



SYNTHESIS AND ANTIFUNGAL ACTIVITY OF NEW AZOLE DERIVATIVES CONTAINING AN OXATHIANE RING

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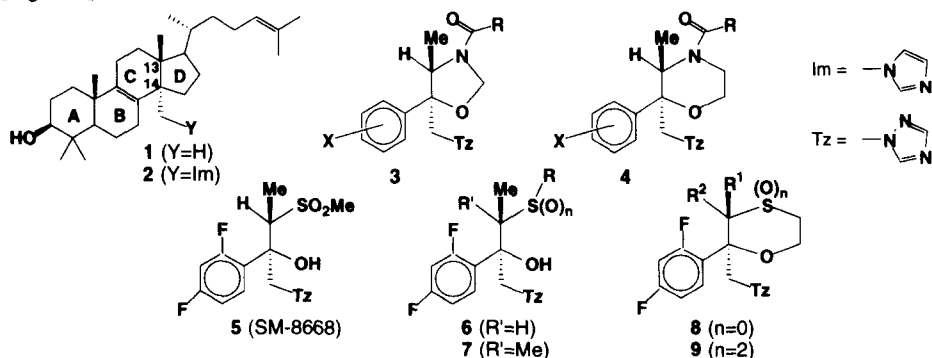
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Abstract: A series ofazole derivatives containing an oxathiane ring, which were designed to simulate the D ring of lanosterol, were synthesized and evaluated for their antifungal activity. 3,3-Dimethyl derivatives showed potent activity against murine systemic candidosis and aspergillosis, whereas (2*R**,3*R**)-3-monomethyl derivatives showed only weak activity in both *in vitro* and *in vivo*. Copyright © 1996 Elsevier Science Ltd

Azole antifungals are known to potent inhibitors of the cytochrome P450 lanosterol-14- α -demethylase in the process of fungal biosynthesis of ergosterol.¹⁾ They are believed to inhibit this enzyme by binding of heterocyclic nitrogen atom (3- position of imidazole or 4-position of triazole) to the protoheme iron atom and exclude oxygen which would normally take part in the reaction.^{1,2)} Since the target of the enzyme is 14- α -methyl group of lanosterol (**1**), a logical inhibitor could be a lanosterol derivative such as **2** with a heme binding component at the 14- α -methyl position.³⁾ Thus, 3-acyl-5-aryl-4-methyl-5-triazolylmethyl oxazolidines (**3**) were designed by Konosu et al. to fit on lanosterol skeleton.⁴⁾ Bartroli et al. recently reported *N*-acylmorpholine analogs **4** as a series of the improved analogs of **3**.⁵⁾ They claimed in the paper that the structure **4** should adopt a conformation in which the 2-triazolylmethyl group and the 3-methyl group were diaxial and antiperiplanar to one another, resembling the spatial disposition of the lanosterol D-ring substituents.⁵⁾ On the other hand, we previously reported that sulfur-containing triazole antifungals SM-8668 (**5**)⁶⁾ and its derivatives **6**⁷⁾ and **7**⁸⁾

[Figure 1]



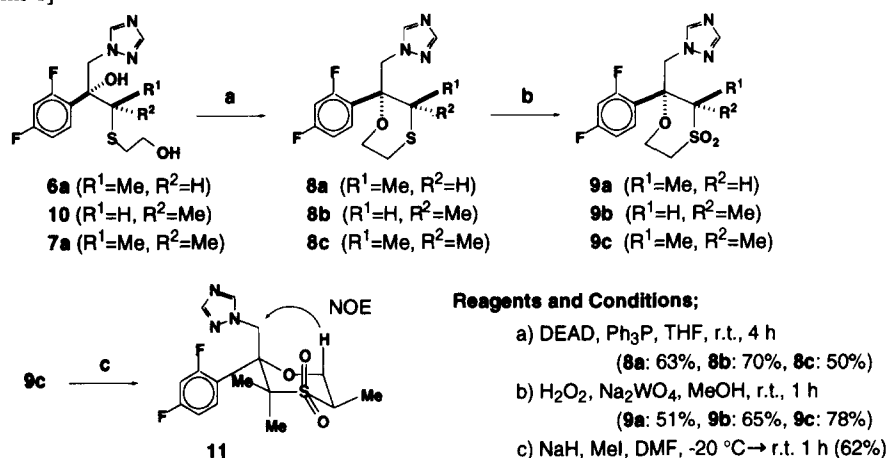
showed potent antifungal activity in both *in vitro* and *in vivo*. As a part of our search for active antifungal agents, we designed and synthesized triazole derivatives **8** and **9** containing an oxathiane ring as hybridized analogs of six-membered ring analogs **4** and sulfur-containing analogs **5**, **6**, and **7**.

