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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 oryzaepv. oryzae* (Xoo), *Xanthomonas axonopodispv. 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 (EC_{50}) value of 4 and 4 μg/mL, which were better than the control drugs bismerthiazol (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 bismerthiazol 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). Research over the years has shown 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.

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2014). Piperazine is an important intermediate in medicine, pesticide and dye. Due to the special chemical structure of piperazine. Piperazine and its series of compounds are important products connecting the chemical industry and the pharmaceutical industry (Suleman et al. 2020), widely used in medicine (Alina et al. 2020), pesticides (Peng and Wang 2018) and other fields. As a kind of pharmacophore group with extensive biological activities in antibacterial (Nadia and Mona 2020), weeding (Chen et al. 2018), anticancer (Štěpánková et al. 2020), antioxidant (Soliman et al. 2020) etc., sulfonamide group has shown excellent activity and great value in the field of medicine and pesticides. Therefore, the structure of sulfonylpiperazine 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 have become more and more extensively. For example, some of the myricetin derivatives containing acylhydrazone showed excellent anticancer activity (Xue et al. 2015). Meanwile, some myricetin derivatives containing piperazine amide also showed good anticancer activity (Ruan et al. 2018a, b). And there were also reported some agricultural antibacterial activities of myricetin derivatives (Li et al. 2019; Chen et al. 2019; Jiang et al. 2020a, 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 of research group, so as to synthesize the new myricetin derivatives containing both piperazine and sulfonyl structure (Fig. 1), and investigated their antibacterial efficacy against Xoo, Xac and Rs in vitro. The antibacterial mechanism of compounds **4** were preliminarily studied by SEM. Compared with the previous work of research group, the inhibitory activity of this series of compounds **4** on Rs has been greatly improved. This article attempts to optimize the superposition of these active fragments to find drugs with high antibacterial activity, and provide a reliable research direction for the screening of new antibacterial drugs.

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). Myricetrin (1 mmol) and methyl iodide (15 mmol) were stirred 43 °C for 48 h, and then suction filtration and the filter was extracted with CH_2Cl_2, most of the solvent in the filtrate was removed by spin evaporation and hydrochloric acid

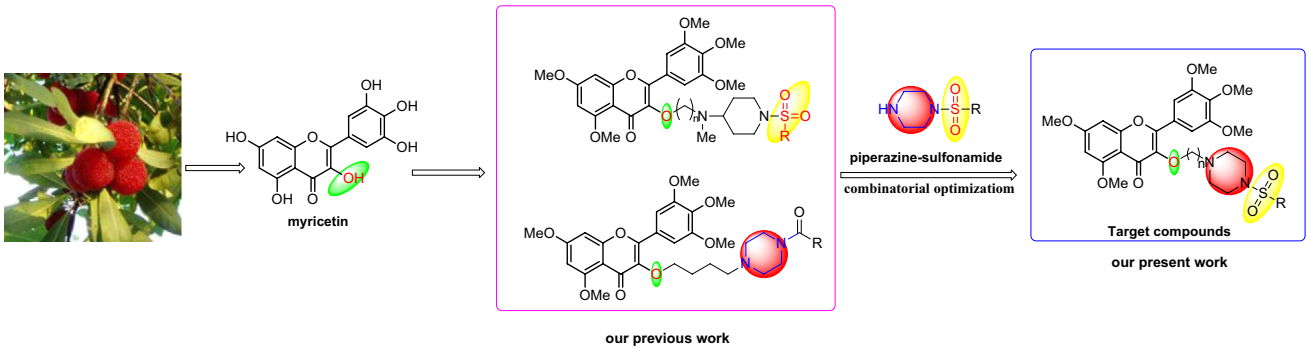
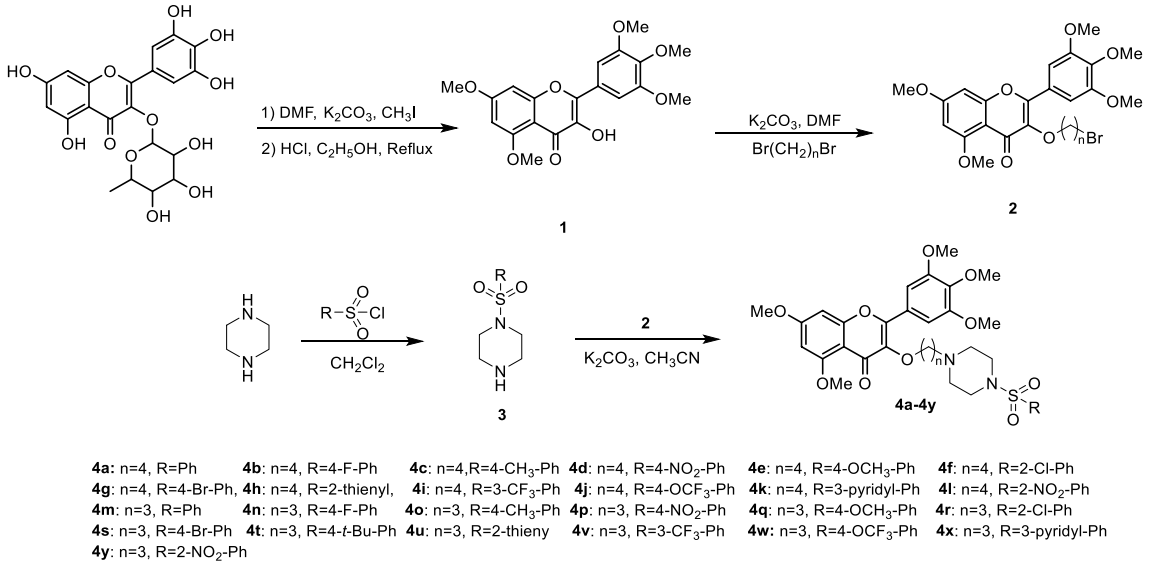


