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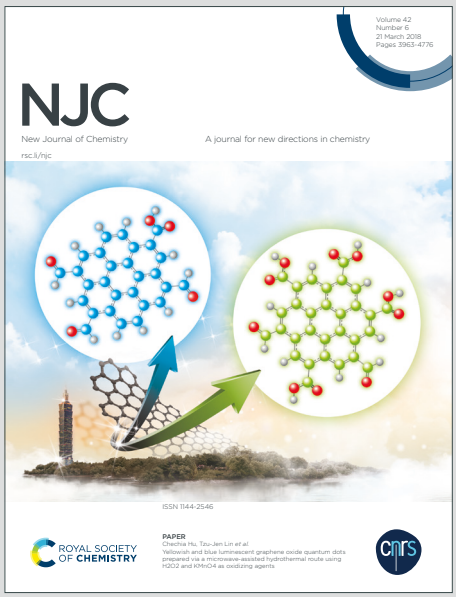

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ARTICLE

Synthesis and Antiviral Activity of Novel Myricetin Derivatives Containing a Ferulic Acid Amide Scaffolds

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Abstract: A variety of myricetin derivatives bearing ferulic acid amide scaffolds were designed and synthesized. The structures of all title compounds were determined by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and HRMS. Preliminary bioassays suggested that some of the target compounds exhibited remarkable antiviral activities. In particular, compound **4l** possessed significant protective activity against tobacco mosaic virus (TMV), with an half maximal effective concentration (EC_{50}) value of 196.11 μg/mL, which was better than commercial agent ningnamycin (447.92 μg/mL). Meanwhile, microscale thermophoresis (MST) indicated that compound **4l** have strong binding capability to tobacco mosaic virus coat protein (TMV-CP) with dissociation constant (K_d) values of 0.34 μmol/L, which was better than ningnamycin (0.52 μmol/L). These results suggested that novel myricetin derivatives bearing ferulic acid amide scaffolds may be considered as an activator for antiviralagents.

1.Introduction

Plant diseases cause economic loss and decreases in the quality and quantity of agricultural products around the world. For example, tobacco mosaic virus (TMV) can easily infect economic crops and causes economic losses. It takes millions of dollars to prevent and cure these deseases.[1] Unfortunately, traditional pesticide, such as ningnanmycin and ribavirin, have been eliminated and banned gradually due to their poor efficiencies, high phytotoxicities, environment damages, pesticide residues and resistant from pesticide.[2, 3] It is an urgent need to develop greener and more efficient pesticides to control and prevent plant diseases.

Due to their low toxicities, easy decompositions, novel structures and environmental friendlinesses, natural products have been used to synthesize new pesticides.[4-6] Myricetin is a kind of natural product which can be extracted from several medicinal plant organs, vegetables and fruits,[7] such as *myrica rubra Sieb*,[8] *Abelmoschus manihot* [9] and *onions.*[10] It has been reported that myricetin has various biological activities, such as antiviral,[11, 12] antibacterial,[13, 14] antioxidant,[15] anticancer [16, 17] and so on. In our previous study, we have reported a series of myricetin derivatives with appreciable bioactivities against TMV.[11]

Ferulic acid is a phenolic acid present in many plants, such as *Angelica sinensis*, *Cimicifuga heracleifolia* and *Lignsticum chuangxiong*.[18] According to previous studies, ferulic acid exhibits a wide range of bioactivities, such as antiviral,[19] antibacterial,[20] anticancer.[21, 22] Therefore, it has attracted great attention in the field of medicinal chemistry. In the further development of antiviral agents, a series of novel myricetin derivatives containing a 1,3,4-thiadiazole moiety was found to have excellent anti-TMV activity.[12] In this study, we aimed to use a ferulic acid amide to replace the 1,3,4-thiadiazole system to build novel myricetin derivatives containing a ferulic acid amide moiety for the development of antiviral agents. The preliminary bioassay results indicated that some of target compounds showed excellent antiviral activities. Among them, compound **4l** possessed significant protective activity against TMV. Meanwhile, MST and molecular docking indicated that compound **4l** have strong binding capability to TMV-CP. To the best

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of our knowledge, this is the first report on the synthesis and antiviral activity evaluation of myricetin derivatives containing a ferulic acid amide moiety (**Figure 1**).

