Synthesis and biological activity of myricetin derivatives containing 1,3,4-thiadiazole scaffold

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Abstract
Background: Myricetin and 1,3,4-thiadiazole derivatives were reported to exhibit favorable antiviral and antibacterial activities. Aiming to discover novel myricetin analogues with potent activities, a series of novel myricetin derivatives containing 1,3,4-thiadiazole moiety were synthesized, and their antibacterial and antiviral activities were evaluated.

Result: Bioassay results indicated that some target compounds exhibited potential antibacterial and antiviral activities. Among them, compounds 2, 3a, 3b, 3d, 3f, 3i, 3m and 3p exhibited excellent antibacterial activities against Xanthomonas oryzae pv. Oryzae (Xoo), with EC50 values of 42.7, 38.6, 20.8, 12.9, 22.7, 27.3, 18.3 and 29.4 μg/mL, respectively, which were better than that of thiadiazole-copper (94.9 μg/mL). Compounds 3b, 3d, 3e, 3f, 3i and 3o showed good antibacterial activities against Ralstonia solanacearum (Rs), with EC50 values of 37.9, 72.6, 43.6, 59.6, 60.6 and 39.6 μg/mL, respectively, which were superior to that of thiadiazole-copper (131.7 μg/mL). In addition, compounds 3d, 3f, 3i and 3m showed better curative activities against tobacco mosaic virus (TMV), with EC50 values of 152.8, 99.7, 127.1, and 167.3 μg/mL, respectively, which were better than that of ningnanmycin (211.1 μg/mL).

Conclusions: A series of myricetin derivatives containing 1,3,4-thiadiazole scaffold were synthesized, and their antibacterial activities against Xoo and Rs and their antiviral activity against TMV were evaluated. Bioassays indicated that some target compounds exhibited potential antibacterial and antiviral activities. These results indicated this kind of myricetin analogues could be further studied as potential alternative templates in the search for novel antibacterial and antiviral agents.

Keywords: Myricetin, 1,3,4-thiadiazole, Antibacterial activity, Antiviral activity

Background
The rational use of agrochemicals plays a pivotal role in agricultural production by effectively controlling plant diseases [1, 2]. Unfortunately, the application of traditional pesticides is greatly limited due to their negative impacts on the environment and the rapid emergence of resistance [2, 3]. Therefore, searching for high-efficiency and environmentally friendly agrochemicals remains an arduous challenge in pesticide chemistry [1, 4]. In this process, natural products and their derivatives with new modes of action have been developed as pesticides that are safe to the environment [5, 6].

As one of important natural products in medicinal chemistry, myricetin was reported to exhibit extensive bioactivities including antibacterial [7], antiviral [8], anticancer [9], anti-inflammatory [10], antioxidant [11], and hypoglycemic activities [12]. Our previous study extracted a mixture containing myricetin from the bark of Toona sinensis and found it to exhibit moderate antiviral activity against tobacco mosaic virus (TMV) [13]. Using natural myricetin as the lead molecule, some

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myricetin derivatives bearing Schiff-base moiety, which displayed good inhibitory activity against telomerase and excellent anticancer activity against human breast cancer cells MDA-MB-231, were synthesized by Xue et al. [14]. Furthermore, the acceptable antibacterial activities against Xanthomonas oryzae pv. oryzae (Xoo) and Ralstonia solanacearum (Rs) of myricetin derivatives containing acidamide moiety were also recently reported by us [15]. Obviously, myricetin derivatives as possible active ingredients play a key role in the searching for novel agrochemicals and pharmaceuticals (Fig. 1).

1,3,4-Thiadiazoles, which represent important nitrogenous heterocycles in medicinal chemistry, have attracted much attentions because of their various pharmacological activities, including antibacterial [16], antifungal [17], antiviral [18], anticonvulsant [19], anxiolytic [20], antinociceptive [21] and anticancer [22] activities. Among the above biological activities, acceptable antibacterial and antiviral activities displayed by 1,3,4-thiadiazoles have been reported well by chemists in recent years. For example, Li et al. [23] found that some 1,3,4-thiadiazole sulfone derivatives exhibited satisfactory antibacterial activities against rice bacterial leaf blight and leaf streak. Recently, we also found some 1,3,4-thiadiazole derivatives bearing 1,4-pentadiene-3-one moiety to exhibit remarkable antiviral activities against plant viruses [24].

