Design, Synthesis, Antibacterial Activity, Antiviral Activity, and Mechanism of Myricetin Derivatives Containing a Quinazolinone Moiety

Tingting Liu,† Feng Peng,† Xiao Cao, Fang Liu, Qifan Wang, Liwei Liu, and Wei Xue*†

Cite This: ACS Omega 2021, 6, 30826−30833

ABSTRACT: Plant bacteria such as Xanthomonas axonopodis pv. citri (Xac), Pseudomonas syringae pv. actinidiae (Psa), Xanthomonas oryzae pv. oryzae (Xoo), and tobacco mosaic virus (TMV) have created huge obstacles to the global trade of food and economic crops. However, traditional chemical agents used to control these plant diseases have gradually become disadvantageous due to long-term irregular use. Therefore, finding new and efficient antibacterial and antiviral agents is becoming imperative. In this study, a series of myricetin derivatives containing a quinazolinone moiety were designed and synthesized, and the antibacterial and antiviral activities of these compounds were evaluated. The bioassay results showed that some target compounds exhibited good antibacterial activities in vitro and antiviral activities in vivo. Among them, the median effective concentration (EC50) value of compound L18 against Xac was 16.9 μg/mL, which was better than those of the control drugs bismethiazol (BT) (62.2 μg/mL) and thiadiazole copper (TC) (97.5 μg/mL). Scanning electron microscopy (SEM) results confirmed that compound L18 inhibited the growth of Xac by affecting the morphology of cells. Microscale thermophoresis (MST) test results indicated that the dissociation constant (Kd) value of compound L11 against TMV-CP was 0.012 μM, which was better than that of the control agent ningnanmycin (2.726 μM). This study reveals that myricetin derivatives containing a quinazolinone moiety are potential antibacterial and antiviral agents.

1. INTRODUCTION

Plant pathogens are invisible foe of crop production and economic trade all over the world. It can result in a loss of crop yield of 20−30% annually.1−4 Plant bacteria (Xac, Psa, Xoo) and plant viruses (TMV) are highly infectious in food and cash crops, which are the two main pathogens of plant infectious diseases.5 Traditional chemical agents used to prevent and control these plant diseases, such as BT, TC, and ningnanmycin, have increased the drug resistance of crops due to their long-term large-scale use.6,9 In addition, the low degradation rate and high toxicity of traditional agents have also brought a certain degree of burden to the environment.8,9 Therefore, it has become an urgent need to find new and efficient antibacterial and antiviral agents with low toxicity, high efficiency, and environmentally friendly.

Quinazolinone is an important class of nitrogen-containing heterocyclic compounds, whose skeleton is composed of benzene and pyrimidine, and widely exists in a variety of natural alkaloids, such as luotonin F and febrifugine (Figure 1).10,11 A number of studies have shown that quinazolinone derivatives have anticancer,12 antioxidant,13 antibacterial,14 antitumor,15 and other pharmacological activities. In recent years, quinazolinones have gradually attracted the attention of scholars in the creation of new pesticides. The existing research results showed that quinazolinone derivatives have antiviral,16,17 antibacterial,18 antifungal,19 and other activities in the prevention and treatment of plant diseases. As an important pharmacophore of the antibacterial agents, such as fluquinconazole and proquinazid (Figure 1), quinazolinone has received high attention due to its simple and variable structure.20

Myricetin (3,5,7-trihydroxy-2-(3′,4′,5′-trihydroxyphenyl)-4H-chromen-4-one) is a natural flavonol compound that can be found in many kinds of plants, such as bayberry, vine tea, grape, and pomegranate.21 Many reports indicated that myricetin and its derivatives showed anti-inflammatory,22,23 antitumor,24 antioxidant,25 antibacterial,26 and other activities. Despite its high research interest, myricetin has been rarely studied and applied in pesticides. Based on this, our group

Received: September 22, 2021
Accepted: October 27, 2021
Published: November 4, 2021
obtained some myricetin derivatives with excellent antibacterial and antiviral activities in the previous work, which provided new ideas for the creation of new pesticides.27

In this paper, the principle of active splicing was used to introduce the quinazolinone skeleton with multiple biological activities into the structure of the natural product myricetin. A series of myricetin derivatives containing a quinazolinone moiety were designed and synthesized. The turbidimetric method and the half-leaf blight spot method were used to evaluate the antibacterial and antiviral activities of the synthesized compounds, and the preliminary mechanism of the highly active compounds (Figure 2) was studied.