Figure 1. Design of novel myricetin derivatives containing ferulic acid amide scaffolds

2. Experimental

2.1. Methods and materials

The melting points were determined by X-4B microscopic melting point meter (Shanghai Yi Dian Physical Optics Instrument Co., Ltd. China); proton nuclear magnetic resonance (NMR) spectra were obtained on JEOL-ECX500 NMR spectrometer (JEOL, Tokyo, Japan) and Bruker Ascend-400 spectrometer (Bruker, Germany) with DMSO or $CDCl_3$ as the solvent and TMS as the internal standard. High-resolution mass spectral (HRMS) data were performed with Thermo Scientific Q Exactive (Thermo Scientific, USA). The micro thermophoresis of the compound and TMV CP was determined by a micro thermophoresis instrument (NanoTemper Tchnologies GmbH, Germany); the fluorescence spectroscopy of the compound interacting with TMV CP was determined by FluoroMax-4 fluorescence spectrometer (HORIBA Scientific, France). All reagents (analytical grade) were purchased from commercial suppliers.

2.2. General synthesis procedure for intermediate 1

Ferulic acid (3.01 g, 15.45 mmol) was added into round bottom flask and dissolved by 10 % NaOH (30 mL), then acetic anhydride (1.97 g, 19.31 mmol) was added. The mixture was stirred at room temperature for 1 h. Then 200 mL H_2O was added into the reaction mixture. 10 % Aqueous HCl was added into the above mixture till pH = 4-5. Then the mixture was filtered and the precipitate was washed by H_2O to obtained the intermediate **1**.[16]

2.3. General synthesis procedure for intermediate 2

Intermediate **1** (0.55 g, 2.33 mmol), 1-Hydroxybenzotriazole (0.38 g, 2.79 mmol) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (0.54 g, 2.79 mmol) were added dropwise into acetonitrile (20 mL), the mixture was stirred at room temperature for 3 h. Then substituted aniline (0.27 g, 2.56 mmol) in acetonitrile (20 mL) was slowly added into the mixture, stirred and refluxed at 90 °C for 5 h until the reaction was completed (monitored by TLC: $V_{ethyl\ acetate}$: $V_{methanol}$ = 10:1). Then the reaction mixture was extracted by ethyl acetate and evaporated under reduced pressure. The product was dissolved in acetonitrile again, added hydrazine hydrate (0.24 g, 4.66 mmol), and stirred at room temperature for 2 h to obtained the intermediate **2**.[19, 23]

2.4. General synthesis procedure for intermediate 3

Preparation of the intermediate **3** has been previously described.[24] The mixture of myricitrin (0.55 g, 5.01 mmol), CH_3I (2.02 g, 60.02 mmol), and K_2CO_3 (0.19 g, 6.13 mmol) was dissolved in *N,N*-dimethyl formamide (DMF, 30 mL), and stirred at 40 °C for 2 d until the reaction was complete (as indicated by TLC analysis). The reaction mixtures were then filtered, and the filtrate was dissolved in 50 mL water and finally extracted three times with dichloromethane (30 mL×3), combined the dichloromethane and concentrated under reduced pressure. The concentrated solution was diluted with 20 mL of absolute ethanol, stirred, and refluxed for 1 h. The concentrated hydrochloric acid (3 mL) was slowly added to the above obtained, for 2 h in reflux. The solid was precipitated

