Synthesis and Antifungal Activity of 5,8-Quinazolinedione Derivatives Modified at Positions 6 and 7

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5,8-Quinazolinediones modified at positions **6** and **7** were synthesized and tested for *in vitro* antifungal activities against *Candida* species and *Aspergillus niger*. Most of 5,8-quinazolinediones 3-5 generally exhibited potent antifungal activity. 6-Arylamino-7-chloro-5,8-quinazolinediones (**3**) generally showed more potent antifungal activity than 7-arylthio-5,8-quinzolinediones (**4**) and 6,7-bis-(arylthio)-5,8-quinazolinediones (**5**).

Key words: 5,8-Quinazolinediones, Antifungal, MIC, Candida species, A. niger

INTRODUCTION

Heterocyclic quinone compounds represent an important class of biologically active molecules (Middleton and Parrick, 1988). 6,7-Disubstituted-5,8-quinolinedione, a heterocyclic quinone, displays various biological activities, including antifungal, antimalarial and antitumor activities (Roberts *et al.*, 1978; Jeschke *et al.*, 1993). The 5,8-quinolinediones, as antimetabolites of coenzyme Q, inhibit the cytochrome bc complex by the blockade of mito-chondrial electron transport in *Saccaromyces cerevisiae*, which is different from commonly used antifungal drugs (Roberts *et al.*, 1978). In our previous papers (Ryu and Kim, 1994; Ryu *et al.*, 2002b), 6-arylamino-7-chloro-5,8-quinolinediones (**1**) and 6,7-bis-(arylthio)-5,8-quinolinediones (**2**) were reported as potent antifungal agents (Fig. 1). Structure-activity relationship studies on quinonoid compounds indicated that the number and position of nitrogen (N) atoms substituted in the heterocyclic ring are considerably important factors to affect the biological activities (Shaikh *et al.*, 1986). Generally, increasing the number of substituent nitrogen atoms in the ring enhance the activities. We speculated that incorporation of a nitrogen atom into the ring of the quinone skeleton in compounds **1** and **2** would change the physicochemical properties, and lead to a new pharmacophore with a

different biological profile from compounds **1** and **2**. We assumed that incorporating an additional arylamino, arylthio, phenoxy or chloro moiety to the quinone would contribute to the improvement in efficacy. Based on this speculation, 6-arylamino-7-chloro-5,8-quinazolinediones (**3**), 7-arylthio-5,8-quinazolinediones (**4**) and 6,7-bis-(arylthio)-5,8-quinazolinediones (**5**), as bioisosteres of 5,8-quinolinediones **1** or **2**, were synthesized and their antifungal activity was evaluated (Scheme 1).

There have been a few reports on 5,8-quinazolinedione derivatives, exhibiting potent biological properties including cytotoxicity against cancer cell lines (Giorgi-Renault *et al.*, 1991; Park *et al.*, 2004; Renault *et al.*, 1983) and inhibitory activity of endothelium-dependent vasorelaxation (Ryu *et al.*, 2002a). However, antifungal properties of 5,8-quinazolinedione compounds have not been reported. We report, therefore, the synthesis and the antifungal activity of the 5,8-quinazolinedione series **3**, **4**, and **5**.

MATERIALS AND METHODS

All melting points were measured in open capillary tubes with a Buchi melting point B-545 and were uncorrected. TLC was performed on precoated silica gel (60G 254, Merck) using chloroform as the solvent. The compounds were detected under UV light (254 nm) or by heating to 110 °C after spraying with a 30% H_2SO_4-vanillin solution. Column chromatography was performed on silica gel G60 (70-230) mesh, NMR spectra were recorded on a Brucker DPX 250 MHz spectrometer using DMSO-d_6 as a solvent, and chemical shifts were given in ppm with

