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Synthesis and antifungal activity of 1*H*-pyrrolo[3,2-*g*]quinoline-4,9-diones and 4,9-dioxo-4,9-dihydro-1*H*-benzo[*f*]indoles

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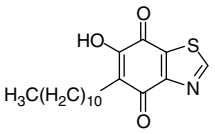
ABSTRACT

1*H*-Pyrrolo[3,2-*g*]quinoline-4,9-diones and 4,9-dioxo-4,9-dihydro-1*H*-benzo[*f*]indoles were synthesized and tested for in vitro antifungal activity against fungi. Among them tested, many compounds showed good antifungal activity. The results suggest that 1*H*-pyrrolo[3,2-g]quinoline-4,9-diones and 4,9-dioxo-4,9-dihydro-1*H*-benzo[*f*]indoles would be potent antifungal agents.

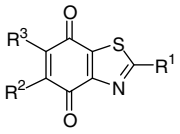
Heterocyclic quinone scaffolds represent often an important class of biologically active molecules.[1] The quinones such as 5-*n*-undecyl-6-hydroxy-4,7-dioxobenzothiazole (UHDBT, **1**) blockade a mitochondrial electron transport in *Saccharomyces cerevisiae*.[2] UHDBT (**1**) has been reported as an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

Structure–activity relationship studies from quinonoid compounds indicated that the number and position of nitrogen (N) atoms substituted in the heterocyclic ring were considerably important factors to affect the biological activities.[5,6] Generally, increase of the number of substituent nitrogen atoms and the ring enhances the activities. We speculated that incorporation of aromatic ring to the quinone skeleton in compounds **3** would change the physicochemical properties, and lead to a new pharmacophore with a different biological profile from compounds **3**. The presence of aryl, alkyl, amino, and halo substituents of quinones was considerably important factor to affect their antifungal activity.[5,6] Based on this information, we further extended to synthesize 1*H*-pyrrolo[3,2-*g*]quinoline-4,9-diones **4** and 4,9-dioxo-4,9-dihydro-1*H*-benzo[*f*]indoles **5** which would be analogs of compounds **3**, and evaluated their antifungal activity.

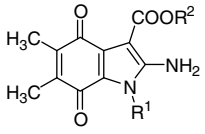
There have been a few reports on 1*H*-pyrrolo[3,2-*g*]quinoline-4,9-diones and 4,9-dioxo-4,9-dihydro-1*H*-benzo[*f*]indoles, exhibiting cytotoxic activities against cancer cell lines.[7,8] However, the inhibitory activity of compounds **4** and **5** on the antifungal properties has not been reported to the best of our knowledge. Therefore, 2-amino-1-aryl-4,9-dioxo-4,9-dihydro-1*H*-pyrrolo[3,2-*g*]quinoline-3-carboxylates **4a–m** and 1-alkyl or aryl-2-amino-4,9-dioxo-4,9-



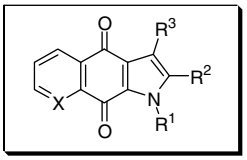
UHDBT (**1**)



2 : R^1, R^2, R^3= H, thio, amino, alkyl, aryl, ..



3 : R^1 = alkyl or aryl
R^2 = alkyl



4: X=N, **5**: X=CH
R^1, R^2 and R^3 = H, NH_2, alkyl, aryl, ester or CN

Figure 1. Heterocyclic quinone compounds.

