Synthesis and antibacterial activity of novel myricetin derivatives containing sulfonylpiperazine

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Abstract
Myricetin derivatives containing sulfonylpiperazine were synthesized and their structures were confirmed by NMR and HRMS. The antibacterial activity results indicated that some compounds showed good antibacterial activity against Xanthomonas oryzae pv. oryzae (Xoo), Xanthomonas axonopodis pv. citri (Xac) and Ralstonia solanacearum (Rs). Among them, compounds 4m and 4p revealed excellent antibacterial activities against Rs with a concentration for 50% of maximal effect (EC50) value of 4 and 4 μg/mL, which were better than the control drugs bismuthiazol (13 μg/mL) and thiodiazole-copper (185 μg/mL). As observed using scanning electron microscope (SEM), these compounds act by causing folding and deformation of the bacterial surface, resulting in incomplete bacterial structure, so as to achieve the goal of bacteriostasis. The myricetin derivatives synthesized are expected to guide the research direction of new antibacterial agents.

Keywords Myricetin derivative · Sulfonylpiperazine · Antibacterial activity · Concentration for 50% of maximal effect · Scanning electron microscope

Introduction
Plant diseases have always been a headache in agricultural production. The plant bacterial diseases are extremely difficult to control in agricultural production, such as rice bacterial blight, tobacco bacterial wilt, citrus canker and so on (Zou et al. 2011; Li et al. 2017). Since the earliest fungicide bordeaux liquid, a lot of agricultural fungicides have been developed successively. With the development of chemistry, new types of nano-antibacterial agents have also come into the sight of chemists (Khatoon et al. 2017, 2018). Until today, there have been many commercial antibacterial agents with good activity, such as bismuthiazol and thiodiazole-copper etc. However, with the increase in the use of traditional fungicides, the resistance of plant bacteria to them has gradually increases (Yan et al. 2016; Jiang et al. 2020a, b). Therefore, the development of new antibacterial agents is of great significance.

Flavonoids are widely existed in plants in nature, and belong to the secondary metabolites of plants (Manthey and Guthrie 2002). It plays an important role in plant growth, development, flowering, fruiting, antibacterial and disease prevention. Moreover, many studies in recent years have shown that flavonoid-based scaffolds as multi-target-directed ligands (MTDLs) have shown an important role in the treatment of Alzheimer’s disease (Jalili-Baleh et al. 2018). Therefore flavonoids have become a research hotspot in the pharmaceutical and pesticide industries due to their extensive biological activities. Myricetin is a common plant-derived flavonol derived from fruits, vegetables, berries, nuts, tea, etc. (Zhang et al. 2020). Studies have found that myricetin has a wide range of biological activities. Such as antibacterial (Mo et al. 2020), anticancer (Sun et al. 2012), anti-inflammatory (Wang et al. 2010), antiviral (Yu et al. 2012) and antioxidant activities (Guitard et al. 2016). Studies have found that myricetin has the least cytotoxicity to TZM-bl, HeLa, PBMC and H9 cells at a concentration of 100 μM, with cell viability above 85%, which is better than quercetin and pinocembrin (Pasetto et al. 2010).
Piperazine is an important intermediate in medicine, pesticide and dye. Due to the special chemical structure of piperazine, it is widely used in medicine, pesticides, and dyes. As a kind of pharmacophore group with extensive biological activities in antibacterial, weeding, anticancer, antioxidant, etc., the sulfonamide group has shown excellent activity and great value in the field of medicine and pesticides. Therefore, the structure of sulfonlpiperazine is often used in new drug design and development (Xu et al. 2015).

As a flavonoid with good biological activity, the application of myricetin derivatives has become more and more extensively. For example, some of the myricetin derivatives containing acylhydrazone showed excellent anticancer activity (Xue et al. 2015). Meanwhile, some myricetin derivatives containing piperazine amide also showed good anticancer activity (Ruan et al. 2018a, b). At the cellular level, chalcone containing myricetin can be influenced by inhibiting the differentiation of Gaoyou duck embryonic osteoclasts in vitro (Fu et al. 2019). Tobacco mosaic virus has a great harm to plant growth and development. Some of the myricetin derivatives containing oxadiazole (Zhang et al. 2019) or ferulic acid (Tang et al. 2020) showed good anti-TMV activity.