2. RESULTS AND DISCUSSION

2.1. Chemistry. The synthetic routes are shown in Scheme 1; myricetin underwent methylation and deglycosylation steps to obtain intermediate a. Intermediate b was obtained by reacting 1,3-dibromopropane or 1,4-dibromobutane with intermediate a. Intermediate c was obtained by reacting substituted anthranilic acid with formamide at 135 °C for 3−6 h. Intermediates b and c were reacted in N,N-dimethylformamide with NaH at 90 °C for 4−6 h to obtain the target compounds. The structures of L1−L20 were characterized by 1H nuclear magnetic resonance (NMR), 13C NMR, 19F NMR, and high-resolution mass spectrometry (HRMS), and the detailed data was included in the Supporting Information.

2.2. Antibacterial Activity In Vitro. The antibacterial activity data is shown in Table 1. Some of the target compounds exhibited good antibacterial activities against Xac, Psa, and Xoo. Compounds L11, L13−L15, and L17−L20 exhibited good in vitro antibacterial activities against Xac when concentrations were 100 and 50 μg/mL; the inhibition...
rates were better than those of BT (60.2 and 44.6%, respectively) and TC (53.6 and 36.8%, respectively). Compounds L11, L14, and L18 displayed good in vitro antibacterial activities against Psa, with inhibition rates being better than those of BT (54.7 and 39.4%, respectively) and TC (49.0% and 33.3%, respectively). Compounds L11, L13, and L18 showed good in vitro antibacterial activities against Xoo, with inhibition rates being better than those of BT (54.0 and 42.9%, respectively) and TC (54.2% and 28.7%, respectively).

Based on preliminary bioassay results, the EC50 values of some target compounds were also determined (Table 2). The EC50 values for compounds L11, L13, L14, L17, and L18 against Xac ranged from 16.9 to 27.0 μg/mL. These results were better than those for BT (62.2 μg/mL) and TC (97.5 μg/mL). The EC50 values for compounds L11, L14, and L18 against Psa ranged from 28.1 to 46.4 μg/mL. These results were better than those for BT (64.7 μg/mL) and TC (35.8 μg/mL). Compounds L11, L13, and L18 have good inhibitory
activity against Xoo. The EC_{50} values of these compounds ranged from 20.4 to 50.4 μg/mL, which were better than those of the control agents BT (63.7 μg/mL) and TC (86.1 μg/mL). The results showed that compound L18 has broad-spectrum antibacterial activity, with EC_{50} values 17.8, 29.7, and 22.1 μg/mL.

2.3. Morphological Change. The SEM results are shown in Figure 3. When Xac cells were not treated with the compound, the cell morphology was full and uniform; when the compound concentration was 50 μg/mL, the cell surface was pitted; and when the compound concentration was 100 μg/mL, the cell morphology was broken. This result indicated that compound L18 can achieve the purpose of inhibiting the growth of Xac by affecting the morphology of Xac cells.

2.4. Antiviral Activity In Vivo. As shown in Table 3, antiviral activity test results showed that the curative, protective, and inactivating activities of L1−L20 for TMV ranged from 20.1 to 63.1%, 12.3 to 68.7%, and 35.1 to 69.8%, respectively. In particular, compound L11 showed 63.1% curative effects at 500 μg/mL, which was better than ningnanmycin (54.1%). In addition, compound L11 exhibited significant protective activity against TMV at 500 μg/mL, and

