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ジャスモン酸生合成に関わるアレンオキシド合成酵素（CYP74A）を阻害する新規トリアゾール類の合成
Synthesis of novel triazole derivatives as potent inhibitor of allene oxide synthase (CYP74A), a key enzyme in jasmonic acid biosynthesis

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A series of new triazole derivatives was synthesized and their inhibitory activity against allene oxide synthase (AOS, CYP74A), a key enzyme in jasmonic acid biosynthesis, was evaluated. Structure-activity relationship studies revealed that methyl 8-[1-(naphthalen-2-yl)-2-(1,2,4-triazol-1-yl)ethoxy]octanate (4i) and methyl 8-[1-(2,4-dichlorophenyl)-2-(1,2,4-triazol-1-yl)ethoxy]octanate (4g) exhibit potent inhibitory activity to allene oxide synthase, with IC50 values of 0.75±0.30 and 0.84±0.60 μM, respectively.

Keywords: allene oxide synthase inhibitor, jasmonic acid, crop protection.

Introduction

Plants respond to pathogen infection and herbivore attack by activation signals, such as salicylic acid and/or jasmonates (JAs), which regulate defense gene expression in plant tissues.1 One of the major signaling events is the activation of JA biosynthesis and JA signal transduction pathways.2 JAs are central signal mediators of defense gene expression in plants3 and also play key roles in several developmental processes.2 They are present at trace levels in undamaged healthy plants but are emitted in large quantities in plant tissues after mechanical wounding or herbivore induced damage.4 Exogenous application of JAs to plant tissues induces defense gene expression.5 Mutations that disrupt the enzymes in JA biosynthesis reduce the response to mechanical wounding.5 Studies on the roles of JAs in vegetative development and pollen viability have provided evidence that they play a key role in flower development.6 The necessity of JAs in male fertility was established by the characterization of an Arabidopsis mutant that failed to produce linolenic acid,7 the substrate of JA biosynthesis. Mutations that disrupt other steps in the pathway of JA biosynthesis were also shown to cause male sterility.8

The importance of JAs in plant defense and development has attracted increasing interest for understanding the defense functions and developmental processes of higher plants.2 Genetic studies on JA biosynthesis have shown that controlling JA biosynthesis might be a possible means of regulating the defense dynamics of higher plants.9 Thus, studies on the regulation mechanism of JA biosynthesis may be a challenging approach for elucidating the plant defense system against herbivore attack and pathogen infection. Consequently, chemical regulation of JA biosynthesis based on design- and synthesis-specific inhibitors is a straightforward strategy. Towards this end, we carried out a systemic search to design specific inhibitors of JA biosynthesis.10-12

A challenge for design-specific inhibitors of JAs biosynthesis is to elucidate the target enzyme. Studies on the functions of enzymes of the JA biosynthesis pathway have shown that AOS (allene oxide synthase), a cytochrome P450 enzyme (CYP74A) that catalyzes the first reaction in the specific pathway of JA biosynthesis,13 is an important site for regulating overall JA biosynthesis.14 Strategies to design P450 inhibitors may thus be applied to the identification of AOS inhibitors. The inhibition mechanism of the cytochrome P450 enzyme has been studied in considerable detail.15 It is known that imidazole and triazole derivatives have widespread ability as P450 inhibitors, apparently due to the intrinsic affinity of the nitrogen electron pair in heterocyclic molecules for the prosthetic heme iron. The azoles bind not only to lipophilic regions of the protein but also simultaneously to the prosthetic heme iron.16 On the bases of these observations, we have previously shown the design and synthesis novel imidazole derivatives as potent inhibitor of AOS (JM series).10 In the course of our research, we found that heptyl 8-[1-(2,4-dichlorophenyl)-2-(imidazol-1-yl)ethoxy]octanate (JM-8686, the chemical structure shown in Fig. 1) exhibits potent inhibitory activity against AOS.9 The key structure of JM-8686 analogues was 1-(2,4-dichlorophenyl)-2-(imidazol-1-yl)ethoxy moiety, using which we introduced different carboxylic acid esters moiety into the JM series to study the structure-activity relationships (SAR).10 We found that the length of the chain of carboxylic acid moiety markedly affects the potency of AOS inhibition, and octanoic acid esters analogues exhibit potent inhibitory activity against AOS.10

