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Synthesis and Fungicidal Activity of Macrolactams and Macrolactones with an Oxime Ether Side Chain

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Three series of novel macrolactams and macrolactones — 12-alkoxyimino-tetradecanlactam, 12-alkoxyiminopentadecanlactam, and 12-alkoxyiminodecanlactone derivatives (**7A**, **7B**, and **7C**) — were synthesized from corresponding 12-oxomacrolactams and 12-oxomacrolactone. Their structures were confirmed by ^{1}H NMR and elemental analysis. The *Z* and *E* isomers of **7A** and **7B** were separated, and their configurations were determined by ^{1}H NMR. These compounds showed fair to excellent fungicidal activities against *Rhizoctonia solani* Kühn. It is interesting that the *Z* and *E* isomers of most of the compounds have quite different fungicidal activities. The fact that the compounds have a gradual increase of fungicidal activity in the order of **7A**, **7C**, and **7B** indicated that the macrocyclic derivatives with a hydrogen-bonding acceptor (=N−O−) and a hydrogen-bonding donor (−CONH−) on the ring, and a three methylenes distance ($CH_2CH_2CH_2$) between these two functional groups, exhibited the best fungicidal activity. The bioassay also showed that **7B** not only has good fungicidal activity but also may have a broad spectrum of fungicidal activities.

KEYWORDS: Macrolactam; macrolactone; synthesis; fungicidal activity; fungicide; pesticide

1. INTRODUCTION

Pesticides play a key role in our life, not only for crop protection in agriculture, but also for human health. However, the unrestricted use of highly toxic pesticides over several decades has resulted in negative effects on the environment and poisoning of nontargeted species. To reduce the negative impacts of the pesticides, new compounds with high efficacy and selectivity against target species are desirable. Imitating the chemistry of biologically active natural products is one approach for developing such pesticides. Macrolactams and macrolactones are a large family of natural products that are isolated from a number of sources, including marine sponges, marine bacteria, and terrestrial bacteria. This class of compounds has attracted considerable interest of chemists and the natural products community because they display a diverse range of biological activities including antitumor, antifungal, cytotoxicity, antimicrobial activities, and inhibition of superoxide generation. Several examples include rifamycin S (*1*), a potent inhibitor of DNA-dependent RNA polymerase (RNAP) of *E.* coli and other prokaryotes, maytansine (*2*), which shows significant inhibitory activity in vitro against cells derived from human carcinoma of the nasopharynx (KB) and against five standard animal tumor systems, and discodermide (*3*), maltophilin (*4*), and xanthobaccin A (*5*), which show antifungal activity. It is also well-known that avermectins, obtained from the fermentation broth of *Streptomyces avermitilis*, are unique, naturally occurring macrolactones (*6*) with a broad spectrum of anthelmintic and insecticidal activities (*7*). In the search for potential pesticides, more than ten series of cyclododecane derivatives have been synthesized, and their biological activities have been evaluated in our laboratory. Among them, 2-monosubstituted cyclododecanone derivatives, such as **1** (*8*), **2** (*9*), or 2-monosubstituted cyclododecanone oxime derivatives, such as **3** (*10*), were found to be active against some important agricultural fungi species (**Figure 1**). On the contrary, monosubstituted cyclododecane derivatives, for example, **4**, **5**, and **6**, were found to be completely ineffective as fungicides (unpublished results).

We postulate that the coexistence of two polarizable groups on the cyclododecane ring is necessary for fungicidal activity of the cyclododecanone class of compounds. Therefore, our approach to improving their fungicidal activity through structural derivation is to use natural macrolactam or marolactone as a template (the −CONH− or –COO− moiety acts as one polarizable group). Thus, a series of 12-alkoxyiminotetradecanlactams (**7A**) were synthesized. It is known that there are two geometric isomers about the C=N bond of oxime deriva-

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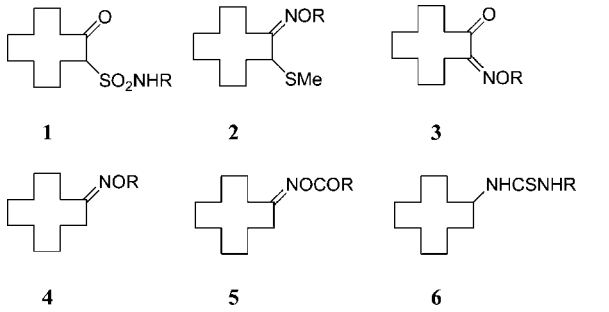
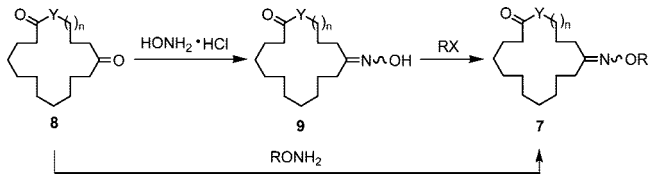


Figure 1. Compounds **1**−**6**.

Scheme 1. Synthetic route of the compounds **7**



tives and that they may have different biological activities (*11, 12*). Therefore, *Z* and *E* isomers of compounds **7A** were separated, and their fungicidal activities against cotton soreshin (*Rhizoctonia solani* Kühn), an important agricultural fungus species, were evaluated. At the same time, their pentadecanlactam and pentadecanlactone analogous (**7B** and **7C**) were also synthesized to study the effect of lactam and lactone rings, as well as the distance between the oxime and amide/ester functional groups on their fungicidal activities. Then, a very active representative of **7B** was screened against 13 important agricultural fungi. The synthetic route of the compounds **7** is shown in **Scheme 1**.

Compounds **7** were prepared from compounds **8** (*13–15*) by reaction with hydroxylamine hydrochloride to give compounds **9**, which were then alkylated using alkyl or benzyl halides (Procedure 1) or directly from compounds **8** by reaction with alkoxyamines (Procedure 2).

2. MATERIALS AND METHODS

2.1. General. NMR spectra were recorded in CD_3COCD_3 or $CDCl_3$ with a Bruker DPX300 spectrometer, using TMS as internal standard; elemental analysis was performed by the analytical center at the Institute of Chemistry (Beijing), Chinese Academy of Science; melting points were measured on a Yanagimoto melting-point apparatus and are uncorrected. The solvents and reagents were used as received or were dried prior to use as needed.