Table 3. Antiviral Activities of the Target Compounds Against TMV In Vivo at 500 μg/mL

| compd. | R   | n   | regression equation | r   | EC_{50} (μg/mL) |
|--------|-----|-----|---------------------|-----|-----------------|
| L1     | 7-F | 3   | y = 0.8272x + 3.0010 | 0.9798 | 261.0 ± 2.1 |
| L2     | 7-Cl| 3   | y = 0.6087x + 3.4754 | 0.9990 | 319.7 ± 4.7 |
| L3     | 6,8-di-Cl| 3   | y = 0.9648x + 2.7679 | 0.9743 | 205.8 ± 4.1 |
| L4     | 8-CH_{3} | 3  | y = 0.9198x + 2.6743 | 0.9810 | 341.3 ± 3.9 |

Average of three replicates. Commercial antiviral agent ningnanmycin.
its inhibition rate was 68.7%, which was even better than that of ningnanmycin (57.1%).

The EC₅₀ value of compound L₁₁ was determined to understand its potential inhibitory ability to TMV. It can be seen from Table 4 that the EC₅₀ values of the curative and protective activities of compound L₁₁ against TMV were 261.0 and 205.8 μg/mL, respectively, which were better than those of ningnanmycin of 319.7 and 341.3 μg/mL, respectively. The tobacco leaf morphology effects of compound L₁₁ and ningnanmycin against tobacco mosaic virus in vivo are shown in Figure 4.

Table 5. Dissociation Constant of Compound L₁₁, Myricetin, and Ningnanmycin with TMV-CP

| compd. | K_d (μM) |
|--------|----------|
| L₁₁    | 0.012 ± 0.008 |
| myricetin | 62.180 ± 22.236 |
| ningnanmycin | 2.726 ± 1.301 |

L₁₁ to TMV-CP was 0.012 ± 0.008 μM, which was better than that of the lead compound myricetin (62.180 ± 22.236 μM) and the control agent ningnanmycin (2.726 ± 1.301 μM).

It shows that myricetin, the lead compound, can greatly enhance its binding ability with TMV-CP after structural modification.

2.6. Molecular Docking. As shown in Figure 6, compound L₁₁ (A, a), myricetin (B, b), and ningnanmycin (C, c) all achieved good docking with the tobacco mosaic virus coat protein. The hydrogen bond length between SER323 and compound L₁₁ was 2.42 Å, which was less than between SER215 and ningnanmycin (3.64 Å). However, the length of the hydrogen bond between SER323 and unmodified myricetin was 3.93 Å. It can be seen that the modified myricetin can significantly enhance the binding force with TMV-CP.

2.7. Structure–Activity Relationship (SAR). According to the antibacterial activity data in Table 1, the results of SAR analysis are as follows. The antibacterial activities of the compounds with 4 methylene groups (n = 4) against three plant pathogens (Xac, Psa, Xoo) were significantly higher than those of the compounds with 3 methylene groups (n = 3).

SAR analysis was performed according to the antiviral activity data in Table 3. When R was 7-F, 7-Cl, 6,8-di-Cl, and 6-F, the antiviral activities of the target compounds were significantly increased. Among them, compound L₁₁ (R = 7-F) had the best curative and protection activities, with the inhibition rates of 63.1 and 68.7%, respectively. It can be known from these data that the target compound showed better antiviral activity when R was an electron-withdrawing group.

3. CONCLUSIONS

In summary, a series of myricetin derivatives containing a quinazolinone moiety were designed and synthesized. The antibacterial and antiviral activities of all target compounds were evaluated. The results showed that compound L₁₈ has the best inhibitory activity on Xac, with an EC₅₀ value of 16.9 μg/mL, which was better than those of the control agents BT (62.2 μg/mL) and TC (97.5 μg/mL). Compound L₁₁ has the best protective activity against TMV, with an EC₅₀ value of 205.6 μg/mL, which was better than ningnanmycin (341.3 μg/mL). Preliminary mechanism studies demonstrated that compound L₁₈ inhibited the growth of Xac cells by affecting their morphology. The MST test showed that the K_d value of compound L₁₁ to TMV-CP was 0.012 μM, which was better than ningnanmycin 2.726 μM. The molecular docking results revealed that compound L₁₁ formed a variety of hydrogen bonds with TMV-CP, and its binding force was stronger than ningnanmycin. The above results are consistent with the bioassay results. These research results displayed that myricetin derivatives containing a quinazolinone moiety have the...
potential to become new and highly effective antibacterial and antiviral agents.

