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Design, Synthesis, and Fungicidal Activity of Macrolactones and Macrolactams with a Sulfonamide Side Chain

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Four series of novel macrolactones and macrolactams—12-alkylsulfonamido-1,15-pentadecanlactones (**5**), 12-alkylsulfonamido-15-methyl-1,15-pentadecanlactones (**6**), 12-alkylsulfonamido-1,15-pentadecanlactams (**7**), and *N*-(alkylsulfonamidoethyl)-1,12-dodecanlactams (**8**)—were designed and synthesized from readily available 2-nitrocyclododecanone or cyclododecanone. Their structures were confirmed by ^{1}H NMR, IR, and elemental analysis. The bioassay showed that these compounds displayed fair to excellent fungicidal activity against *Rhizoctonia solani* Kühn and have a gradual increase of fungicidal activity in the order of **6**, **7**, **8**, and **5**. Among them, compounds **5a**, **5b**, and **5c** displayed excellent fungicidal activity against *R. solani* comparable with the commercial fungicide carbendazim. Above results illustrated that the rule on the relationship between the activity and hydrogen-bonding, namely the macrocyclic compounds with a hydrogen-bonding acceptor and a hydrogen-bonding donor on the ring and having a three methylenes distance between two polarizable groups have the best fungicidal activity against *R. solani*, has a general suitability to the macrocyclic compounds, and pesticide molecules may combine with a target enzyme by hydrogen-bonding. The facts, which compound **6** has a much lower fungicidal activity against *R. solani* than compound **5** but their difference in chemical structure is only that there is a methyl group on the C15 for compound **6** and none but hydrogen atom on the C15 for compound **5**, indicated that a methyl group plays an inhibitory role to the fungicidal activity. It suggests that the existence of a methyl group with a great volume between two polarizable groups would interfere in the interaction of pesticide molecules and the target enzyme.

KEYWORDS: Macrolactone; macrolactam; sulfonamide; synthesis; fungicidal activity; fungicide; pesticide; *Rhizoctonia solani* Kühn

INTRODUCTION

Cotton soreshin (*Rhizoctonia solani* Kühn) is an important agricultural fungus species that causes serious damage to cotton production in China (*1*). Several chemical fungicides have been approved for the control of *R. solani* on cotton including carbendazim. Unfortunately, resistance to these fungicides has been observed, thus, leading to the continuing need of further research to discover new classes of fungicides, especially those with novel modes of action. Our strategy for discovering new fungicides was to imitate the chemistry of biologically active natural products. In a previous paper (*2*), we reported the design and synthesis of macrolactam and macrolactone derivatives with an oxime ether side chain to improve fungicidal activity of general macrocyclic compounds. Bioassay showed that they have good fungicidal activity against *R. solani*. Among them, those with a hydrogen-bonding acceptor (═N—O—) and a hydrogen-bonding donor (—CONH—) on the ring and having a three methylenes distance between two polarizable groups have the best fungicidal activity. Namely, 12-alkyloxyimino-1,15-pentadecanlactams (**1**) have the best fungicidal activity. On the other hand, it is well-known that sulfonamides have a broad spectrum of biological activities. For example, sulfanilamide (**2**) was the first synthetic antibacterial agent active against a wide range of infection (*3*), and flusulfamide (**3**) is used as a soil fungicide for the control of *plasmodiophora brassicae* on Chinese cabbage (*4*). In addition, we also reported that 2-oxo-cyclododecyl sulfonamides (**4**) have some fungicidal activity and found that those with a hydrogen atom on the nitrogen atom have better activity than those without a hydrogen atom on the

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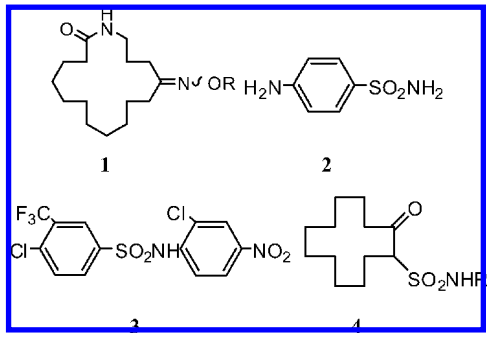
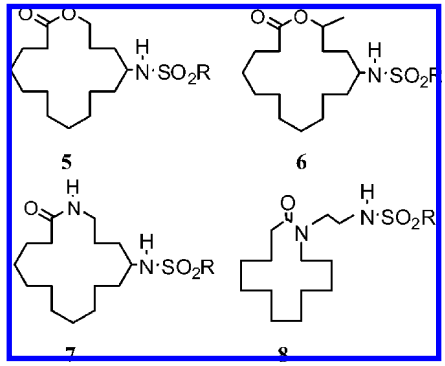
nitrogen atom, showing the importance of a hydrogen-bonding donor in the molecule to the fungicidal activity (*5*).

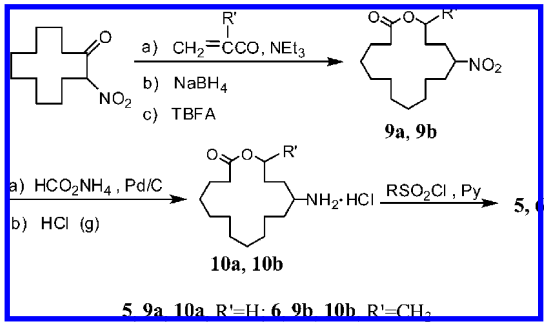


In view of the above-mentioned facts, we introduce a sulfonamide group into pentadecanlactone, synthesizing a series of novel 12-alkylsulfonamido-1,15-pentadecanlactones (**5**), which retain a hydrogen-bonding acceptor (here, it is −CO−O−) and a hydrogen-bonding donor (here, it is −NH−SO_2−) on the large ring and still have a three methylenes distance between two polarizable groups, and expecting that designed compounds have a better fungicidal activity than compound **1** or comparable fungicidal activity with compound **1**. In order to investigate if the rule on the relationship between the activity and hydrogen-bonding has a general suitability to the macrocyclic compounds, further structural derivation on compound **5** was carried out: (a) A methyl group was introduced at the C15 position, and the 12-alkylsulfonamido-15-methyl-1,15-pentadecanlactones (**6**) were synthesized. (b) The lactone ring was replaced by a lactam ring, and the 12-alkylsulfonamido-1,15-pentadecanlactams (**7**) were synthesized. (c) The sulfonamide group was transferred to the terminal of the side chain and still kept a suitable distance between the two polarizable groups, and the *N*-(alkylsulfonamidoethyl)-1,12-dodecanlactams (**8**) were synthesized.