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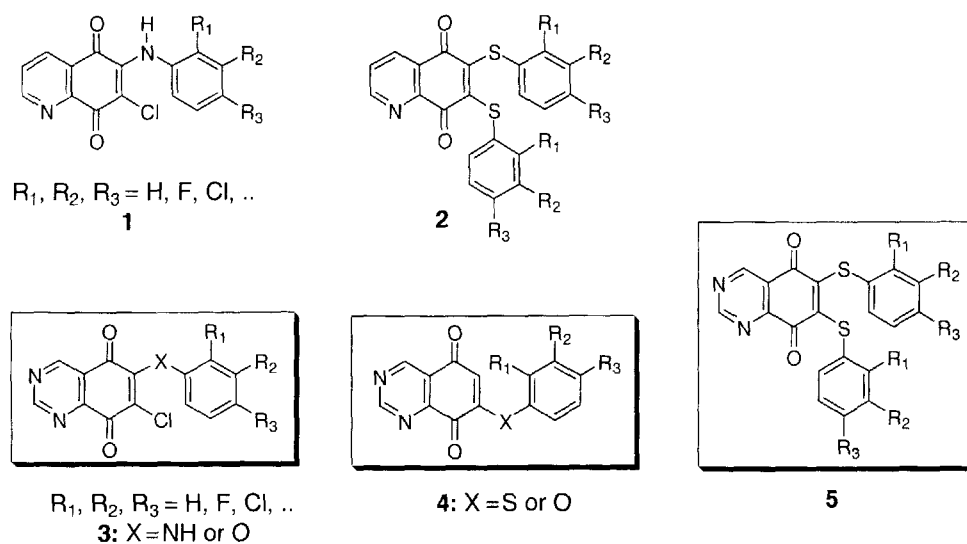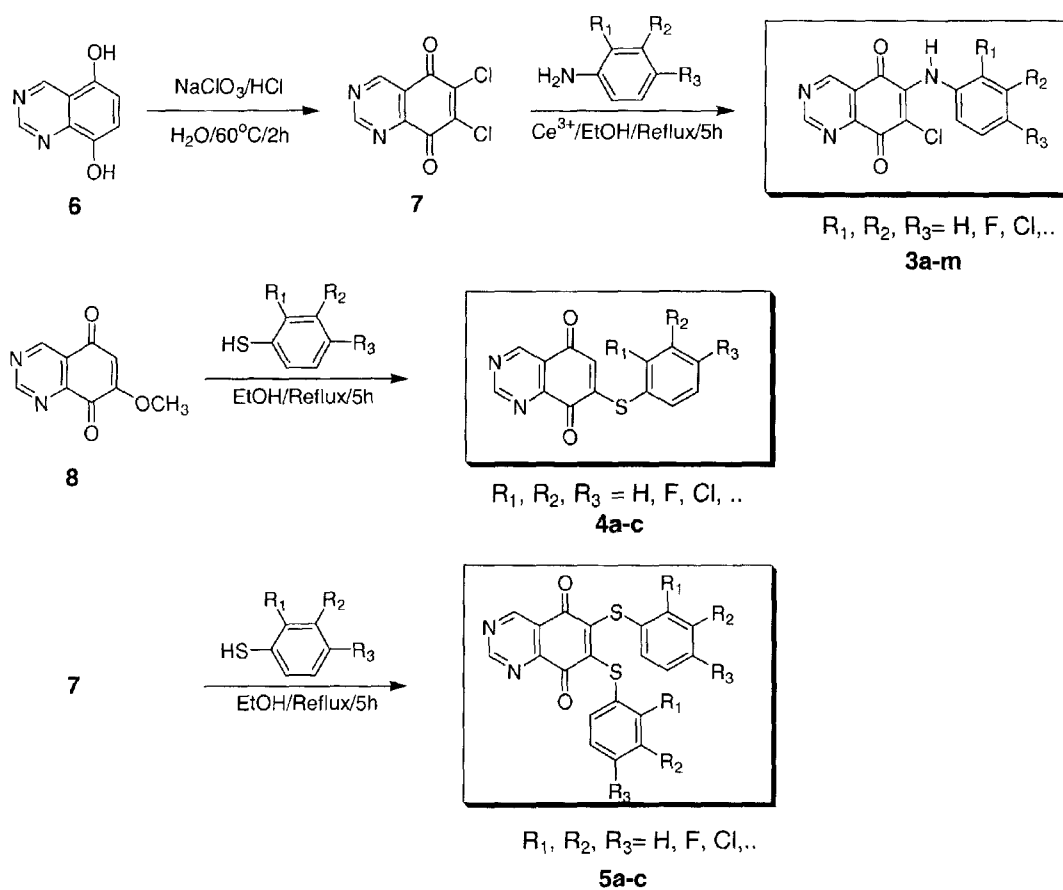E-mail: ckryu@mm.ewha.ac.kr