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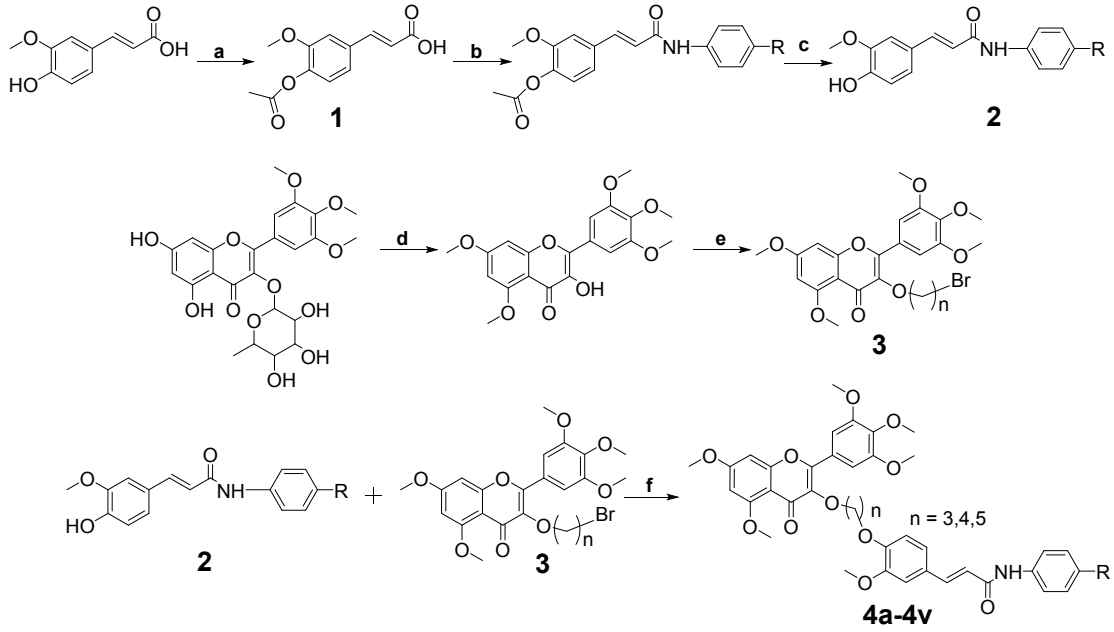
from the clear solution. After cooling to room temperature, the reaction mixture was filtered, and the obtained solid product was dried at 40 °C for 2 h. Finally, dibromoalkanes and DMF were added reflux 6h to obtained intermediate **3**.

2.5. General synthesis procedure for target compounds 4a–4v.

A mixture of intermediate **2** (0.31 g, 1.08 mmol), anhydrous K_2CO_3 (0.41 g, 2.94 mmol) in DMF (30 mL) was stirred at 85 °C for 1 h, then DMF (20 mL) containing intermediate 3 (0.50 g, 0.98 mmol) was dropped slowly to the mixture and reacted at 105 °C for 6 h. After cooling to the room temperature, the reaction mixture was added about 200 mL H_2O and adjusted pH to 4-5 by 10 % HCl, filtered and washed by H_2O. Finally, compounds **4a–4v** were gained by recrystallization from methanol.



reation condition: **a** : acetic anhydride, 5 % NaOH; **b** : R-PhNH$_2$, HOBt, EDCl; **c** :NH$_2$NH$_2$H$_2$O, CH$_3$CN; **d** : DMF, K_2CO_3, CH_3I, conc HCl; **e** :DMF, Br(CH$_2$CH$_2$)$_n$Br; **f** : DMF, K_2CO_3

4a : R = 4-CH_3, n = 3; **4b** : R = 4- OCH_3, n = 3; **4c** : R = 4-CH_3, n = 4; **4d** : R = 4-OCH_3, n = 4;
4e : R = 3-Cl, n = 3; **4f** : R = 3-Cl, n = 4; **4g** : R = 4-Cl, n = 4; **4h** : R = H, n = 4;
4i : R = H, n = 3; **4j** : R = 3,4-di-CH_3, n = 3; **4k** : R = 3,4-di-CH_3, n = 4; **4l** : R = 3,4-di-OCH_3, n = 3;
4m: R = 3,4-di-OCH_3, n = 4 **4n** : R = 4-Br, n = 3; **4o** : R = 4-Br, n = 4; **4p** : R = 3,4-di-Cl, n = 3;
4q : R = 3,4-di-Cl, n = 4;**4r** : R = 4-Cl, n = 5; **4s**: R = 3-Cl, n = 5; **4t** : R = 4-OCH_3, n = 5;
4u : R = 2-F, n = 3; **4v** : R = 2-F, n = 4