The synthetic route of compounds **5** and **6** is shown in **Scheme 1**. The 12-nitropentadecanlactones (**9**), synthesized

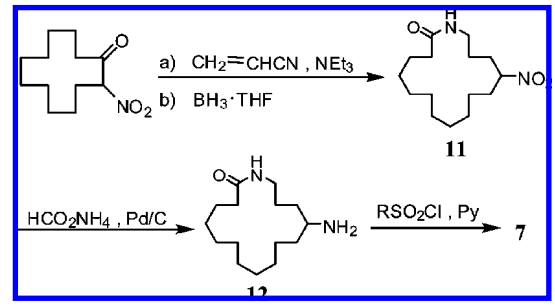
Scheme 1



starting from 2-nitrocyclododecanone by Michael addition to acrolein or methyl vinyl ketone followed by selective reduction of the carbonyl at the side chain and ring expansion, were converted into the corresponding amines (**10**) by transfer hydrogenation (*6*) using ammonium formate and palladium on carbon. The amines **10** were sulfonylated with alkylsulfonyl chloride to afford target compounds **5** and **6**.

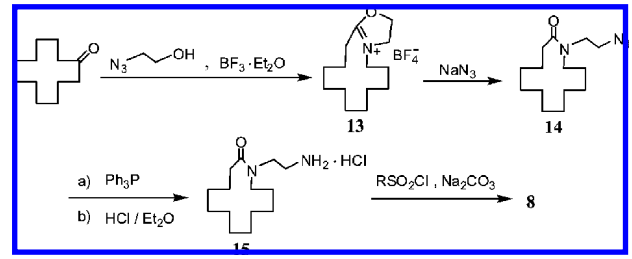
The synthetic route of compound **7** is shown in **Scheme 2**. Michael addition of 2-nitrocyclododecanone to acrylonitrile followed by selective reduction of a nitrile group gave 12-nitropentadecanlactam (**11**), which was converted into the corresponding amine (**12**) followed by sulfonylation with alkylsulfonyl chloride to afford target compound **7**.

Scheme 2



The synthetic route of compound **8** is shown in **Scheme 3**. Schmidt reaction (*7*) of cyclododecanone with 2-azidoethanol followed by treating with sodium azide (*8*) gave *N*-(2-azidoethyl)dodecanlactam (**14**), which was reduced and sulfonylated to afford target compound **8**.

Scheme 3



In this paper, we would like to report the design, synthesis, and fungicidal activity of compounds **5**, **6**, **7**, and **8**.

MATERIALS AND METHODS

General. ^{1}H NMR spectra were recorded in $CDCl_3$, with a Bruker DPX300 spectrometer, using TMS as the internal standard; infrared spectra were recorded on potassium bromide disks or liquid films on a Shimadzu IR-435 spectrophotometer; elemental analysis was performed by the analytical center in 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.

Chemical Synthesis. *Synthesis of 12-Nitro-1,15-pentadecanlactone (***9a***).* Compound **9a** was prepared according to the method given in ref (*7*).

*Synthesis of 15-Methyl-12-nitro-1,15-pentadecanlactone (***9b***).* Compound **9b**was prepared according to the method given in ref (*9*) just using methyl vinyl ketone instead of acrolein. Colorless liquid: yield (based on 2-nitrocyclododecanone), 68%; ^{1}H NMR δ 1.23(3H, d, J = 6.2 Hz), 1.32−1.37 (14H, m), 1.54−2.03 (8H, m), 2.30−2.35 (2H, m), 4.41−4.60 (1H, m), 4.89−5.10 (1H, m).

General Procedure for the Synthesis of Compounds **10** *(6).* A mixture of compound **9** (0.01 mol), ammonium formate (3.18 g, 0.05 mol), and palladium on carbon (10%, 0.1 g) in methanol was stirred at room

temperature for 1 h and then filtered, and the filtrate was concentrated to dryness at reduced pressure to give a viscous liquid, which was dissolved in diethyl ether. The resulting solution was passed in dry hydrogen chloride at 0 °C until no precipitate could be observed. Filtration gave the desired products. **10a**: yield, 82%; mp 167−168 °C (lit.: mp 167−168 °C (*10*)). **10b**: yield, 88%; mp 156−157 °C; ^{1}H NMR δ 1.24−1.33 (25H, m), 2.04−2.33 (2H, m), 3.10−3.35 (1H, m), 4.91−5.05 (1H, m), 8.04 (3H, s).

General Procedure for the Synthesis of Compounds **5** *and* **6.** To a stirred solution of compound **10** (0.005 mol) and pyridine (1.20 g, 0.015 mol) in 50 mL of anhydrous acetonitrile at room temperature under a nitrogen atmosphere was added alkylsulfonyl chloride (0.01 mol), and the mixture stirred under reflux for 6 h. Concentration at reduced pressure gave a viscous liquid, which was dissolved in aqueous sodium hydroxide solution. The resulting solution was neutralized to pH 2 with hydrochloric acid and extracted with dichloromethane (30 mL × 3). The combined organic layer was washed with water and brine, dried over sodium sulfate, and evaporated under reduced pressure to give a crude product. Further purification on silica gel column chromatography with petroleum and ethyl acetate gave the target compounds **5** or **6**. The physical and elemental data of the target compounds are given in **Table 1**, and the ^{1}H NMR and IR data are listed in **Table 2**.

*Synthesis of 12-Nitro-1,15-pentadecanlactam (***11***).* Compound **11** was prepared according to the method given in ref (*11*).