4. MATERIALS AND METHODS

4.1. Chemicals and Instruments. All solvents and reagents were purchased from Tianjin Zhi Yuan Regent Co., Ltd. (Tianjin, China), Shanghai Titan Chemical Co., Ltd. (Shanghai, China), and Adamas Reagent, Ltd. (Shanghai, China), which were all of analytical grade and used directly without further purification or drying. The melting point was determined under an X-4B microscope melting point apparatus (Shanghai Yi Dian Physical Optics Instrument Co., Ltd., China). The 1H, 13C, and 19F NMR spectra of the target compounds were obtained on a JEOL-ECX500 MHz (JEOL, Tokyo, Japan). High-resolution mass spectra (HRMS) were procured with a Thermo Scientific Q Exactive (Thermo, Missouri). The interaction between the target compounds and TMV-CP was studied using a micro thermophoresis instrument (NanoTemper Technologies GmbH, Germany). SEM experiments used the Nova NanoSEM 450 (Field Electron and Ion Co.).

4.2. General Synthesis Procedure for Intermediates a and b. Myricetin with a purity of 98% was used as a raw material. Intermediates a and b were synthesized by methods reported in the literature.31

4.3. General Synthesis Procedure for Intermediate c. The substituted anthranilic acid (15 mmol) and formamide (200 mmol) were reacted at 135 °C for 3–6 h (monitored by TLC). Then, intermediate c was obtained by filtration under reduced pressure and drying.

4.4. General Synthesis of Target Compounds L1–L20. Intermediates b (2.75 mmol) and c (3.30 mmol) were reacted in N,N-dimethylformamide (20 mL) with NaH (8.02 mmol) at 90 °C for 4–6 h (monitored by TLC). The reaction mixture was poured into 500 mL of ice water and stirred, and a solid was precipitated out. Then, the crude product was obtained by filtration under reduced pressure. The target compounds were purified by column chromatography with ethyl acetate/methanol (25:1, V/V).

4.5. Antibacterial Activity Assay In Vitro. The method previously reported in the literature was used to determine the antibacterial activity of the target compounds L1–L20.32

4.6. Antiviral Activity Assay In Vivo. The antiviral activity of the target compounds was determined by the method previously reported in the literature.33

4.7. SEM Analysis. The influence of the compound L18 on the morphology of Xac was studied using the previous scanning electron microscopy test method.34

4.8. MST Analysis. The MST test was used to further analyze the interaction between the compounds and TMV-CP. We used Monolith NT.115 software (NanoTemper Technologies, München, Germany) to obtain the Kd value of the compounds for TMV-CP.35

4.9. Molecular Docking. Molecular docking study was obtained using DS-CDoking implemented in Discovery Studio (version 4.5). Compound L11 was selected for docking with TMV-CP (PDB code: 1EI7).36

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c05256.

Extraction and purification of TMV; synthetic procedures of target compounds; and characterization data and spectra, including 1H, 13C, 19F NMR, and HRMS (PDF)

AUTHOR INFORMATION

Corresponding Author
Wei Xue — State Key Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Research and Development Center for Fine Chemicals, Guizhou University, Guiyang 550025, P. R. China; orcid.org/0000-0003-4471-5414; Email: wxue@gzu.edu.cn
Authors

Tingting Liu — State Key Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Research and Development Center for Fine Chemicals, Guizhou University, Guiyang 550025, P. R. China

Feng Peng — State Key Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Research and Development Center for Fine Chemicals, Guizhou University, Guiyang 550025, P. R. China

Xiao Cao — State Key Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Research and Development Center for Fine Chemicals, Guizhou University, Guiyang 550025, P. R. China

Fang Liu — State Key Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Research and Development Center for Fine Chemicals, Guizhou University, Guiyang 550025, P. R. China

Qifan Wang — State Key Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Research and Development Center for Fine Chemicals, Guizhou University, Guiyang 550025, P. R. China

Liwai Liu — State Key Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Research and Development Center for Fine Chemicals, Guizhou University, Guiyang 550025, P. R. China

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.1c05256

Author Contributions
T.L. and F.P. contributed equally to this work.