2.2. Chemical Synthesis. *2.2.1. General Procedure for the Synthesis of Compounds* **9.** To a stirred solution of compound **8** (0.01 mol) and sodium carbonate (1.06 g, 0.01 mol) in 20 mL of methanol, a solution of hydroxylamine hydrochloride (0.76 g, 0.011 mol) in 5 mL of water was added dropwise. After the mixture was refluxed for 4 h, cold water was added. Filtration gave a mixture of *Z* and *E* isomers of **9**. **9A**: yield: 90%, m.p.:152–154°; **9B**: yield: 87%, m.p.:162–164°; **9C**: yield: 93%, m.p.: 57∼62°. **9A, 9B**, and **9C** were used in the next step without purification.

2.2.2. General Procedure for the Synthesis of Compounds **7** *(Procedure 1) (16).* A mixture of compound **9** (2 mmol) and sodium hydride (0.10 g, 2.2 mmol) in anhydrous DMSO was stirred at room temperature for 1.5 h, an alkyl halide (2.2 mmol) was then added dropwise, and the mixture was stirred for 6 h at room temperature. The excess sodium hydride was destroyed by carefully adding 20 mL water, and then the mixture was extracted with methylene chloride (3 × 20 mL). The combined organic layer was washed with brine, dried over sodium sulfate, and then concentrated under vacuum to give a crude product. Further purification on silica gel column chromatography with methylene chloride and ethyl acetate gave *Z* and *E* isomers of the target compounds, and the minor mixture in the order of *Z* isomer (**1**), mixture, and then *E* isomer (**2**). The physical and elemental data of the target compounds are given in **Table 1** (in which the total yields of the *Z* and *E* isomers are given), and the ^{1}H NMR data is presented in **Table 2**.

2.2.3. General Procedure for the Synthesis of Compounds **7** *(Procedure 2). 2.2.3.1. Synthesis of Alkoxyamines.* A solution of triethylamine (1.05 g, 10.3 mmol) in DMF (10 mL) was added to a solution of alkyl chloride (10 mmol) and N-hydroxy phthalimide (9.3 mmol) in DMF (12 mL) at 0–5 °C. After stirring for 3 days, the mixture was poured into a 10% hydrochloric acid solution (60 mL), and the resulting mixture was then filtered. The solid was dissolved in ethanol (10 mL), and a solution of hydrazine hydrate (10 mmol) in ethanol was added. The mixture was refluxed for 2 h, cooled, and then filtered. The filter cake was washed with ethanol. The combined filtrates were saturated with gaseous hydrochloric acid, and then ether was added until no further precipitate was observed. Filtration gave a white solid (alkoxyamine hydrochloride) that was used in the next step without purification.

2.2.3.2. Synthesis of Compounds **7.** A mixture of compounds **8** (2.5 mmol) and alkoxyamine hydrochloride (4 mmol) in pyridine (10 mL) was stirred for 16 h, concentrated to 2 mL at reduced pressure, poured into water (20 mL), and then extracted with methylene chloride (3 × 20 mL). The combined organic extracts were washed with dilute hydrochloride acid, water, and brine successively, dried over sodium sulfate, and evaporated to give a white solid, which was purified and separated by the same procedure as in Section 2.2.2.

2.3. Bioassay of Fungicidal Activities. *2.3.1. Method.* Fungicidal activities of compounds **7** against *Rhizoctonia solani* Kühn were evaluated using the mycelium growth rate test (*17*).

2.3.2. Fungicidal Activities of Compounds **7.** Inhibition rate of compounds **7** against *Rhizoctonia solani* Kühn at the concentrations of 100, 50, 25, 12.5 and 6.25 μg/mL was first determined. Then, EC_{50} values were estimated using logistic analysis (*18*). As a control, fungicidal activity of the commercial fungicide carbendazim against the above-mentioned fungi was evaluated at the same condition. The results are shown in **Table 3**.

2.3.3. Spectrum of Fungicidal Activities of Compound **7B3.** Inhibition rate of compounds **7B3** (a mixture of *Z* and *E* isomers) against pear black spot (*Alternaria kikuchiana*), tomato southern blight (*Phyllospicpa physaleos* Sacc), cotton rhizoctonia rot (*Rhizoctonia solani* Kühn), cucumber gray mold (*Botrytis cinerea* Pers), asparagus stem blight (*Phomopsis asparagi* Sacc), apple ring spot (*Physalospora piricola* Nose), cotton verticillium wilt (*Vercicillium alboatrum* Reinke et Berthold), cucumber anthracnose (*Colletotrichum lagenarium*), cotton fusarium wilt (*Fusarium vasinfectum* Atkimson), cotton damping-off (*Pythium aphanibermatum (Eds.)* Fipzp), tomato early blight (*Alternaria solani* Jones et Grout), tomato leaf mold (*Cladosporium fulvum* Cooke), peppers fruit rot (*Phytophthora capsici* Len) at concentrations of 100, 50, 25, 12.5, and 6.25 μg/mL was determined and then EC_{50} values were estimated. The results were shown in **Table 4**.

3. RESULTS AND DISCUSSION

3.1. Geometric Isomers of Compounds 7. The *Z* and *E* isomers of compounds **7A** and **7B** (**Figure 2**) were isolated by column chromatography and were distinguished based on the ^{1}H NMR features of the compounds.

In the case of the *Z* isomers, the electronegative oxygen atom on the side chain is closer to 13-CH_2 and further away from the 11-CH_2. The resonance lines of 13-CH_2 would be expected to shift downfield and that of 11-CH_2 shifted upfield from the corresponding CH_2 of the *E* isomers. Taking **7A3** as an example, the resonance peak corresponding to 11-CH_2 displayed a triplet at δ 2.2, and that of 13-CH_2 was a multiplet at δ 2.52–2.57 in the spectrum of **7A3** (**1**), but the corresponding two CH_2 in **7A3** (**2**) displayed a multiplet due to the downfield shift of the 11-CH_2 peak and the upfield shift of the 13-CH_2 peak. Therefore, **7A3** (**1**) is the *Z* isomer and **7A3** (**2**) is the *E* isomer. The *Z* and *E* isomers of compounds **7C** could not be separated because of an insufficient polarity difference.