*Synthesis of 12-Amino-1,15-pentadecanlactam (***12***).* The reaction was run similarly to that used to synthesize **10**. After the reaction was completed, catalyst was removed and water added. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over sodium sulfate, and evaporated under reduced pressure to give the desired product **12**: yield, 94%; mp 103−104 °C; ^{1}H NMR δ 0.95−1.61 (24H, m), 2.01−2.07 (2H, m), 2.50−2.65 (1H, m), 2.89−3.01 (1H, m), 3.15−3.21 (1H, m).

General Procedure for the Synthesis of Compound **7.** The reaction was run similarly to that used to synthesize **5** and **6**. The crude products obtained were recrystallized in methanol and water to give the desired compound **7**. The physical and elemental data of the target compounds are given in **Table 1**, and the ^{1}H NMR and IR data are listed in **Table 2**.

Synthesis of Compound **13.** To a stirred solution of cyclododecanone (4.92 g, 0.027 mol) and azidoethanol (3.5 g, 0.040 mol) in 50 mL of dichloromethane at −5 °C was added 47% boron trifluoride etherate (14.2 g, 0.1 mol). The mixture was further stirred for 3 h at the same temperature and then stirred under reflux for 192 h. Concentration at reduced pressure gave a viscous liquid, which was dissolved in dichloromethane (20 mL), washed with water (10 mL × 3), dried over sodium sulfate, and evaporated under reduced pressure to give the desired product **13** (viscous liquid, 0.76 g): yield, 90%; ^{1}H NMR δ 1.29−1.45 (14H, m), 1.78−1.90 (4H, m), 2.81 (2H, t, J = 6.9 Hz), 3.79 (2H, t, J = 6.5 Hz), 4.24 (2H, t, J = 10.3 Hz), 5.03 (2H, t, J = 10.3 Hz).

Synthesis of Compound **14.** To a stirred solution of compound **13** (3.1 g, 0.01 mol) in 20 mL of anhydrous DMF was added sodium azide (1.3 g, 0.02 mol) portion by portion. The mixture was stirred at 70 °C for 16 h. Water (25 mL) was poured into the mixture, and the resulting mixture was extracted with diethyl ether (10 mL × 4). The combined organic layer was washed with water and brine, dried over sodium sulfate, and evaporated under reduced pressure to give a crude product. Further purification on silica gel column chromatography with petroleum and ethyl acetate gave the desired compound **14** (viscous liquid, 1.9 g): yield, 70%; ^{1}H NMR δ 1.34−1.44 (14H, m), 1.61−1.70 (4H, m), 2.40 (2H, t, J = 7.0 Hz), 2.90 (2H, t, J = 6.5 Hz), 3.13 (2H, t, J = 4.6 Hz), 4.32 (2H, t, J = 4.6 Hz).

Synthesis of Compound **15.** A mixture of compound **14** (5.5 g, 0.021 mol) and triphenyl phosphine (11 g, 0.042 mol) in 100 mL of anhydrous acetonitrile was stirred at room temperature for 13 h; water (20 mL) was then added, and resulting mixture was stirred at room temperature for 4 h. After filtration, the filtrate was extracted with diethyl ether (100 mL × 4). The combined organic layer was washed with brine, dried over sodium sulfate, and evaporated under reduced pressure to give a crude product (viscous liquid), which was dissolved in anhydrous diethyl ether (100 mL), and a solution of hydrogen chloride in diethyl ether was added dropwise at 0 °C until no precipitate could be observed. The filtration gave the desired product **15** (white solid, 4.3 g): yield, 75%; mp 103−106 °C; ^{1}H NMR δ 1.18−1.38 (14H, m), 1.54−1.85 (4H, m), 2.43 (2H, t, J = 7.8 Hz), 3.26 (2H, t, J = 6.1 Hz), 3.40 (2H, t, J = 7.6 Hz), 3.71 (2H, t, J = 6.1 Hz), 8.37 (3H, s).

General Procedure for the Synthesis of Compound **8.** To a stirred mixture of compound **15** (0.28 g, 0.001 mol) and sodium carbonate (0.45 g, 0.004 mol) in 20 mL of THF and water (1/1, v/v) was added alkylsulfonyl chloride (0.001 mol), and the mixture was stirred at room temperature for 6 h. Water (10 mL) was added, and the resulting mixture was extracted with dichloromethane (10 mL × 3). The combined organic layer was washed with brine, dried over sodium sulfate, and evaporated under reduced pressure to give a crude product (viscous liquid). Further purification on silica gel column chromatography with dichloromethane and methanol gave the desired compound **8**. The physical and elemental data of the target compounds are given in **Table 1**, and the ^{1}H NMR and IR data are listed in **Table 2**.

Bioassay of Fungicidal Activity. *Method.* Fungicidal activity of compounds **5**, **6**, **7**, and **8** against *R. solani* were evaluated using the mycelium growth rate test (*12*).

Fungicidal Activity of Compounds **5**, **6**, **7**, *and* **8.** The inhibition rates of compounds **5**, **6**, **7**, and **8** against *R. solani* at the concentrations of 100, 50, 25, 12.5, and 6.25 μg /mL were determined first. Then, EC_{50} values were estimated using logit analysis (*13*). 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**.

RESULTS AND DISCUSSION

Chemistry. Compounds **5**, **6**, and **8** were purified by silica gel column chromatography eluting with petroleum ether−ethyl acetate (compounds **5** and **6**) or dichloromethane−methanol (compound **8**). The yields were 30−44% (compound **5**), 36−56% (compound **6**), and 23−49% (compound **8**), respectively (**Table 1**). Because of good crystallizability, compound **7** was purified by recrystallization from methanol−water to give higher yields (72−84%) than compounds **5**, **6**, and **8** (**Table 1**).

The structures of the target compounds **5**, **6**, **7**, and **8** were characterized by ^{1}H NMR, IR, and elemental analysis (**Table 2**).

There are two diastereoisomers for compound **6** containing two different chiral carbons (C12 and C15). Existence of two isomers can be observed in the ^{1}H NMR spectrum of several of compound **6** (e.g., the resonance peak corresponding to the methyl group at the side chain displayed two singlets at δ 2.97 and 2.98 in the spectrum of **6l** (a mixture of two isomers)). Similarly, the methoxycarbonyl group on the benzene ring displayed two singlets at δ 3.98 and 3.99 for compound **6i**, and the methylene group of benzyl displayed two singlets at δ 4.25 and 4.26 for compound **6k**. (Note: All of these isomers have not been separated; therefore, the mixture of two diastereoisomers was used in the bioassay.)

