Synthesis and bioactivity evaluation of penta-1,4-diene-3-one oxime ether derivatives

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A series of penta-1,4-diene-3-one oxime ether derivatives were synthesized, and their antiviral and antifungal activities were evaluated. Bioactivity evaluations showed that most target compounds had significant antiviral effects against tobacco mosaic virus (TMV). Among them, (1E,3Z,4E)-1-(4-(benzyloxy)phenyl)-5-(furan-2-yl)penta-1,4-dien-3-one O-(3-fluorobenzyl) oxime (5e) was found to have good curative activity against TMV, with an inhibition rate of 64.6%, which was better than that of ribavirin (45.2%). (1E,3Z,4E)-1-(4-(benzyloxy) phenyl)-5-(furan-2-yl)penta-1,4-dien-3-one O-((6-chloropyridin-3-yl)methyl) oxime (5d) had a remarkable protective effect against TMV, with an inhibitory rate of 66.9%, which was better than that of ribavirin (61.8%). The inhibitory rate of (1E,3Z,4E)-1-(2-(benzyloxy)phenyl)-5-(furan-2-yl)penta-1,4-dien-3-one O-(4-chlorobenzyl) oxime (5m) in inactivation activity against TMV was 87.0%, which was better than that of ribavirin (77.9%). Further molecular docking studies indicated that compound 5m shows strong binding affinities toward the coat protein of tobacco mosaic virus. This result indicates that penta-1,4-diene-3-one oxime ether derivatives can play a significant role in discovering new antiviral agents.

Keywords: penta-1,4-diene-3-one, oxime ether, biological activity, molecular docking.

Electronic supplementary materials: The online version of this article contains supplementary materials (Supplemental Figs. S1–S39), which are available at http://www.jstage.jst.go.jp/browse/jpestics/

Introduction

Tobacco mosaic virus (TMV), also called plant cancer, is a serious plant virus that is difficult to control due to its absolute parasitism. TMV is the most persistent plant virus that can survive in plant debris for up to 100 years. More than 885 individual species in 65 plant families can be infected by this virus, with plant diseases caused by TMV resulting in the loss of $100 million annually worldwide. Ribavirin is a successful antiviral drug that widely used to prevent TMV. However, its antiviral activity is always less than 50% at 500 µg/mL. Furthermore, antiviral agent research is different from drug research. Many pharmaceutical studies, such as those on the structure and function of a target protein or on the signal transduction pathway of target proteins, have been conducted. However, in anti-plant virus agent research, only very limited molecular targets are studied and can be used in agrochemical design and discovery, and this increases the difficulty of discovering antiviral agents for plants. Therefore, the research and development of new bioactive molecules with fine anti-TMV effects have attracted attentions of more and more researchers.

Natural product-derived compounds, which feature unique action mechanisms and environmental friendliness, play a pivotal role in effective control against plant diseases. As important structural cores of curcumin, penta-1,4-diene-3-one fragments have been widely used in designing medicines and agrochemicals that give corresponding compounds various biological activities, such as anticancer, bactericidal, anti-inflammatory, antiviral, and insecticidal properties. Among these, the potent activities against plant viruses have been well studied by chemists in previous decades. For example, a series of N-heterocyclic groups, including pyridinium, benzotriazinone, quinazoline, and parazole moieties, were introduced to penta-1,4-diene-3-ones (Fig. 1, A1–A4). These compounds were found to...
have remarkably increased biological activities. In our previous works, a TMV coat protein was found as the potential anti-TMV target protein of penta-1,4-diene-3-one oxime ether derivatives containing a quinazolin-4(3H)-one scaffold (Fig. 2, B).\textsuperscript{16}

Similarly, possessing outstanding characteristics, including high efficiencies, broad activities, and low toxicities against mammals,\textsuperscript{17,18} oxime ethers play important roles in the search for effective plant virucides. In our previous researches, we synthesized a series of oxime ether derivatives containing a pyridine moiety\textsuperscript{17} that exhibited good antiviral activities against TMV (Fig. 3, C).

Based on the findings above, we speculated that exchanging the carbonyl group in penta-1,4-dien-3-one scaffolds with an oxime ether group might generate novel molecules with potent biological activities against TMV. Thus, a series of penta-1,4-dien-3-one oxime ether derivatives were synthesized, and their antiviral and antifungal activities were evaluated (Fig. 4). The synthetic route of title compounds is shown in Scheme 1.