Synthesis

A series of triazole analogs containing an oxathiane ring were synthesized as shown in Scheme 1. Oxathianes **8a**, **8b**, and **8c** were obtained by intramolecular Mitsunobu reaction⁹⁾ of racemic diols **6a**⁷⁾, **10**¹⁰⁾, and **7a**⁸⁾, respectively. These oxathianes were respectively oxidized with hydrogen peroxide in presence of catalytic amount of sodium tungstate¹¹⁾ to give 4,4-dioxo oxathianes **9a-c**.¹²⁾

Furthermore, **9c** was deprotonated with sodium hydride and treated with methyl iodide to afford a 5-substituted derivative **11**¹²⁾ as a single isomer. The relative configuration of **11** was determined to be (2*R**, 5*R**) as shown in Scheme 1, since the nuclear Overhauser effect (NOE) was observed on one of the methylene protons of the triazolylmethyl group when the 6-axial proton was irradiated.

[Scheme 1]



Antifungal activity

The minimum inhibitory concentration values (MIC, $\mu\text{g/ml}$) against *Candida albicans* KB-8 and *Aspergillus fumigatus* MTU6001 are presented in Table 1.¹³⁾ Oxathianes **8a-c** showed higher activity against *C. albicans* and *A. fumigatus* than the corresponding 4,4-dioxo derivatives **9a-c**. Among the 4,4-dioxo derivatives, only compound **11** showed activity as potent as SM-8668 (**5**) *in vitro*. However, these *in vitro* results were not reflected on their *in vivo* activity.¹⁴⁾

The results on the prophylactic efficiency against murine systemic candidosis and aspergillosis are also summarized in Table 1.¹³⁾ Almost all control mice died within 3 days after infection, whereas a considerable number of mice treated by oral administration of azole compounds (10 mg/kg/dose for candidosis or 50 mg/kg/dose for aspergillosis) survived significantly longer.

(2*R**, 3*R**)-3-Monomethyl and 3,3-dimethyl oxathianes were expected to fit on lanosterol skeleton as well as *N*-acymorpholine analogs **4**. Actually, 3,3-dimethyl derivatives **8c**, **9c**, and **11** showed potent activity

against both murine systemic candidosis and aspergillosis. However, (2*R**,3*R**)-2-monomethyl derivatives **8a** and **9a** showed only weak activity against candidosis and no activity against aspergillosis. Because of a conformational flexibility, the 2-triazolyl methyl group and the 3-methyl group on **8a** and **9a** would prefer a diequatorial configuration to a diaxial and antiperiplanar configuration, which is different from those on *N*-acylmorpholine analogs **4** taking a rigid antiperiplanar configuration by the effect of 1,3-allylic strain.⁵⁾ Therefore, 3,3-dimethylation should be of value to fix the conformation of oxathiane ring. In comparison, (2*R**,3*S**)-isomers **8b** and **9b** did not show any activity *in vivo*, since their 2-triazolyl methyl group and the 3-methyl group exist in *cis*-configuration and cannot take such an antiperiplanar configuration as 13-methyl group and 14-methyl group of lanosterol.

[Table 1] Antifungal activities of oxathiane derivatives.

Compound	MIC (μg/ml)		Mean survival days (d) *1	
	<i>C. albicans</i>	<i>A. fumigatus</i>	<i>C. albicans</i> *2	<i>A. fumigatus</i> *3
fluconazole*4	0.78	400	10 (0.7)	2.8 (2.0)*5
SM-8668 (5)	0.39	25	10 (1.6)	10 (2.1)
(2 <i>R</i> *,3 <i>R</i> *)				
8a (n=0)	0.20	50	4.9 (0.5)	1.5 (1.7)
9a (n=2)	6.25	> 100	6.9 (0.6)	1.1 (1.1)
(2 <i>R</i> *,3 <i>S</i> *)				
8b (n=0)	0.10	25	2.0 (0.2)	1.9 (2.1)
9b (n=2)	3.13	> 100	1.2 (0.2)	1.8 (2.1)
2,2-dimethyl				
8c (n=0)	0.10	3.13	8.6 (0.7)	9.8 (2.4)
9c (n=2)	3.13	100	9.4 (1.8)	10 (1.5)
11 (n=2)	0.39	12.5	10 (0.7)	9.4 (1.4)

*1; *In vivo* activity was determined in mice. The triazole derivative administered orally. Mean survival days of control mice on the same conditions are given in parentheses. *2; 10 mg/kg/dose of a triazole derivative was used. *3; 50 mg/kg/dose of a triazole derivative was used. *4; See reference 15. *5; Only in this case, 100 mg/kg/dose of fluconazole was used.

