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Synthesis and antifungal activity of 1*H*-indole-4,7-diones

Chung-Kyu Ryu,* Jung Yoon Lee, Rae-Eun Park, Mi-Young Ma and Ji-Hee Nho

College of Pharmacy, Ewha Womans University, Seodaemun-ku, Seoul 120-750, Republic of Korea

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Abstract—1*H*-Indole-4,7-diones were synthesized and tested for in vitro antifungal activity against fungi. The synthesized 1*H*-indole-4,7-diones generally showed good antifungal activity against *Candida krusei*, *Cryptococcus neoformans*, and *Aspergillus niger*. The results suggest that 1*H*-indole-4,7-diones would be potent antifungal agents.

Heterocyclic quinone compounds represent an important class of biologically active molecules.[1] The quinones such as 5-*n*-undecyl-6-hydroxy-4,7-dioxobenzothiazole (UHDBT, **1**) blockade a mitochondrial electron transport in *Saccharomyces cerevisiae*.[2] The UHDBT (**1**) has been reported as inhibitors of mitochondrial cytochrome complex in yeast[3] and bacteria.[4] In our previous report, [5] 4,7-dioxobenzothiazoles **2** which could be analogues of UHDBT have demonstrated potent antifungal activity against pathogenic fungi (Fig. 1).

A variety of heterocyclic quinones with different substituents could exhibit the biological activities through different action and sometimes improve upon the activities. The presence of thio, amino, halo, and alkyl substituents of quinones was considerably important factor to affect their antifungal activity.[5] Based on this speculation, we further extended to synthesize 1*H*-indole-4,7-dione derivatives **3** and **4** which would be bioisosteres of quinones **2**, and evaluated their antifungal activity.

There have been many reports on 1*H*-indole-4,7-diones, exhibiting cytotoxic activities[6–10] against cancer cell lines, and antibacterial activity.[11] However, the inhibitory activity of compounds **3** and **4** on the antifungal properties has not been reported to the best of our knowledge. Therefore, the 1*H*-indole-4,7-diones **3** and **4** with various substituents were designed and synthesized to elucidate their contribution to the antifungal activity. The in vitro antifungal activity of compounds **3** and **4** against pathogenic fungi was determined by the 2-fold broth dilution method.

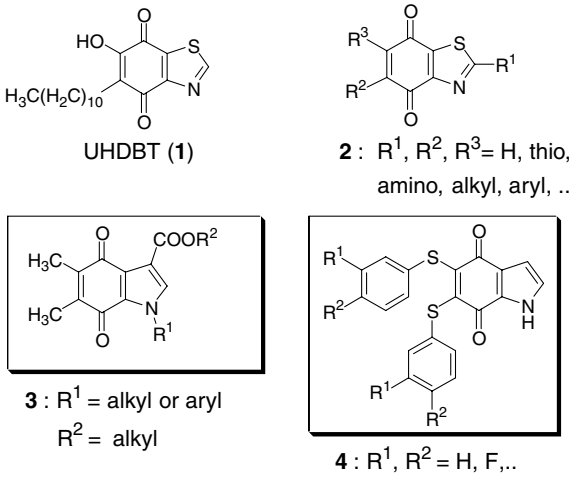

Figure 1. 1*H*-Indole-4,7-dione derivatives.

A method for the synthesis of 1*H*-indole-4,7-diones **3a**–**m** (Table 1) is shown in (Scheme 1). 2,3-Dichloro-5,6-dimethylcyclohexa-2,5-diene-1,4-dione (**5**) was prepared by oxidizing 2,3-dimethylbenzene-1,4-diol with HNO_3/HCl according to known method.[12] Methyl or ethyl 2-(2-chloro-4,5-dimethyl-3,6-dioxocyclohexa-1,4-dienyl)-2-cyanoacetate (**6a** or **6b**) was synthesized by nucleophilic substitution of compound **5** with equivalent of methyl or ethyl cyanoacetate in EtOH in the presence of NH_4OH. When equivalent amounts of compound **6a** and appropriate arylamines were mixed in EtOH and refluxed for 5 h, compounds **3c**–**m** were formed. In

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* Corresponding author. Tel.: +82 2 3277 3027; fax: +82 2 3277 3051; e-mail: ckryu@mm.ewha.ac.kr

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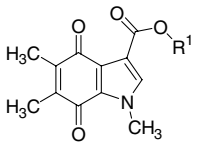
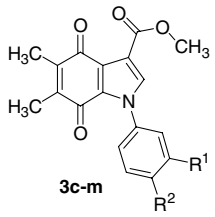
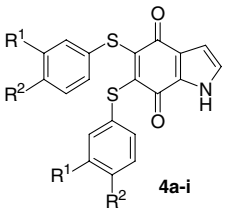
Table 1. Structures and in vitro antifungal activity for 1*H*-indole-4,7-diones