In summary, we hope to develop a fast and efficient method for constructing the partial skeleton of piperazine and sulfonamides structure with the lead of myricetin by consulting a large number of literatures and combining our previous work. A Bruker Ascend 400 NMR spectrometer (Bruker Optics, Switzerland) was used to record the $^1$H, $^{13}$C and $^{19}$F nuclear magnetic resonance (NMR), with tetramethylsilane (TMS) as the internal standard, and CDCl$_3$ as solvent. The melting point tests were conducted in an XT-4 binocular microscope (Beijing Tech Instrument Co., Ltd.). A WFH-203B with three UV analyzer (Shanghai Jingke Industrial Co., Ltd.) was used for thin-layer chromatography (TLC). Deionizing water purifier (Hokee). Vertical High-Pressure Steam Sterilization Pot (Shanghai ShenAn Medical instrument Factory). Multiskan FC (Thermo Fisher Scientific (Shanghai) Co., Ltd.).

**Experimental**

**Materials**

Piperazine and arylsulfonyl chloride were obtained from Shanghai Titanchem Co., Ltd., and all other reagents were analytical grade. A Bruker Ascend 400 NMR spectrometer (Bruker Optics, Switzerland) was used to record the $^1$H, $^{13}$C and $^{19}$F nuclear magnetic resonance (NMR), with tetramethylsilane (TMS) as the internal standard, and CDCl$_3$ as solvent. The melting point tests were conducted in an XT-4 binocular microscope (Beijing Tech Instrument Co., Ltd.). A WFH-203B with three UV analyzer (Shanghai Jingke Industrial Co., Ltd.) was used for thin-layer chromatography (TLC). Deionizing water purifier (Hokee). Vertical High-Pressure Steam Sterilization Pot (Shanghai ShenAn Medical instrument Factory). Multiskan FC (Thermo Fisher Scientific (Shanghai) Co., Ltd.).

**Chemicals**

**General procedure for preparing the intermediates 1, 2 and 3**

As shown in Scheme 1, intermediate 1 and 2 were prepared via the reported methods (Chen et al. 2019). Myricetin (1 mmol) and methyl iodide (15 mmol) were stirred at 43 °C for 48 h, and then suction filtration and the filter was washed with CH$_2$Cl$_2$, most of the solvent in the filtrate was removed by spin evaporation and hydrochloric acid.
(10 mL) was added under reflux in the ethanol to obtain the intermediate 1. Finally, the intermediate 1 (10 mmol) was stirred in DMF at room temperature for 1 h and dibromoalkane (30 mmol) was added; this reaction was allowed to continue for 12 h and pour into water to obtain the intermediate 2. And the intermediate 3 was prepared by known methods (Henderson et al. 2011). Arylsulfonyl chloride (10 mmol) was added in one portion to a solution of piperazine (60 mmol) in CH₂Cl₂ at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, diluted with CH₂Cl₂, quenched by the addition of saturated NaHCO₃ (aq), washed with brine, and concentrated in vacuo to obtain the intermediate 3.

Synthesis of the target compounds 4a–4y

The synthetic route to the title compounds, the myricetin derivatives containing sulfonylpiperazine (4a–4y) are shown in Scheme 1. The intermediate 3 (2.4 mmol) and potassium carbonate (3.0 mmol) were stirred in 30 mL acetonitrile for 30 min, then the intermediate 2 (2.0 mmol) was added, the temperature was increased to 90 °C for 5 h, the potassium carbonate was removed by filtration, and the acetonitrile was removed by spin evaporation. The target compounds 4a–4y were obtained by column chromatography (ethyl acetate:petroleum ether = 1:2–2:1), with different yields. Their physical properties and spectral data are listed in the Supporting Information, and the ¹H NMR, ¹³C NMR, ¹⁹F NMR and HRMS spectra attached in the Supporting Information.

Results and discussion

Chemistry

Twenty-five myricetin derivative containing sulfonylpiperazine were obtained in this study, all their structures were identified via ¹H NMR, ¹³C NMR, ¹⁹F NMR and HRMS. The data of 4a was shown and discussed below. In the ¹H NMR spectrum, multiplet signals at δ 7.68–6.28 ppm revealed the presence of aromatic nuclei, and a triplet peak at δ 3.91–3.94 ppm indicated the presence of O–CH₂–C group. In addition, the high-frequency single peaks at δ 3.89–3.83 ppm revealed the presence of five –OCH₃. The nuclear magnetic signal at δ 2.93–2.38 ppm revealed the presence of nuclear magnetic signal peak of piperazine’s hydrogen proton. Finally, and three absorption signals at δ 2.28–1.40 ppm indicated the presence of C–CH₂CH₂CH₂–N group. The absorption signals at δ 174.02 and 72.12 ppm in ¹³C NMR spectra confirmed the presence of –C=O and –OCH₂– groups, respectively. When fluorine is substituted on the benzene ring, carbon atoms attached to fluorine will migrate to the low field and the fluorine atom will split the two adjacent carbon atoms in ¹³C NMR spectra. For example, compound 4b had an absorption peak at δ 163.99 ppm, which represented the nuclear magnetic peak of C–F. The absorption peak of the carbon atom at the same position in 4a was shown at δ 132.83 ppm. In addition, two adjacent carbon atoms of a carbon atom substituted by fluorine split into two adjacent absorption peaks at δ 116.42 and 116.19 ppm. The
two carbons at the same position in 4a showed a single absorption peak at δ 132.83 ppm. The high resolution mass spectrometry (HRMS) spectra of title compounds show characteristic absorption signals of [M + H]+ ions, which are consistent with their molecular weight.