Scheme 1. Synthesis of the title compounds **4a–4v**

3. Results and discussion

3.1. Spectral properties

The structures of all title compounds were determined by ^{1}H NMR, ^{13}C NMR , ^{19}F NMR and HRMS, and the spectra data were shown in the Supplementary Materials. The data of **4a** was shown and discussed below. In the ^{1}H NMR, multiplet signals at δ 8.01–6.36 ppm revealed the presence of nitrogen hydrogen bond, protons in olefinic bonds and aromatic nuclei, and triplet singlets at δ 4.23 and 4.18 ppm indicate the presence of –CH_2– group. In addition, the four high-frequency single peaks and doublets peaks at 3.94 –3.77 ppm revealed the presence of five –OCH_3, and double peak at δ 2.31 ppm indicate the presence of –CH_3 group. Absorption signals at δ 174.07, 164.12 and 20.91 ppm in ^{13}C NMR spectra confirm the presences of –C=O– , –C=O–NH– and –CH_3 groups, respectively. The high-resolution mass spectrometry (HRMS) spectra of title compounds show characteristic absorption signals of $[M + H]^+$ ions, which is consistent with their molecular weight.

3.2. Antiviral activity of title compounds against TMV *in vivo*

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Using *N. tabacun L*. leaves under the same age as that of test subjects, the curative and protective activities against TMV (*in vivo*) at a concentration of 500 μg/mL were evaluated by the half-leaf blight spot methods.[25, 26] The obtained results were shown in **Table 1**. The preliminary bioassay results indicated that the inhibitory rates of target compounds (**4a–4v**) against TMV ranged from 15.8 to 55.5 % in terms of their curative activities, while their protective activities ranged from 5.3 to 62.1 %. Especially, compound **4n** showed 55.5 % curative effects at 500 μg/mL, which was better than that of myricetin (35.7 %) and ningnanmycin (53.2 %). In addition, compound **4l** exhibited significant protective activities against TMV at 500 μg/mL, the inhibition rate was 62.1 %, which was even better than that of myricetin (41.5 %) and ningnanmycin (55.7 %).

Table 1 Inhibition effect (%) of the compounds **4a–4v** against TMV [a]

Compd.	R	n	Curative Activity (%)	Protection Activity (%)
4a	4-CH_3	3	33.0 ± 2.1	11.6 ± 0.9
4b	4-OCH_3	3	42.1 ± 1.2	35.6 ± 3.7
4c	4-CH_3	4	39.6 ± 3.3	21.2 ± 2.1
4d	4-OCH_3	4	15.8 ± 0.6	5.3 ± 0.8
4e	3-Cl	3	37.5 ± 1.1	51.6 ± 3.3
4f	3-Cl	4	32.1 ± 4.2	52.3 ± 4.1
4g	4-Cl	4	38.1 ± 0.8	40.3 ± 5.2
4h	H	4	41.3 ± 4.3	48.5 ± 7.2
4i	H	3	43.5 ± 0.8	31.2 ± 3.6
4j	3,4-di-CH_3	3	39.4 ± 0.3	46.4 ± 0.8
4k	3,4-di-CH_3	4	21.1 ± 0.9	25.9 ± 2.1
4l	3,4-di-OCH_3	3	37.4 ± 1.1	62.1 ± 7.2
4m	3,4-di-OCH_3	4	31.2 ± 4.2	13.5 ± 0.6
4n	4-Br	3	55.5 ± 7.3	53.3 ± 4.5
4o	4-Br	4	28.4 ± 6.1	19.5 ± 5.5
4p	3,4-di-Cl	3	37.2 ± 0.9	58.1 ± 4.1
4q	3,4-di-Cl	4	34.2 ± 0.7	43.9 ± 7.2
4r	4-Cl	5	40.4 ± 5.2	44.1 ± 4.1
4s	3-Cl	5	43.2 ± 4.1	37.8 ± 0.8
4t	4-OCH_3	5	39.9 ± 3.8	24.1 ± 2.2
4u	2-F	3	37.0 ± 8.2	41.1 ± 3.1
4v	2-F	4	21.8 ± 2.7	32.5 ± 4.2
MY [b]	-	-	35.7 ± 5.2	41.5 ± 3.3
NNM [c]	-	-	53.2 ± 0.6	55.7 ± 4.5

[a] Average of three replicates; [b] The lead compound of (MY, myricetin);
[c] The commercial agent (NNM, ningnamycin) was used for comparison of antiviral activity

To confirm the potential inhibitory capacity of these compounds against TMV, we further evaluated the EC_{50} of some title compounds against TMV based on our preliminary bioassay. As shown in **Table 2**, compounds **4l**, **4n** and **4p** exhibit excellent protective activities against TMV with the EC_{50} values of 196.1, 425.3 and 386.7 μg/mL respectively, which were superior to ningnamycin (447.9 μg/mL). Compound **4n** shows good curative activity against TMV with an EC_{50} value of 472.4 μg/mL, which was closed to ningnamycin (428.8 μg/mL).