Considering these above results, we speculated that introducing 1,3,4-thiadiazole fragment into myricetin might generate novel lead compounds with greater biological activities. Thus, a series of myricetin derivatives containing 1,3,4-thiadiazole scaffold were synthesized (Scheme 1), and their antibacterial activities against Xoo and Rs and their antiviral activity against TMV were evaluated.

**Results and discussion**

**Chemistry**

A series of myricetin derivatives containing thiadiazole moiety were successfully prepared in two steps in our current work. All of the target compounds 2, 3a–3q were characterized by infrared spectrum (IR), nuclear magnetic resonance (NMR) spectroscopy, and high resolution mass spectrum (HRMS) analysis. The IR spectral data of compounds 2, 3a–3q showed characteristic frequencies at 1723–1709 cm⁻¹ and 1640–1621 cm⁻¹, which are assigned to the characteristic vibrations of C=O and C=N–, respectively. In the ¹H NMR spectra, the characteristic –CH₂—groups between myricetin scaffold and 1,3,4-thiadiazole heterocycle was observed.
as a signal at approximately 5.27–5.21 ppm. The chemical shifts at 165.59–161.63 and 161.70–154.04 ppm in the $^{13}$C NMR spectra confirmed the existence of C=O and C=N-groups, respectively.

**Antibacterial activity screening of the title compounds against Xac and Rs in vitro**

Using *Ralstonia solanacearum* (strain MR111, Guizhou University, China) and *Xanthomonas oryzae pv. oryzae* (strain PXO99A, Nanjing Agricultural University, China) as the tested bacterial strains, the antibacterial activities of title compounds have been evaluated by the turbidimeter test [1, 3, 4, 6], and the commercial agent thiadiazole-copper was tested as the control. Some compounds with good antibacterial activity against Xoo and Rs were tested at five double-declining concentrations (100, 50, 25, 12.5 and 6.25 μg/mL) to obtain the corresponding EC$_{50}$ values.

The title compounds (2, 3a–3q) were evaluated for antibacterial activities against Xoo and Rs in vitro. Results in Table 1 indicated that most synthesized compounds exhibited appreciable antibacterial activities against Xoo and Rs. For example, compounds 2, 3a, 3b, 3d, 3f, 3i, 3m and 3p showed excellent antibacterial activities against Xoo at 100 μg/mL, with inhibition rates of 84.5, 84.9, 99.6, 87.3, 77.5, 84.5, 99.3 and 84.3%, respectively, which were better than that of thiadiazole-copper (52.3%). The inhibition rates of compounds 2, 3a, 3b, 3d, 3f, 3i, 3m and 3p against Xoo at 50 μg/μL were 54.6, 60.1, 65.2, 90.7, 82.6, 68.2, 80.8 and 71.2%, respectively, which were better than that of thiadiazole-copper (28.7%). Additionally, compounds 3b, 3d, 3e, 3f, 3i and 3o demonstrated good antibacterial activities against Rs at 100 μg/mL, with inhibition rates of 81.4, 64.3, 75.7, 69.3, 64.3 and 65.4%, respectively, which were superior to that of thiadiazole-copper (46.7%). Compounds 3b, 3d, 3e, 3f, 3i and 3o showed good antibacterial activities against Rs at 50 μg/μL (60.2, 30.4, 65.5, 40.5, 52.2 and 52.1%, respectively), which were better than thiadiazole-copper (32.2%).

To further understand antibacterial activity of synthesized compounds, the EC$_{50}$ values of some target compounds, which exhibited better antibacterial activities against Xoo and Rs than thiadiazole-copper, were calculated and summarized in Table 2. Notably, compounds 2, 3a, 3b, 3d, 3f, 3i, 3m and 3p exhibited excellent antibacterial activities against Xoo, with EC$_{50}$ values of 42.7, 38.6, 20.8, 12.9, 22.7, 27.3, 18.3 and 29.4 μg/mL, respectively, which were better than that of thiadiazole-copper (94.9 μg/mL). Meanwhile, compounds 3b, 3d, 3e, 3f, 3i and 3o showed remarkable antibacterial activities against Rs, with EC$_{50}$ values of 37.9, 72.6, 43.6, 59.6, 60.6 and 60.6 μg/mL.