Fig. 1. Structures of 5,8-quinolinedione 1, 2 and 5,8-quinazolinedione derivates 3, 4, and 5

Scheme 1. Synthesis of 5,8-quinazolinediones

TMS as a standard. Mass spectra were obtained on a JMS AX 505 WA spectrometer (electronic impact at 70 eV). Elemental analyses were performed by CE instruments EA1110 with sulfanilamide as the standard material, and analytical results for C, H and N were within (0.4% of theoretical values. Arylamines, DMSO-d_6 and other reagents were obtained from Aldrich Chemical Co. Reagents for biological screening were obtained from Sigma Co.

Synthesis of 6,7-dichloro-5,8-quinazolinedione (7)

6,7-Dichloro-5,8-quinazolinedione (7) was prepared according to the procedure described in a previous paper (Ryu *et al.*, 2004). 5,8-Dihydroxyquinazoline (6) was prepared according to the known procedure (Melesani *et al.*, 1970). To a solution of compound 6 (1.62 g, 10 mmol) in 18 mL of conc-HCl, a solution of $NaClO_3$ (1 g) was added over 30 min at 60°C. The mixture was stirred at 50-60°C for 30 min and then was poured into 100 mL of ice water. The precipitate was filtered and crystallized from n-BuOH. 6,7-Dichloro-5,8-quinazolinedione (7) was obtained (0.7 g, 71%); mp 135°C (Shaikh *et al.*, 1986; Ryu *et al.*, 2004).

General procedure for the synthesis of 6-arylamino-7-chloro-5,8-quinazolinediones 3a-m

A solution of compound 7 (0.229 g, 1 mmol) and $CeCl_3·7H_2O$ (0.373 g, 1 mmol) in 15 mL of 95% EtOH was added to the solution of the arylamine (1.1 mmol) in 5 mL of 95% EtOH and stirred at r.t. for 2 h and then refluxed for 4-5 h. After the mixture was kept overnight in a refrigerator or poured into 20 mL of ice water, the precipitate was collected by filtration. The filtered crude product was purified by silica gel column chromatography with $CHCl_3$ or crystallized from 95% EtOH.

The physical data of compounds 3i-m were previously reported (Ryu *et al.*, 2004).

6-(4-Methoxyphenyl)amino-7-chloro-5,8-quinazolinedione (3a)

Dark brown powder (60% yield); mp 205-208°C; IR (KBr) 3390 (s, NH), 2900 (m), 1640 (s, C=O), 1450-1560, 1230 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 9.9 (s, 1H, NH), 9.5 (s, 1H, H2), 9.3 (s, 1H, H4), 7.1-6.8 (m, 4H, benzene), 3.5 (s, 3H, OCH_3); MS (m/z) 315 (M⁺); *Anal. Cald* for $C_{15}H_{10}ClN_3O_3$ (315.71): C, 57.06; H, 3.19; N, 13.31; Found : C, 57.01; H, 3.20; N, 13.30.