Author Contributions
T.L., F.P., and W.X. conceived and designed the study. T.L. completed the experiment and took the required photos. T.L., F.P., and X.C. analyzed and interpreted the data. T.L., F.L., and Q.W. wrote the manuscript. L.L. provided material support. W.X. supervised and funded the acquisition for this work. All authors have read and reviewed the manuscript.

Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the National Nature Science Foundation of China (No. 21867003), the Science Foundation of Guizhou Province (No. 20192452), the Natural Science research project of Guizhou Education Department (No. 2018009), the Frontiers Science Center for Asymmetric Synthesis and Medicinal Molecules, Department of Education, Guizhou Province [Qianjiaohe KY number (2020)004], and the Program of Introducing Talents of Discipline to Universities of China (111 Program, D20023).

REFERENCES

(1) Kashyap, P. L.; Kumar, S.; Srivastava, A. K. Nanodiagnostics for plant pathogens. Environ. Chem. Lett. 2017, 15, 7–13.

(2) Silva, R. N.; Monteiro, V. N.; Steinadorff, A. S.; Gomes, E. V.; Noronha, E. F.; Ulhoa, C. J. Trichoderma/pathogen/plant interaction in pre-harvest food security. Fungal Biol. 2019, 123, 565–583.

(3) Shasmia; Mohapatra, D.; Mohapatra, P. K.; Naik, S. K.; Mukherjee, A. K. Priming with salicylic acid induces defense against bacterial blight disease by modulating rice plant photosystem II and antioxidant enzymes activity. Physiol. Mol. Plant Pathol. 2019, 108, No. 101427.

(4) Ren, X.; Li, X.; Yin, L.; Jiang, D.; Hu, D. Design, synthesis, antiviral bioactivity, and mechanism of the ferulic acid ester-containing sulfonamide moiety. ACS Omega 2020, 5, 19721–19726.

(5) Zhou, X.; Ye, Y.; Liu, S.; Shao, W.; Liu, L.; Yang, S.; Wu, Z. Design, synthesis and anti-TMV activity of novel α-amino phosphonate derivatives containing a chalcone moiety that induce resistance against plant disease and target the TMV coat protein. Pestic. Biochem. Physiol. 2021, 172, No. 104749.

(6) Buttner, C.; McAuliffe, O.; Ross, R. P.; Hill, C.; O’Mahony, J.; Coffey, A. A. Bacteriophages and bacterial plant diseases. Front. Microbiol. 2017, 8, No. 34.

(7) Wu, S.; Shi, J.; Chen, J.; Hu, D.; Zang, L.; Song, B. Synthesis, antibacterial activity, and mechanisms of novel 6-sulfonyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole derivatives. J. Agric. Food Chem. 2021, 69, 4645–4654.

(8) Tang, X.; Zhang, C.; Chen, M.; Xue, Y.; Liu, T.; Xue, W. Synthesis and antiviral activity of novel myricetin derivatives containing ferulic acid amide scaffolds. New J. Chem. 2020, 44, 2374–2379.

(9) Wei, C.; Zhao, L.; Sun, Z.; Hu, D.; Song, B. Discovery of novel indole derivatives containing dithiocasal as potential antiviral agents for plants. Pestic. Biochem. Physiol. 2020, 166, No. 104568.

(10) Mahdavi, M.; Lotfi, V.; Vaeedi, M.; Kianmehr, E.; Siafiee, A. Synthesis of novel fused quinazolinone derivatives. Mol. Divers. 2016, 20, 677–685.

(11) Peng, J.; Yin, X.; Li, H.; Ma, K.; Zhang, Z.; Zhou, R.; Wang, Y.; Hu, G.; Liu, Y. Design, synthesis, and structure-activity relationship of quinazolinone derivatives as potential fungicides. J. Agric. Food Chem. 2021, 69, 4604–4614.