**Table 1** Inhibition effect of the compounds 4, 5a–5q against Xoo and Rs

| Compd. | R | Xoo 100 μg/mL | Rs 50 μg/mL | Xoo 50 μg/mL | Rs 100 μg/mL | Rs 50 μg/mL |
|--------|---|---------------|-------------|--------------|--------------|-------------|
| 2      |   | 84.5 ± 3.9    | 54.6 ± 8.5  | 46.5 ± 9.7   | 28.1 ± 7.8   |             |
| 3a     | H | 84.9 ± 5.8    | 60.1 ± 2.5  | 36.0 ± 2.6   | 32.4 ± 6.1   |             |
| 3b     | 4-NO$_2$Ph | 81.4 ± 4.6    | 65.2 ± 9.0  | 81.5 ± 6.7   | 60.2 ± 6.9   |             |
| 3c     | 2-MePh | 47.2 ± 1.5    | 25.9 ± 3.7  | 49.3 ± 6.7   | 30.3 ± 3.8   |             |
| 3d     | 4-CIPh | 99.6 ± 0.1    | 90.7 ± 4.0  | 64.3 ± 8.8   | 30.4 ± 4.1   |             |
| 3e     | Me | 58.2 ± 5.1    | 27.4 ± 5.4  | 75.7 ± 8.1   | 65.5 ± 9.9   |             |
| 3f     | 2-CIPh | 87.3 ± 2.5    | 82.6 ± 2.6  | 69.3 ± 0.8   | 46.5 ± 9.1   |             |
| 3g     | 2-FPh | 79.7 ± 3.6    | 21.0 ± 4.9  | 45.2 ± 5.9   | 38.3 ± 2.4   |             |
| 3h     | 4-OMePh | 37.3 ± 6.2    | 15.5 ± 8.9  | 28.1 ± 7.6   | 27.1 ± 6.0   |             |
| 3i     | 2,4-di-CIPh | 77.5 ± 1.4 | 68.2 ± 5.4  | 64.3 ± 6.1   | 52.1 ± 2.8   |             |
| 3j     | 3-NO$_2$Ph | 30.0 ± 1.2    | 79.8 ± 9.7  | 45.2 ± 8.3   | 31.1 ± 4.3   |             |
| 3k     | 4-BrPh | 47.3 ± 4.7    | 23.3 ± 7.5  | 26.4 ± 2.6   | 10.7 ± 1.6   |             |
| 3l     | 2-BrPh | 50.7 ± 1.9    | 31.6 ± 4.5  | 24.0 ± 4.7   | 16.2 ± 0.7   |             |
| 3m     | 2-CI-thiazol-5-s-y | 99.4 ± 3.9 | 80.8 ± 3.7  | 26.3 ± 3.2   | 25.0 ± 6.6   |             |
| 3n     | Ph | 38.3 ± 4.5    | 17.7 ± 0.1  | 45.3 ± 5.6   | 44.7 ± 5.1   |             |
| 3o     | 4-MePh | 52.6 ± 3.3    | 37.6 ± 5.5  | 65.4 ± 1.7   | 52.1 ± 5.7   |             |
| 3p     | Pyridin-3-y | 84.3 ± 3.8    | 71.2 ± 5.3  | 38.0 ± 6.2   | 12.8 ± 6.0   |             |
| Myricetin* | – | 40.1 ± 8.3    | 21.0 ± 5.6  | 28.6 ± 2.2   | 17.5 ± 3.3   |             |
| Thiadiazole-copper* | – | 52.4 ± 2.0    | 28.7 ± 4.1  | 46.7 ± 2.0   | 32.2 ± 2.1   |

Average of three replicates

*Thiadiazole-copper and myricetin were used for comparison of antibacterial activity*
39.6 μg/mL, respectively, which were superior to that of thiadiazole-copper (131.7 μg/mL).

The inhibitory rates in Tables 1 and 2 indicated that most synthesized compounds bearing the same substituted fragment were found to exhibit better antibacterial activity against Xoo than Rs. For example, the EC_{50} values of title compounds 3b, 3d, 3f and 3i against Xoo were respectively 20.8, 12.9, 22.7 and 27.3 μg/mL, which were better than that against Rs (37.9, 72.6, 59.6 and 60.6 μg/mL, respectively). The antibacterial results in Tables 1 and 2 also indicated that the different groups on R had significant effects on the antibacterial activity of the target compounds. Obviously, the presence of heterocycles can effectively enhance the antibacterial activity against Xoo. As examples of this phenomenon, the compounds 3m and 3p, which contain respectively 2-Cl-thiazol-5-yl and pyridin-3-yl groups, exhibited fine antibacterial activities against Xoo at 50 μg/mL, with the inhibition rates of 80.8 and 71.2%, respectively, which were superior to that of thiazazole-copper (28.7%). Meanwhile, when R was substituted with 4-NO_2Ph, 4-ClPh, 2-ClPh and 2,4-di-ClPh groups, the corresponding compounds 3b, 3d, 3f and 3i exhibit remarkable antibacterial activities against Xoo, with the EC_{50} values of 20.8, 12.9, 22.7 and 27.3 μg/mL, respectively, which were better than that of thiazazole-copper (94.9 μg/mL).