Although JM-8686 is a potent inhibitor of AOS and exhibits high binding affinity to recombinant AOS in vitro,11,12 research focused on controlling JA biosynthesis in plant tissues remain to be accomplished. In the present work, we carried out chemical optimization of a JM series by chemical modification of JM-8686 in several points as follows: 1) to improve water solubility of the inhibitors by shortening the ester moiety of JM-8686 using octanoic acid methyl ester as a key structure, 2) to introduce 1,2,4-triazole moiety into the inhibitor instead of imidazole of JM-8686 to evaluate the effect of 1,2,4-triazole moiety on AOS inhibition, and 3) to introduce different aromatic ring structures to inhibitors that
mimic the 2,4-dichlorophenyl moiety of JM-series for structure-activity relationship studies (the general structure of target compounds is shown in Fig. 1). The inhibitory activity of newly synthesized 1,2,4-triazole derivatives against AOS were evaluated. We expect that further development and experimental use of AOS inhibitors in intact plants could provide new information about the defense mechanism of plants to herbivore attack and mechanical wounding.

Materials and Methods

1. General

Chemicals for synthesis were purchased from Acros Organic BVBA (Geel, Belgium), Kanto Chemicals Co. Ltd. (Tokyo, Japan) and Tokyo Kasei Co. Ltd. (Tokyo, Japan). Melting points (mp) were determined with a Yanako melting point apparatus. 

NMR spectra were recorded with a JEOL ECP-400 spectrometer, Fourier transform ion cyclotron resonance mass spectra (ESI-FTICR) were recorded on an Exactive MS System (Thermo Fisher Scientific, USA).

2. Chemistry

Preparation of 13(S)-hydroperoxy-cis,trans,cis-9,11,15-octadecatrienoic acid (13(S)-HPOT). 13(S)-HPOT was prepared according to the method described previously. The stock solution of 13(S)-HPOT was prepared by dissolving 13(S)-HPOT in methanol (10 mM) and was stored at −20°C.

Preparation of 1-phenyl-2-(1,2,4-triazol-1-yl)ethanone (2a). 2a was prepared using phenacyl bromide as the starting material, as described previously. To a vigorously stirred suspension of 1H-1,2,4-triazole (5.52 g, 0.08 mol) and phenacyl bromide 1a (9.95 g, 0.05 mol) in 30 mL acetone, was added triethylamine (8.1 g, 0.05 mol) drop-wise over a period of 1 hr with the temperature below 0°C, and the reaction mixture was stirred for another 30 min at room temperature. The mixture was filtered to remove triethylamine hydrobromide salt precipitates, the precipitates was washed with 3×10 mL acetone, the filtrate was evaporated under reduced pressure, and the residues were dissolved in 50 mL chloroform and then washed with 2×25 mL water. After evaporation of chloroform, the yellow solid was recrystallized with 2-propanol, and 2a was obtained as a white solid with a yield of 66.7%, mp: 100–103°C. 1H NMR (CDCl3) δ: 5.78 (s, 2H), 7.55 (t, J=7.7 Hz, 2H), 7.68 (t, J=7.3 Hz, 1H), 7.98–8.00 (m, 2H), 8.11 (s, 1H), 8.74 (s, 1H). Other compounds (2b–2i) were prepared in a similar way by the reaction of triazole with the corresponding phenacyl bromide.

1-(3-Methoxyphenyl)-2-(1,2,4-triazol-1-yl)ethanone (2b). Yield: 52.7%, mp: 78–80°C. 1H NMR (CDCl3) δ: 5.68 (s, 2H), 7.20–7.23 (m, 1H), 7.44–7.48 (m, 1H), 7.51–7.58 (m, 2H), 8.03 (s, 1H), 8.25 (s, 1H).