3.3. Structure activity relationship (SAR) of the title compounds against TMV

As indicated in **Tables 1** and **2**, the antiviral effects of target compounds were greatly affected by structural variations. Some structure–activity relationships (SAR) analyses were discussed as

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below. The presence of 4-Br, 3-Cl, 4-OCH_3 and H groups at the R position greatly increased the curative activities of the target compounds against TMV. For instance, the target compounds **4b** (4-OCH_3, n=3), **4i** (H, n=3), **4n** (4-Br, n=3) and **4s** (3-Cl, n=5) showed important antiviral activities against TMV, with inhibition rates of 42.1, 43.5, 55.5 and 43.2 %, respectively. Furthermore, when R were 3-Cl, 3,4-di-OCH_3 and 3,4-di-Cl groups, the protective activities of the relevant compounds **4f**, **4l** and **4p** at 500 μg/mL were 52.3, 62.1, and 58.1 %, respectively, which were superior to other substituent groups.

Table 2 The EC_{50} values of **4l**, **4n** and **4p** against TMV [a]

	Compd.	R	n	Toxic regression equation	r	EC_{50} μg/mL
Curative Activity	**4n**	4-Br	3	y=1.4582x+1.1002	0.9902	472.4
	NNM [b]	-	-	y=0.7650x+2.9863	0.9830	428.8
Protection Activity	**4l**	3,4-di-OCH_3	3	y=2.0488x-0.3031	0.9891	196.1
	4n	4-Br	3	y=1.7099x+1.7002	0.9888	425.3
	4p	3,4-di-Cl	3	y=1.4133x+2.3311	0.9970	386.7
	NNM [b]	-	-	y=1.5482x+0.8954	0.9819	447.9

[a] Average of three replicates; [b] The commercial agent (NNM, ningnamycin) was used for comparison of antiviral activity

3.4. Binding sites of 4l, 4m, myricetin and ningnanmycin to TMV-CP

To further analyze the interactions between the compounds **4l**, **4m**, myricetin, ningnanmycin and TMV-CP, MST analysis was carried out.[27-29] The MST results were summarized in **Figure 2** and **Table 3.** The binding of compounds **4l, 4m,** myricetin and ningnanmycin to TMV-CP protein gave K_d values of 0.34 ± 0.09 μmol/L, 2.30 ± 0.77 μmol/L, 92.23 ± 47.54 μmol/L and 0.52 ± 0.25 μmol/L, respectively. As showed in MST, compound **4l** (K_d=0.34 ± 0.09 μmol/L) shared strong affinity, which was better than that of ningnanmycin (K_d=0.52 ± 0.25 μmol/L) and lead compound myricetin (K_d=92.23 ± 47.54 μmol/L). Based on anti-TMV activities and MST results, we can predict that the structural modification of the lead compound myricetin, such as the introduction of the active groups ferulic acid amide, could greatly improved the antiviral activities.