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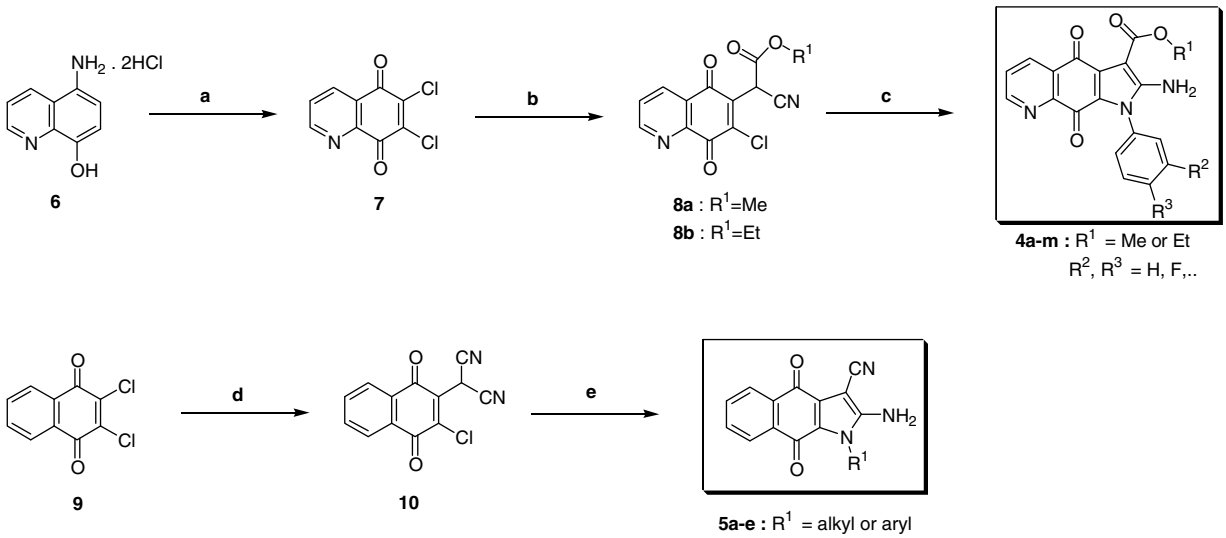
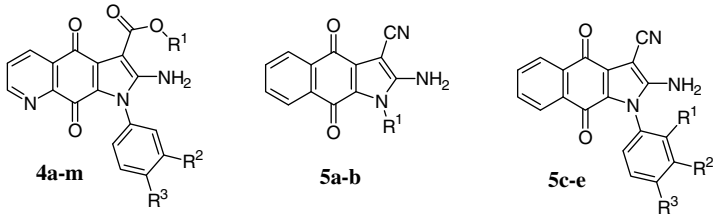


Scheme 1. Reagents and conditions: (a) $NaClO_3$/HCl/H_2O/60° C/30 min; (b) methyl cyanoacetate or ethyl cyanoacetate/EtOH/NH_4OH/rt/10 min (c) **8a** or **8b**/arylamine/EtOH/reflux/5 h; (d) malononitrile/triethylamine/EtOH/reflux/20 min; (e) alkyl or arylamine/EtOH/reflux/5 h.

dihydro-1*H*-benzo[*f*]indole-3-carbonitriles **5a–e** with various substituents were designed and synthesized to elucidate their contribution to the antifungal activity (Scheme 1). The in vitro antifungal activity of compounds **4a–m** and **5a–e** against pathogenic fungi was determined by the twofold broth dilution method. Additional data for properties and antifungal activity of compound **6** is provided.

A method for the synthesis of 1*H*-pyrrolo[3,2-*g*]quinoline-4,9-diones **4a–m** is shown in Scheme 1 and Table 1. 6,7-Dichloroquinoline-5,8-dione (**7**) was prepared by oxidizing commercially available 5-aminoquinolin-8-ol (**6**) with $NaClO_3$/HCl.[9] Methyl or ethyl 2-(7-chloro-5,8-dioxo-5,8-dihydroquinolin-6-yl)-2-cyanoacetate (**8a** or **8b**) was synthesized by nucleophilic substitution of

Table 1
Structures and in vitro antifungal activity for 1*H*-pyrrolo[3,2-*g*]quinoline-4,9-diones and 4,9-dioxo-4,9-dihydro-1*H*-benzo[*f*]indoles.



Compound	R^1	R^2	R^3	MIC[a] (μg/mL)				
				Candida albicans[b]	*Candida tropicalis*	*Candida krusei*	*Cryptococcus neoformans*	*Aspergillus niger*
4a	CH_3	H	H	>100	>100	50	>100	50
4b	CH_3	H	CH_3	100	100	12.5	12.5	>100
4c	CH_3	H	CH_3O	>100	>100	12.5	>100	50
4d	CH_3CH_2	H	H	>100	6.3	>100	50	50
4e	CH_3CH_2	H	CH_3	>100	3.2	12.5	12.5	25
4f	CH_3CH_2	H	CH_3O	>100	12.5	>100	50	25
4g	CH_3CH_2	H	OH	3.2	0.6	12.5	12.5	25
4h	CH_3CH_2	H	F	>100	6.3	>100	25	50
4i	CH_3CH_2	H	Cl	>100	3.2	>100	50	6.3
4j	CH_3CH_2	H	Br	50	3.2	>100	25	50
4k	CH_3CH_2	H	I	25	3.2	25	25	12.5
4l	CH_3CH_2	H	CF_3	6.3	0.8	6.3	12.5	12.5
4m	CH_3CH_2	F	F	1.6	50	25	50	25
5a	CH_3	—	—	12.5	6.3	12.5	12.5	25
5b	CH_3CH_2	—	—	25	25	12.5	12.5	25
5c	H	H	H	100	100	3.2	100	>100
5d	H	H	CH_3	>100	>100	3.2	100	>100
5e	CH_3	H	CH_3	25	25	3.2	12.5	25
6	—	—	—	>100	>100	100	100	>100
Fluconazole	—	—	—	12.5	6.3	25	50	50
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 *C. neoformans*, and 2 days for *A. 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.