**Antibacterial activity examination of the title compounds against Xoo, Xac and Rs in vitro**

The bacteriostatic activity of the compounds were measured by turbidimetric method (Zhong et al. 2017; Li et al. 2013), using Xac, Xoo and Rs as test strains, while using the commercial antibacterial agents bismertiazol and thiodiazole-copper as control drugs. Some of the target compounds exhibited better antibacterial activities against Xac, Xoo and Rs in vitro at 100 and 50 μg/mL, and the observed results would be shown in Table 1. For example, the myricetin has no obvious antibacterial activity, but most of the target compounds showed better antimicrobial activity than the lead compound myricetin. Compounds 4a, 4c and 4d were exhibited favorable antibacterial activity against Xoo at 100 μg/mL, with the inhibition rates of 72, 77 and 75%, which gained an advantage over that of bismertiazol (55%) and thiodiazole-copper (62%). The inhibition rates of compounds 4a, 4c and 4d against Xoo at 50 μg/mL were 52, 53 and 43%, which were better than that of bismertiazol (39%) and thiodiazole-copper (36%). Similarly, compounds 4h and 4p showed higher antibacterial activity against Xac at 100 μg/mL, the calculated inhibition of 74 and 87%, which exceeded that of bismertiazol (63%) and thiodiazole-copper (51%). Compounds 4h and 4p revealed superior antibacterial activities against Xac at 50 μg/mL with the inhibition rates of 42 and 41%, respectively, which were also higher compared to bismertiazol (19%) and thiodiazole-copper.

![Table 1](image)