(12) Wang, H.; Liu, H.; Li, W.; Zhang, S.; Wu, Z.; Li, X.; Li, C.; Liu, Y.; Chen, B. Design, synthesis, antiproliferative and antibacterial evaluation of quinazolinone derivatives. Med. Chem. Res. 2019, 28, 203–214.

(13) El-Sayed, A. A.; Ismail, M. F.; Amr, A. E. E.; Naglah, A. M. Synthesis, Antiproliferative, and Antioxidant Evaluation of 2-pentyquinazolin-4-(3H)-one (thione) derivatives with DFT study. Molecules 2019, 24, 3787.

(14) Zhan, X.; Xu, Y.; Qi, Q.; Wang, Y.; Shi, H.; Mao, Z. Synthesis, cytotoxic, and antibacterial evaluation of quinazolinone derivatives with substituted amino moiety. Chem. Biodiversity 2018, 15, No. e1700513.

(15) El-Bordany, E. A.; Ali, R. S. Synthesis of new benzoazinone, quinazolinone, and pyrazoloquinazolinone derivatives and evaluation of their cytotoxic activity against human breast cancer cells. J. Heterocyclic Chem. 2018, 55, 1223–1231.

(16) Ran, L.; Yang, H.; Luo, L.; Huang, M.; Hu, D. Discovery of potent and novel quinazolinone sulphone inhibitors with anti-ToCV activity. J. Agric. Food Chem. 2020, 68, 5302–5308.

(17) Hao, Y.; Wang, K.; Wang, Z.; Liu, Y.; Ma, D.; Wang, Q. Luotonin A and its derivatives as novel antiviral and antiphathogenic fungus agents. J. Agric. Food Chem. 2020, 68, 8764–8773.

(18) Zhang, L.; Chen, Q.; Li, X.; Wu, S.; Wan, J.; Ouyang, G. Synthesis and antibacterial activity of 2-substituted (3-pyridyl)-quinazolinone derivatives. J. Heterocyclic Chem. 2018, 55, 743–749.

(19) Wang, X.; Li, P.; Li, Z.; Yin, J.; He, M.; Xue, W.; Chen, Z.; Song, B. Synthesis and bioactivity evaluation of novel arylimines containing a 3-aminophenyl-2-((p trifluoromethoxy)anilino)-4-(3H)-quinazolinone moiety. J. Agric. Food Chem. 2013, 61, 9575–9582.
(20) Shao, L.; Gan, Y.; Hou, M.; Tao, S.; Zhang, L.; Wang, Z.; Ouyang, G. Design, synthesis and biological activity of quinazolinone derivatives containing hydrazone structural units. *Chinese J. Org. Chem.* 2020, 40, 1975.

(21) Jiang, S.; Tang, X.; Chen, M.; He, J.; Su, S.; Liu, L.; He, M.; Xue, W. Design, synthesis and antibacterial activities against *Xanthomonas oryzae pv. oryzae*, *Xanthomonas axonopodis pv. citri* and *Ralstonia solanacearum* of novel myricetin derivatives containing sulfonamide moiety. *Pest Manag. Sci.* 2020, 76, 853−860.

(22) Liu, C.; Han, X.; Yu, P.; Chen, L. Z.; Xue, W.; Liu, X. H. Synthesis and biological evaluation of myricetin-pentadienone hybrids as potential anti-inflammatory agents *in vitro* and *in vivo*. *Bioorg. Chem.* 2020, 96, No. 103597.

(23) Jang, J.; Lee, S. H.; Jung, K.; Yoo, H.; Park, G. Inhibitory effects of myricetin on lipopolysaccharide-induced neuroinflammation. *Brain Sci.* 2020, 10, 32.

(24) Yan, T.; Tao, Y.; Wang, X.; Lv, C.; Miao, G.; Wang, S.; Wang, D.; Wang, Z. Preparation, characterization and evaluation of the antioxidant capacity and antitumor activity of myricetin microparticles formed by supercritical antisolvent technology. *Bioorg. Chem.* 2020, 96, No. 103597.