**Materials and Methods**

1. **Chemicals**

   The melting points of the title compounds were determined when left untouched on an XT-4-MP apparatus (Beijing Tech Instrument Co., China). \( ^1 \text{H} \) and \( ^{13} \text{C} \) nuclear magnetic resonance (NMR) spectra were recorded on a JEOL-ECX 500 NMR spectrometer operating at room temperature using tetramethylsilane (TMS) as the internal standard and acetone as the solvent. The infrared (IR) spectra were recorded from KBr disks using a Bruker VECTOR 22 spectrometer. Mass spectra studies were recorded on an organic mass spectrometer (Agilent, USA). Thin-layer chromatography purifications were carried out on 200–300 mesh silica gel. All reagents and reactants were analytical grade, purchased from commercial suppliers. Intermediates 1, 2, and 3 were synthesized via procedures described in the respective literature.\textsuperscript{16–18}

2. **Chemical synthesis**

   2.1. **General procedure for the synthesis of intermediate 4**

   A mixture of 10 mmol of intermediate 3, 40 mmol of hydroxylamine hydrochloride, and 20 mL of pyridine in ethanol (40 mL) was stirred for 12 hr at room temperature. After the reaction was completed, the mixture was filtered, and the filtrate was vacuum-dried. The residue was subjected to column chromatography with petroleum ether/ethyl acetate (\( V:V=3:1 \)) to yield intermediate 4.

   2.2. **General procedure for the synthesis of title compounds**

   Intermediate 4 (1.5 mmol), 2,4-dichlorophenyl (1.80 mmol), and \( \text{K}_2\text{CO}_3 \) (3.00 mmol) were added to 35 mL of acetonitrile. Then the mixture was heated at 85°C for 3.5 hr. After the reaction was completed, the mixture was filtered, and the filtrate was vacuum-dried. The residue was subjected to column chromatography with petroleum ether/ethyl acetate (\( V:V=3:1 \)) to yield the title compounds 5a–5m. The physical characteristics, \( ^1 \text{H} \) NMR, \( ^{13} \text{C} \) NMR, and IR data, for target compounds 5a–5m are listed in the Supporting Information, and the data of 5a are shown below as a representative example.

   \((1E,3Z,4E)-1-(4-(Benzyloxy)phenyl)-5-(furan-2-yl)penta-1,4-dien-3-one O-(2,4-dichlorobenzyl) oxime (5a): brown liquid, yield 39%; IR (KBr, cm\(^{-1}\)): \( \nu \text{max} \) 1603, 1558, 1508, 1244, 1173, 1042, 1014, 966, 820, 741; \( ^1 \text{H} \) NMR (500 MHz, CDCl\(_3\), ppm) \( \delta \): 7.64–7.46 (m, 7H, furan-5-H, Ar(Cl)-3,5-H, Ar-2,6-H), 7.40–7.00 (m, 9H, Ar-3,4,5-H, Ar(OCH\(_2\))-2,6-H, Ar-2,6-H), 7.40–7.00 (m, 9H, Ar-3,4,5-H, Ar(OCH\(_2\))-2,6-H, Ar-2,6-H), 7.40–7.00 (m, 9H, Ar-3,4,5-H, Ar(OCH\(_2\))-2,6-H, Ar-2,6-H), 7.40–7.00 (m, 9H, Ar-3,4,5-H, Ar(OCH\(_2\))-2,6-H, Ar-2,6-H), 7.40–7.00 (m, 9H, Ar-3,4,5-H, Ar(OCH\(_2\))-2,6-H, Ar-2,6-H).
Ar(OCH\(_2\))=CH=, Ar(Cl)-6-H, furan-CH=, Ar(OCH\(_2\))=3,5-H, Ar(OCH\(_2\))=C=CH), 6.85–6.78 (m, 1H, furan-3-H), 6.65–6.50 (m, 2H, furan-C=CH, furan-4-H), 5.31–5.30 (d, \(J = 4.0\) Hz, 2H, CH\(_2\), E-oxime isomer+Z-oxime isomer), 5.16–5.10 (d, \(J = 7.4\) Hz, 2H, CH\(_2\)); \(^{13}\)C NMR (125 MHz, CD\(_3\)COCD\(_3\), ppm) \(\delta\): 159.9, 154.2, 152.6, 144.2, 143.4, 137.2, 137.1, 135.0, 134.1, 133.7, 131.2, 129.2, 129.0, 128.6, 128.0, 127.7, 127.3, 124.8, 121.9, 119.8, 119.2, 115.2, 114.7, 112.8, 112.3, 112.1, 111.0, 72.8, 69.7; MS (ESI, \(m/z\)) calcd for: C\(_{29}\)H\(_{23}\)Cl\(_2\)NO\(_3\) [M+H]+: 504.3, found: 504.2, \(E:Z=1.15:0.68\).