Table 1. Physical and Elemental Data of Compounds 7

compd No.	R	configuration	mp (°)	yield (%)	elemental analysis C (calcd)	H (calcd)	N (calcd)
7A-1(1)	Me	*Z*	107–108	90[b] (50[a])	67.43 (67.13)	10.55 (10.52)	10.42 (10.44)
7A-1(2)	Me	*E*	71–72		67.30 (67.13)	10.42 (10.52)	10.35 (10.44)
7A-2(1)	ethyl	*Z*	112–113	90[b]	68.46 (68.04)	10.77 (10.71)	10.11 (9.92)
7A-2(2)	ethyl	*E*	72–73		67.67 (68.04)	10.72 (10.71)	9.75 (9.92)
7A-3(1)	*n*-propyl	*Z*	82	93[b]	68.87 (68.88)	10.91 (10.88)	9.46 (9.45)
7A-3(2)	*n*-propyl	*E*	68		68.88 (68.88)	10.83 (10.88)	9.51 (9.45)
7A-4(1)	allyl	*Z*	90–91	92[b]	69.39 (69.35)	10.23 (10.27)	9.58 (9.51)
7A-4(2)	allyl	*E*	74–75		69.33 (69.35)	10.29 (10.27)	9.41 (9.51)
7A-5(1)	*n*-butyl	*Z*	89–90	98[b]	69.62 (69.63)	11.07 (11.04)	9.13 (9.02)
7A-5(2)	*n*-butyl	*E*	54–55		69.58 (69.63)	11.07 (11.04)	9.08 (9.02)
7A-6(1)	i-butyl	*Z*	93–94	92[b]	69.66 (69.63)	11.08 (11.04)	9.01 (9.02)
7A-6(2)	i-butyl	*E*	71–72		69.61 (69.63)	10.89 (11.04)	8.98 (9.02)
7A-7(1)	n-heptal	*Z*	74–75	96[b]	71.52 (71.54)	11.33 (11.44)	7.88 (7.95)
7A-7(2)	n-heptal	*E*	55–56.5		71.51 (71.54)	11.49 (11.44)	8.01 (7.95)
7A–8(1)	*n*-tetradecyl	*Z*	73.5–74	96[b]	74.61 (74.61)	11.92 (12.08)	6.22 (6.21)
7A–8(2)	*n*-tetradecyl	*E*	68–68.5		74.75 (74.61)	12.13 (12.08)	6.33 (6.21)
7A-9(1)	*n*-hexadecyl	*Z*	76–77	97[b]	75.33 (75.26)	12.20 (12.21)	5.95 (5.85)
7A–9(2)	*n*-hexadecyl	*E*	69–70		75.22 (75.26)	12.14 (12.21)	5.92 (5.85)
7A1–0(1)	benzyl	*Z*	118–119	92[b]	73.45 (73.22)	9.48 (9.36)	8.28 (8.13)
7A1–0(2)	benzyl	*E*	97–99		73.24 (73.22)	9.37 (9.36)	8.47 (8.13)
7A–11(1)	4-methylbenzyl	*Z*	128–130	94[b]	73.65 (73.70)	9.54 (9.56)	7.93 (7.81)
7A–11(2)	4-methylbenzyl	*E*	97–98		73.74 (73.70)	9.57 (9.56)	7.68 (7.81)
7A–12(1)	4-fluorobenzyl	*Z*	118–119	97[b]	69.86 (69.58)	8.64 (8.62)	7.75 (7.73)
7A–12(2)	4-fluorobenzyl	*E*	92–93		69.41 (69.58)	8.62 (8.62)	7.83 (7.73)
7A–13(1)	4-chlorobenzyl	*Z*	131.5–132	96[b]	66.56 (66.56)	8.29 (8.25)	7.36 (7.39)
7A–13(2)	4-chlorobenzyl	*E*	110–111		66.63 (66.56)	8.33 (8.25)	7.42 (7.39)
7A–14(1)	4-nitrobenzyl	*Z*	148–149	90[b]	64.71 (64.76)	8.08 (8.02)	10.75 (10.79)
7A–14(2)	4-nitrobenzyl	*E*	134–135		64.77 (64.76	7.97 (8.02)	10.69 (10.79)
7A–15(1)	2-chloro-6-fluorobenzyl	*Z*	145–146	90[b]	63.47 (63.54)	7.54 (7.62)	7.02 (7.06)
7A–15(2)	2-chloro-6-fluorobenzyl	*E*	93–94		63.70 (63.54)	7.73 (7.62)	7.05 (7.06)
7A–16(1)	2,4-dichlorobenzyl	*Z*	131–132	91[b]	60.91 (61.02)	7.30 (7.31)	6.73 (6.78)
7A–16(2)	2,4-dichlorobenzyl	*E*	129–130		61.01 (61.02)	7.37 (7.31)	6.75 (6.78)
7A–17(1)	3-pyridylmethyl	*Z*	108–110	95[b]	69.33 (69.53)	9.03 (9.04)	11.83 (12.16)
7A–17(2)	3-pyridylmethyl	*E*	81–82		69.42 (69.53)	8.79 (9.04)	12.31 (12.16)
7B-2(1)	ethyl	*Z*	89–90	67[a]	69.43 (68.88)	11.07 (10.88)	9.24 (9.45)
7B-2(2)	ethyl	*E*	118–119		68.67 (68.88)	10.76 (10.88)	9.04 (9.45)
7B-3(1)	*n*-propyl	*Z*	107–108	71[a]	70.14 (69.63)	11.31 (11.04)	9.04 (9.02)
7B-3(2)	*n*-propyl	*E*	92–93.5		69.71 (69.63)	10.98 (11.04)	9.03 (9.02)
7B–4(1)	allyl	*Z*	90–92	75[a]	70.40 (70.09)	10.54 (10.46)	8.86 (9.08)
7B–4(2)	allyl	*E*	96–97		70.13 (70.09)	10.48 (10.46)	8.77 (9.08)
7B-5(1)	*n*-butyl	*Z*	79–80.5	71[a]	70.65 (70.32)	11.31 (11.18)	8.68 (8.63)
7B-5(2)	*n*-butyl	*E*	70–71		69.08 (70.32)	11.03 (11.18)	8.58 (8.63)
7B–7(1)	n-heptal	*Z*	64–65	73[a]	72.19 (72.08)	11.94 (11.55)	7.42 (7.64)
7B–7(2)	n-heptal	*E*	69–71		71.84 (72.08)	11.63 (11.55)	7.57 (7.64)
7B–9(1)	*n*-hexadecyl	*Z*	80–81	80[a]	75.66 (75.55)	12.46 (12.27)	5.50 (5.68)
7B–9(2)	*n*-hexadecyl	*E*	82–83.5		75.39 (75.55)	12.43 (12.27)	5.65 (5.68)
7B–10(1)	benzyl	*Z*	80–81	80[a]	73.80 (73.70)	9.70 (9.56)	7.70 (7.81)
7B–10(2)	benzyl	*E*	86–87		73.69 (73.70)	9.55 (9.56)	7.87 (7.81)
7B–13(1)	4-chlorobenzyl	*Z*	114–115	88[a]	67.26 (67.24)	8.29 (8.46)	6.96 (7.13)
7B–13(2)	4-chlorobenzyl	*E*	116–117		67.15 (67.24)	8.47 (8.46)	6.95 (7.13)
7B–15(1)	2-chloro-6-fluorobenzyl	*Z*	123–124	82[a]	64.57 (64.30)	7.91 (7.85)	6.60 (6.82)
7B–15(2)	2-chloro-6-fluorobenzyl	*E*	136–137		64.26 (64.30)	7.90 (7.85)	6.69 (6.82)
7C-3	n-propyl	*Z*+*E*	viscous liquid	40[a]	69.53 (69.41)	10.61 (10.68)	4.42 (4.50)
7-C4	allyl	*Z*+*E*	viscous liquid	45[a]	69.84 (69.86)	9.93 (10.10)	4.66 (4.53)
7-C5	n-butyl	*Z*+*E*	viscous liquid	50[a]	69.70 (70.11)	10.45 (10.84)	4.00 (4.30)
7-C7	n-heptal	*Z*+*E*	viscous liquid	42[a]	72.26 (71.89)	11.02 (11.24)	3.59 (3.81)
7-C9	n-hexadecyl	*Z*+*E*	viscous liquid	55[a]	75.33 (75.40)	11.51 (12.04)	2.60 (2.84)
7C–10	benzyl	*Z*+*E*	viscous liquid	45[a]	73.76 (73.50)	9.70 (9.25)	3.61 (3.90)
7C–13	4-chlorobenzyl	*Z*+*E*	viscous liquid	46[a]	67.07 (67.07)	8.48 (8.19)	3.69 (3.56)
7C–15	2-chloro-6-fluorobenzyl	*Z*+*E*	viscous liquid	51[a]	63.74 (64.14)	7.58 (7.59)	3.23 (3.40)