Fungicidal Activity. As shown in **Table 3**, these compounds displayed fair to excellent fungicidal activity against *R. solani* and have a gradual increase of fungicidal activity in the order of **6**, **7**, **8**, and **5**. Compound **5** displayed well to excellent activity except individual compound **5k**. Among them, compounds **5a**, **5b**, and **5c**, the EC_{50} values of which were 2.4, 3.7, and 3.3 μg/mL, respectively, displayed excellent fungicidal activity and were comparable with compound **1** and the commercial fungicide carbendazim with an EC_{50} value of 1.5 μg/mL. As mentioned above, the designed idea of compound **5** was originated from compound **1**. In view of the hydrogen-bonding acceptor and hydrogen-bonding donor, compounds **5** and **1** have similar structural characteristics as shown in **Figure**

Table 1. Physical and Elemental Data of Compounds **5**, **6**, **7**, and **8**

Compds No.	R	Mp (°C)	Yield (%)	Elemental analysis		
				C (calcd)	H (calcd)	N (calcd)
5a	C_6H_5	77-78	30	63.99 (63.76)	8.49 (8.41)	3.78 (3.54)
5b	4-MeC_6H_4	132-133	44	64.76 (64.51)	8.73 (8.61)	3.63 (3.42)
5c	4-ClC_6H_4	Viscous liquid	40	58.59 (58.66)	7.53 (7.50)	3.39 (3.26)
5d	3-$O_2NC_6H_4$	98-99	41	57.38 (57.25)	7.42 (7.32)	6.65 (6.36)
5e	2,5-$Cl_2C_6H_3$	104-105	26	54.58 (54.31)	6.85 (6.73)	3.10 (3.02)
5f	4-FC_6H_4	Viscous liquid	30	60.83 (60.99)	7.75 (7.80)	3.39 (3.39)
5g	2-ClC_6H_4	75-76	37	58.46 (58.66)	7.56 (7.50)	3.32 (3.26)
5h	2-$O_2NC_6H_4$	84-85	36	57.35 (57.25)	7.41 (7.32)	6.65 (6.36)
5i	2-($MeCO_2$)C_6H_4	77-78	39	61.18 (60.90)	7.92 (7.78)	3.38 (3.54)
5j		87-89	36	57.13 (56.83)	7.85 (7.78)	3.42 (3.49)
5k	$C_6H_5CH_2$	95-96	44	64.32 (64.51)	8.72 (8.61)	3.78 (3.42)
5l	CH_3	97-99	36	57.95 (57.62)	9.53 (9.37)	4.54 (4.20)
6a	C_6H_5	102-103	56	64.33 (64.51)	8.57 (8.61)	3.46 (3.42)
6b	4-MeC_6H_4	107-108	50	64.94 (65.21)	8.62 (8.80)	3.21 (3.31)
6c	4-ClC_6H_4	87-88	40	59.27 (59.51)	7.66 (7.72)	3.10 (3.15)
6d	3-$O_2NC_6H_4$	87-88	51	58.29 (58.13)	7.57 (7.54)	6.34 (6.16)
6e	2,5-$Cl_2C_6H_3$	86-87	36	55.38 (55.22)	6.96 (6.95)	2.98 (2.93)
6f	4-FC_6H_4	121-122	55	61.32 (61.80)	7.94 (8.01)	3.23 (3.28)
6g	2-ClC_6H_4	90-91	46	59.51 (59.51)	7.77 (7.72)	3.09 (3.15)
6h	2-$O_2NC_6H_4$	77-78	40	57.97 (58.13)	7.48 (7.54)	6.21 (6.16)
6i	2-($MeCO_2$)C_6H_4	87-88	45	61.47 (61.64)	8.03 (7.98)	3.00 (3.00)
6j		106-107	53	57.77 (57.80)	8.08 (8.00)	3.40 (3.37)
6k	$C_6H_5CH_2$	75-76	52	65.53 (65.21)	9.03 (8.80)	3.51 (3.31)
6l	CH_3	58-59	55	58.86 (58.76)	9.71 (9.57)	3.97 (4.03)
7a	C_6H_5	147.5-148	80	63.98 (63.92)	8.70 (8.69)	7.16 (7.10)
7b	4-MeC_6H_4	175.5-176	75	64.52 (64.67)	8.88 (8.88)	6.84 (6.86)
7c	4-ClC_6H_4	176.5-177.5	78	58.88 (58.79)	7.74 (7.75)	6.51 (6.53)
7d	3-$O_2NC_6H_4$	167-167.5	80	57.47 (57.38)	7.56 (7.57)	9.69 (9.56)
7e	2,5-$Cl_2C_6H_3$	169-169.5	72	54.33 (54.42)	7.04 (6.96)	5.78 (6.04)
7f	4-FC_6H_4	128-128.5	76	61.07 (61.14)	8.10 (8.04)	6.82 (6.79)
7g	2-ClC_6H_4	146.5-147	82	58.85 (58.79)	7.74 (7.75)	6.60 (6.53)
7h	2-$O_2NC_6H_4$	162-163	82	57.23 (57.38)	7.57 (7.57)	9.29 (9.56)
7i	2-($MeCO_2$)C_6H_4	96-96.5	78	61.00 (61.03)	8.00 (8.02)	6.21 (6.19)
7j		121-122	76	57.07 (56.97)	8.09 (8.05)	7.04 (6.99)
7k	$C_6H_5CH_2$	150-150.5	74	64.97 (64.67)	9.02 (8.88)	6.83 (6.86)
7l	CH_3	170.5-171	84	58.12 (57.80)	9.72 (9.70)	8.53 (8.43)
8a	C_6H_5	117-118	49	63.10 (63.12)	8.54 (8.48)	7.17 (7.36)
8b	4-MeC_6H_4	120-121	47	63.77 (63.92)	8.75 (8.69)	6.91 (7.10)
8c	4-ClC_6H_4	145-147	37	57.78 (57.88)	7.63 (7.53)	6.58 (6.75)
8d	3-$O_2NC_6H_4$	131-132	23	56.26 (56.45)	7.43 (7.34)	9.60 (9.87)
8e	2,5-$Cl_2C_6H_3$	112-113	35	53.41 (53.45)	6.86 (6.73)	6.00 (6.23)