compound **7** with equivalent of methyl or ethyl cyanoacetate in EtOH in the presence of NH_4OH according to known method[10] with minor modification. When equivalent amount of compound **8a** and appropriate arylamines were mixed in EtOH and refluxed for 5 h, compounds **4a–c** were formed. Compounds **4d–m** were prepared by cyclization of compound **8b** with arylamines in EtOH.

In similar manner, a method for the synthesis of 2-amino-1-alkyl or aryl-4,9-dioxo-4,9-dihydro-1*H*-benzo[*f*]indole-3-carbonitriles **5a–e** is shown in Scheme 1 and Table 1. The 2-(3-chloro-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-malononitrile (**10**) was synthesized by nucleophilic substitution of 2,3-dichloro-1,4-naphthoquinone (**9**) with equivalent of malononitrile in EtOH in the presence of triethylamine.[11] When equivalent amount of the compound **10** and appropriate alkyl or arylamines were mixed in EtOH and refluxed for 5 h, compounds **5a–e** were formed.

The synthesized 1*H*-pyrrolo[3,2-*g*]quinoline-4,9-diones **4a–m** and 4,9-dioxo-4,9-dihydro-1*H*-benzo[*f*]indoles **5a–e** were tested in vitro for their growth inhibitory activity against pathogenic fungi by the standard method.[12] As indicated in Table 1, the MIC (minimum inhibitory concentration) values were determined by comparison with fluconazole and 5-fluorocytosine as standard agents. Among tested compounds **4a–m**, many compounds generally showed potent antifungal activity against the tested pathogenic fungi. Actually, the activity of compounds **4g** and **4l** was superior or comparable to those of 5-fluorocytosine against all tested fungi. The compounds **4g** and **4l** completely inhibited the growth of all fungal species tested at the MIC level of 1.6–25 μg/mL.

Among tested 4,9-dioxo-4,9-dihydro-1*H*-benzo[*f*]indoles **5a–e**, compounds **5a**, **5b**, and **5e** generally showed potent antifungal activity against the tested pathogenic fungi. In contrast, compounds **5c** and **5d** did not show significant antifungal activity, although these compounds exhibited good activity against *Candida krusei*.

In addition, 5-aminoquinolin-8-ol (**6**) exhibited no or poor, if any, antifungal activity. 1*H*-Pyrrolo[3,2-*g*]quinoline-4,9-diones **4** and 4,9-dioxo-4,9-dihydro-1*H*-benzo[*f*]indoles **5** showed, in general, more potent antifungal activity than compound **6**. Thus, the quinone moiety in compounds **4** and **5** could be essential for the activity, for example, as nonquinonoid compound **6** loses the activity. The structure–activity relationship may not exist between properties of subsistent (R^1, R^2, and R^3) for the 1-aryl moieties of compounds **4a–m** and **5c–e**.

In conclusion, alkyl-2-(7-chloro-5,8-dioxo-5,8-dihydroquinolin-6-yl)-2-cyanoacetate (**8a** or **8b**) was synthesized by nucleophilic substitution of compound **7** with equivalent of alkyl cyanoacetate in the presence of NH_4OH. The compound **10** was prepared by nucleophilic substitution of 2,3-dichloro-1,4-naphthoquinone (**9**) with equivalent of malononitrile in the presence of triethylamine. 1*H*-Pyrrolo[3,2-*g*]quinoline-4,9-diones **4a–m** and 4,9-dioxo-4,9-dihydro-1*H*-benzo[*f*]indoles **5a–e** were synthesized by cyclization of compounds **8a, 8b**, or **10** with amines in EtOH. Among them tested, many of compounds **4a–m** and **5a–e** showed potent antifungal activity against pathogenic fungi. These 1*H*-pyrrolo[3,2-*g*]quinoline-4,9-diones and 4,9-dioxo-4,9-dihydro-1*H*-benzo[*f*]indoles may thus be promising leads for the development of antifungal agents. Moreover, the results should encourage the synthesis of these analogs for improving antifungal properties.

Acknowledgments

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