**Antiviral activity screening of the title compounds against TMV in vivo**

Using growing N. tobacum L. leaves at the same age as the test subjects, the curative and protective activities against TMV were evaluated based on the half-leaf blight spot method [25–27], and the commercial agent ningnanmycin was tested as the control under the same conditions. The antiviral activity against TMV in vivo at 500 μg/mL was listed in Tables 3 and 4. The preliminary bioassays results indicated that the inhibitory rates of title compounds against TMV at 500 μg/mL ranged from 18.2 to 68.4% in terms of their curative activity, and ranged from 21.5 to 60.8% in terms of their protective activity. Among them, the inhibitory rates of compounds 3d, 3f, 3i and 3m in curative activity were 59.8, 68.4, 66.8 and 57.1%, respectively, which were better than that of ningnanmycin (51.8%). Moreover, compounds 3c, 3i and 3m were found to exhibit significant protective activities (58.4, 60.8 and 56.7%, respectively), which were similar to ningnanmycin (58.3%).

To further understand antiviral activity of synthesized compounds, the EC_{50} values of 3d, 3f, 3i and 3m were calculated and summarized in Table 4. Notably, the EC_{50} values of 3d, 3f, 3i and 3m were respectively 152.8, 99.7, 127.1 and 167.3 μg/mL, which were better than that of ningnanmycin (211.1 μg/mL).

The antiviral results in Tables 3 and 4 indicated that most of synthesized compounds bearing the same substituted fragment exhibited better protective activity than curative activity against TMV. Meanwhile, Results in Tables 3 and 4 also indicated that the different groups on R had significant effects on the anti-TMV activity of the target compounds. Obviously, the presence of benzyl chloride groups can effectively enhance the curative activity of title compounds against TMV. For example, compounds 3d, 3f, 3i and 3m, which contain respectively 2-ClPh, 4-ClPh, 2,4-di-ClPh and 2-Cl-thiazol-5-yl groups, exhibited excellent curative activities against TMV, with the EC_{50} values of 152.8, 99.7, 127.1 and 167.3 μg/mL, respectively, which were better than that of ningnanmycin (211.1 μg/mL). Furthermore, when the R was 2-MePh,

| Compd. | Xoo          | Regression equation | r   | EC_{50} (μg/mL) | Rs          | Regression equation | r   | EC_{50} (μg/mL) |
|--------|--------------|---------------------|-----|----------------|-------------|---------------------|-----|----------------|
| 2      | y = 2.513x + 0.902 | 0.99 | 42.7 ± 2.6 | /             | /           | /                   | /   | /              |
| 3a     | y = 2.885x + 0.454 | 0.99 | 38.6 ± 1.4 | /             | /           | /                   | /   | /              |
| 3b     | y = 1.199x + 3.420 | 0.99 | 208 ± 3.6  | y = 2.685x + 0.762 | 0.99 | 37.9 ± 1.0 |
| 3d     | y = 2.328x + 2.418 | 0.97 | 129 ± 5.8  | y = 2.770x + 0.154 | 0.99 | 72.6 ± 1.6 |
| 3e     | /             | /   | /           | y = 2.485x + 0.925 | 0.98 | 43.6 ± 3.8 |
| 3f     | y = 1.982x + 2.314 | 0.98 | 227 ± 3.6  | y = 3.004x - 0.332 | 0.99 | 59.6 ± 2.0 |
| 3i     | y = 1.401x + 2.989 | 0.99 | 273 ± 1.8  | y = 2.365x + 0.786 | 0.99 | 60.6 ± 2.1 |
| 3m     | y = 2.723x + 1.565 | 0.98 | 183 ± 3.6  | /             | /           | /                   | /   | /              |
| 3p     | y = 2.058x + 1.979 | 0.99 | 294 ± 1.0  | /             | /           | /                   | /   | /              |
| 3o     | /             | /   | /           | y = 1.017x + 3.375 | 0.96 | 39.6 ± 5.3 |
| Thiazazole-copper | y = 1.999x + 1.047 | 0.99 | 94.9 ± 2.2 | y = 0.930x + 3.028 | 0.98 | 131.7 ± 2.9 |