1, although compound **5** is a macrolactone with a sulfonamide side chain and compound **1** is a macrolactam with an oxime ether side chain. The results showed that the rule on the relationship between the fungicidal activity and hydrogen-bonding has a general suitability to the macrocyclic compounds. Compound **8** has somewhat lower fungicidal activity against *R. solani* than that of compound **5**. Although the former is a 13-membered lactam derivative and the latter is a 16-membered lactone derivative, they are similar in chemical structure (the active moiety is similar and all of the lipophilic moiety are 10−11 methylenes of large rings). The difference is that the greater part of the active moiety of compound **8** is out of the large ring as the skeleton of the side chain, which is flexible instead of rigid (**Figure 1**). The flexible characteristic of the

Table 2. ^{1}H NMR Data of Compounds **5**, **6**, **7**, and **8**

Compds No.	^{1}H NMR ($CDCl_3$, δ)	IR
5a	1.10∼1.39 (m, 17H), 1.47∼1.75 (m, 5H), 2.30 (t, 2H, J = 6.8 Hz), 3.26∼3.31 (m, 1H), 4.00∼4.04 (m, 2H), 4.84 (d, 1H, J = 8.5 Hz), 7.48∼7.60 (m, 3H), 7.88∼7.91 (m, 2H)	3300, 2920, 2870, 1730, 1450, 1335, 1165, 1100, 970
5b	1.16∼1.38 (m, 17H), 1.51∼1.66 (m, 5H), 2.30 (t, 2H, J = 6.8 Hz), 2.43 (s, 3H), 3.26∼3.27 (m, 1H), 4.01−4.05 (m, 2H), 4.59 (d, 1H, J = 8.5 Hz), 7.27∼7.31 (m, 2H), 7.76 (dd, 2H, J = 1.7 Hz, J = 6.6 Hz)	3310, 2920, 2870, 1725, 1600, 1440, 1375, 1230, 1155, 1095
5c	1.13∼1.43 (m, 17H), 1.50∼1.70 (m, 5H), 2.31 (t, 2H, J = 6.8 Hz, 3.29∼3.31 (m, 1H), 4.04∼4.09 (m, 2H), 4.75 (d, 2H, J = 8.6 Hz), 7.46∼7.51 (m, 2H), 7.79∼7.84 (m, 2H)	3300, 2920, 2870, 1730, 1580, 1450, 1335, 1250, 1090
5d	1.13∼1.46 (m, 17H), 1.55∼1.73 (m, 5H), 2.32 (t, 2H, J = 6.8 Hz, 3.37∼3.43 (m, 1H), 4.06∼4.11 (m, 2H), 4.75 (d, 1H, J = 8.8 Hz), 7.72−7.78 (m, 1H), 8.19∼8.23 (m, 1H), 8.41∼8.45 (m, 1H), 8.71−8.73 (m, 1H)	3250, 2920, 2870, 1720, 1535, 1460, 1360, 1170, 1020, 970
5e	1.17∼1.43 (m, 17H), 1.56∼1.72 (m, 5H), 2.31 (t, 2H, J = 6.8 Hz), 3.34∼3.35 (m, 1H), 4.06∼4.10 (m, 2H), 4.87 (d, 1H, J = 8.7 Hz), 7.43∼7.50 (m, 2H), 8.09∼8.10 (m, 1H)	3300, 2920, 2870, 1710, 1435, 1330, 1170
5f	1.17∼1.41 (m, 17H), 1.51∼1.72 (m, 5H), 2.31 (t, 2H, J = 6.8 Hz, 3.26∼3.32 (m, 1H), 4.02∼4.11 (m, 2H), 4.55 (d, 1H, J = 8.6 Hz), 7.15∼7.22 (m, 2H), 7.86∼7.93 (m, 2H)	3300, 2920, 2870, 1710, 1590, 1490, 1450, 1330, 1150, 1095, 1020
5g	1.12∼1.42 (m, 17H), 1.56∼1.71 (m, 5H), 2.30 (t, 2H, J = 6.8 Hz, 3.28∼3.33 (m, 1H), 4.01∼4.06 (m, 2H), 4.96 (d, 1H, J = 8.6 Hz), 7.39∼7.54 (m, 3H), 8.09∼8.12 (m, 1H)	3250, 2920, 2870, 1725, 1550, 1445, 1335, 1170, 1050
5h	1.14∼1.39 (m, 17H), 1.57∼1.76 (m, 5H), 2.32 (t, 2H, J = 6.8 Hz, 3.48∼3.53 (m, 1H), 3.99∼4.05 (m, 1H), 4.09∼4.16 (m, 1H), 5.17 (d, 1H, J = 8.4 Hz), 7.72∼7.77 (m, 2H), 7.84∼7.88 (m, 1H), 8.13∼8.17 (m, 1H)	3330, 2920, 2870, 1730, 1595, 1525, 1470, 1435, 1365, 1180, 1010
5i	1.09∼1.42 (m, 17H), 1.55∼1.71 (m, 5H), 2.31 (t, 2H, J = 6.8 Hz, 3.38∼3.42 (m, 1H), 3.98 (s, 3H), 4.02∼4.07 (m, 2H), 5.81 (d, 1H, J = 7.9 Hz), 7.59∼7.66 (m, 2H), 7.79∼7.82 (m, 1H), 8.08∼8.11 (m, 1H)	3300, 2920, 2870, 1725, 1435, 1335, 1290, 1170, 1065