(25) Bertin, R.; Chen, Z.; Marin, R.; Donati, M.; Feltrinelli, A.; Montopoli, M.; Zambon, S.; Manzato, E.; Froldi, G. Activity of myricetin and other plant-derived polyhydroxyl compounds in human LDL and human vascular endothelial cells against oxidative stress. *Biomed. Pharmacother.* 2016, 82, 472−478.

(26) Arita-Morioka, K.; Yamanaka, K.; Mizunoe, Y.; Tanaka, Y.; Ogura, T.; Sugimoto, S. Inhibitory effects of myricetin derivatives on curli-dependent biofilm formation in *Escherichia coli*. *Sci. Rep.* 2018, 8, No. 8452.

(27) Chen, Y.; Li, P.; Su, S.; Chen, M.; He, J.; Liu, L.; He, M.; Wang, H.; Xue, W. Synthesis and antibacterial and antiviral activities of myricetin derivatives containing a 1,2,4-triazole Schiff base. *RSC Adv.* 2019, 9, 23045−23052.

(28) Jiang, S.; Su, S.; Chen, M.; Peng, F.; Zhou, Q.; Liu, T.; Liu, L.; Xue, W. Antibacterial activities of novel dithiocarbamate-containing 4H-chromen-4-one derivatives. *J. Agric. Food Chem.* 2020, 68, 5641−5647.

(29) He, J.; Tang, X.; Liu, T.; Peng, F.; Zhou, Q.; Liu, L.; He, M.; Xue, W. Synthesis and antibacterial activity of novel myricetin derivatives containing sulfonylpiperazine. *Chem. Pap.* 2021, 75, 1021−1027.

(30) Chen, M.; Su, S.; Zhou, Q.; Tang, X.; Liu, T.; Peng, F.; He, M.; Luo, H.; Xue, W. Antibacterial and antiviral activities and action mechanism of flavonoid derivatives with a benzimidazole moiety. *J. Saudi Chem. Soc.* 2021, 25, No. 101194.

(31) Xue, W.; Song, B.; Zhao, H. J.; Qi, X. B.; Huang, Y. J.; Liu, X. H. Novel myricetin derivatives: Design, synthesis and anticancer activity. *Eur. J. Med. Chem.* 2015, 97, 155−163.

(32) Song, X.; Li, P.; Li, M.; Yang, A.; Yu, L.; Luo, L.; Hu, D.; Song, B. Synthesis and investigation of the antibacterial activity and action mechanism of 1,3,4-oxadiazole thioether derivatives. *Pestic. Biochem. Physiol.* 2018, 147, 11−19.

(33) Zhang, J.; He, F.; Chen, J.; Wang, Y.; Yang, Y.; Hu, D.; Song, B. Purine nucleoside derivatives containing a sulfa ethylamine moiety: design, synthesis, antiviral activity, and mechanism. *J. Agric. Food Chem.* 2021, 69, 5575−5582.

(34) Guo, T.; Xia, R.; Liu, T.; Peng, F.; Tang, X.; Zhou, Q.; Luo, H.; Xue, W. Synthesis, biological activity and action mechanism study of novel chalcone derivatives containing malonate. *Chem. Biodivers.* 2020, 17, No. e2000025.

(35) Wang, Y.; He, F.; Wu, S.; Luo, Y.; Wu, R.; Hu, D.; Song, B. Design, synthesis, anti-TMV activity, and preliminary mechanism of cinnamic acid derivatives containing dithioacetal moiety. *Pestic. Biochem. Physiol.* 2020, 164, 115−121.

(36) Peng, F.; Liu, T.; Wang, Q.; Liu, F.; Cao, X.; Yang, J.; Liu, L.; Xie, C.; Xue, W. Antibacterial and antiviral activities of 1,3,4-oxadiazole thioether 4H-chromen-4-one derivatives. *J. Agric. Food Chem.* 2021, 69, 11085−11094.