6-(4-Ethylphenyl)amino-7-chloro-5,8-quinazolinedione (3b)

Black powder (75% yield); mp 149-150°C; IR (KBr) 3430 (m, NH), 2930 (m), 1650 (s, C=O), 1560 (m), 1500(m), 1380 (s), 1270 (m), 820 (m), 750 (m), 660 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 9.9 (s, 1H, NH), 9.6 (s, 1H, H2), 9.3 (s, 1H, H4), 7.5-7.0 (m, 4H, benzene), 2.5 (q, J=7.5, 2H, CH_2), 1.1-1.2 (t, J=7.5, 3H, CH_3); MS (m/z) 313 (M⁺).

6-(3,4-Dimethylphenyl)amino-7-chloro-5,8-quinazolinedione (3c)

Gray violet powder (60% yield); mp 210-213°C; IR (KBr) 3430 (s, NH), 2920 (m), 1650 (s, C=O), 1450-1550, 1280 (m), 1030 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 10.2 (s, 1H, NH), 9.7 (s, 1H, H2), 9.5 (s, 1H, H4), 7.0-6.1 (m, 4H, benzene), 2.1 (s, 3H, H3), 1.9 (s, 3H, CH_3). MS (m/z) 313

(M⁺); *Anal. Cald* for $C_{16}H_{12}ClN_3O_2$ (313.06): C, 61.25; H, 3.86; N, 13.39; Found: C, 61.21; H, 3.4o; N, 13.37.

6-(4-Hexylphenyl)amino-7-chloro-5,8-quinazolinedione (3d)

Dark violet powder (80% yield); mp 136-139°C; IR (KBr) 3400 (s, NH), 2920 (m), 1650 (s, C=O), 1380 (m), 1270 (m), 970 (m), 750 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 9.6 (s, 1H, NH), 9.3 (m, 2H, H2, H4), 7.1-7.0 (m, 6H, benzene), 2.5 (s, 2H, C_6H_{13}), 1.2-1.5 (m, 8H, C_6H_{13}), 0.8 (t, J=7.7, 3H, C_6H_{13}); MS (m/z) 369 (M⁺); *Anal. Cald* for $C_{20}H_{20}ClN_3O_2$ (369.12): C, 64.95; H, 5.45; N, 11.36; Found: C, 63.80; H, 5.74; N, 11.16.

6-(2,3,4-Trifluorophenyl)amino-7-chloro-5,8-quinazolinedione (3e)

Shiny purple powder (65% yield); mp 385-386°C; IR (KBr) 3460 (m, NH), 1640 (m, C=O), 1470-1550, 1380 (s), 1270 (m), 1050 (m), 750 (m), 660 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 10.2 (s, 1H, NH), 9.9 (s, 2H, H2, H4), 7.4 (m, 4H, benzene); MS (m/z) 339 (M⁺).

6-(3,4-Difluorophenyl)amino-7-chloro-5,8-quinazolinedione (3f)

Violet powder (65% yield); mp >385°C; IR (KBr) 3430 (s, NH), 2950 (m), 1640 (s, C=O), 1500 (m), 1380 (m), 1270 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 10.2 (s, 1H, NH), 9.9 (s, 1H, H2), 9.4 (s, 1H, H4), 7.4-7.0 (m, 4H, benzene); MS (m/z) 321 (M⁺).

6-(4-Bromophenyl)amino-7-chloro-5,8-quinazolinedione (3g)

Dark purple powder (69% yield); mp 259-260°C; IR (KBr) 3400 (s, NH), 2890 (m), 1640 (s, C=O), 1470-1540, 1380 (s), 1270 (m), 740 (m), 680 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 10.2 (s, 1H, NH), 9.6 (s, 2H, H2, H4), 7.5-6.9 (m, 4H, benzene); MS (m/z) 363 (M⁺); *Anal. Cald* for $C_{14}H_7ClBrN_3O_2$ (362.96): C, 46.12; H, 1.94; N, 11.53; Found: C, 46.10; H, 1.94; N, 11.50.