3. Bioactivity assay

3.1. Antiviral activities in vivo

3.1.1. Curative activity of the target compounds against TMV in vivo

Growing leaves of *Nicotiana tabacum* under same ages were selected. The leaves were inoculated with TMV (6×10\(^{-3}\) mg/mL) by dipping and brushing the whole leaves, which were previously sprinkled with silicon carbide. The leaves were then washed with water after inoculation for 0.5 hr. The compound solution was smeared on the left side of the leaves, and the solvent was smeared on the right side as the control. Three or four days after inoculation, lesions on each of the leaves were recorded. Three replicates were set up for each. The inhibitory rate (\(I\%\)) of the compound was calculated according to the following formula.

\[
(I\%) = \frac{(C_{num} - T_{num})}{C_{num}} \times 100\%
\]

\(T_{num}\): average local lesion number smeared with compounds

\(C_{num}\): average local lesion number of control (not treated with compounds)

3.1.2. Protection activity of the target compounds against TMV in vivo

The compound solutions were smeared on the left side of the *Nicotiana tabacum* leaves, and the solvents were smeared on the right side as the control sample for growing *Nicotiana tabacum* leaves. After 12 hr, crude TMV (6×10\(^{-3}\) mg/mL) was inoculated onto whole leaves at the same concentration on each side of the leaves, which were previously sprinkled with silicon carbide. After 0.5 hr, the leaves were washed with water and then dried. Three or four days after inoculation, lesions on each of the leaves were recorded. Three replicates were used for each compound. The I\% of the compound was calculated according to the following formula.

\[
(I\%) = \frac{(C_{num} - T_{num})}{C_{num}} \times 100\%
\]

\(T_{num}\): average local lesion number smeared with compounds

\(C_{num}\): average local lesion number of control (not treated with compounds)

3.1.3. Inactivation activity of the title compounds against TMV in vivo

The virus was inhibited after it was mixed with a compound solution of the same volume for 30 min. The right side of the *Nicotiana tabacum* leaves was then inoculated with the solvent and virus mixture for control. All of the leaves were previously sprinkled with silicon carbide. Three or four days after inoculation, lesions on each of the leaves were recorded. Three replications were reproduced for each compound. The I\% of the compounds was calculated according to the following formula.

\[
(I\%) = \frac{(C_{num} - T_{num})}{C_{num}} \times 100\%
\]

\(T_{num}\): average local lesion number smeared with compounds

\(C_{num}\): average local lesion number of control (not treated with compounds)

3.2. Molecular docking

The molecular docking was performed using a DS-CDock® implemented in Discovery Studio (version 4.5). The coat protein subunit amino acid sequence of TMV was searched for in the UniProt database. The Protein BLAST server was used to
search for the template protein, and the homologies of TMV-CP sequences were aligned. Homology modeling of TMV-CP was carried out using Create Homology Models, which is a module integrated into Discovery Studio. The obtained models were evaluated using Ramachandran plots. The three-dimensional structures of the compounds were constructed using the Sketching module and optimized using the Full Minimization module. All parameters are the default ones during the docking process.

Results

1. Chemical synthesis

A series of penta-1,4-diene-3-one oxime ether derivatives were successfully prepared in five steps in our current work. All of the target compounds, 5a–5m, were identified by IR, 1H NMR, 13C NMR, and ESI-MS. In the IR spectra, the characteristic absorptions at 1500–1620 cm−1 and 1210–1260 cm−1 indicate the presence of –C= and –C–O–N– groups, respectively. In the 1H NMR spectra of the title compounds 5a–5m, the multiplet at 6.50–8.20 ppm reveals the presence of aromatic protons, and the characteristic absorption peaks of –CH2– show a high-frequency downfield singlet at 5.00–5.50 ppm. In addition, the typical shifts in the 13C NMR spectra at approximately 155–165 ppm and 65–75 ppm show the presence of –C= and –CH2– groups, respectively. In the ESI-MS spectra, the greater abundance of [M+H]+ ions reveals that the title compounds are stable.