Fig. 1 Design route of the target compounds **4a**–**4y**



4a: n=4, R=Ph **4b**: n=4, R=4-F-Ph **4c**: n=4,R=4-CH_3-Ph **4d**: n=4, R=4-NO_2-Ph **4e**: n=4, R=4-OCH_3-Ph **4f**: n=4, R=2-Cl-Ph
4g: n=4, R=4-Br-Ph, **4h**: n=4, R=2-thienyl, **4i**: n=4, R=3-CF_3-Ph **4j**: n=4, R=4-OCF_3-Ph **4k**: n=4, R=3-pyridyl-Ph **4l**: n=4, R=2-NO_2-Ph
4m: n=3, R=Ph **4n**: n=3, R=4-F-Ph **4o**: n=3, R=4-CH_3-Ph **4p**: n=3, R=4-NO_2-Ph **4q**: n=3, R=4-OCH_3-Ph **4r**: n=3, R=2-Cl-Ph
4s: n=3, R=4-Br-Ph **4t**: n=3, R=4-*t*-Bu-Ph **4u**: n=3, R=2-thieny **4v**: n=3, R=3-CF_3-Ph **4w:** n=3, R=4-OCF_3-Ph **4x**: n=3, R=3-pyridyl-Ph
4y: n=3, R=2-NO_2-Ph

Scheme 1 Synthetic route of the target compounds **4a–4y**

(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 CH_2Cl_2 at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, diluted with CH_2Cl_2, quenched by the addition of saturated $NaHCO_3$ (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 ^{1}H NMR, ^{13}C NMR, ^{19}F 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 ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and HRMS. The data of **4a** was shown and discussed below. In the ^{1}H 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–CH_2–C group. In addition, the high-frequency single peaks at δ 3.89–3.83 ppm revealed the presence of five –OCH_3. 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–$CH_2CH_2CH_2$–N group. The absorption signals at δ 174.02 and 72.12 ppm in ^{13}C NMR spectra confirmed the presence of –C=O and –OCH_2– 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 ^{13}C 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 bismerthiazol 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 bismerthiazol (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 bismerthiazol (39%) and thiadiazole-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 bismerthiazol (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 bismerthiazol (19%) and thiadiazole-copper

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	10 ± 4
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	7 ± 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[b]	55 ± 2	39 ± 2	63 ± 1	19 ± 6	60 ± 6	52 ± 0
TC[b]	62 ± 5	36 ± 4	51 ± 2	19 ± 2	38 ± 4	21 ± 2

Average of three replicates

BT bismerthiazol, *TC* thidiazole-copper

[b]The commercial antibacterial agents bismerthiazol and thiodiazole-copper was used as positive control

(19%). In addition, compounds **4b**, **4k**, **4m**, **4o**, **4p**, **4u** 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%, 86 and 80%, 82 and 77%, respectively, which were over the control agents bismerthiazol (60 and 52%) and thiodiazole-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 bismerthiazol (13 μg/mL) and thiodiazole-copper (185 μg/mL) signally. We can clearly observe the difference in activity against Rs between compound **4p**, myricetin, control drugs bismerthiazol and thiodiazole-copper in Fig. 2.