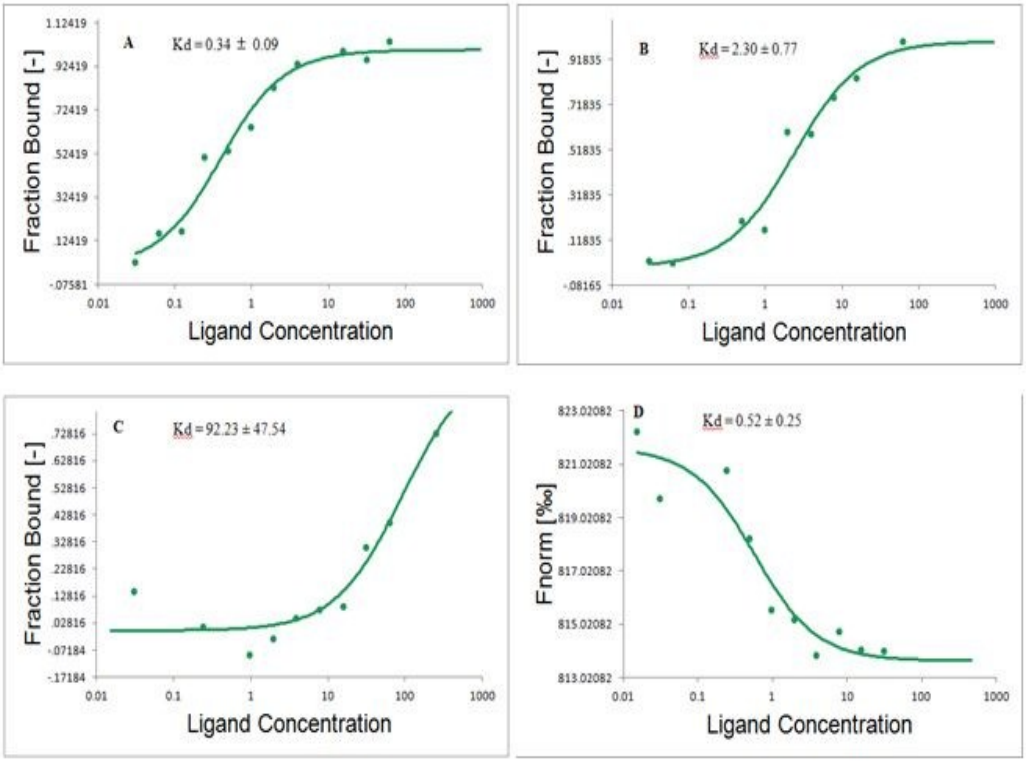

Figure 2. Microscale thermophoresis results of compounds **4l** (**A**), **4m** (**B**),myricetin (**C**) and ningnamycin (**D**)

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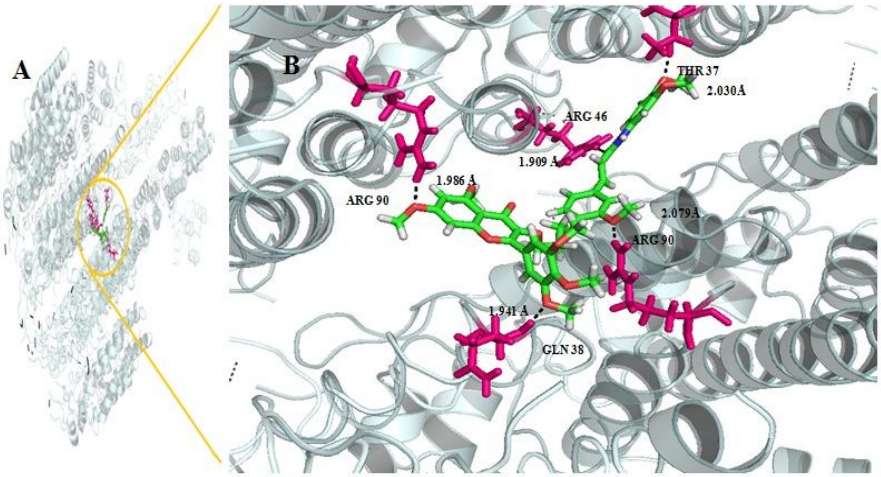
Table 3. The dissociation constant of **4l**, **4m**, myricetin and ningnanmycin with TMV-CP

Compd.	K_d (μmol/L)
4l	0.34 ± 0.09
4m	2.30 ± 0.77
myricetin	92.23 ± 47.54
ningnanmycin	0.52 ± 0.25

3.5. Molecular docking of 4l and myricetin with TMV-CP

To identify the **4l** and myricetin recognition sites in TMV-CP (Protein Data Bank (PDB) code: 1EI7),we performed molecular docking using the gold method with 200 cycles.[27, 29, 30] As shown in the **Figure 3**, the compound **4l** was well-embedded between the two subunits of TMV-CP. Previous reports have shown that these residues play key roles in the self-assembly of TMV particles.[31] The binding orientation of compound **4l** was clearly shown in **Figure 3** (A and B), it forms one hydrogen bond with ARG-46, with the highest docking score (1.909 Å) among the designed molecules. Besides, compound **4l** deep into the active pocket formed by amino-acid residue, including ARG-90, CLN-38 and THR-37. These interactions between small molecules and the TMV-CP may impair the interaction of twoTMV-CP subunits, hence preventing self-assembly of the TMV particle. As shown in the **Figure 3**, The hydrogen bond strength of compound **4l** was stronger than that of myricetin (C and D). Based on molecular docking results of compound **4l** and myricetin, we can predict that the structural modification of the lead compound myricetin could greatly improve the antiviral activities.