5j	1.21∼1.42(m, 17H), 1.56∼1.72 (m, 5H), 2.23 (t, 2H, J = 6.8 Hz, 3.35∼3.39 (m, 1H), 4.05∼4.10 (m, 2H), 4.66 (d, 1H, J = 4.5 Hz), 7.07∼7.10 (m, 1H), 7.57∼7.59 (m, 1H), 7.60∼7.62 (m, 1H)	3300, 2920, 2870, 1720, 1445, 1335, 1210, 1145, 1020
5k	1.25∼1.58 (m, 17H), 1.59∼1.71 (m, 5H), 2.31 (t, 2H, J = 6.8 Hz, 3.32∼3.37 (m, 1H), 3.99 (d, 1H, J = 8.7 Hz), 4.08∼4.13 (m, 2H), 4.24 (s, 2H), 7.35∼7.44 (m, 5H)	3310, 2920, 2870, 1710, 1470, 1305, 1150, 1070, 1010
5l	1.32∼1.82 (m, 22H), 2.33 (t, 2H, J = 6.8 Hz), 2.97 (s, 3H), 3.42∼3.48 (m, 1H), 4.10∼4.24 (m, 2H), 4.30 (d, 1H, J = 8.0 Hz)	3300, 2920, 2870, 1720, 1320, 1260, 1150
6a	1.09∼1.37 (m, 21H), 1.52∼1.67 (m, 4H), 2.24−2.29 (m, 2H), 3.23 (br, 1H),.4.51−4.53 (m, 1H), 4.79∼4.88 (m, 1H), 7.48∼7.61 (m, 3H), 7.88∼7.91 (m, 2H)	3300, 2950, 2870, 1730, 1450, 1330, 1170, 1030
6b	1.09∼1.52 (m, 24H), 1.60∼1.67 (m, 1H), 2.24−2.29 (m, 2H), 2.43 (s, 3H), 3.26∼3.29 (m, 1H), 4.35−4.38 (m, 1H), 4.81∼4.86 (m, 1H), 7.29∼7.32 (m, 2H), 7.74∼7.79 (m, 2H)	3300, 2930, 2870, 1730, 1440, 1330, 1270, 1160, 820
6c	1.14∼1.44 (m, 21H), 1.53∼1.70 (m, 4H), 2.25∼2.30 (m, 2H), 3.18∼3.27 (m, 1H), 4.46∼4.63 (m, 1H), 4.80∼4.89 (m, 1H), 7.46∼7.51 (m, 2H), 7.79∼7.84 (m, 2H)	3300, 2930, 2870, 1730, 1330, 1170, 1100
6d	1.14∼1.43 (m, 21H), 1.51∼1.71 (m, 4H), 2.26−2.31 (m, 2H), 3.29∼3.34 (m, 1H), 4.76∼4.89 (m, 2H), 7.75 (t, 1H, J = 8.0 Hz), 8.19∼8.23 (m, 1H), 8.42∼8.45 (m, 1H), 8.72∼8.73 (m, 1H)	3300, 2930, 2870, 1730, 1540, 1450, 1350, 1180, 1060
6e	1.15∼1.37 (m, 20H), 1.47∼1.70 (m, 7H), 2.25−2.31 (m, 2H), 3.34∼3.38 (m, 1H), 4.80∼4.92 (m, 2H), 7.43∼7.50 (m, 2H), 8.09∼8.11 (m, 1H)	3310, 2930, 2870, 1730, 1450, 1380, 1150
6f	1.14∼1.37 (m, 21H), 1.53∼1.68 (m, 4H), 2.25−2.30 (m, 2H), 3.19−3.23 (m, 1H), 4.38−4.56 (m, 1H), 4.82∼4.88 (m, 1H), 7.16∼7.22 (m, 2H), 7.86∼7.92 (m, 2H)	3270, 2910, 2850, 1710, 1590, 1490, 1450, 1330, 1170, 1105, 1010
6g	1.11∼1.36 (m, 19H), 1.45∼1.67 (m, 6H), 2.24−2.29 (m, 2H), 3.22∼3.36 (m, 1H), 4.81∼4.91 (m, 2H), 7.40∼7.54 (m, 3H), 8.09∼8.13 (m, 1H)	3300, 2930, 2870, 1710, 1470, 1450, 1350, 1170, 1050
6h	1.11∼1.47 (m, 21H), 1.55∼1.76 (m, 4H), 2.26−2.31 (m, 2H), 3.41∼3.50 (m, 1H), 4.83∼4.92 (m, 1H), 5.16∼5.19 (m, 1H), 7.71∼7.78 (m, 2H), 7.85∼7.88 (m, 1H), 8.13∼8.16 (m, 1H)	3300, 2930, 2870, 1730, 1530, 1440, 1360, 1160
6i	1.08∼1.40 (m, 17H), 1.47∼1.74 (m, 6H), 2.25−2.30 (m, 2H), 3.33∼3.45 (m, 1H), 3.98 (s) + 3.99 (s) (3H), 4.80∼4.90 (m, 1H), 5.76∼5.83 (m, 1H), 7.60∼7.65 (m, 2H), 7.79∼7.82 (m, 1H), 8.07∼8.12 (m, 1H)	3310, 2950, 2870, 1730, 1430, 1340, 1280, 1170, 1060, 950
6j	1.14∼1.45 (m, 21H), 1.54∼1.69 (m, 4H), 2.25−2.30 (m, 2H), 3.27∼3.33 (m, 1H), 4.43−4.47 (m, 1H), 4.83∼4.90 (m, 1H), 7.07∼7.10 (m, 1H), 7.57∼7.62 (m, 2H)	3300, 2950, 2890, 1730, 1330, 1170
6k	1.01∼1.70 (m, 25H), 2.26−2.33 (m, 2H), 3.24∼3.29 (m, 1H), 3.86−3.96 (m, 1H), 4.25 (s) + 4.26 (s) (2H), 4.83∼4.96 (m,1H), 7.36∼7.51 (m, 4H), 7.75∼7.79 (m, 1H)	3300, 2930, 2870, 1730, 1540, 1460, 1130
6l	1.21∼1.79 (m, 25H), 2.28−2.33 (m, 2H), 2.97 (s) + 2.98 (s) (3H), 3.35∼3.38 (m, 1H), 4.08∼4.17 (m, 1H), 4.90∼5.04 (m, 1H)	2930, 2870, 1730, 1480, 1310, 1160
7a	1.14∼1.53 (m, 22H), 1.99∼206 (m, 2H), 2.88∼2.98 (m, 3H), 3.94 (s, 1H), 7.51∼7.65 (m, 4H), 7.69∼7.73 (m, 1H), 7.78∼7.81 (m, 2H)	3300, 2900, 2800, 1650, 1550, 1450, 1350, 1150, 1070