[a] Procedure 1. [b] Procedure 2.

3.2. Fungicidal Activity. As shown in **Table 3**, compounds **7A** have fair to good fungicidal activity against *Rhizoctonia solani* Kühn. Among them, compounds **7A3** (**2**), **7A5** (**2**), and **7A10** (**2**), the EC_{50} values of which were 9.11, 7.21, and 7.24 μg/mL, respectively, displayed the highest fungicidal activity, but they were inferior to the commercial fungicide carbendazin. In general, the following structure–activity relationship in compounds **7A** was observed: (1) the compounds with a C3−C4 straight chain alkyl and benzyl without substituents have better fungicidal activity; (2) *E* isomers are more active than Z isomers, except for the individual compounds **7A14**. The replacement of the tetradecanlactam ring with a pentadecanlactam ring (compounds **7B**) results in significantly improved fungicidal activity. The EC_{50} values of compounds **7B3(2)**, **7B5(1)**, **7B5(2)**, and **7B15(1)** were 3.62, 3.97, 2.34, and 2.34 μg/mL, respectively, and are

Table 2. ^{1}H NMR Data of Compounds **7** ($CDCl_3$, δ)

compds No.	11-CH_2	13-CH_2	others
7A-1(1)	2.14–2.24 (4H, m) (+2-CH_2)	2.51–2.55 (2H, m)	1.23–1.42 (12H, m), 1.57–1.72 (4H, m), 3.44–3.50 (2H, m), 3.87 (3H, s), 6.14 (1H, br s)
7A-1(2)	2.31 (2H, t, J = 6.5 Hz)	2.38 (2H, t, J = 5.4 Hz)	1.23–1.37 (12H, m), 1.51–1.60 (2H, m), 1.60–1.66 (2H, m), 2.17–2.22 (2H, m), 3.53–3.49 (2H, m), 3.85 (3H, s), 6.25 (1H, br, s)
7A-2(1)	2.23 (2H, t, J = 6.9 Hz)	2.52–2.56 (2H, m)	1.56–1.70 (4H, m), 1.23–1.41 (15H, m), 2.12–2.16 (2H, m) 3.43–3.50 (2H, m), 4.13 (2H, q, J = 6.9 Hz), 6.26 (1H, br)
7A-2(2)	2.30–2.40 (4H, m)		1.24–1.30 (15H, m), 1.54–1.68 (4H, m), 2.17–2.21 (2H, m), 3.54–3.59 (2H, m), 4.10 (2H, q, J = 7.0 Hz,), 6.28 (1H, br)
7A-3(1)	2.22 (2H, t, J = 7.0 Hz)	2.52–2.57 (2H, m)	0.97 (3H, t, J = 7.4 Hz), 1.20–1.42 (12H, m), 1.50–1.78 (6H, m), 2.10–2.17 (2H, m), 3.43–3.50 (2H, m), 4.03 (2H, t, J = 6.8 Hz), 6.23 (1H, br)
7A-3(2)	2.30–2.40 (4H, m)		0.98 (3H, t, J = 7.4 Hz), 1.23–1.29 (12H, m), 1.51–1.75 (6H, m), 2.15–2.21 (2H, m), 3.50–3.60 (2H, m), 4.00 (2H, t, J = 6.6 Hz), 6.26 (1H, br)
7A-4(1)	2.21–2.26 (2H, m)	2.54–2.59 (2H, m)	1.23–1.39 (12H, m), 1.58–1.72 (4H, m), 2.12–2.16 (2H, m), 3.44–3.50 (2H, m), 4.55–4.59 (2H, m), 5.21–5.37 (2H, m), 5.99–6.09 (1H, m), 6.29 (1H, br)
7A-4(2)	2.32–2.39 (4H, m)		1.26–1.35 (12H, m), 1.55–1.68 (4H, m), 2.13–2.18 (2H, m), 3.52–3.58 (2H, m), 4.54–4.59 (2H, m), 5.21–5.37 (2H, m), 5.95–6.08 (1H, m), 6.30 (1H, br, s)
7A-5(1)	2.22 (2H, t, J = 6.9 Hz)	2.51–2.56 (2H, m)	0.96 (3H, t, J = 7.4 Hz), 1.20–1.46 (14H, m), 1.57–1.72 (6H, m), 2.12–2.17 (2H, m), 3.43–3.50 (2H, m), 4.07 (2H, t, J = 6.7 Hz), 6.24 (1H, br)
7A-5(2)	2.29–2.39 (4H, m)		0.96 (3H, t, J = 7.3 Hz), 1.25–1.57 (14H, m), 1.57–1.70 (6H, m), 2.16–2.21 (2H, m), 3.53–3.59 (2H, m), 4.05 (2H, t, J = 6.45 Hz), 6.29 (1H, br)
7A–6(1)	2.22 (2H, t, J = 7.0 Hz)	2.53–2.57 (2H, m)	0.96 (6H, d, J = 6.7 Hz), 1.24–1.39 (12H, m) 1.54–1.70 (4H, m), 1.95–2.05 (1H, m), 2.12–2.17 (2H, m), 3.45–3.51 (2H, m), 3.85 (2H, d, J = 6.7 Hz), 6.18 (1H, br)
7A-6(2)	2.31–2.40 (4H, m)		0.96 (6H, d, J = 6.7 Hz), 1.26–1.35 (12H, m), 1.55–1.70 (4H, m), 1.93–2.03 (1H, m), 2.15–2.20 (2H, m), 3.53–3.59 (2H, m), 3.82 (2H, d, J = 6.6 Hz), 6.26 (1H, br)
7A-7(1)	2.22 (2H, t, J = 6.9 Hz)	2.51–2.56 (2H, m)	0.86–0.91 (3H, t, J = 6.7), 1.23–1.40 (20H, m), 1.59–1.73 (6H, m), 2.12–2.17 (2H, m), 3.43–3.49 (2H, m), 4.06 (2H, t, J = 6.8 Hz), 6.23 (1H, br)
7A-7(2)	2.29–2.39 (4H, m)		0.87–0.91 (3H, t, J = 6.8), 1.26–1.41 (26H, m), 2.16–2.21 (2H, m), 3.53–3.59 (2H, m), 4.03 (2H, t, J = 6.6 Hz), 6.27 (1H, br)
7A-8(1)	2.22 (2H, t, J = 6.9 Hz)	2.52–2.56 (2H, m)	0.88 (3H, t, J = 6.7 Hz), 1.20–1.41 (34H, m), 1.55–1.73 (6H, m), 2.13–2.17 (2H, m), 3.43–3.49 (2H, m), 4.05 (2H, t, J = 6.8 Hz), 6.22 (1H, br)
7A-8(2)	2.29–2.39 (4H, m)		0.88 (3H, t, J = 6.9 Hz), 1.26–1.40 (34H, m), 1.50–1.78 (6H, m), 2.16–2.20 (2H, m), 3.53–3.59 (2H, m), 4.03 (2H, t, J = 6.53 Hz), 6.26 (1H, br)
7A-9(1)	2.22 (2H, t, J = 6.92 Hz)	2.51–2.56 (2H, m)	0.88 (3H, t, J = 6.7 Hz), 1.20–1.42 (38H, m), 1.55–1.72 (6H, m), 2.10–2.16 (2H, m), 3.43–3.49 (2H, m), 4.05 (2H, t, J = 6.81 Hz), 6.22 (1H, br)
7A-9(2)	2.30–2.39 (4H, m)		0.88 (3H, t, J = 6.8 Hz), 1.26–1.40 (38H, m), 1.50–1.71 (6H, m), 2.16–2.21 (2H, m), 3.53–3.59 (2H, m), 4.03 (2H, t, J = 6.53 Hz), 6.27 (1H, br)
7A-10(1)	2.20 (2H, t, J = 6.9 Hz)	2.53–2.57 (2H, m)	1.18–1.40 (12H, m), 1.54–1.65 (4H, m), 1.91–1.95 (2H, m), 3.40–3.46 (2H, m), 5.09 (2H, s), 5.98 (1H, br), 7.26–7.42 (5H, m)
7A-10(2)	2.28–2.36 (4H, m)		1.08–1.20 (12H, m), 1.39–1.58 (4H, m), 1.84–1.90 (2H, m), 3.40–3.52 (2H, m), 5.05 (2H, s), 5.82 (1H, br), 7.26–7.41 (5H, m)
7A-11(1)	2.22 (2H, t, J = 6.8 Hz)	2.51–2.56 (2H, m)	1.16–1.34 (12H, m), 1.55–1.63 (4H, m), 1.89–1.92 (2H, m), 2.35 (3H, s), 3.38–3.44 (2H, m), 5.04 (2H, s) 5.99 (1H, br), 7.18 (2H, d, J = 7.5 Hz), 7.24–7.31 (2H, m)
7A-11(2)	2.26–2.34 (4H, m)		1.06–1.26 (12H, m), 1.38–1.45 (2H, m), 1.50–1.56 (2H, m), 1.82–1.86 (2H, m), 2.35 (3H, s), 3.45–3.51 (2H, m), 5.00 (2H, s), 5.80 (1H, br), 7.2 (2H, d, J = 7.7 Hz),7.26–7.31 (2H, m)
7A-12(1)	2.21 (2H, t, J = 7.0 Hz)	2.52–2.56 (2H, m)	1.15–1.39 (12H, m), 1.54–1.66 (4H, m), 1.95–1.99 (2H, m), 3.40–3.46 (2H, m), 5.04 (2H, s), 5.94 (1H, br), 7.34–7.40 (2H, m), 7.02–7.09 (2H, m)
7A-12(2)	2.29–2.35 (4H, m)		1.11–1.29 (12H, m), 1.44–1.59 (4H, m), 1.90–1.95 (2H, m), 3.47–3.53 (2H, m), 5.01 (2H, s), 5.81 (1H, br), 7.02–7.10 (2H, m), 7.33–7.39 (2H, m)
7A-13(1)	2.21 (2H, t, J = 7.0 Hz)	2.52–2.56 (2H, m)	1.15–1.38 (12H, m), 1.55–1.67 (4H, m), 1.96–2.05 (2H, m), 3.41–3.47 (2H, m), 5.04 (2H, s), 5.75 (1H, br), 7.33 (4H, s)