Average of three replicates

* The commercial agricultural antibacterial agent thiazazole-copper was used for comparison of antibacterial activity
were similar to that of ningnanmycin. Average of three replicates

Table 3 Antiviral activities of the title compounds against TMV in vivo at 500 µg/mL

| Compd. | Curative activity (%) | Protection activity (%) | Compd. | Curative activity (%) | Protection activity (%) |
|--------|-----------------------|-------------------------|--------|-----------------------|-------------------------|
| 2      | 18.2 ± 7.3            | 21.5 ± 9.1              | 3j     | 28.7 ± 3.8            | 39.4 ± 3.1              |
| 3a     | 46.7 ± 5.2            | 50.3 ± 9.3              | 3k     | 28.0 ± 8.6            | 33.0 ± 7.5              |
| 3b     | 53.8 ± 9.0            | 54.1 ± 9.4              | 3l     | 33.9 ± 9.4            | 34.2 ± 5.4              |
| 3c     | 37.0 ± 9.1            | 58.4 ± 1.0              | 3m     | 57.1 ± 9.6            | 56.7 ± 8.2              |
| 3d     | 59.8 ± 9.2            | 54.3 ± 9.0              | 3n     | 48.4 ± 5.9            | 42.1 ± 7.1              |
| 3e     | 28.7 ± 8.3            | 35.4 ± 5.1              | 3o     | 50.8 ± 3.6            | 47.3 ± 2.9              |
| 3f     | 68.4 ± 7.4            | 54.4 ± 7.7              | 3p     | 34.6 ± 5.4            | 36.5 ± 1.6              |
| 3g     | 36.4 ± 3.8            | 386 ± 7.7               | 3q     | 288 ± 6.7             | 34.4 ± 7.2              |
| 3h     | 44.8 ± 9.4            | 45.2 ± 1.5              | 3r     | 51.8 ± 4.3            | 58.3 ± 2.9              |
| 3i     | 66.8 ± 9.8            | 60.8 ± 8.3              |        |                       |                         |

Average of three replicates

* Ningnanmycin and myricetin were used for comparison of antiviral activity

Table 4 The EC50 values of 5d, 5f, 5i and 5m against TMV

| Compd. | TMV 500 µg/mL | Regression equation | r      | EC50 (µg/mL) |
|--------|---------------|---------------------|--------|---------------|
| 3d     | 59.8 ± 6.2    | y = 0.473x - 3.967  | 0.98   | 152.8 ± 3.2   |
| 3f     | 68.4 ± 7.4    | y = 0.744x - 3.512  | 0.99   | 99.7 ± 2.7    |
| 3i     | 66.8 ± 9.8    | y = 0.816x + 3.823  | 0.99   | 127.1 ± 2.6   |
| 3m     | 57.1 ± 9.6    | y = 0.361x + 4.197  | 0.99   | 167.3 ± 4.8   |
| Ningnanmycin* | 51.3 ± 2.6 | y = 0.203x + 4.154 | 0.97   | 211.1 ± 3.6   |

Average of three replicates

* The commercial agricultural antiviral agent ningnanmycin was used for comparison of antiviral activity

2,4-di-ClPh and 2-Cl-thiazol-5-y1 groups, the protective activities of corresponding compounds 3c, 3i and 3m at 500 µg/mL were 58.4, 60.8 and 56.7%, respectively, which were similar to that of ningnanmycin (58.3%).

Methods and materials

Chemistry

The melting points of the products were determined on an XT-4 binocular microscope (Beijing Tech Instrument Co.). The 1H NMR and 13C NMR (CDCl3 or DMSO as solvents) spectroscopies were performed on a JEOL-ECX 500 NMR spectrometer at room temperature using TMS as an internal standard. The IR spectra were recorded on a Bruker VECTOR 22 spectrometer using KBr disks. High-performance liquid chromatography mass spectrometry was performed on a Thermo Scientific Q Exactive (USA). Unless noted, all solvents and reagents were purchased from Shanghai Titan Scientific Co., Ltd, and were treated with standard methods. Based on the synthesis procedures described in our previous work [14], intermediates 1 (2-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)aceto-hydrazide) were prepared using myricetin (5,7-dihydroxy-3-(3,4,5-trihydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2-(3,4,5-trihydroxyphenyl)-4H-chromen-4-one) as the starting material.