1-(4-Methoxyphenyl)-2-(1,2,4-triazol-1-yl)ethanone (2c). Yield: 43.5%, mp: 84–86°C. 1H NMR (CDCl3) δ: 5.64 (s, 2H), 6.99–7.02 (m, 2H), 7.97–8.00 (m, 2H), 8.01 (s, 1H), 8.26 (s, 1H).

1-(2,4-Dichlorophenyl)-2-(1,2,4-triazol-1-yl)ethanone (2d). Yield: 48.7%, mp: 170–172°C. 1H NMR (CDCl3) δ: 5.67 (s, 2H), 7.37–7.59 (m, 3H), 7.70 (d, J=8.1 Hz, 2H), 7.70 (d, J=8.1 Hz, 2H), 8.01 (d, J=4.0 Hz, 2H), 8.02 (s, 1H), 8.32 (s, 1H).

1-(2,4-Dichlorophenyl)-2-(1,2,4-triazol-1-yl)ethanone (2d). Yield: 54.7%, mp: 116–118°C. 1H NMR (CDCl3) δ: 5.66 (s, 2H), 7.21–7.25 (m, 2H), 8.02 (s, 1H), 8.03–8.07 (m, 2H), 8.25 (s, 1H).

1-( Chlorophenyl)-2-(1,2,4-triazol-1-yl)ethanone (2f). Yield: 46.5%. mp: 144–146°C. 1H NMR (CDCl3) δ: 5.69 (s, 2H), 7.53 (d, J=8.4 Hz, 2H), 7.94 (d, J=8.4 Hz, 2H), 8.07 (s, 1H), 8.45 (s, 1H).

1-(2,4-Dichlorophenyl)-2-(1,2,4-triazol-1-yl)ethanone (2g). Yield: 52.6%, mp: 107–109°C. 1H NMR (CDCl3) δ: 5.33 (s, 2H), 6.92 (s, 1H), 7.02 (s, 1H), 7.38 (d, J=9.1 Hz, 1H), 7.51 (s, 2H), 7.57 (d, J=9.1 Hz, 1H).

1-(3,4-Dichlorophenyl)-2-(1,2,4-triazol-1-yl)ethanone (2h). Yield: 65.2%, mp: 161–163°C. 1H NMR (CDCl3) δ: 5.65 (s, 2H), 7.65 (d, J=8.4 Hz, 1H), 7.83 (dd, J=2.2, 8.4 Hz, 1H), 8.03–8.09 (m, 1H), 8.21 (s, 1H), 8.25 (s, 1H).

1-Naphthalen-2-yl-2-(1,2,4-triazol-1-yl)ethanone (2i). Yield: 52.1%. mp: 152–154°C. 1H NMR (CDCl3) δ: 5.84 (s, 2H), 7.60–7.70 (m, 2H), 7.91–8.03 (m, 5H), 8.32 (s, 1H), 8.52 (s, 1H).

Preparation of 1-phenyl-2-(1,2,4-triazol-1-yl)ethanethiol (3a). 3a was prepared by reduction of 2a using NaBH4 in methanol as described previously. Yield: 72.7%, mp: 102–104°C. 1H NMR (CDCl3) δ: 4.29–4.43 (m, 2H), 5.12–5.15 (m, 1H), 7.32–7.41 (m, 5H), 7.97 (s, 1H), 8.04 (s, 1H). Other compounds (3b–3i) were prepared in a similar way by reduction of the corresponding ketones.

1-(3-Methoxyphenyl)-2-(1,2,4-triazol-1-yl)ethanethiol (3b). Yield: 62.6%, colorless oil. 1H NMR (CDCl3) δ: 4.28–4.42 (m, 2H), 5.10

Fig. 1. Chemical structure of target compound.
48.2%. mp: J=8.4Hz, lH, 7.06-7.10 (m, 2H), 7.32-7.35 (m, 2H), 7.99 (s, 1H), 8.04 (s, 1H).