**Table 1** Antibacterial activities of compounds 4a–4y

| Compounds | Xoo  | Xac  | Rs   |
|-----------|------|------|------|
|           | 100 μg/mL | 50 μg/mL | 100 μg/mL | 50 μg/mL | 100 μg/mL | 50 μg/mL |
| 4a        | 74 ± 4 | 52 ± 4 | 55 ± 3 | 31 ± 2 | 27 ± 3 | 25 ± 2 |
| 4b        | 25 ± 4 | 24 ± 1 | 55 ± 6 | 27 ± 1 | 93 ± 4 | 66 ± 3 |
| 4c        | 77 ± 7 | 53 ± 2 | 47 ± 2 | 33 ± 0 | 34 ± 4 | 104 ± 0 |
| 4d        | 75 ± 6 | 43 ± 5 | 53 ± 1 | 36 ± 2 | 63 ± 2 | 51 ± 5 |
| 4e        | 41 ± 1 | 26 ± 1 | 57 ± 2 | 31 ± 3 | 38 ± 5 | 28 ± 2 |
| 4f        | 26 ± 3 | 20 ± 2 | 42 ± 2 | 33 ± 2 | –     | –     |
| 4g        | 46 ± 5 | 33 ± 3 | 40 ± 3 | 39 ± 2 | 80 ± 5 | 39 ± 3 |
| 4h        | 41 ± 1 | 33 ± 5 | 74 ± 2 | 42 ± 1 | –     | –     |
| 4i        | 38 ± 5 | 33 ± 5 | 33 ± 3 | 11 ± 5 | 69 ± 4 | 51 ± 3 |
| 4j        | 40 ± 2 | 36 ± 2 | 54 ± 2 | 40 ± 3 | 73 ± 6 | 39 ± 1 |
| 4k        | 57 ± 3 | 25 ± 6 | 46 ± 6 | 23 ± 4 | 100 ± 2 | 96 ± 5 |
| 4l        | 24 ± 2 | 21 ± 3 | 55 ± 3 | 29 ± 3 | 68 ± 1 | 37 ± 5 |
| 4m        | 28 ± 5 | 25 ± 3 | 26 ± 3 | 25 ± 1 | 100 ± 3 | 86 ± 5 |
| 4n        | 22 ± 2 | 21 ± 5 | 48 ± 1 | 37 ± 3 | 48 ± 2 | 17 ± 2 |
| 4o        | 22 ± 4 | 13 ± 2 | 38 ± 4 | 23 ± 2 | 98 ± 1 | 90 ± 3 |
| 4p        | 57 ± 1 | 29 ± 6 | 87 ± 2 | 41 ± 1 | 100 ± 4 | 90 ± 2 |
| 4q        | 12 ± 5 | 7 ± 1 | 33 ± 4 | 28 ± 1 | 51 ± 4 | 19 ± 2 |
| 4r        | 42 ± 1 | 19 ± 7 | 36 ± 2 | 33 ± 3 | 57 ± 3 | 55 ± 1 |
| 4s        | 28 ± 9 | 3 ± 3 | 36 ± 3 | 26 ± 2 | 16 ± 2 | 10 ± 1 |
| 4t        | 60 ± 1 | 70 ± 0 | 37 ± 7 | 16 ± 4 | 36 ± 3 | 29 ± 3 |
| 4u        | 29 ± 6 | 17 ± 5 | 32 ± 3 | 26 ± 3 | 86 ± 0 | 80 ± 3 |
| 4v        | 35 ± 5 | 5 ± 2 | 25 ± 1 | 26 ± 3 | 69 ± 3 | 30 ± 5 |
| 4w        | 19 ± 6 | 8 ± 6 | 22 ± 0 | 11 ± 4 | 75 ± 1 | 73 ± 3 |
| 4x        | 14 ± 2 | 9 ± 4 | 32 ± 6 | 17 ± 2 | 41 ± 1 | 22 ± 6 |
| 4y        | 33 ± 2 | 15 ± 2 | 37 ± 6 | 26 ± 7 | 82 ± 3 | 77 ± 3 |
| Myricetin | 11 ± 4 | 9 ± 5 | –     | –     | 21 ± 2 | 8 ± 5 |
| **BT**    | 55 ± 2 | 39 ± 2 | 63 ± 1 | 19 ± 6 | 60 ± 6 | 52 ± 0 |
| **TC**    | 62 ± 5 | 36 ± 4 | 51 ± 2 | 19 ± 2 | 38 ± 4 | 21 ± 2 |

Average of three replicates

*BT* bismertiazol, *TC* thiodiazole-copper

bThe commercial antibacterial agents bismertiazol and thiodiazole-copper was used as positive control
In addition, compounds 4b, 4k, 4m, 4o, 4p and 4y exhibited better antibacterial activities against Rs at 100 and 50 µg/mL, with the inhibition rates of 93 and 66%, 100 and 96%, 100 and 86, 98 and 90%, 100 and 90%, and 86 and 80%, 82 and 77%, respectively, which were over the control agents bismertiazol (60 and 52%) and thidiazole-copper (38 and 20%).

According to the preliminary screening results of antibacterial activity, EC$_{50}$ values of some of the compounds showed excellent antibacterial activities against Xoo, Xac and Rs, as shown in Table 2. We can know from Table 2, the compounds 4a, 4c and 4d exerted distinct activity against Xoo with the EC$_{50}$ values were 36, 38 and 40 µg/mL, respectively, which preceded that of bismerthiazol (89 µg/mL) and thiodiazole-copper (68 µg/mL). Compound 4p revealed preferable antibacterial activity against Xac with EC$_{50}$ values of 41 µg/mL, which was superior to bismerthiazol (93 µg/mL) and thiodiazole-copper (70 µg/mL). Compounds 4k, 4m, 4o, 4p, 4u and 4y against Rs with EC$_{50}$ values of 6, 4, 10, 4, 5 and 5 µg/mL, respectively, which prevailed over that of bismertiazol (13 µg/mL) and thiodiazole-copper (185 µg/mL) signal.