General synthesis procedure for 5,7-dimethoxy-2-(3,4,5-trimethoxyphenyl)-3-((5-mercapto-1,3,4-thiadiazol-2-yl)methoxy)-4H-chromen-4-one (2)

To a solution of intermediate 1 (1.00 g, 2.17 mmol) in methanol (30 mL), potassium hydroxide (0.20 mL, 3.16 mmol) and carbon disulfide (0.21 mL, 3.47 mmol) were added, and the reaction mixture was heated under reflux for 16 h. After the reaction was cooled to room temperature, 50 mL of water was added to the mixture, and the pH of the solution was adjusted to five with dilute HCl. Then, a solid precipitated was filtered and recrystallized with ethanol to obtain the intermediate 2. white solid, m. p. 154–155 °C, yield 50.1%; IR (KBr, cm−1): 3229, 2939, 2837, 1639, 1634, 1575, 1498, 1466, 1357, 1253, 1211, 1130, 944, 816; 1H NMR (500 MHz, DMSO- d6) δ 7.24 (s, 2H, Ar–H), 6.87 (d, J = 2.1 Hz, 1H, Ar–H), 6.53 (d, J = 2.1 Hz, 1H, Ar–H), 5.09 (s, 2H, CH2), 3.91 (s, 3H, OCH3), 3.86 (s, 9H, 3 OCH3), 2.91 (s, 3H, OCH3), 13C NMR (125 MHz, DMSO-d6) δ 183.1, 176.9, 169.4, 165.6,
164.6, 163.5, 158.2, 157.9, 145.03, 143.4, 129.9, 113.5, 111.2, 101.5, 98.6, 67.3, 65.5, 61.5, 61.4, 61.3; HRMS (HPLC) m/z: 519.0890, found 519.0883 ([M+H]^+).

**General synthesis procedures for title compounds 3a–3p**

To a solution of 2 (1.16 mmol) in acetonitrile (30 mL), sodium carbonate (1.74 mmol) and CH3I (1.74 mmol) were added, and the reaction mixture was stirred at 40 °C for 5 h. After the reaction was completed and cooled to room temperature, a solid precipitated was filtered and recrystallized with methanol to obtain the title compound 3a. Based on the similar method, the title compounds 3b–3p were prepared.

5,7-Dimethoxy-2-(3,4,5-trimethoxyphenyl)-3-((5-(methylthio)-1,3,4-thiadiazol-2-yl)methoxy)-4H-chromen-4-one (3a)

A white solid, m. p. 124–125 °C; yield 30.1%; IR (KBr, cm⁻¹): 2942, 1700, 1637, 1604, 1575, 1519, 1477, 1451, 1349, 1362, 1243, 1211, 1164, 1126, 108, 856, 821; ¹H NMR (500 MHz, DMSO-d₆) δ 8.06 (d, J = 8.7 Hz, 2H, Ar–H), 7.62 (d, J = 8.7 Hz, 2H, Ar–H), 7.18 (s, 2H, Ar–H), 6.82 (d, J = 2.1 Hz, 1H, Ar–H), 6.50 (d, J = 2.1 Hz, 1H, Ar–H), 5.21 (s, 2H, CH₂), 4.48 (s, 2H, CH₂), 3.87 (s, 3H, OCH₃); ¹³C NMR (125 MHz, DMSO-d₆) δ 173.3, 165.7, 164.9, 163.3, 161.1, 159.0, 154.3, 152.9, 140.1, 138.6, 125.1, 109.3, 106.1, 96.2, 92.7, 62.3, 61.03, 56.5, 56.4, 56.9, 14.1; HRMS (HPLC) m/z: 555.0866, found 555.0870 ([M+Na]^+).

5,7-Dimethoxy-2-(3,4,5-trimethoxyphenyl)-3-((5-((4-nitrobenzyl)thio)-1,3,4-thiadiazol-2-yl)methoxy)-4H-chromen-4-one (3b)

A yellow solid, m. p. 124–125 °C; yield 30.1%; IR (KBr, cm⁻¹): 2953, 2836, 1645, 1538, 1492, 1472, 1452, 1414, 1357, 1215, 1169, 113, 1105, 992, 817; ¹H NMR (500 MHz, DMSO-d₆) δ 7.81 (s, 2H, Ar–H), 6.81 (s, 1H, Ar–H), 6.49 (s, 1H, Ar–H), 5.22 (s, 2H, CH₂), 3.87 (s, 3H, OCH₃); ¹³C NMR (125 MHz, DMSO-d₆) δ 173.3, 165.7, 164.9, 163.3, 161.2, 159.0, 154.1, 152.9, 140.2, 138.7, 134.1, 133.9, 130.6, 129.0, 125.1, 109.4, 106.1, 96.2, 92.7, 62.4, 61.1, 56.6, 56.4, 56.0, 35.9; HRMS (HPLC) m/z: 665.0798, found 665.0766 ([M+Na]^+).