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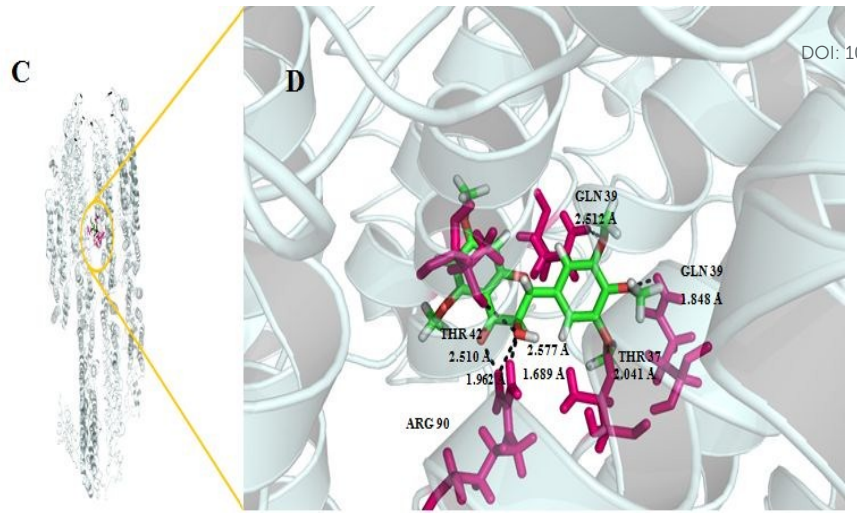

Figure 3 Molecular docking studies of compounds **4l** (**A**–**B**) and myricetin (**C**–**D**)

4. Conclusions

A series of myricetin derivatives bearing ferulic acid amide scaffolds were designed and synthesized. Preliminary bioassays suggested that these compounds exhibit favorable curative and protective activities against TMV. Among them, compound **4l** showed remarkable protective activity against TMV, with the EC_{50} values of 196.11 μg/mL, which was superior to ningnamycin (447.92 μg/mL). Further the microscale thermophoresis studies revealed that compound **4l** have strong binding capability with TMV-CP, and the molecular docking studies were consistent with the experimental results. All these results support that the myricetin derivatives bearing ferulic acid amide scaffolds possess antiviral activities, and thus could be further studied as potential alternative templates in the search for novel antiviral agents.

Competing interests

The authors declare that they have no competing interests.