3a-b



3c-m

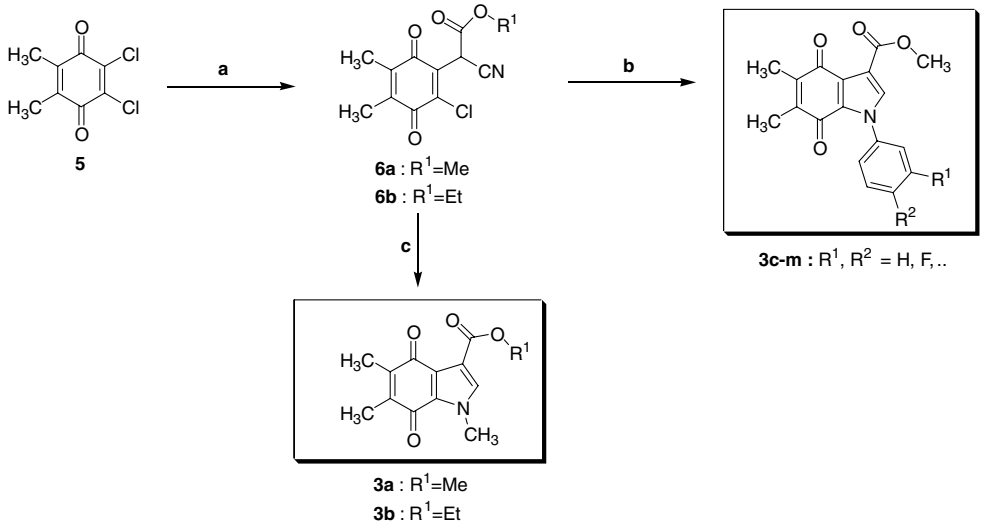


4a-i

Compound	R^1	R^2	MIC[a] (μg/mL)				
			Candida albicans[b]	*Candida tropicalis*	*Candida krusei*	*Cryptococcus neoformans*	*Aspergillus niger*
3a	CH_3	—	>100	>100	3.2	1.6	>100
3b	CH_3CH_2	—	>100	25	50	100	>100
3c	H	H	3.2	12.5	1.6	6.3	25
3d	H	F	>100	>100	3.2	3.2	12.5
3e	H	Cl	12.5	12.5	0.8	12.5	25
3f	H	Br	50	6.3	50	50	3.2
3g	H	I	25	12.5	50	50	100
3h	H	CH_3	>100	>100	3.2	0.8	>100
3i	H	CH_3O	>100	50	3.2	100	>100
3j	CH_3	CH_3	12.5	>100	0.8	1.6	6.3
3k	H	CF_3O	>100	>100	6.3	1.6	3.2
3l	H	CH_3CH_2	25	50	50	50	3.2
3m	H	$(CH_3)_2CH$	12.5	12.5	100	100	3.2
4a	H	H	>100	>100	>100	12.5	50
4b	H	F	100	25	3.2	6.3	100
4c	H	Cl	>100	12.5	25	3.2	>100
4d	H	Br	>100	>100	>100	3.2	12.5
4e	CH_3	H	>100	12.5	>100	3.2	50
4f	CH_3	CH_3	>100	>100	>100	50	100
4g	F	F	>100	>100	12.5	50	>100
4h	Cl	H	6.3	1.6	25	3.2	25
4i	H	OH	50	50	>100	25	>100
6a	—	—	>100	>100	100	6.3	>100
6b	—	—	>100	>100	100	25	>100
5-Fluorocytosine			6.3	12.5	6.3	12.5	50

[a] The MIC value was defined as the lowest concentration of the antifungal agent. MIC values were read after 1 day for *Candida* species and *Cryptococcus neoformans*, and 2 days for *Aspergillus niger* in 37 °C. The inoculum sizes contained approximately 1×10^5 cells/mL. Culture media tested were the modified Sabouraud dextrose broth (Difco Lab.). The final concentration of antifungal agents was between 0.2 and 100 μg/mL.

[b] Fungi tested: *Candida albicans* Berkout KCCM 50235, *Candida tropicalis* Berkout KCCM 50662, *Candida krusei* Berkout KCCM 11655, *Cryptococcus neoformans* KCCM 50564 and *Aspergillus niger* KCTC 1231.



Scheme 1. Synthesis of 1*H*-indole-4,7-diones. Reagents and conditions: (a) methyl cyanoacetate or ethyl cyanoacetate/EtOH/NH_4OH/rt/10 min; (b) **6a**/arylamine/EtOH/reflux/5 h; (c) **6a** or **6b**/methylamine/EtOH/reflux/5 h.