**Table 2** EC$_{50}$ values of some compounds against Xoo, Xac and Rs

| Tested Compounds | Regression equation | r | EC$_{50}$ (µg/mL) |
|------------------|---------------------|---|------------------|
| Xoo 4a           | y = 1.0037x + 3.4383 | 0.9627 | 36               |
| 4c               | y = 1.3975x + 2.7873 | 0.9754 | 38               |
| 4d               | y = 1.2546x + 2.9887 | 0.9715 | 40               |
| TC               | y = 1.8570x + 1.5964 | 0.9910 | 68               |
| BT              | y = 1.2079x + 2.6426 | 0.9844 | 89               |
| Xac 4h           | y = 1.2056x + 2.7741 | 0.9589 | 70               |
| 4p               | y = 2.0575x + 1.6741 | 0.9550 | 41               |
| TC               | y = 1.2141x + 2.7624 | 0.9752 | 70               |
| BT              | y = 1.1147x + 2.8064 | 0.9878 | 93               |
| Rs 4b            | y = 2.3189x + 1.6664 | 0.9921 | 27               |
| 4d               | y = 0.8746x + 3.9683 | 0.9632 | 15               |
| 4i               | y = 0.6887x + 3.9954 | 0.9585 | 29               |
| 4j               | y = 1.5022x + 2.8776 | 0.9636 | 26               |
| 4k               | y = 1.8641x + 3.5488 | 0.9507 | 6                |
| 4m               | y = 1.3204x + 4.2077 | 0.9633 | 4                |
| 4o               | y = 1.9801x + 3.0192 | 0.9934 | 10               |
| 4p               | y = 1.3149x + 4.2120 | 0.9617 | 4                |
| 4r               | y = 0.6145x + 4.1342 | 0.9938 | 26               |
| 4u               | y = 0.8169x + 4.2210 | 0.9904 | 5                |
| 4w               | y = 1.3517x + 3.1764 | 0.9582 | 22               |
| 4y               | y = 1.0833x + 4.2902 | 0.9604 | 5                |
| TC               | y = 0.6931x + 3.4289 | 0.9773 | 185              |
| BT              | y = 0.8701x + 4.0372 | 0.9747 | 13               |

Average of three replicates

BT bismertiazol, TC thidiazole-copper

The commercial antibacterial agents bismertiazol and thidiazole-copper was used as positive control

**Fig. 2** Antibacterial activities of compound 4p (a), myricetin (b), thidiazole-copper (c) and bismertiazol (d) against Rs test in vitro at 100, 50, 25, 12.5 and 6.25 µg/mL.
inhibition rates of 48 and 41%. When R was substituted with 4–NO₂–Ph, compounds 4d and 4p showed certain inhibitory activity against Xoo, Xac and Rs at 100 µg/mL. The inhibitory activity of compound 4d against Xoo is better when n = 4. Similarly, the inhibitory activity of compound 4p against Xac and Rs is best when n = 3. Compared with the previous work of research group, this article introduced sulfonylpiperazine to the structure of myricetin, and some compounds show better inhibitory activity against Rs with EC₅₀ values between 4 and 10 µg/mL, which is superior to the myricetin derivatives containing thiodiazole sulfide with EC₅₀ values between 28 and 185 µg/mL (Ruan et al. 2018a, b). And the antibacterial activity of these compounds were verified by SEM.

**Scanning electron microscopy (SEM) studies**

To further explore the mechanism of antibacterial action against Rs, scanning electron microscopy (SEM) studies were carried out using the designated compound 4p and the observed SEM micrographs are shown in Fig. 3. Obviously, when there is no drug action, the form of the strain is plump and short and thick. However, the surface of the bacteria began to appear wrinkle at 50 µg/mL, which became more pronounced as the concentration of the drug increased to 100 µg/mL. It was obtained by SEM, the bacteriostatic mechanism of compound 4p is to act on the surface of bacteria by drugs, thus causing the bacteria to fold and shrink, resulting in incomplete bacterial structure, so as to achieve the goal of bacteriostasis.

**Conclusion**

In summary, 25 myricetin derivatives containing sulfonylpiperazine were designed and synthesized. And test their in vitro activity on the three strains Xoo, Xac and Rs. Some compounds showed excellent inhibitory activity against Rs with EC₅₀ values between 4 and 10 µg/mL. Among them, compound 4p against Xac and Rs with EC₅₀ value of 41 and 4 µg/mL, which far exceeded that of bismertiazol (93 and 13 µg/mL, respectively) and thiodiazole-copper (67 and 185 µg/mL), respectively. Meanwhile, the inhibitory rate of compound 4p on Xoo is 57% at 100 µg/mL, which was slightly better than the control drug bismertiazol (55 µg/mL). Meanwhile, compound 4m against Rs with EC₅₀ value of 4 µg/mL, which better than the control drug bismertiazol (13 µg/mL) and thiodiazole-copper (185 µg/mL). Scanning electron microscopy analysis further confirmed that the title compounds caused the bacteria to shrink by acting on the surface of the bacteria, so as to achieve antibacterial effect. Therefore, the designed compounds can be used as potential antibacterial drugs for further research to find new antibacterial drugs.

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