6-(4-Methylphenyl)amino-7-chloro-5,8-quinazolinedione (3h)

Dark brown powder (72% yield); mp 236-238°C; IR (KBr) 3400 (m NH), 2950 (m), 1650 (m, C=O), 1420-1550, 1380 (s), 1270 (m), 740 (m), 680 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 9.6 (s, 1H, NH), 9.3 (s, 2H, H2, H4), 7.1-6.9 (m, 4H, benzene), 2.3 (s, 3H, CH_3); MS (m/z) 299 (M⁺); *Anal. Cald* for $C_{15}H_{10}ClN_3O_2$ (299.05): C, 60.11; H, 3.36; N, 14.02; Found: C, 56.95; H, 3.38; N, 14.05.

General procedure for synthesis of 7-arylthio-5,8-quinazolinediones 4a-c

7-Methoxy-5,8-quinazolinedione (8) was prepared as

the known procedure (Renault et al., 1983). A mixture of compound **8** (0.261 g, 1 mmol) and an appropriate arylthiol (1 mmol) in 15 mL of 95% EtOH was refluxed for 6-10 h. After the reaction mixture was kept overnight in the refrigerator, the precipitate was collected by filtration. The product was purified by silica gel column chromatography with $CHCl_3$ and recrystallized from 95% EtOH. The crystallized compounds **4a-c** were filtered, washed with cold 95% EtOH and dried (Table II).

7-(4-Methoxyphenyl)thio-5,8-quinazolinedione (4a)

Dark brown powder (32% yield); mp 169-172°C; IR (KBr) 3050 (m), 1680 (s, C=O), 1446-1551, 1380 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 10.19 (s, 2H, H2, H4), 7.42 (d, J=7.4, 2H, benzene), 7.96 (d, J=7.4, 2H, benzene), 6.52 (s, 1H, H6), 3.75 (s, 3H, OCH_3); MS (m/z) 298 (M⁺). Anal. Calcd for $C_{15}H_{10}N_2O_3S$ (298.32): C, 60.39; H, 3.38; N, 9.39; Found: C, 60.36; H, 3.30; N, 9.37.

7-(4-Fluorophenyl)thio-5,8-quinazolinedione (4b)

Dark brown powder (25% yield); mp 137-140°C; IR (KBr) 3021 (m), 1675 (s, C=O), 1442-1550, 1260 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 10.19 (s, 2H, H2, H4), 7.56 (d, J=7.8, 2H, benzene), 7.25 (d, J=7.8, 2H, benzene), 6.51 (s, 1H, H6); MS (m/z) 286 (M⁺).

7-(4-Chlorophenyl)thio-5,8-quinazolinedione (4c)

Dark brown powder (28% yield); mp 269-272°C; IR (KBr) 3033 (m), 1670 (s, C=O), 1455-1570, 1263 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 10.19 (s, 2H, H2, H4), 7.53 (d, J=7.6, 2H, benzene), 7.47 (d, J=7.4, 2H, benzene), 6.52 (s, 1H, H6); MS (m/z) 302 (M⁺).

General procedure for synthesis of 6,7-bis-(arylthio)-5,8-quinazolinediones 5a-c

A solution of compound **7** (0.227 g, 1 mmol) in 15 mL of 95% EtOH was added to the solution of the arylthiol (2.1 mmol) in 5 mL of 95% EtOH and stirred at room temperature for 2 h and then refluxed for 45 h. After the reaction mixture was kept overnight in the refrigerator or poured into 20 mL of ice water, the precipitate was collected by filtration. The crude product was purified by silica gel column chromatography with $CHCl_3$ or crystallized from 95% EtOH or MeOH. Crystallization from aq. EtOH afforded the 6,7-bis-(arylthio)-5,8-quinolinediones **5a-c**.

6,7-Bis-[(4-methylphenyl)thio]-5,8-quinazolinedione (5a)

Dark violet powder (53% yield); mp 98-102°C; IR (KBr) 3249 (m), 1679 (s, C=O), 1459-1556, 1281 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 9.58 (s, 1H, H2), 9.30 (s, 1H, H4), 7.40 (d, J=7.2, 1H, benzene), 7.34 (m, 2H, benzene), 7.20 (d, J=7.2, 1H, benzene), 7.15 (m, 4H, benzene), 2.35 (s, 6H, 2CH_3); MS (m/z) 404 (M⁺); Anal. Calcd for $C_{22}H_{16}N_2O_2S_2$

(404.07): C, 65.32; H, 3.99; N, 6.93; Found: C, 65.25; H, 3.98; N, 6.91.

