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Bioorganic & Medicinal Chemistry Letters 15 (2005) 679–682
Bioorganic & Medicinal Chemistry Letters

Synthesis and antifungal activity of noble 5-arylamino- and 6-arylthio-4,7-dioxobenzoselenazoles

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Received 23 September 2004; revised 10 November 2004; accepted 11 November 2004
Available online 7 December 2004

Abstract—5-Arylamino- and 6-arylthio-4,7-dioxobenzoselenazoles **4** and **5** were synthesized and tested for in vitro antifungal activity against *Candida* and *Aspergillus* species. 5-Arylamino-4,7-dioxobenzoselenazoles **4** showed, in general, more potent antifungal activity than 6-arylthio-4,7-dioxobenzoselenazoles **5**. The results suggest that 5-arylamino-4,7-dioxobenzoselenazoles **4** would be potent antifungal agents.

1. Introduction

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**) block mitochondrial electron transport in *Saccaromyces cerevisiae*.[2] UHDBT (**1**) was reported as an inhibitor of mitochondrial cytochrome complex in yeast,[3,4] malaria,[5] bacteria[6] and mammals.[7] In our previous reports,[8] 5-arylamino- and 6-arylthio-4,7-dioxobenzothiazoles **2** and **3**, which have 1′-sulfur (S) as analogues of UHDBT, demonstrated potent antifungal activity against pathogenic fungi (Fig. 1). This fact prompted us to consider a bioisosteric substitution of the 1′-sulfur by selenium (Se). The quinone analogues containing selenium such as 5-arylamino-4,7-dioxobenzoselenazoles **4** and 6-arylthio-4,7-dioxobenzoselenazoles **5** could have similar activity as compounds **2** and **3** since selenium is isoelectronic with sulfur.

A variety of heterocyclic quinones with different substituents could exhibit the activities through different action and sometimes improve the activities. The presence of arlyamino, arylthio, alkyl group or hetero atoms substituted in quinones was a considerably important factor to affect their antifungal activity.[8–10] Based on these considerations, the 4,7-dioxobenzoselenazoles **4** and **5** with various substituents were designed and synthesized to elucidate their contribution to the antifungal activity (Scheme 1).

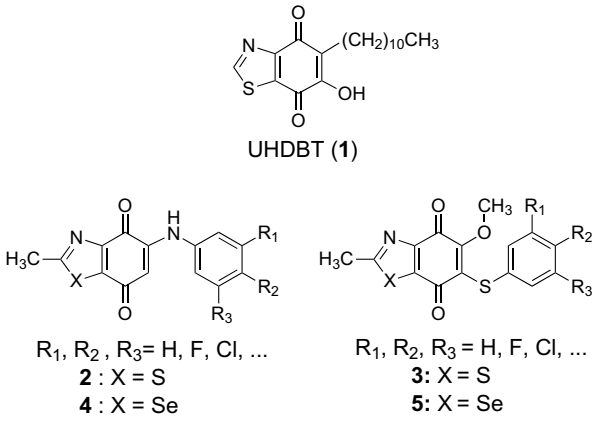

Figure 1. Antifungal 4,7-dioxobenzoselenazole derivatives.

The in vitro antifungal activity of the 4,7-dioxobenzoselenazoles **4** and **5** against pathogenic fungi was determined by the twofold broth dilution method. Additional data for properties and antifungal activity of 4,7-dioxobenzoselenazoles are provided.

Keywords: 4,7-Dioxobenzoselenazole; Antimicrobial compounds; Antifungal; Fungi; Substitution effects.
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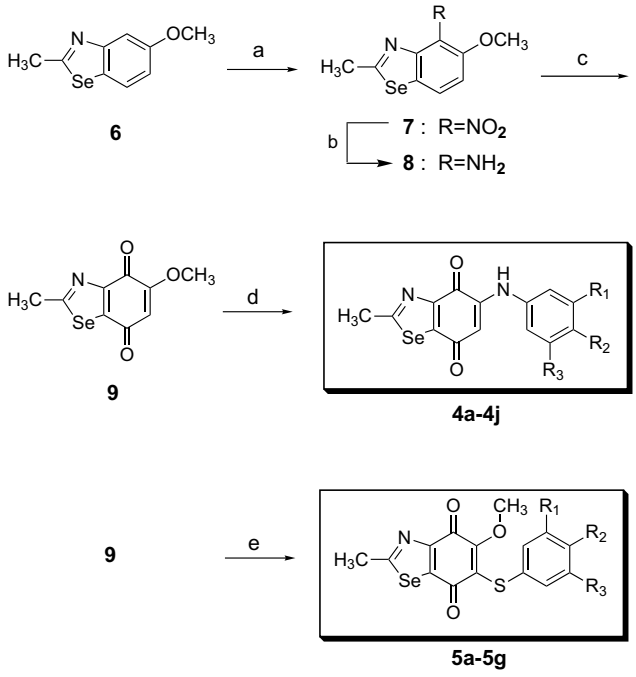
doi:10.1016/j.bmcl.2004.11.027



Scheme 1. Synthesis of 4,7-dioxobenzoselenazoles **4** and **5**. Reagents and conditions: (a) HNO_3/H_2SO_4/rt/5 h; (b) $SnCl_2$/HCl/60 °C/1 h; (c) Fremy's salt (2 equiv) in 0.3 M KH_2PO_4/H_2O/rt/5 h; (d) arylamine (1 equiv)/EtOH/reflux/4–6 h; (e) arylthiol (1 equiv)/EtOH/reflux/4–10 h.