Table 2. Continued

compds No.	11-CH_2	13-CH_2	others
7A–13(2)	2.29–2.35 (4H, m)		1.11–1.28 (12H, m), 1.42–1.60 (4H, m), 1.88–1.93 (2H, m), 3.45–3.51 (2H, m), 5.00 (2H, s), 5.75 (1H, br), 7.33 (4H, s)
7A–14(1)	2.21 (2H, t, J = 7.3 Hz)	2.56–2.60 (2H, m)	1.23–1.37 (12H, m), 1.53–1.66 (4H, m), 2.04–2.10 (2H, m), 3.48–3.54 (2H, m), 5.17 (2H, s), 5.84 (1H, br), 7.51–7.55 (2H, m), 8.20–8.25 (2H, m)
7A–14(2)	2.34–2.40 (4H, m)		1.14–1.25 (12H, m), 1.43–1.60 (4H, m), 1.92–2.05 (2H, m), 3.47–3.52 (2H, m), 5.16 (2H, s), 5.77 (1H, br), 7.53–7.57 (2H, m), 8.22–8.26 (2H, m)
7A–15(1)	2.20 (2H, t, J = 6.7 Hz)	2.51–2.56 (2H, m)	1.10–1.30 (12H, m), 1.56–1.65 (4H, m), 2.03–2.07 (2H, m), 3.38–3.44 (2H, m), 5.25 (2H, d, J_{H-F} = 1.9 Hz), 5.94 (1H, br), 7.00–7.07 (1H, m), 7.20–7.32 (2H, m)
7A–15(2)	2.27–2.32 (4H, m)		1.00–1.24 (12H, m), 1.43–1.60 (4H, m), 2.02–2.08 (2H, m), 3.48–3.55 (2H, m), 5.26 (2H, d, J_{H-F} = 1.9 Hz), 6.14 (1H, br), 7.20–7.30 (2H, m), 7.01–7.07 (1H, m)
7A–16(1)	2.21 (2H, t, J = 7.0 Hz)	2.55–2.59 (2H, m)	1.18–1.36 (12H, m), 1.54–1.66 (4H, m), 2.04–2.07 (2H, m), 3.44–3.50 (2H, m), 5.14 (2H, s), 5.88 (1H, br), 7.37–7.42 (2H, m), 7.23–7.27 (1H, m)
7A–16(2)	2.31–2.36 (4H, m)		1.11–1.28 (12H, m), 1.44–1.57 (4H, m), 1.97–2.05 (2H, m), 3.47–3.54 (2H, m), 5.13 (2H, s), 5.88 (1H, br), 7.37–7.43 (2H, m), 7.24–7.28 (1H, m)
7A–17(1)	2.21 (2H, t, J = 7.1 Hz)	2.54–2.57 (2H, m)	1.13–1.40 (12H, m), 1.55–1.66 (4H, m), 2.00–2.05 (2H, m), 3.42–3.51 (2H, m), 5.10 (2H, s), 5.94 (1H, br), 7.27.7.33 (1H, m), 7.71–7.74 (1H, m), 8.57–8.65 (2H, m)
7A–17(2)	2.31–2.36 (4H, m)		1.12–1.61 (16 h, m), 1.97–2.05 (2H, m), 3.48–3.54 (2H, m), 5.07 (2H, s), 5.84 (1H, br), 7.27–7.34 (1H, m), 7.72 (1H, d, J = 7.8 Hz), 8.58–8.66 (2H, m)
7B–2(1)	2.08–2.17 (m, 4H) (+2- CH_2)	2.27–2.33 (m, 2H)	1.17 (t, J = 7.2 Hz, 3H), 1.28–1.35 (m, 12H), 1.43–1.50 (m, 2H), 1.60–1.71 (m, 4H), 3.20–3.26 (m, 2H), 3.98 (q, J = 7.2 Hz, 2H), 7.23 (s, 1H)
7B–2(2)	2.13–2.19 (m, 4H) (+2- CH_2)	2.22–2.29 (m, 2H)	1.17 (t, J = 7.2 Hz, 3H), 1.20∼1.38 (m, 12H), 1.43–1.50 (m, 2H), 1.60–1.72 (m,4H), 3.23–3.29 (m, 2H), 3.98 (q, J = 7.2 Hz, 2H), 7.23 (s, 1H)
7B–3(1)	2.08–2.17 (m, 4H) (+2- CH_2)	2.28–2.34 (m, 2H)	0.89 (t, J = 7.5 Hz, 3H), 1.25∼1.34 (m, 12H), 1.37–1.50 (m, 2H), 1.55–1.71 (m, 6H), 3.20–3.26 (m, 2H), 3.90 (t, J = 6.3 Hz, 2H), 7.22 (s, 1H)
7B–3(2)	2.13–2.22 (m, 4H) (+2- CH_2)	2.25–2.30 (m, 2H)	0.89 (t, J = 7.5 Hz, 3H), 1.24∼1.33 (m, 12H), 1.49–1.72 (m, 8H), 3.23–3.29 (m, 2H), 3.89 (t, J = 6.3 Hz, 2H), 7.22 (s, 1H)