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[a]	$y=1.8570x+1.5964$	0.9910	68
	BT[a]	$y=1.2079x+2.6426$	0.9844	89
Xac	**4h**	$y=1.2056x+2.7741$	0.9589	70
	4p	$y=2.0575x+1.6741$	0.9550	41
	TC[a]	$y=1.2141x+2.7624$	0.9752	70
	BT[a]	$y=1.1147x+2.8064$	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	$y=1.0833+4.2902$	0.9604	5
	TC[a]	$y=0.6931x+3.4289$	0.9773	185
	BT[a]	$y=0.8701x+4.0372$	0.9747	13

Average of three replicates

BT bismerthiazol, *TC* thidiazole-copper

[a]The commercial antibacterial agents bismerthiazol and thidiazole-copper was used as positive control

Structure–activity relationship analysis of antibacterial activities

Table 1 revealed that the antibacterial activities of the title compounds were considerably affected by the length of the carbon chain and different substituents on sulfonyl groups. For instance, When $n=3$ and R were substituted with phenyl, 4–CH_3–Ph, 4–NO_2–Ph, thienyl or 2–NO_2–Ph, these compounds exhibited significant Rs inhibitory activity with the inhibition rates of 100, 98, 100 and 82% at 100 μg/mL, respectively, which were better than the compounds with $n=4$ on the same substituent group with the inhibition rates of 27, 34, 63 and 68%. When $n=4$ and R were substituted with 4–F–Ph or pyridyl, these compounds performed better Rs inhibitory activity with the inhibition rates of 93 and 100% at 100 μg/mL, which were exceeded than the compounds with $n=3$ on the same substituent group with the

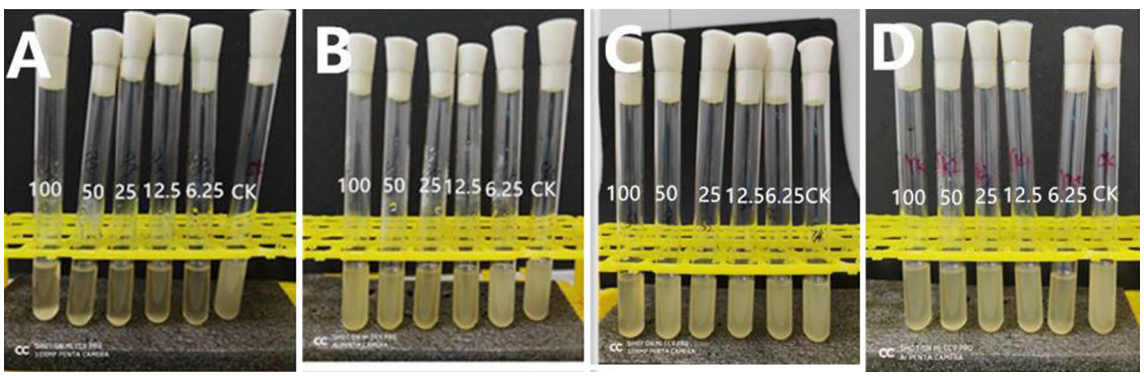


Fig. 2 Antibacterial activities of compound **4p** (**a**), myricetin (**b**), thiodiazole-copper (**c**) and bismerthiazol (**d**) against Rs test in vitro at 100, 50, 25, 12.5 and 6.25 μg/mL

Fig. 3 SEM images for Rs after incubated in different concentration of compound **4p**. **a** 0 mg/mL, **b** 50 μg/mL and **c**100 μg/mL. Scale bar for **a**–**c** are 2 μm

inhibition rates of 48 and 41%. When R was substituted with 4–NO_2–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 EC_{50} values between 4 and 10 μg/mL, which is superior to the myricetin derivatives containing thiadiazole sulfide with EC_{50} values between 28 and 39 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 EC_{50} values between 4 and 10 μg/mL. Among them, compound **4p** against Xac and Rs with EC_{50} value of 41 and 4 μg/mL, which far exceeded that of bismerthiazol (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 bismerthiazol (55 μg/mL). Meanwhile, compound **4m** against Rs with EC_{50} value of 4 μg/mL, which better than the control drug bismerthiazol (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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