2. Antifungal and antiviral activities of the target compounds 5a–5m

The anti-TMV activities of the target compounds 5a–5m at 500 µg/mL were tested using the half-leaf spot method,13,16) and ribavirin as the commercial agent was tested under the same condition. The results of bioassays, shown in Table 1, indicated that these title compounds had preferable curative, protective, and inactivation activities against TMV, with inhibitory rates ranging from 32.7 to 64.6%, from 34.4 to 66.9%, and from 74.0 to 87.0%, respectively. Among them, compounds 5c, 5e, and 5h were found to have good curative activity against TMV, with inhibition rates of 59.9, 64.6, and 63.5%, respectively, which were

| Compounds | R          | -X-          | Curative activity(%) | Protective activity(%) | Inactivation activity(%) |
|-----------|------------|--------------|-----------------------|------------------------|-------------------------|
| 5a        | 2,4-di-Cl-Ph | 4-O-yl       | 47.8±1.2               | 51.5±6.2                | 81.5±8.1                |
| 5b        | 4-NO2-Ph    | 4-O-yl       | 52.1±3.1               | 54.5±7.2                | 81.5±3.0                |
| 5c        | 4-OMe-Ph    | 4-O-yl       | 59.9±2.7               | 59.6±4.7                | 81.1±1.2                |
| 5d        | 2-Cl-5-pyridyl | 4-O-yl    | 58.3±4.2               | 66.9±3.6                | 78.5±3.0                |
| 5e        | 3-F-Ph      | 4-O-yl       | 64.6±3.3               | 61.3±2.6                | 80.8±2.9                |
| 5f        | 2,4-di-Cl-Ph | 2-O-yl       | 47.9±0.7               | 62.4±1.5                | 78.2±4.7                |
| 5g        | 4-NO2-Ph    | 2-O-yl       | 51.4±0.9               | 60.8±1.8                | 81.8±7.1                |
| 5h        | 3-F-Ph      | 2-O-yl       | 63.5±4.1               | 34.4±5.1                | 74.0±1.3                |
| 5i        | 2-Cl-Ph     | 2-O-yl       | 44.3±0.8               | 65.4±0.5                | 81.7±3.1                |
| 5j        | 4-OMe-Ph    | 2-O-yl       | 34.9±2.5               | 60.4±2.9                | 82.8±3.5                |
| 5k        | 2-Cl-5-pyridyl | 2-O-yl    | 46.7±5.2               | 62.5±0.8                | 83.3±4.2                |
| 5l        | -Ph         | 2-O-yl       | 57.1±7.1               | 44.9±7.7                | 81.3±6.4                |
| 5m        | 4-Cl-Ph     | 2-O-yl       | 32.7±3.1               | 57.6±6.1                | 87.0±6.0                |
| Ribavirin | —           | —            | 45.2±2.2               | 61.8±3.8                | 77.9±6.5                |

Table 1. Inhibitory effect of the title compounds 5a–5m against TMV at 500 µg/mL.

[a] Average of three replicates; [b] the commercial anti-plant virus agents ribavirin was tested for comparison of activity.
better than that of ribavirin (45.2%). Compounds 5d, 5i, and 5k had better protective effects against TMV, and their inhibitory rates were 66.9, 65.4, and 62.5%, respectively, which were superior to that of ribavirin (61.8%). The inhibitory rates of compounds 5j, 5k, and 5m in inactivation activity against TMV were 82.8, 83.3, and 87.0%, respectively, which were better than that of ribavirin (77.9%). This also showed that these compounds have important inhibitory effects against TMV and that they can be used as lead structures in discovering new antiviral agents. As shown in Table 2, the target compounds have certain inhibitory effects on three plant-pathogenic fungi, but all of them are lower than that of the control drug epoxiconazole.

3. Molecular docking studies

Molecular docking studies (Fig.5) for 5m with the tobacco mosaic virus coat protein (TMV-CP) (PDB code: 1EI7) revealed that compound 5m was the most effective one, followed by 5k and so on (Table 1, inactivation activity of the compound). The binding orientation of compound 5m is clearly shown in Fig. 5; it forms one hydrogen bond with ALAA:74, with the highest docking score (2.49 Å) among the designed molecules. In addition, oxime ether showed a carbon–hydrogen bond interaction with residue SERB:255 and a π-Alkyl interaction with the phenyl-group residue ALAA:74. These interactions between small molecules and the TMV-CP may impair the interaction of two TMV-CP subunits, hence preventing self-assembly of the TMV particle. The molecular docking results showed that the binding of the TMV-CP to the molecule was consistent with the initial screening activity against TMV (the inactivation activity of the compound).