7B–4(1)	2.06–2.10 (m, 4H) (+2- CH_2)	2.28–2.32 (m, 2H)	1.21–1.78 (m, 20H), 3.19–3.29 (m, 2H), 4.45–4.48 (m, 2H), 5.10–5.15 (m, 1H), 5.20–5.27 (m, 1H), 5.91–6.03 (m, 1H), 7.25 (s, 1H)
7B–4(2)	2.10–2.20 (m, 4H) (+2- CH_2)	2.23–2.32 (m, 2H)	1.21–1.78 (m, 20H), 3.21–3.31 (m, 2H), 4.45–4.48 (m, 2H), 5.09–5.14 (m, 1H), 5.20–5.27 (m, 1H), 5.90–6.03 (m, 1H), 7.17 (s, 1H)
7B–5(1)	2.04–2.14 (m, 4H) (+2- CH_2)	2.16–2.33 (m, 2H)	0.91 (t, J = 7.2 Hz, 3H), 1.33–1.72 (m, 24H), 3.20–3.26 (m, 2H), 3.95 (t, J = 6.0 Hz, 3H), 7.20 (s, 1H)
7B–5(2)	2.13–2.19 (m, 4H) (+2- CH_2)	2.21–2.29 (m, 2H)	0.91 (t, J = 7.2 Hz, 3H), 1.33–1.72 (m, 24H), 3.23–3.29 (m, 2H), 3.94 (t, J = 6.6 Hz, 3H), 7.20 (s, 1H)
7B–7(1)	2.08–2.18 (m, 4H) (+2- CH_2)	2.22–2.32 (m, 2H)	0.88 (t, J = 6.8 Hz), 1.24–1.33 (m, 21H), 1.49–1.72 (m, 8H), 3.21–3.31 (m, 2H), 3.94 (t, J = 6.5 Hz, 2H), 7.16 (s, 1H)
7B-7(2)	2.10–2.22 (m, 4H) (+2- CH_2)	2.20–2.28 (m, 2H)	0.88 (t, J = 6.8 Hz, 3H), 1.23–1.33 (m, 21H), 1.48–1.72 (m, 8H), 3.21–3.31 (m, 2H), 3.95 (t, J = 6.5 Hz, 2H), 7.17 (s, 1H)
7B–9(1)	2.11–2.16 (m, 4H) (+2- CH_2)	2.28–2.34 (m, 2H)	0.88 (t, J = 6.7 Hz, 3H), 1.27–1.35 (m, 42H), 1.43–1.51 (m, 2H), 1.59–1.71 (m, 6H), 3.20–3.26 (m, 2H), 3.95 (t, J = 6.5 Hz, 2H), 7.19 (s, 1H)
7B–9(2)	2.13–2.19 (m, 4H) (+2-CH_2)	2.22–2.30 (m, 2H)	0.88 (t, J = 6.6 Hz, 3H), 1.27–1.35 (m, 40H), 1.47–1.74 (m, 9H), 3.23–3.29 (m, 2H), 3.95 (t, J = 6.5 Hz, 2H), 7.16 (s, 1H)
7B–10(1)	2.09–2.16 (m, 4H) (+2-CH_2)	2.33–2.39 (m, 2H)	1.25∼1.32 (m, 12H), 1.47–1.50 (m, 2H), 1.60–1.73 (m, 4H), 3.20–3.26 (m, 2H), 4.97 (s, 2H), 7.22 (s, 1H), 7.24–7.39 (m, 5H)
7B–10(2)	2.13–2.23 (m, 4H) (+2-CH_2)	2.29–2.34 (m,2H)	1.22∼1.31 (m, 12H), 1.45–1.53 (m, 2H), 1.55–1.71 (m, 4H), 3.24–3.28 (m, 2H), 5.02 (s, 2H), 7.19 (s, 1H), 7.24–7.37 (m, 5H)
7B–13(1)	2.09–2.16 (m, 4H) (+2-CH_2)	2.32–2.38 (m, 2H)	1.22∼1.29 (m, 12H), 1.39–1.49 (m, 2H), 1.57–1.67 (m, 4H), 3.19–3.26 (m, 2H), 5.01 (s, 2H), 7.18 (s, 1H), 7.29–7.45 (m, 4H)
7B–13(2)	2.12–2.22 (m, 4H) (+2-CH_2)	2.24–2.36 (m, 2H)	1.22∼1.28 (m, 12H), 1.41–1.54 (m, 2H), 1.59–1.72 (m, 4H), 3.20–3.27 (m, 2H), 5.01 (s, 2H), 7.18 (s, 1H), 7.29–7.45 (m, 4H)
7B–15(1)	2.06–2.14 (m, 4H) (+2– CH_2)	2.25–2.31 (m, 2H)	1.21∼1.38 (m, 12H), 1.43–1.49 (m, 2H), 1.57–1.67 (m, 4H), 3.15–3.21 (m, 2H), 5.16 (d, J_{H-F} = 1.7, 2H), 7.12–7.41 (m, 4H)
7B–15(2)	2.10–2.20 (m, 4H) (+2-CH_2)	2.21–2.26 (m, 2H)	1.25∼1.39 (m, 12H), 1.40–1.51 (m, 2H), 1.59–1.70 (m, 4H), 3.21–3.27 (m, 2H), 5.16 (d, J_{H-F} = 1.7 Hz, 2H), 7.12–7.41 (m, 4H)