2. Chemistry

A method for the synthesis of 5-arylamino-/6-arylthio-4,7-dioxobenzoselenazoles **4a–j**, and **5a–g** (Table 1) is shown in Scheme 1. Nitration of 5-methoxy-2-methyl-benzoselenazole (**6**) by HNO_3/H_2SO_4 afforded 5-methoxy-2-methyl-4-nitro-benzoselenazole (**7**) in about 92% yield. 4-Amino-5-methoxy-2-methyl-benzoselenazole (**8**) was prepared by reduction of the compound **7** with $SnCl_2$/HCl variation in about 70% yield. 5-Methoxy-2-methyl-4,7-dioxobenzoselenazole (**9**) was synthesized by oxidizing the compound **8** with Fremy's salt (potassium nitrosodisulfonate) in 59% yield. 5-Arylamino-2-methyl-4,7-dioxobenzoselenazoles **4a–j** were synthesized by regioselective nucleophilic substitution of compound **9** with appropriate arylamines. It is well known that the displacement of the methoxy group in quinones with the arylamine produces regioselective arylaminated quinones.[8] The substitution was similar to the regioselective arylamination on 6-position of 6-methoxy-4,7-dioxobenzothiazole in previously reported papers.[8,10]

6-Arylthio-5-methoxy-4,7-dioxobenzoselenazoles **5a–g** were synthesized by reaction of compound **9** with appropriate arylthiols. In the reactions, 6-arylthio compounds **5a–g** were exclusively formed. The regioselective reaction was similar to the substitution of arylthiols on 6-position of 5-methoxy-2-methyl-4,7-dioxobenzothiazole in the reported paper.[10]

Experimental details and data for this procedure are cited in References and notes.[11,12]

3. Antifungal activity

The synthesized 4,7-dioxobenzoselenazoles **4** and **5** were tested in vitro for their growth inhibitory activity against pathogenic fungi by the standard method.[13] The MIC (minimum inhibitory concentration) values were determined by comparison with 5-fluorocytosine as a standard

Table 1. Structures and in vitro antifungal activity for 4,7-dioxobenzoselenazoles **4** and **5**

Compds	R_1	R_2	R_3	MIC[a] (μg/mL)				
				C. albicans[b]	*C. tropicalis*	*C. krusei*	*A. niger*	*A. flavus*
4a	H	H	H	6.3	6.3	6.3	6.3	6.3
4b	H	F	H	6.3	6.3	6.3	6.3	12.5
4c	H	Cl	H	12.5	12.5	25.0	12.5	12.5
4d	H	Br	H	12.5	50.0	50.0	25.0	50.0
4e	H	I	H	25.0	25.0	25.0	25.0	25.0
4f	H	CH_3	H	6.3	25.0	25.0	6.3	12.5
4g	H	OCH_3	H	12.5	12.5	12.5	12.5	12.5
4h	H	CF_3	H	25.0	3.2	3.2	12.5	25.0
4i	F	H	H	12.5	3.2	6.3	12.5	12.5
4j	Cl	H	Cl	1.6	3.2	25.0	12.5	12.5
5a	H	H	H	6.3	6.3	6.3	12.5	12.5
5b	H	F	H	25.0	3.2	25.0	50.0	50.0
5c	H	Cl	H	25.0	12.5	25.0	25.0	25.0
5d	H	CH_3	H	12.5	6.3	25.0	25.0	50.0
5e	H	OCH_3	H	25.0	12.5	12.5	12.5	25.0
5f	F	F	H	12.5	6.3	6.3	25.0	25.0
5g	H	NO_2	H	3.2	1.6	25.0	50.0	12.5
9				50.0	12.5	25.0	25.0	50.0
5-Fluorocytosine				12.5	12.5	50.0	12.5	50.0

[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 2 days for *A. niger* in 37 °C. The inoculum sizes contained approximately 1×10^5 CFU/mL. Culture media tested were the modified Sabouraud dextrose broth (Difco Lab.). The final concentration of antifungal agents was between 0.4 and 100 μg/mL.

[b] Fungi tested: *Candida albicans* ATCC 10231, *C. tropicalis* ATCC 28775, *C. krusei* ATCC 749, *Aspergillus niger* KCTC 1231 and *A. flavus* KCCM 11899.