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

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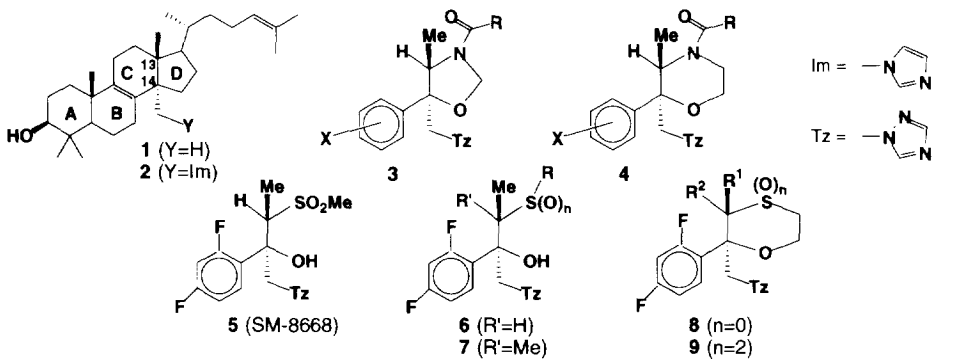
Abstract: A series of azole derivatives containing an oxathiane ring, which were designed to simulate the D ring of lanosterol, were synthesized and evaluated for their antifungal activity. 3,3-Dimethyl derivatives showed potent activity against murine systemic candidosis and aspergillosis, whereas (2*R**,3*R**)-3-monomethyl 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 P_{450} 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]



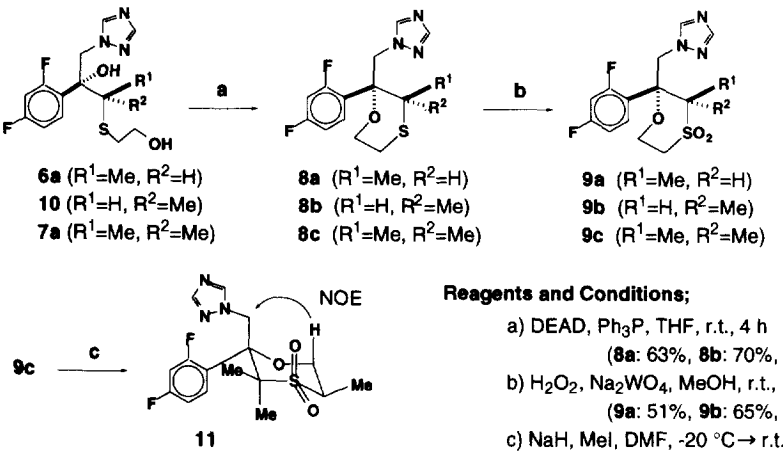
showed potent antifungal activity in both *in vitro* and *in vivo*. As a part of our search for active antifungal agents, we designed and synthesized triazole derivatives **8** and **9** containing an oxathiane ring as hybridized analogs of six-membered ring analogs **4** and sulfur-containing analogs **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 reaction[9] 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 tungstate[11] to give 4,4-dioxooxathianes **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]



6a (R^1=Me, R^2=H)
10 (R^1=H, R^2=Me)
7a (R^1=Me, R^2=Me)

8a (R^1=Me, R^2=H)
8b (R^1=H, R^2=Me)
8c (R^1=Me, R^2=Me)

9a (R^1=Me, R^2=H)
9b (R^1=H, R^2=Me)
9c (R^1=Me, R^2=Me)

Reagents and Conditions;
a) DEAD, Ph_3P, THF, r.t., 4 h
(**8a**: 63%, **8b**: 70%, **8c**: 50%)
b) H_2O_2, Na_2WO_4, MeOH, r.t., 1 h
(**9a**: 51%, **9b**: 65%, **9c**: 78%)
c) NaH, MeI, DMF, -20 °C→ r.t. 1 h (62%)

Antifungal activity

The minimum inhibitory concentration values (MIC, μg/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*-acylmorpholine 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 diequatrial 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	
	C. albicans	*A. fumigatus*	*C. albicans* *2	*A. fumigatus**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*R**,3*R**)				
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*R**,3*S**)				
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.