Table 2. Continued

compds No.	11-CH_2	13-CH_2	others
7C–3	0.90∼0.95 (m, 3H), 1.33∼1.34 (m, 12H), 1.50∼1.52 (m, 2H), 1.61∼1.68 (m, 4H), 1.86∼1.89 (m, 2H), 2.12∼2.17 (m, 2H), 2.24∼2.42 (m, 5H), 3.93∼3.98 (m, 2H), 4.13∼4.18 (m, 2H)		
7C–4	1.32∼1.41 (m, 12H), 1.52∼1.54 (m, 2H), 1.63∼1.65 (m, 2H), 1.83∼1.88 (m, 2H), 2.13∼2.18 (m, 1H), 2.25∼2.43 (m, 5H), 4.09∼4.16 (m, 2H), 4.46∼4.97 (m, 2H), 5.10∼5.15 (m, 1H), 5.20∼5.27 (m, 1H), 5.92∼6.02 (m, 1H)		
7C–5	0.93 (t, 3H, J = 7.3 Hz), 1.26∼1.41 (m, 14H), 1.49∼1.69 (m, 7H), 1.85∼1.90 (m, 2H), 2.25∼2.37 (m, 5H), 3.97∼4.02 (m, 2H), 4.12∼4.18 (m, 2H)		
7C–7	0.86–0.92 (m, 3H), 1.25–1.33 (m, 22H), 1.49–1.54 (m, 2H), 1.61–1.69 (m, 2H), 1.82–1.92 (m, 2H), 2.24–2.37 (m, 6H), 3.96–4.00 (m, 2H), 4.14–4.18 (m, 2H)		
7C–9	0.86–0.95 (m, 3H), 1.25–1.35 (m, 40H), 1.49–1.54 (m, 2H), 1.57–1.68 (m, 2H), 1.84–1.92 (m, 2H), 2.24–2.37 (m, 6H), 3.96–4.00 (m, 2H), 4.15–4.20 (m, 2H)		
7C–10	1.31∼1.35 (m, 12H), 1.48∼1.54 (m, 2H), 1.58∼1.68 (m, 2H), 1.83∼1.90 (m, 2H), 2.13∼2.18 (m, 1H), 2.25∼2.45 (m, 5H), 4.06∼4.17 (m, 2H), 5.05 (d, 2H, J = 2.8 Hz), 7.26∼7.35 (m, 5H)		
7C–13	1.26∼1.33 (m, 12H), 1.47∼1.53 (m, 2H), 1.59∼1.68 (m, 2H), 1.81∼1.90 (m, 2H), 2.24∼2.36 (m, 5H), 4.15 (t, 2H, J = 5.6 Hz), 5.00 (d, 2H, J = 2.6 Hz), 7.24∼7.33 (m, 4H)		
7C–15	1.23∼1.33 (m, 12H), 1.43∼1.48 (m, 2H), 1.61∼1.66 (m, 2H), 1.80∼1.89 (m, 2H), 2.11∼2.16 (m, 1H), 2.23∼2.37 (m, 5H), 4.06∼4.14 (m, 2H), 5.18∼5.20 (m, 2H), 6.96∼7.03 (m, 1H), 7.17∼7.27 (m, 2H)		