4. Antiviral activity and structure activity relationship against TMV

The results in Table 1 show that some title compounds had potential antiviral activities against TMV. Substituted benzyl chlorides were introduced into penta-1,4-diene-3-one oxime ethers to establish a structure–activity relationship of antiviral activities against TMV based on the experimental data. The plant viricide commercially available in China, ribavirin, was used as the control. When R was the 3-F-Ph group, the corresponding target compounds 5e (X=4-O-yl) and 5h (X=2-O-yl) exhibited excellent curative activity against TMV, with inhibition rates of 64.6 and 63.5%, respectively, which were superior to that of ribavirin (45.2%). When X was 4-O-yl and R was substituted with the 2-Cl-5-pyridyl group, the target compound 5d exhibited the best protective activity against TMV, with an inhibition rate of 66.9%, which was better than that of ribavirin (61.8%). When X was 2-O-yl and R was substituted with the 4-Cl-Phe group, the inhibition rate of the relative compound 5m was 87.0%, which was better than that of ribavirin (77.9%).

Discussion

Aiming to find novel compounds with potential antiviral activities, we synthesized a series of novel penta-1,4-diene-3-one oxime ether derivatives and evaluated their antiviral activities against TMV. The results showed that most of the target compounds had significant activities against TMV. Among them, compound 5e was found to have good curative activity against TMV, with an inhibition rate of 64.6%, which was better than that of ribavirin (45.2%). Compound 5d had a remarkable protective effect against TMV, with an inhibitory rate of 66.9%, which was better than that of ribavirin (61.8%). The inhibitory rate of compound 5m in inactivation activity against TMV was 87.0%, which was better than that of ribavirin (77.9%). Furthermore, these compounds were investigated using molecular docking studies. Compound 5m with an highest docking score and showed strong binding affinity toward the binding sites of target protein ALAA:74. This result indicates that penta-1,4-diene-3-one oxime ether derivatives can play significant roles in discovering new antiviral agents.

Table 2. Inhibition effect of compounds 5a–5m against three fungi

| Compounds | R- | X- | Wheat scab (%)a | Chilli wilt (%)a | Valsa mali (%)a |
|-----------|----|----|----------------|----------------|----------------|
| 5a        | 2,4-di-Cl-Ph | 4-O-yl | 2.1±0.5 | 2.5±0.9 | 1.8±0.8 |
| 5b        | 4-NO₂-Ph | 4-O-yl | n.d. | 3.4±1.1 | 9.0±1.1 |
| 5c        | 4-OMe-Ph | 4-O-yl | n.d. | n.d. | 2.4±0.9 |
| 5d        | 2-Cl-5-pyridyl | 4-O-yl | 3.9±0.8 | 4.8±1.0 | n.d. |
| 5e        | 3-F-Ph | 4-O-yl | n.d. | 0.3±1.4 | 1.2±0.8 |
| 5f        | 2,4-di-Cl-Ph | 2-O-yl | n.d. | n.d. | n.d. |
| 5g        | 4-NO₂-Ph | 2-O-yl | n.d. | 8.4±1.2 | n.d. |
| 5h        | 3-F-Ph | 2-O-yl | 0.7±0.9 | 0.7±1.0 | 0.3±1.1 |
| 5i        | 2-Cl-Ph | 2-O-yl | 5.1±0.8 | 1.1±1.1 | 1.1±1.3 |
| 5j        | 4-OMe-Ph | 2-O-yl | 1.7±0.8 | n.d. | 5.2±0.9 |
| 5k        | 2-Cl-5-pyridyl | 2-O-yl | 4.1±1.0 | 5.3±1.1 | n.d. |
| 5l        | -Ph | 2-O-yl | n.d. | 3.1±1.0 | n.d. |
| 5m        | 4-Cl-Ph | 2-O-yl | 2.4±0.9 | 4.9±1.1 | n.d. |
| Epoxiconazole | — | — | 100.0±3.9 | 100.0±5.4 | 100.0±8.4 |

a) Average of three replicates; b) the commercial anti-plant fungi agents epoxiconazole was tested for comparison of activity.
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Fig. 5. Three- and two-dimensional diagrams of compound 5m docked with TMV-CP. The two-dimensional diagram contains conventional hydrogen bonds, carbon–hydrogen bonds, Pi-Pi T-shaped bonds and Pi-Alkyl bonds.
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