1-Biphenyl-4-yl-2-(1,2,4-triazol-1-yl)ethanol (3d), Yield: 62.8%. mp: 168–170°C. 1H NMR (CDCl3) δ: 4.37-4.48 (m, 2H), 5.19 (dd, J=4.0, 7.7 Hz, 1H), 7.35–7.39 (m, 1H), 7.43-7.48 (m, 4H), 7.61 (dd, J=8.8, 10.6 Hz, 4H), 8.01 (s, 1H), 8.09 (s, 1H).

1-(4-Fluorophenyl)-2-(1,2,4-triazol-1-yl)ethanol (3e), Yield: 42.8%. mp: 76–78°C. 1H NMR (CDCl3) δ: 4.27–4.40 (m, 2H), 5.12–5.14 (m, 1H), 7.06–7.10 (m, 2H), 7.32–7.35 (m, 2H), 8.00 (s, 1H), 8.05 (s, 1H).

1-(4-Chlorophenyl)-2-(1,2,4-triazol-1-yl)ethanol (3f), Yield: 48.6%. mp: 109–111°C. 1H NMR (CDCl3) δ: 4.29 (dd, J=8.2, 14.1 Hz, 1H), 4.39 (dd, J=3.3, 13.9 Hz, 1H), 5.11–5.15 (m, 1H), 7.30 (d, J=8.8 Hz, 2H), 7.36 (d, J=8.8 Hz, 2H). 1H NMR (CDCl3) δ: 4.27–4.40 (m, 2H), 5.12–5.14 (m, 1H), 7.06–7.10 (m, 2H), 7.32–7.35 (m, 2H), 8.00 (s, 1H), 8.05 (s, 1H).

1-(2,4-Dichlorophenyl)-2-(1,2,4-triazol-1-yl)ethanol (3g), Yield: 55.2%. mp: 85–87°C. 1H NMR (CDCl3) δ: 4.23 (dd, J=7.9, 14.1 Hz, 1H), 4.55 (dd, J=2.4, 14.1 Hz, 1H), 5.41–5.43 (m, 1H), 7.29 (dd, J=1.8, 8.4 Hz, 1H), 7.42 (d, J=2.2 Hz, 1H), 7.49 (d, J=8.4 Hz, 1H), 7.98 (s, 1H), 8.07 (s, 1H).

1-(3,4-Dichlorophenyl)-2-(1,2,4-triazol-1-yl)ethanol (3h), Yield: 43.6%. mp: 93–95°C. 1H NMR (CDCl3) δ: 4.23–4.29 (m, 1H), 4.36–4.41 (m, 1H), 5.11 (dd, J=2.7, 8.2 Hz, 1H), 7.20 (dd, J=2.0, 8.2 Hz, 1H), 7.44–7.53 (m, 2H), 7.96 (s, 1H), 8.08 (s, 1H). 1H NMR (CDCl3) δ: 4.38–4.53 (m, 2H), 5.28–5.33 (m, 1H), 7.47–7.53 (m, 2H), 7.83–7.89 (m, 5H), 8.02 (s, 1H), 8.08 (s, 1H).

Preparation of methyl 8-[1-phenyl-2-(1,2,4-triazol-1-yl)ethoxy]octanate (4a), 4a was prepared from 3a by a method as described previously.28 Yield: 44.6%. light yellow oil. 1H NMR (CDCl3) δ: 1.21–1.28 (m, 6H), 1.40–1.42 (m, 2H), 1.56–1.55 (m, 2H), 2.29 (t, J=7.5 Hz, 2H), 3.13–3.16 (m, 1H), 3.32–3.37 (m, 1H), 3.67 (s, 3H), 4.37–4.35 (m, 2H), 4.62 (dd, J=5.3, 7.5 Hz, 1H), 7.30–7.41 (m, 5H), 7.95 (s, 1H), 8.08 (s, 1H). HRMS [M+Na]+: Calcd. For C29H31N3O3Na: 444.2258, Found: 444.2258. Other compounds (4b–4i) were prepared in a similar way by reaction of the corresponding alcohol with methyl 8-bromooctanoate.