Table 3. Fungicidal Activity of Compounds **7** against *Rhizoctonia solani* Kühn[a]

compds No.	EC_{50} (μg/mL)	compds No.	EC_{50} (μg/mL)	compds No.	EC_{50} (μg/mL)
7A–1(1)	51.34				
7A–1(2)	55.80				
7A-2(2)	25.84	7B–2(2)	22.73		
7A–3(1)	22.10	7B–3(1)	13.14	7C–3	8.08
7A–3(2)	9.11	7B–3(2)	3.62		
7A–4(1)	44.03	7B–4(1)	45.61	7C–4	12.76
7A–4(2)	21.76	7B–4(2)	15.92		
7A–5(1)	55.10	7B–5(1)	3.97	7C–5	13.36
7A–5(2)	7.21	7B–5(2)	2.34		
7A–6(1)	48.40				
7A–6(2)	30.38				
7A–7(1)	209.43	7B–7(1)	19.25	7C–7	9.68
7A–7(2)	50.35	7B–7(2)	27.88		
7A–8(1)	101.13				
7A–8(2)	69.12				
7A–9(1)	135.04	7B–9(1)	47.75	7C–9	40.39
7A–9(2)	127.22	7B–9(2)	51.48		
7A–10(1)	18.15	7B10(1)	5.84	7C–10	45.13
7A–10(2)	7.24	7B10(2)	8.28		
7A–11(1)	111.31				
7A–11(2)	50.55				
7A–12(1)	74.91				
7A-12(2)	12.07				
7A–13(1)	97.25	7B–13(1)	68.37	7C-13	19.61
7A–13(2)	84.79	7B–13(2)	164.28		
7A–14(1)	49.32				
7A-14(2)	166.33				
7A–15(1)	1734.74	7B-15(1)	2.34	7C–15	51.27
7A–15(2)	42.99	7B-15(2)	6.21		
7A–16(1)	100.00				
7A-16(2)	105.66				
7A–17(1)	56.43				
7A–17(2)	52.55				
carbendazim	1.54				

[a] Regression equations and correlation coefficients are omitted.

comparable with the commercial fungicide carbendazin (with EC_{50} = 1.54 μg/mL). The pentadecanlactone derivatives (**7C**) have somewhat improved fungicidal activity against *Rhizoctonia solani* Kühn than that of **7A** but are less active than 7B. Namely, in the order of **7A**, **7C**, and **7B**, the compounds have a gradual increase of fungicidal activity. It can be seen from **Table 4** that compound **7B3** has a broad spectrum of fungicidal activities and has especially excellent fungicidal activities against *Alternaria kikuchiana* and *Phyllospicpa physaleos* Sacc.The EC_{50} values were 1.2 and 1.9 μg/mL, respectively.

Table 4. Fungicidal Spectrum of **7B3** (a mixture of *Z* and *E* isomers)

pathogen	EC_{50} (μg/mL)
pear black spot (*Alternaria kikuchiana*)	1.2
tomoto southern blight (*Phyllospicpa physaleos* Sacc)	1.9
cotton rhizoctonia rot (*Rhizoctonia solani* Kühn)	4.6
cucumber gray mold (*Botrytis cinerea* Pers)	8.6
asparagus stem blight (*Phomopsis asparagi* Sacc)	12.0
apple ring spot (*Physalospora piricola* Nose)	13.8
cotton verticillium wilt (*Vercicillium alboatrum* Reinke et Berthold)	19.3
cucumber anthracnose (*Colletotrichum Lagenarium*)	23.9
cotton fusarium wilt (*Fusarium vasinfectum* Atkimson)	29.0
cotton damping-off (*Pythium aphanibermatum (Eds.)* Fipzp)	33.3
tomoto early blight (*Alternaria solani* Jones et Grout)	44.2
tomoto leaf mold (*Cladosporium fulvum* Cooke)	53.1
peppers fruit rot (*Phytophthora capsici* Len)	57.8

In conclusion, all of above results confirmed our original judgment: macrocyclic compounds with two polarizable groups on the ring may have certain fungicidal activity. In this research, all of tetradecanlactam and pentadecanlactam derivatives, containing two polarizable groups –CONH− and =N−O− on the ring (**7A** and **7B**), and pentadecanlactone derivatives, containing –COO− and =N−O− on the ring (**7C**), displayed fair to excellent fungicidal activity against *Rhizoctonia solani* Kühn. In the macrocyclic derivatives with two polarizable groups on the ring, the compounds in which there is a three methylene distance ($CH_2CH_2CH_2$) between the two polarizable groups (**7B** and **7C**) are more active than those in which there is a two-methylene distance (CH_2CH_2) between the two polarizable groups (**7A**). The fact that compounds **7B** have higher fungicidal activity than compounds **7C** indicates that the macrocyclic derivatives with a hydrogen-bonding acceptor (here, it is =N−O−) and a hydrogen-bonding donor (here, it is −CONH−) have the best fungicidal activity among the macrocyclic derivatives with two polarizable groups and a three methylenes distance between these groups. The information can be very useful for designing new macrocyclic fungicides. The

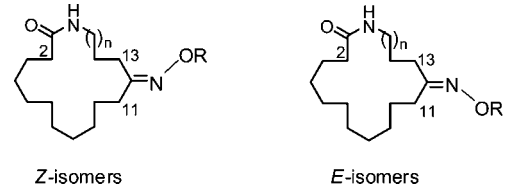


Figure 2. *Z* and *E* Isomers of Compounds **7A** (n = 0) and **7B** (n = 1).

fungicidal activity is also closely associated with R on the side chain; further study on the effect of R on the activity may be fruitful.

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