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References

1. L.J. Chen, R.J. Xia, X. Tang, Y. Chen, C. Zhang, W. Xue, *Molecules*, 2019, **24**, 925.
2. P.Y. Wang, L. Zhou, J. Zhou, Z.B. Wu, W. Xue, B.A. Song, *Bioorg. Med. Chem. Lett*. 2016, **26**, 1214–1217.
3. X.H. Gan, D.Y. Hu, P. Li, J. Wu, X.W. Chen, W. Xue, B.A. Song, *Pest Manag. Sci.* 2016, **72**, 534–543.
4. X.H. Qian, P.W. Lee, C. Song, *J. Agric. Food Chem*. 2010, **58**, 2613–2623.
5. G.C. Leonard, O.D. Stephen, *Pest Manag. Sci*. 2007, **63**, 524–554.
6. P.G. Marrone, *Out Look AGR*. 1999, **28**, 149–154.
7. B. Sultana, F. Anwar, *Food Chem*. 2008, **108**, 879–884.
8. Y. Tong, X.M. Zhou, S.J. Wang, Y. Yang, Y.L. Cao, *Arch. Pharm. Res*. 2009, **32**, 527–533.
9. X.R. Wang, Z.Q. Wang, Y. Li, *Acta. Botanica. Sinica*. 1981, **23**, 222–227.
10. K.W. Lee, N.J. Kang, E.A. Rogozin, H.G. Kim, Y.Y. Cho, A.M. Bode, H. Joo , Y.J. Surh, G.T. Bowden, Z. Dong, *Carcinogenesis*, 2007, **28**, 1918–1927.
11. X.W. Su, D.H. D'Souza, *Food Environ. Virol*. 2013, **5**, 97–102.
12. X.M. Zhong, X.B. Wang, L.J. Chen, X.H. Ruan, Q. Li, J.P. Zhang, Z. Chen, W. Xue, *Chem. Cent. J*. 2017, **11**,106.
13. C.C. Chen, C.Y. Huang, *Protein J.* 2011, **30**, 59–65.
14. K. Rashed, A. Ćirić, J. Glamočlija, M. Soković, *Ind. Crop. Prod.* 2014, **59**, 210–215.
15. V. Chobot, F. Hadacek, *Redox. Rep*. 2011, **16**, 242–247.
16. W. Xue, B.A. Song, H.J. Zhao, X.B. Qi. Y.J. Huang, X.H. Liu, *Eur. J. Med. Chem.* 2015, **97**, 155–163.
17. T.K. Ha, I. Jung, M.E. Kim, S.K. Bae, *Biomed. Pharmacother*. 2017, **91**, 378–384.
18. S. Ou, K.C. Kwok, *J. Sci. Food Agric*. 2004, **84**, 1261–1269.

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19. Z.X. Wu, J. Zhang, J.X. Chen, J.K. Pan, L. Zhao, D.Y. Liu, A.W. Zhang, J. Chen, D.Y. Hu, B.A. Song, *Pest Manag. Sci*. 2017, **73**, 2079–2089.
20. Y.G. Shi, Y. Wu, X.Y. Lu, Y.P. Ren, Q. Wang, C.M. Zhu, L. Yu, H. Wang, *Food Chem.* 2017, **220**, 249–256.
21. C. Eroğlu, M. Seçme, G. Bağcı, Y. Dodurga, *Tumor biol.* 2015, **36**, 9437–9446.
22. N. Kumar, S. Kumar, S. Abbat, K. Nikhil, S. M. Sondhi, P.V. Bharatam, P. Roy, V. Pruthi, *Med. Chem. Res.* 2016, **25**, 1175–1192.
23. J.X. Chen, Y.Z. Chen, X.H. Gan, B.J. Song, D.Y. Hu, B.A. Song, *J. Agric. Food Chem*. 2018, **66**, 9616–9623.
24. H.R. Liu, L.B. Liu, X.H. Gao, Y.Z. Liu, W.J. Xu, W. He, H. Jiang, J.J. Tang, H.Q. Fan, X.H. Xia, *Eur. J. Med. Chem.* 2017, **126**, 810–822.
25. J. Chen, J. Shi, L. Yu, D. Liu, X.H. Gan, B.A. Song, D.Y. Hu, *J. Agric. Food Chem*. 2018, **66**, 5335–5345.
26. Z.X. Wu, J. Zhang, J.X. Chen, J.K. Pan, L. Zhao, D.Y. Liu, A.W. Zhang, J. Chen, D.Y. Hu, B.A. Song, *Pest Manag. Sci*. 2017, **73**, 2079–2089.
27. X.Y. Li, J. Liu, X. Yang, Y. Ding, J. Wu, D.Y. Hu, B.A. Song, *Bioorg. Med. Chem*. 2015, **23**, 3629–3637.
28. C.J. Wienken, P. Baaske, U. Rothbauer, D. Braun, S. Duhr, *Nat. Commun*. 2010, **1**, 100.
29. L.J. Chen, T. Guo, R.J. Xiao, X. Tang, Y. Chen, C. Zhang, W. Xue, *Molecules*, 2019, **24**, 925.
30. X. Tang, S.J. Su, M. Chen, J. He, R.J. Xia, T. Guo, Y. Chen, C. Zhang, J. Wang, W. Xue, *RSC Adv*. 2019, **9**, 6011–6020.
31. A. C. Bloomer, J. N. Champness, G. Bricogne, *Nature*, 1978, **276**, 362–368.