6,7-Bis-[(4-fluorophenyl)thio]-5,8-quinazolinedione (5b)

Dark violet powder (50% yield); mp 102-105°C; IR (KBr) 3094 (w), 1674 (s, C=O), 1488-1556, 1224 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 9.90 (s, 1H, H2), 9.54 (s, 1H, H4), 7.50 (m, 4H, benzene), 7.20 (m, 4H, benzene); MS (m/z) 412 (M⁺).

6,7-Bis-[(4-chlorophenyl)thio]-5,8-quinazolinedione (5c)

Dark red brown powder (59% yield); mp 112-115°C; IR (KBr) 2922 (w), 1679 (s, C=O), 1472-1557 cm⁻¹; ¹H-NMR (DMSO-d_6) δ 9.71 (s, 1H, H2), 9.53 (s, 1H, H4), 7.20 (s, 1H, benzene), 7.07 (s, 1H, benzene), 6.94 (s, 1H, benzene); MS (m/z) 443 (M⁺).

Antifungal in vitro susceptibility testing

The MIC (minimum inhibitory concentration) values of compounds **3, 4**, and **5** were determined by the standard broth dilution method (Mcginnis and Rinaldi, 1996). The antifungal activity was tested in modified Sabouraud dextrose broth against the following fungal strains: Candida albicans ATCC 10231, C. krusei ATCC 749, C. tropicalis ATCC 28775 and Aspergillus niger KCTC 1231. Ketoconazole as an antifungal standard agent was used. The compounds were tested in the 0.1-100 μg/mL range and added to the modified Sabouraud dextrose broth for fungi over a final concentration range of 0.1 to 100 μg/mL. The inoculum sizes contained approximately 1×10^5 CFU/mL. They were incubated at 37°C for appropriate periods of time that sufficed to show clearly visible growth on drug-free control broths. The MIC value was defined as the lowest concentration of the antifungal agent, at which showed optically clear. MIC values were read after 1 day for Candida species and 2 days for A. niger in 37°C.

RESULTS AND DISCUSSION

Chemistry

The method used to synthesize the 5,8-quinazolinediones **3a-m** is shown in Scheme 1. 6,7-Dichloro-5,8-quinazo-linedione (**7**) was prepared by oxidizing 5,8-dihydroxy-quinazoline (**6**) with the $NaClO_3/HCl$ variation as the method previously reported (Melesani et al., 1970; Park et al., 2004). 6-Arylamino-7-chloro-5,8-quinazolinediones **3a-m** were formed by regioselective nucleophilic substitution of the quinazolinedione **7** with appropriate arylamines in the presence of $CeCl_3$.

From the results of catalytic action of Ce^{3+} ions in the substitution reaction, the regioselectivity should have originated from the selective increment of the electrophilicity of the 6-position of **7** by the formation of Ce(III) chelate
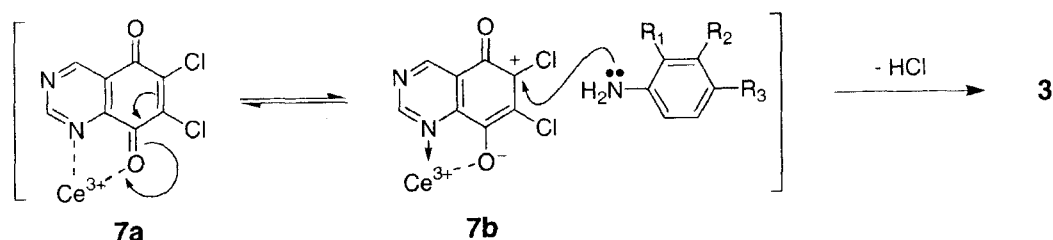
Scheme 2. Regioselective nucleophilic substitution

between nitrogen at the 1-position and carbonyl oxygen at the 8-position (Scheme 2). The catalysis by the Ce^{3+} ion is understood from the intermediate **7b**. The arylaminated products **3** were formed by a Michael-type addition of arylamines to **7b** and subsequent dechlorination. These substitutions were similar to the regioselective substitution of arylamines on 8-quinazolinedione in the presence of Ce(III) (Ryu *et al.*, 2002a). Most of these substitutions went as expected.