5,7-Dimethoxy-2-(3,4,5-trimethoxyphenyl)-3-((5-((2-chlorobenzyl)thio)-1,3,4-thiadiazol-2-yl)methoxy)-4H-chromen-4-one (3c)

A white solid, m. p. 112–113 °C; yield 36.6%; IR (KBr, cm⁻¹): 2997, 2942, 2838, 1636, 1603, 1578, 1572, 1505, 1490, 1470, 1454, 1415, 1350, 1245, 1211, 1164, 1127, 1108, 1018, 1003, 853, 820; ¹H NMR (500 MHz, CDCl₃) δ 7.52 (d, J = 7.4 Hz, 1H, Ar–H), 7.38–7.34 (m, 1H, Ar–H), 7.20 (m, 2H, Ar–H), 7.15 (s, 2H, Ar–H), 6.49 (d, J = 2.2 Hz, 1H, Ar–H), 6.37 (d, J = 2.1 Hz, 1H, Ar–H), 5.28 (s, 2H, CH₂), 4.45 (s, 2H, CH₂), 3.97 (s, 3H, OCH₃), 3.91 (s, 3H, OCH₃), 3.90 (s, 3H, OCH₃), 3.88 (s, 6H, 2 OCH₃), 2.31 (s, 3H, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ 173.3, 165.7, 164.4, 163.3, 161.2, 159.0, 154.1, 153.0, 153.3, 153.1, 140.2, 138.5, 125.2, 108.8, 106.3, 96.7, 93.8, 62.2, 60.7, 56.7, 56.6, 56.5, 26.9, 15.1; HRMS (HPLC) m/z: 569.0923, found 569.0983 ([M+Na]^+).
5,7-Dimethoxy-2-(3,4,5-trimethoxyphenyl)-3-((5-((2-fluorobenzyl)thio)-1,3,4-thiadiazol-2-yl) methoxy)-4H-chromen-4-one (3l)

A white solid, m. p. 154–155 °C; yield 90.1%; IR (KBr, cm⁻¹): 2942, 1700, 1637, 1604, 1575, 1519, 1471, 1455, 1349, 1362, 1243, 1121, 1164, 1126, 1108, 1017, 856, 821; ¹H NMR (500 MHz, CDCl₃) δ 7.51 (d, J = 8.3 Hz, 1H, Ar–H), 7.17 (d, J = 8.3 Hz, 1H, Ar–H), 7.14 (s, 1H, Ar–H), 7.13 (s, 2H, Ar–H), 6.49 (d, J = 2.2 Hz, 1H, Ar–H), 6.38 (d, J = 2.2 Hz, 1H, Ar–H), 5.26 (s, 2H, CH₂), 4.27 (s, 2H, CH₂), 3.98 (s, 6H, OCH₃), 3.91 (s, 6H, OCH₃), 3.88 (s, 6H, OCH₃); ¹³C NMR (125 MHz, CDCl₃) δ 173.3, 165.5, 164.4, 163.6, 161.2, 159.0, 154.0, 153.0, 140.2, 138.7, 134.3, 133.5, 131.6, 129.8, 129.7, 127.2, 125.1, 109.4, 106.0, 96.2, 92.6, 62.4, 61.1, 56.8, 56.4, 56.0, 34.5; HRMS (HPLC) m/z: 665.0789, found 665.0747 ([M+Na]⁺).

5,7-Dimethoxy-2-(3,4,5-trimethoxyphenyl)-3-((5-((3-nitrobenzyl)thio)-1,3,4-thiadiazol-2-yl) methoxy)-4H-chromen-4-one (3j)