Methyl 8-[1-(3-methoxyphenyl)-2-(1,2,4-triazol-1-yl)ethoxy]octanate (4b), Yield: 44.2%, light yellow oil. 1H NMR (CDCl3) δ: 1.21–1.28 (m, 6H), 1.38–1.47 (m, 2H), 1.54–1.63 (m, 2H), 2.30 (dd, J=6.7, J=14.0 Hz, 2H), 3.11–3.17 (m, 1H), 3.34–3.41 (m, 1H), 3.67 (s, 3H), 3.81 (s, 3H), 4.30 (t, J=3.5 Hz, 2H), 4.59 (t, J=6.4 Hz, 1H), 6.82–6.90 (m, 3H), 7.30 (dd, J=5.7, J=9.7 Hz, 1H), 7.95 (s, 1H), 8.09 (s, 1H). HRMS [M+Na]+: Calcd. For C29H31O3Na: 436.1165, Found: 436.1165.

Methyl 8-[1-naphthalen-2-yl-2-(1,2,4-triazol-1-yl)ethoxy]octanate (4l), Yield: 36.2%. light yellow oil. 1H NMR (CDCl3) δ: 1.22–1.28 (m, 6H), 1.48 (t, J=6.6 Hz, 2H), 1.54–1.62 (m, 2H), 2.24–2.35 (m, 2H), 3.12–3.22 (m, 1H), 3.35–3.41 (m, 1H), 3.66 (s, 3H), 4.34–4.44 (m, 2H), 4.79 (dd, J=4.4, 8.1 Hz, 1H), 7.43–7.54 (m, 3H), 7.77–7.89 (m, 4H), 7.96 (s, 1H), 8.11 (s, 1H). HRMS [M+Na]+: Calcd. For C31H33N3O3Na: 448.2106, Found: 448.2106.

3. Biology
Expression and purification of recombinant AOS. The coding region of AOS cDNA that was restricted by the enzymes BamHII
and KpnI was inserted into an E. coli expression vector pQE30 (Qiagen, Valencia, CA, USA). E. coli M15, transformed with this construct, was kindly provided by Prof. E. W. Weiler (Lehrstuhl für Pflanzenphysiologie, Fakultät für Biologie Ruhr-Universität, Germany). Expression and purification of recombinant AOS were performed as described previously.39

In vitro assays for AOS inhibitors. The inhibitory activity of test compounds was evaluated by a method described previously.12 The enzyme reaction mixture contained 50 mM sodium phosphate buffer (pH 7.0, 0.1% Tween 20), enzyme (AOS, 5 nM), and designated concentrations of substrate (13(S)-HPOT) at 25°C. Activity was measured by following the decrease in absorption at 235 nm using a Shimadzu UV3100 spectrophotometer (Shimadzu, Kyoto Japan). An absorption coefficient of 22.8 mM⁻¹ cm⁻¹ was used.

Results and Discussion

In vitro inhibitory activity of synthesized compounds against purified recombinant AOS is shown in Table 1. We used phenyl analogue (4a) as the standard for structure-activity relationship studies. Compound 4a inhibits AOS activity in a dose-dependent manner (data not shown) with an IC₅₀ value of 1.6 ± 0.2 μM. Introduction of a methoxy moiety at position 4 of the phenyl group (4c) slightly reduced the activity of AOS inhibition, with an IC₅₀ value of 2.6 ± 0.7 μM. Moving the methoxy group to position 3 of the phenyl group (4b) markedly reduced the activity with an IC₅₀ value of 22.5 ± 5.7 μM. This result indicates that a methoxy substituent on the phenyl ring may have a negative effect on promoting activity for AOS inhibition. Introduction of a phenyl group at position 4 of the phenyl ring (4d) markedly reduced the activity with an IC₅₀ value of 54.3 ± 5.7 μM. This result suggests that the presence of a bulky biphenyl group weakens the affinity of the molecule to the binding site on AOS. A strong electron-withdraw group of fluorine atom at position 4 of the phenyl moiety (4e) also markedly reduced the activity for AOS inhibition, with an IC₅₀ value of 14.5 ± 3.7 μM, indicating that the electron-withdraw substituent has a negative effect on promoting the inhibitory activity of this synthesized series. Introduction of a chlorine atom to the phenyl at position 4 (4f) slightly enhanced the inhibitory activity with an IC₅₀ value of 1.2 ± 0.7 μM. Introduction of two chlorines to the phenyl ring at positions 2 and 4 (4g) and at positions 3 and 4 (4h) enhanced AOS inhibition with IC₅₀ values of 0.84 ± 0.60 μM and 0.93 ± 0.30 μM, respectively. This result suggests that the substituent of chlorine atom(s) on the phenyl moiety enhanced the inhibition activity of this synthetic series to AOS. Interestingly, the naphthalene analogue (4i) is a more potent inhibitor than 4a, with an IC₅₀ value of 0.75 ± 0.30 μM. Among the 9 analogues synthesized and examined for their AOS inhibitory activities in the present study, compounds 4g and 4h, which have two chlorine atoms on the phenyl moiety, exhibit potent inhibitory activity against AOS. In contrast, the naphthalene analogue is the best inhibitor among this synthetic series.