Table 2. Continued

Compds No.	^{1}H NMR ($CDCl_3$, δ)	IR
7b	1.11∼1.50 (m, 22H), 1.99∼2.03 (m, 2H), 2.38 (s, 3H), 2.90∼3.01 (m, 3H), 7.38 (d, 2H, J = 8.2 Hz), 7.45 (d, 1H, J = 7.7 Hz), 7.67 (d, 2H, J = 8.2 Hz), 7.71−7.75 (m, 1H)	3300, 2900, 2800, 1650, 1550, 1430, 1320, 1150, 1070
7c	1.12∼1.52 (m, 22H), 1.99∼2.04 (m, 2H), 2.93∼3.04 (m, 3H), 7.65∼7.70 (m, 3H), 7.71∼7.75 (m, 1H), 7.77∼7.82 (m, 2H)	3300, 2900, 2800, 1650, 1550, 1450, 1350, 1150, 1070, 820, 760
7d	1.19∼1.52 (m, 22H), 1.99∼2.04 (m, 2H), 2.87∼3.14 (m, 3H), 7.66−7.78 (m, 1H), 7.88∼7.95 (m, 2H), 8.21∼8.24 (m, 1H), 8.46∼8.53 (m, 2H)	3300, 2900, 2800, 1650, 1550, 1450, 1350, 1170, 1120, 680
7e	1.19∼1.52 (m, 22H), 2.00∼2.04 (m, 2H), 2.89∼3.10 (m, 3H), 7.69∼7.76 (m, 3H), 7.93∼7.94 (m, 1H), 8.04 (d, 1H, J = 8.6 Hz)	3300, 2900, 2800, 1650, 1530, 1450, 1350, 1250, 1170, 830
7f	1.21∼1.52 (m, 22H), 1.99∼2.04 (m, 2H), 2.93∼3.04 (m, 3H), 7.38∼7.47 (m, 2H), 7.50−7.60 (m, 1H), 7.70∼7.74 (m, 1H), 7.82∼7.88 (m, 2H)	3300, 2900, 2800, 1650, 1580, 1550, 1480, 1450, 1320, 1250, 1150, 1070, 820, 650
7g	1.19∼1.52 (m, 22H), 1.99∼2.06 (m, 2H), 2.87∼3.06 (m, 3H), 7.50∼7.55 (m, 1H), 7.60∼7.71 (m, 3H), 7.79 (d, 1H, J = 8.5 Hz), 7.98∼8.01 (m, 1H)	3300, 2900, 2800, 1650, 1540, 1450, 1350, 1250, 1150, 1040, 760
7h	1.16∼1.52 (m, 22H), 2.00∼2.05 (m, 2H), 2.91∼3.20 (m, 3H), 7.71∼7.76 (m, 1H), 7.82∼8.03 (m, 5H)	3300, 2900, 2800, 1650, 1550, 1450, 1350, 1250, 1170, 1070, 750
7i	1.13∼1.52 (m, 22H), 1.99∼2.04 (m, 2H), 2.90∼3.33 (m, 3H), 3.84 (s, 3H), 7.26 (d, 1H, J = 8.2 Hz), 7.60∼7.63 (m, 1H), 7.70∼7.75 (m, 3H), 7.89∼7.93 (m, 1H)	3300, 2900, 2800, 1720, 1650, 1550, 1450, 1350, 1370, 1250, 1120, 1050, 760
7j	1.16∼1.55 (m, 23H), 1.99∼2.04 (m, 2H), 2.91∼3.10 (m, 3H), 7.15∼7.18 (m, 1H), 7.54∼7.56 (m, 1H), 7.72∼7.76 (m, 2H), 7.89∼7.91 (m, 1H)	3300, 2900, 2800, 1650, 1550, 1440, 1400, 1350, 1250, 1150
7k	1.14∼1.53 (m, 22H), 1.99∼2.06 (m, 2H), 3.02∼3.17 (m, 3H), 4.28 (s, 2H), 6.99 (d, 1H, J = 8.0 Hz), 7.33∼7.40 (m, 5H), 7.77∼7.81 (m, 1H)	3300, 2900, 2800, 1650, 1550, 1450, 1350, 1260, 1130,
7l	1.19∼1.56 (m, 22H), 2.02∼2.06 (m, 2H), 2.87 (s, 3H), 3.01∼3.05 (m, 1H), 3.12∼3.18 (m, 2H), 6.92 (d, 1H, J = 8.0 Hz), 7.76∼7.80 (m, 1H)	3300, 2900, 2800, 1630, 1550, 1450, 1320, 1150
8a	1.30∼1.40(m, 14H), 1.56∼1.73(m, 4H), 2.26(t,J = 7.6 Hz,2H), 3.02∼3.21(m, 4H), 3.42(t, J = 5.8 Hz, 2H), 6.06(t, J = 5.2 Hz, 1H), 7.46∼7.58(m, 3H), 7.84∼7.87(m, 2H)	3411, 3146, 2932, 2857, 1678, 1623, 1529, 1447, 1330, 1161, 1091, 980
8b	1.23∼1.40 (m, 14H), 1.56∼1.74 (m, 4H), 2.26 (t, J = 7.6 Hz, 2H), 2.42 (s, 3H), 3.11∼3.19 (m, 4H), 3.42 (t, J = 5.4 Hz, 2H), 5.57 (t, J = 5.0 Hz, 1H), 7.28∼7.34 (m, 2H), 7.71∼7.75(m, 2H)	3172, 2930, 2860, 1621, 1457, 1335, 1186, 1092, 812
8c	1.23∼1.38 (m, 14H), 1.54∼1.70(m, 4H), 2.23∼2.30 (m, 2H), 3.07∼3.21 (m, 4H), 3.41∼3.51 (m, 2H), 6.23 (s, br, 1H), 7.26∼7.54 (m, 2H), 7.71∼7.81 (m, 2H)	3320, 2933, 2859, 1640, 1550, 1472, 1341, 1156, 1090, 765
8d	1.23∼1.29 (m, 14H), 1.58∼1.75 (m, 4H), 2.30 (t, J = 7.7 Hz, 2H), 3.17∼3.26 (m, 4H), 3.47(t, J = 5.5 Hz, 2H), 6.41 (t, J = 4.8 Hz, 1H), 7.69−7.75 (m, 1H), 8.18∼8.21 (m, 1H), 8.39∼8.43(m, 1H), 8.67−8.69 (m, 1H)	3159, 2931, 2958, 1629, 1528, 1456, 1349, 1168, 1093, 881
8e	1.26∼1.43 (m, 14H), 1.57∼1.79 (m, 4H), 2.33 (t, J = 7.7 Hz, 2H), 3.12∼3.18 (m, 2H), 3.26 (t, J = 7.6 Hz, 2H), 3.48 (t, J = 5.6 Hz, 2H), 6.16 (t, J = 5.0 Hz, 1H), 7.42∼7.61 (m, 2H), 8.05∼8.07 (m, 1H)	3143, 2933, 2858, 1624, 1451, 1374, 1335, 1242, 1162, 1098, 1041, 829