A white solid, m. p. 131–132 °C; yield 39.4%; IR (KBr, cm⁻¹): 2945, 1634, 1605, 1558, 1471, 1426, 1352, 1246, 1212, 1163, 1130, 1018, 820; ¹H NMR (500 MHz, CDCl₃) δ 7.43 (d, J = 8.3 Hz, 2H, Ar–H), 7.28 (s, 1H, Ar–H), 7.25 (s, 1H, Ar–H), 7.13 (s, 2H, Ar–H), 6.49 (d, J = 2.2 Hz, 1H, Ar–H), 6.38 (d, J = 2.2 Hz, 1H, Ar–H), 5.26 (s, 2H, CH₂), 4.27 (s, 2H, CH₂), 3.98 (s, 3H, OCH₃), 3.91 (s, 3H, OCH₃), 3.88 (s, 3H, OCH₃); ¹³C NMR (125 MHz, CDCl₃) δ 173.3, 165.7, 164.4, 163.8, 161.2, 159.0, 154.0, 153.0, 140.3, 138.8, 134.1, 133.1, 132.5, 129.4, 125.7, 125.1, 109.4, 106.1, 96.2, 92.7, 62.4, 61.0, 56.6, 56.0, 34.2; HRMS (HPLC) m/z: 676.1030, found 676.1012 ([M+Na]⁺).
5,7-Dimethoxy-2-(3,4,5-trimethoxyphenyl)-3-((S-((2-chlorothiazol-5-yl)methyl)thio)-1,3,4-thiadiazol-2-yl) methoxy)-4H-chromen-4-one (3p)

A white solid, m. p. 155–156 °C, yield 60.1%; IR (KBr, cm⁻¹): 2979, 2942, 1643, 1602, 1579, 1505, 1492, 1470, 1454, 1416, 1351, 1246, 1211, 1163, 1128, 1108, 1000, 823; ¹H NMR (500 MHz, DMSO-d₆) δ 7.34 (d, J = 6.9 Hz, 2H, Ar–H), 7.25 (d, J = 10.3 Hz, 3H, Ar–H), 7.18 (s, 2H, Ar–H), 6.82 (t, J = 4.6 Hz, 1H, Ar–H), 6.49 (d, J = 2.1 Hz, 1H, Ar–H), 5.22 (s, 2H, CH₂), 4.34 (s, 2H, CH₂), 3.87 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 3.79 (d, J = 13.8 Hz, 6H, 2 OCH₃), 3.70 (d, J = 7.8 Hz, 3H, OCH₃); ¹³C NMR (125 MHz, CDCl₃) δ 172.1, 164.9, 164.4, 164.0, 160.9, 158.8, 153.3, 151.1, 141.8, 138.1, 137.8, 125.2, 108.8, 106.4, 94.8, 93.8, 62.3, 60.7, 56.7, 56.6, 56.5, 28.4; HRMS (HPLC) m/z: 672.0362, found 672.0262 ([M+Na]^+).

Conclusions

Aiming to discover novel myricetin analogues with potent activities, a series of novel myricetin derivaties containing 1,3,4-thiadiazole moiety were synthesized, and their antibacterial activities against Xoo and Rs and their antiviral activity against TMV were evaluated. Bioassays indicated that some target compounds exhibited potential antibacterial and antiviral activities. Among them, compounds 2, 3a, 3b, 3d, 3f, 3i, 3m and 3p exhibited excellent antibacterial activities against Xoo, with EC₅₀ values of 42.7, 38.6, 20.8, 12.9, 22.7, 27.3, 18.3 and 29.4 μg/mL, respectively, which were better than that of thiadiazole-copper (94.9 μg/mL). Compounds 3b, 3d, 3e, 3f and 3o showed good antibacterial activities against Rs, with EC₅₀ values of 37.9, 72.6, 43.6, 59.6, 60.6 and 39.6 μg/mL, respectively, which were superior to that of thiadiazole-copper (131.7 μg/mL). In addition, compounds 3d, 3f, 3i and 3m showed better curative activities against TMV, with EC₅₀ values of 152.8, 99.7, 127.1, and 167.3 μg/mL, respectively, which were better than that of ningnamycin (211.1 μg/mL). Given the above results, this kind of myricetin analogues could be further studied as potential alternative templates in the search for novel antibacterial and antiviral agents.

Additional file

Additional file 1. All the copies of IR, ¹H NMR, ¹³C NMR and HRMS for the title compounds.

Authors’ contributions

The current study is an outcome of constructive discussion with WX, XZ, LC and XR carry out their synthesis and characterization experiments; XZ, XW, QL, JZ and CZ performed the antiviral and antibacterial activities; WX, XZ,
LC and QL carried out the $^1$H NMR, $^{13}$C NMR, IR and HRMS spectral analyses; WX and XW were involved in the drafting of the manuscript and revising the manuscript. All authors read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
We have presented all our main data in the form of tables and figures. Meanwhile, all the copies of IR, $^1$H NMR, $^{13}$C NMR and HRMS for the title compounds were presented in the Additional file 1. The datasets supporting the conclusions of the article are included within the article and the Additional file 1.

Consent for publication
This section is not applicable for this manuscript.

Ethics approval and consent to participate
This section is not applicable for this manuscript.

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