References and notes

1) a) Aoyama, Y.; Yoshida, Y.; Sato, R. *J. Biol. Chem.* **1984**, *259*, 1661. b) Aoyama, Y.; Yoshida, Y. *Biochem Pharmacol.* **1987**, *36*, 229.

2) a) Gadher, P.; Mercer, E. I.; Baldwin, B. C.; Wiggens, T. E. *Pestic. Biochem. Physiol.* **1983**, *19*, 1. b) Trzaskos, J. M.; Bowen, W. D.; Shafiee, A.; Fisher, R. T.; Gaylor, J. T. *J. Biol. Chem.* **1984**, *259*, 13402. c) Schroeper, G. T. *Ann. Rev. Biochem.* **1982**, *51*, 603.

3) Cooper, A. B.; Wright, J. J.; Ganguly, A. K.; Desai, J.; Loebenberg, D.; Parmegiani, R.; Feingold, D. S.; Sud, I. J. *J. Chem. Soc. Chem. Commun.* **1989**, 898.

4) Konosu, T.; Tajima, Y.; Takeda, N.; Miyaoka, T.; Kasahara, M.; Yasuda, H.; Oida, S. *Chem. Pharm. Bull.* **1990**, *38*, 2476.

5) Bartroli, J.; Turmo, E.; Algueró, M.; Boncompte, E.; Vericat, M. L.; García-Rafanell, J.; Forn, J. *J. Med. Chem.* **1995**, *38*, 3918.

6) Tanio, T.; Ichise, K.; Nakajima, T.; Okuda, T. *Antimicrob. Agents Chemother.* **1990**, *34*, 980.

7) a) Miyauchi, H.; Kozuki, K.; Tanio, T.; Ohashi, N. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1479. b) Miyauchi, H.; Kozuki, K.; Tanio, T.; Ohashi, N. *Bioorg. Med. Chem.* **1996**, *4*, 263.

8) Miyauchi, H.; Kozuki, K.; Tanio, T.; Ohashi, N. *Chem. Pharm. Bull.* **1996**, *44*, 785.

9) Mitsunobu, O. *Synthesis* **1981**, 1.

10) *erythro*-Diol **10** was prepared by the same method as described for *threo*-diol **6a**. For the details, see ref. 7 and 11.

11) Saji, I.; Tamoto, K.; Tanaka, Y.; Miyauchi, H.; Fujimoto, K.; Ohashi, N. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1427.

12) ^{1}H-NMR data (270 MHz, $CDCl_3$) of sulfones: **9a**; δ1.24 (3H, d, *J*=7 Hz, 3-CH_3), 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-CH_2), 5.01 (1H, dt, *J*=2, 14 Hz, H-6ax), 5.96 (1H, d, *J*=15 Hz, 2-CH_2), 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-CH_3), 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-CH_2), 4.98 (1H, d, *J*=15 Hz, 2-CH_2), 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-CH_3), 1.57 (3H, d, *J*=4 Hz, 3-CH_3, 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-CH_2), 5.88 (1H, d, *J*=16 Hz, 2-CH_2), 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-CH_3), 1.40 (3H, d, *J*=7 Hz, 5-CH_3), 1.58 (3H, d, *J*=4 Hz, 3-CH_3, 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-CH_2), 5.83 (1H, d, *J*=16 Hz, 2-CH_2), 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.

14) *In vitro* antifungal activity among azols is sometimes recognized to be unreliable in predicting *in vivo* activity. For typical examples, see, a) Graybill, J. R.; Craven, P. C. *Drugs* **1983**, *25*, 41. b) Mullen, G. B.; DeCory, T. R.; Mitchell, J. T.; Allen, S. D.; Kinsolving, C. R.; St. Georgiev, V. *J. Med. Chem.* **1988**, *31*, 2008. c) Konosu, T.; Takeda, N.; Tajima, Y.; Yasuda, H.; Oida, S. *Chem. Pharm. Bull.* **1990**, *38*, 1258.

15) a) Richardson, K.; Brammer, K. W.; Marriott, M. S.; Troke, P. F. *Antimicrob. Agents Chemother.* **1985**, *27*, 832. b) Richardson, K.; Cooper, K.; Marriott, M. S.; Tarbit, M. H.; Troke, P. F.; Whittle, P. J. *N. Y. Acad. Sci.* **1988**, *544*, 12.

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