Comparing JM-8686 with compound 4g, two structural factors were modified in the present study: the imidazole moiety was modified to 1,2,4-triazole, and the heptyl ester was shortened to a methyl ester. Thus, JM-8645 (shown in Fig. 1) is a good analogue of the JM series to discuss the effect of the azole moiety on AOS inhibition, as JM-8645 and compound 4g shared the same chemical structure, except for the azole moiety. We found no significant difference in AOS inhibition between JM-8645 (IC₅₀ = 0.85 ± 0.30 μM) and compound 4g (IC₅₀ = 0.84 ± 0.60 μM). Nevertheless, it is worth mentioning here that triazoles have been widely used as fungicide and plant growth regulators, apparently due to their bioavailability.30 Consequently, triazole analogues synthesized in the present work may exhibit good properties for the regulation of JA biosynthesis in plants. Another structural factor was modified by shortening the length of the ester moiety by introducing the methyl instead of heptyl moiety of JM-8686 in order to improve water solubility. Software was used to calculate the prediction Log P of the compounds of interest.21 As shown in Table 1, the prediction Log P of the compounds synthesized in this work is between 3.38 and 4.98, while JM-8686 is 7.32. This result indicates that the triazoles synthesized in the present work are more water soluble than JM-8686.

We thus identified a new class of AOS inhibitors with triazole moiety. Structure-activity relationship studies revealed that compound 4i with naphthalene moiety is the best AOS inhibitor among this synthetic series, with an IC₅₀ value of 0.75 ± 0.30 μM. We expect that further development and experimental use of AOS inhibitors may provide new methods to control JA biosynthesis in plants.

### Table 1. Effect of R substitution on the AOS inhibition of synthesized compounds

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*All the data shown were determined independently three times.*

*Values were calculated using ALOGPS 2.1.*

*IC₅₀ values of JM-8686 and JM-8645 were adopted from previously reported results.*
Acknowledgment

We would like to thank Prof. E. W. Weiler (Lehrstuhl für Pflanzenphysiologie, Ruhr-Universität, Bochum, Germany) for his generous gift of the Arabidopsis AOS clone.

References

ジャスモン酸生合成に関わるアレンオキシド合成酵素
（CYP74A）を阻害する新規トリアゾール類の合成

王 敬銘，中居宏太，山田和弘，吉澤紘子

アレンオキシド合成酵素（CYP74A）はジャスモン酸の生合成酵素である。本研究では、アレンオキシド合成酵素阻害剤を開発するために、新規トリアゾール系化合物を合成した。合成した化合物のアレンオキシド合成酵素阻害活性は、大腸菌で調製・精製した組み換え型酵素を用いて検討した。構造活性相関解析研究の結果、8-[1-(ナフタレン-2-イル)-2-(1,2,4-トリアゾール-1-イル)エトキシ]オクタン酸メチルエステル(4i) およびメチル8-[1-(2,4-ジクロロフェニル)-2-(1,2,4-トリアゾール-1-イル)エトキシ]オクタン酸メチルエステル(4g) が強いアレンオキシド合成酵素阻害活性を示し、そのIC50が0.75±0.3および0.84±0.6μMであった。