Table 3. Fungicidal Activity of Compounds **5**, **6**, **7**, and **8** against *R. solani*[a]

Compds No.	EC_{50} (μg/mL)	Compds No.	EC_{50} (μg/mL)	Compds No.	EC_{50} (μg/mL)	Compds No.	EC_{50} (μg/mL)
5a	2.4	**6a**	51.3	**7a**	55.3	**8a**	11.6
5b	3.7	**6b**	57.0	**7b**	13.4	**8b**	8.8
5c	3.3	**6c**	69.6	**7c**	19.6	**8c**	18.7
5d	18.7	**6d**	86.0	**7d**	27.6	**8d**	10.7
5e	28.4	**6e**	30.0	**7e**	30.4	**8e**	5.3
5f	4.5	**6f**	25.1	**7f**	36.7		
5g	25.0	**6g**	37.9	**7g**	59.5		
5h	22.3	**6h**	93.3	**7h**	21.5		
5i	20.9	**6i**	53.4	**7i**	12.8		
5j	5.1	**6j**	20.3	**7j**	18.3		
5k	52.4	**6k**	28.2	**7k**	8.1		
5l	12.2	**6l**	56.4	**7l**	45.1		
carbendazim	1.5	carbendazim	1.5	carbendazim	1.5	carbendazim	1.5

[a] Regression equations and correlation coefficients are omitted.

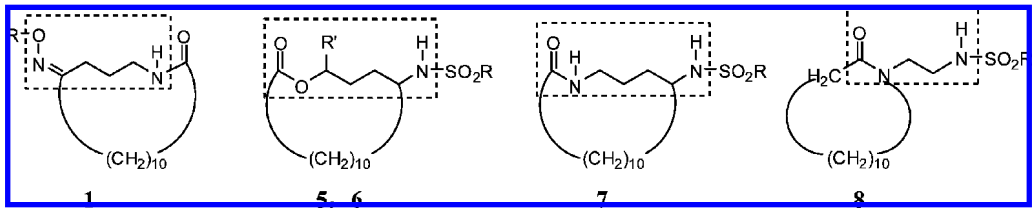


Figure 1. Comparison of structures of compounds **1**, **5**, **6**, **7**, and **8**. Structures of active moiety of compounds in the square frames are similar.

active moiety reduces the reactivity of the molecule in combination with the target enzyme. This is the reason why the fungicidal activity of compound **8** is somewhat lower than that of compound **5**.

Compound **6** has a much lower fungicidal activity against *R. solani* (the EC_{50} values of all compound **6**'s are larger than 20 μg/mL) than that of compound **5**. However, their difference in chemical structure is only that there is a methyl group on the C15 for compound **6** and none but a hydrogen atom on the C15 for compound **5**, which indicated that the methyl group plays an inhibitory role to the fungicidal activity. We postulate that maybe the existence of a methyl group with a great volume between two polarizable groups will interfere in the interaction of pesticide molecules with the target enzyme, as shown in **Figure 2**. Further experimental research would be needed to confirm such a mode of action.

In the molecule of compound **7**, the carbonyl of the amide bond can play the role as hydrogen-bonding acceptor; therefore, they have good fungicidal activity, but the active hydrogen on the nitrogen atom adjacent to the carbonyl would interfere in

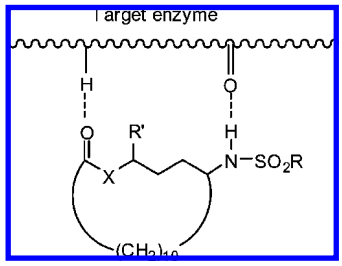


Figure 2. Sketch map of the interaction of compounds **5**, **6**, and **7** with target enzyme. Pesticide molecules combine with target enzyme by hydrogen-bonding. Interaction of pesticide molecule with target enzyme is interfered by a methyl group for compound **6** (R′ is methyl group and X is O), and the interaction is interfered by an active hydrogen on the nitrogen atom for compound **7** (X is NH and R′ is H).

the interaction of pesticide molecules and the target enzyme. This is the reason why fungicidal activity of compound **7** is lower than compound **5**.

In conclusion, all of the above results once again confirmed our judgment: macrocyclic compounds with a hydrogen-bonding acceptor and a hydrogen-bonding donor on the ring and having a three methylenes distance between two polarizable groups have the best fungicidal activity against *R. solani*. At the same time, the results also showed that the existence of any greater group other than a hydrogen atom or an active hydrogen between two polarizable groups would reduce their fungicidal activity possibly due to the interfering with the interaction of pesticides molecules with the target enzyme. The rule obtained on the relationship between the activity and hydrogen-bonding can be very useful for designing new classes of macrocyclic fungicides, especially those with novel modes of action.

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