls, respectively.

The inhibition rate (I) of the tested compound was determined based on the following formula:

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

In this formula, the C represents the average mycelial diameter of negative control and T represents the average mycelial diameter of test compound-treated PDA.

Results and discussion

Synthesis

The synthetic procedures of target compounds **4a**–**4r** are summarized in Scheme 1. In brief, 1,2,4-triazole-substituted benzaldehyde **1** was reacted with anthranilamide in hot DMSO to furnish the intermediate quinazolinone **2**, which was then treated with *N*-(substituted phenyl)-2-bromoacetamide **3a**–**3r** in hot DMF containing anhydrous K_2CO_3 as catalyst to afford target compounds **4a**–**4r** in 43–67% yield. All the target compounds were fully characterized by ^{1}H NMR, ^{13}C NMR and HRMS spectra, which were in good accordance with the proposed structures in Scheme 1.

Crystal structure

A single crystal of compound **4a** suitable for X-ray diffraction analysis was obtained by slow evaporation of **4a** in a CH_2Cl_2-EtOH (5/1, *v*/*v*) solution at room temperature. As shown in Fig. 3, the acetamide group was directly attached to 4-position oxygen atom of quinazoline nucleus, rather than 3-position of nitrogen atom. Crystallographic data for **4a**: colorless crystal, $C_{24}H_{18}N_6O_2$, M_r=422.43, triclinic, space group P-1; a = 4.6875(9) Å, b = 19.043(4) Å, c = 22.820(5) Å; α = 99.38(3)°, β = 90.00(3)°, γ = 90.00(3)°, V = 2009.8(7) Å^3, T = 293 K, Z = 4, Dc = 1.393 g/cm^3, $F(000)$ = 876.0, reflections collected/independent reflections = 9776/3657, goodness-of-fit on F^2 = 1.031, $R1$ = 0.13, $wR2$ = 0.2653. CCDC 1573558.

Antibacterial activity

Antibacterial activity of compounds **4a**–**4r** against three pathogenic bacteria (*Xoo*, *Xac* and *Rs*) was firstly assessed in vitro at 200 and 100 μg/mL, using a turbidimetric method. As shown in Table 1, nearly half of this class of compounds demonstrated stronger inhibition activities against *Xoo* than control bismerthiazol at 100 μg/mL, with compounds **4q** and **4c** being the two most effective (having the inhibition rates of 84.6% and 83.4%, respectively). Significantly improved antibacterial activity toward *Xoo* was observed for these compounds, compared with recently reported quinazolinylether derivatives having a 1,2,4-triazolylstyryl moiety [21]. Furthermore, a few compounds also demonstrated moderate antibacterial activity against *Xac*. For example, compounds **4h**, **4i**, **4j**, **4n**, **4o** and **4q** possessed inhibition rates of 41.9%, 39.2%, 47.6%, 32.6%, 32.0% and 32.8% at 100 μg/mL, respectively. As for the bacterium *Rs*, only compounds **4a**, **4i** and **4j** were found to display modest inhibition activities against this pathogen under a higher concentration of 200 μg/mL.

To better evaluate antibacterial activities of these compounds against *Xoo*, their EC_{50} values were then determined using serial dilution method. As summarized in Table 2, compounds **4a**, **4c**, **4d**, **4g**, **4i**, **4n**, **4o** and **4q** were found to have EC_{50} values of 55.6, 35.0, 53.2, 36.5, 72.0, 54.4, 79.6 and 32.4 μg/mL against this pathogen, respectively, which were indeed superior to the control bismerthiazol (EC_{50} = 89.8 μg/mL). In particular, the efficacy of compounds **4c**, **4g** and **4q** was nearly 1.5 times more active than commercial bactericide bismerthiazol. A preliminary structure–activity relationship analysis was performed, and some tentative conclusions could be drawn as follows: (1) The three most effective compounds (namely compounds **4c**, **4g** and **4q**) included halogen substitutions, which favored the binding interactions between small molecules and proteins [29]; (2) Among these compounds, methyl-substituted compounds (compounds **4k**, **4l** and **4r**) exhibited a poor antibacterial activity, with compound **4r** (having a bulky 2,6-*di*-CH_3-Ph group) being the worst (EC_{50} = 240.7 μg/mL); (3) The position effect of certain substitutions on the benzene ring exerted a pronounced influence on the antibacterial activity, such as compounds **4c** (3-F-Ph) vs **4b** (2-F-Ph) as well as **4g** (2-CF_3-Ph) vs **4h** (4-CF_3-Ph), displaying approximately threefold differences in the antibacterial activity.

Table 2 EC_{50} values of compounds **4a**–**4r** against *Xoo*

Compd.	Toxic regression equation	Correlation coefficient (r)	$EC_{50}^{a} \pm SD$ (μg/mL)
4a	$y = 1.3010x + 2.7296$	0.9919	55.6 ± 3.2
4b	$y = 1.3381x + 2.3536$	0.9972	95.0 ± 3.5
4c	$y = 2.3456x + 1.3783$	0.9969	35.0 ± 2.0
4d	$y = 1.5035x + 2.4050$	0.9963	53.2 ± 3.5
4e	$y = 1.9568x + 1.0010$	0.9856	110.6 ± 5.2
4f	$y = 1.5323x + 1.7691$	0.9983	128.4 ± 3.2
4g	$y = 1.3058x + 2.9602$	0.9904	36.5 ± 1.8
4h	$y = 1.8485x + 1.2993$	0.9954	100.5 ± 4.1
4i	$y = 2.0656x + 1.1635$	0.9948	72.0 ± 2.5
4j	$y = 1.3564x + 2.2261$	0.9796	110.9 ± 4.8
4k	$y = 1.5009x + 1.7858$	0.9988	138.5 ± 3.1
4l	$y = 1.7944x + 1.0503$	0.9846	158.9 ± 8.1
4m	$y = 2.2084x + 0.5627$	0.9919	102.2 ± 6.4
4n	$y = 1.0030x + 3.2595$	0.9966	54.4 ± 3.6
4o	$y = 1.6493x + 1.8650$	0.9796	79.6 ± 3.5
4p	$y = 1.8201x + 1.2201$	0.9995	119.3 ± 7.5
4q	$y = 2.1648x + 1.7293$	0.9981	32.4 ± 2.2
4r	$y = 1.7696x + 0.7858$	0.9988	240.7 ± 3.2
BMT[b]	$y = 2.1405x + 0.8190$	0.9908	89.8 ± 1.8