In conclusion, we synthesized a series of azole derivatives containing an oxathiane ring and found that 3,3-dimethyl derivatives **8c**, **9c**, and **11** showed excellent activity against murine systemic candidosis and aspergillosis. Further investigation on 5-substituted analogs of **9c** is currently in progress in order to improve its activity and physical properties such as solubility in water.

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- 12) ¹H-NMR data (270 MHz, CDCl₃) of sulfones: **9a**; δ1.24 (3H, d, *J*=7 Hz, 3-CH₃), 3.01 (1H, br.d, *J*=14 Hz, H-5eq), 3.43 (1H, dt, *J*=5, 14 Hz, H-5ax), 3.65 (1H, q, *J*=7 Hz, H-3), 4.44 (1H, ddd, *J*=2, 5, 14 Hz, H-6eq), 4.67 (1H, d, *J*=15 Hz, 2-CH₂), 5.01 (1H, dt, *J*=2, 14 Hz, H-6ax), 5.96 (1H, d, *J*=15 Hz, 2-CH₂), 6.73-6.94 (2H, m, H-3' and 5'), 7.19 (1H, m, H-6'), 7.29 (1H, s, Tz-H), and 7.73 (1H, s, Tz-H). **9b**; δ1.72 (3H, d, *J*=7 Hz, 3-CH₃), 3.13 (1H, ddd, *J*=3, 7, 14 Hz, H-5), 3.36 (1H, ddd, *J*=3, 8, 14 Hz, H-5), 3.73 (1H, q, *J*=7 Hz, H-3), 4.38 (1H, ddd, *J*=3, 8, 14 Hz, H-6), 4.62 (1H, ddd, *J*=3, 7, 14 Hz, H-6), 4.85 (1H, d, *J*=15 Hz, 2-CH₂), 4.98 (1H, d, *J*=15 Hz, 2-CH₂), 6.80-6.88 (2H, m, H-3' and 5'), 7.25 (1H, m, H-6'), 7.69 (1H, s, Tz-H), and 7.78 (1H, s, Tz-H). **9c**; δ1.23 (3H, s, 3-CH₃), 1.57 (3H, d, *J*=4 Hz, 3-CH₃, long-range coupling with F atom), 3.08 (1H, br.d, *J*=14 Hz, H-5eq), 3.61 (1H, dt, *J*=5, 14 Hz, H-5ax), 4.44 (1H, ddd, *J*=2, 5, 14 Hz, H-6eq), 5.08 (1H, dt, *J*=2, 14 Hz, H-6ax), 5.31 (1H, d, *J*=16 Hz, 2-CH₂), 5.88 (1H, d, *J*=16 Hz, 2-CH₂), 6.81-6.92 (2H, m, H-3' and 5'), 7.57 (1H, m, H-6'), 7.72 (1H, s, Tz-H), and 7.75 (1H, s, Tz-H). **11**; δ1.23 (3H, s, 3-CH₃), 1.40 (3H, d, *J*=7 Hz, 5-CH₃), 1.58 (3H, d, *J*=4 Hz, 3-CH₃, long-range coupling with F atom), 3.63 (1H, m, H-5ax), 4.20 (1H, dd, *J*=5, 14 Hz, H-6eq), 4.68 (1H, dd, *J*=12, 14 Hz, H-6ax), 5.29 (1H, d, *J*=16 Hz, 2-CH₂), 5.83 (1H, d, *J*=16 Hz, 2-CH₂), 6.81-6.92 (2H, m, H-3' and 5'), 7.56 (1H, m, H-6'), 7.71 (1H, s, Tz-H), and 7.74 (1H, s, Tz-H).
- 13) The *in vitro* and *in vivo* activities of the compounds were tested by the same methods as we described previously. For the details, see ref. 7.
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