[a]The average of three trials
[b]Commercial agrobactericide bismerthiazol (BMT) was used as control agent

Antifungal activity

Antifungal activities of compounds **4a**–**4r** against six phytopathogenic fungi were tested in vitro at 50 μg/mL, using mycelial growth rate method. As listed in Table 3, all the compounds displayed moderate to good antifungal activity against *Gloeosporium fructigenum*. It is worth mentioning that inhibition rates of compounds **4j** and **4p** were determined to be 44.4% and 44.0% against this pathogen, respectively, close to commercial fungicide Hymexazol (49.8%).

Conclusions

In conclusion, a series of 2-((2-(4-(1*H*-1,2,4-triazol-1-yl)phenyl)quinazolin-4-yl) oxy)-*N*-phenyl acetamide deriva-

Table 3 Antifungal activities of compounds **4a**–**4r** at 50 μg/mL

Compd.	Inhibition rate (%)[a]					
	GF	VD	PI	FO	PS	CM
4a	39.4 ± 1.1	12.3 ± 1.8	10.3 ± 1.5	9.6 ± 2.8	30.1 ± 3.3	24.6 ± 8.6
4b	36.1 ± 1.7	6.9 ± 0.6	14.8 ± 2.6	11.4 ± 0.6	26.8 ± 6.7	14.1 ± 7.2
4c	36.5 ± 2.4	8.7 ± 1.3	16.6 ± 5.7	8.6 ± 3.9	32.4 ± 1.3	23.5 ± 6.7
4d	36.1 ± 4.0	12.3 ± 1.8	16.0 ± 1.9	8.2 ± 1.6	28.1 ± 4.9	21.7 ± 5.6
4e	35.7 ± 1.3	6.0 ± 0.4	12.2 ± 2.4	9.6 ± 1.0	20.8 ± 2.4	19.4 ± 3.8
4f	29.1 ± 2.4	12.9 ± 0.4	13.9 ± 2.6	9.3 ± 2.7	25.3 ± 3.2	20.1 ± 5.9
4g	31.1 ± 1.7	15.4 ± 0.8	14.5 ± 2.1	7.9 ± 0.6	17.9 ± 2.4	21.4 ± 2.4
4h	39.0 ± 2.6	0	13.4 ± 1.0	13.2 ± 1.2	18.4 ± 4.6	21.3 ± 4.3
4i	41.9 ± 2.5	16.3 ± 1.4	14.2 ± 0.7	12.9 ± 1.8	16.8 ± 3.1	17.5 ± 4.6
4j	44.4 ± 2.1	34.7 ± 1.6	15.7 ± 2.5	24.3 ± 1.2	30.0 ± 4.0	18.0 ± 2.6
4k	27.1 ± 1.4	12.6 ± 4.4	14.5 ± 1.5	13.6 ± 2.4	16.9 ± 1.9	17.1 ± 4.9
4l	36.4 ± 2.1	12.6 ± 0.9	14.5 ± 2.1	17.1 ± 1.0	16.1 ± 3.1	23.5 ± 6.8
4m	39.4 ± 2.0	10.8 ± 2.6	13.6 ± 1.5	17.5 ± 0.7	19.2 ± 4.5	18.2 ± 6.0
4n	38.5 ± 2.5	14.7 ± 3.2	13.3 ± 1.6	12.8 ± 2.1	27.3 ± 3.6	27.3 ± 3.4
4o	35.7 ± 2.7	16.3 ± 1.7	14.5 ± 2.1	9.3 ± 1.3	20.8 ± 1.1	0
4p	44.0 ± 0.7	15.3 ± 2.2	16.3 ± 2.0	8.9 ± 2.5	27.3 ± 0.7	18.6 ± 5.4
4q	37.3 ± 0.8	16.5 ± 2.5	12.4 ± 1.2	10.4 ± 0.6	19.6 ± 3.4	19.0 ± 8.9
4r	35.3 ± 4.3	18.4 ± 1.6	16.3 ± 2.0	12.1 ± 0.7	22.9 ± 4.1	21.4 ± 2.2
Hymexazol[b]	49.8 ± 2.4	84.7 ± 0.8	64.9 ± 3.2	72.7 ± 1.4	74.5 ± 3.2	66.2 ± 0.1

GF Gloeosporium fructigenum, *VD Verticillium dahliae*, *PI Phytophthora infestans*, *FO Fusarium oxysporum*, *PS Pellicularia sasakii*, *CM Cytospora mandshurica*

[a]The average of three trials

[b]Commercial agrofungicide Hymexazol was used as control agent

tives were synthesized and evaluated for their antimicrobial activity against the phytopathogenic bacteria and fungi in agriculture. The work presented herein demonstrated the potential of this new molecular framework for being a useful molecular platform for developing more efficient agrobactericides against the pathogen *Xoo*.

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