7-Methoxy-5,8-quinazolinedione (**8**) was prepared according to the known method (Renault *et al.*, 1983) with minor modification. 7-Arylthio-5,8-quinzolinediones **4a-c** (Table II) were synthesized by the regioselective substitution of compound **8** with appropriate arylthiols.

The 6,7-bis-(arylthio)-5,8-quinazolinediones **5a-c** were synthesized by nucleophilic substitution on 6,7-dichloro-5,8-quinazolinedione (**7**) with two equivalents of the arylthiols. Most of the substitutions went as expected and

had an overall high yield.

We also attempted to synthesize 6-arylthio-7-chloro-5,8-quinazolinediones by the substitution on compound **7** with one equivalent arylthiol under various reaction conditions. Unfortunately, we failed to obtain compounds. By the reactions, only the 6,7-bis-(arylthio)-5,8-quinazolinediones **5a-c** were formed exclusively.

Antifungal activity

The quinones **3a-m**, **4a-c**, and **5a-c** were tested *in vitro* for their growth inhibitory activity against *Candida* sp. and *A. niger* according to the standard protocol by the broth dilution method (Mcginnis and Rinaldi, 1996). The MIC values were determined by comparison with those of ketoconazole as a standard agent. As represented in Table I, II, most of the 5,8-quinazolinedione series **3-5** showed potent antifungal activity against all tested fungal species, and the activity against *C. tropicalis* was prominent.

Table I. Structures and *in vitro* antifungal activities for 6-arylamino-7-chloro-5,8-quinazolinediones **3**

Compds	R_1	R_2	R_3	MIC[a] (μg/mL)			
				C. albicans[b]	*C. tropicalis*	*C. krusei*	*A. niger*
3a	H	H	CH_3O	6.3	3.2	12.5	12.5
3b	H	H	C_2H_5	3.2	6.3	12.5	6.3
3c	H	CH_3	CH_3	6.3	6.3	25.0	6.3
3d	H	H	C_6H_{13}	3.2	1.6	3.2	12.5
3e	F	F	F	6.3	3.2	25.0	25.0
3f	H	F	F	25.0	25.0	12.5	50.0
3g	H	H	Br	6.3	3.2	3.2	0.8
3h	H	H	CH_3	6.3	3.2	6.3	3.2
3i	H	H	F	3.2	25	1.6	3.2
3j	H	H	Cl	3.2	3.2	3.2	3.2
3k	H	H	I	3.2	3.2	12.5	3.2
3l	H	H	H	3.2	3.2	12.5	3.2
3m	H	H	NO_2	6.3	3.2	3.2	12.5
Ketoconazole				6.3	6.3	12.5	12.5

[a] The MIC value was defined as the lowest concentration of the antifungal agent at which showed optically clear. 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 and *Aspergillus niger* KCTC 1231.

Table II. Structures and *in vitro* antifungal activities for 7-arylthio- and 6,7-bis-(arylthio)-5,8-quinazolinediones **4** and **5**

Compds	R₁	R₂	R₃	MIC (μg/mL)			
				C. albicans	C. tropicalis	C. krusei	A. niger
4a	H	H	CH₃O	100	0.8	50.0	25.0
4b	H	H	F	12.5	1.6	12.5	12.5
4c	H	H	Cl	12.5	0.8	100	12.5
5a	H	H	CH₃	25.0	0.8	>100	6.3
5b	H	H	F	12.5	0.8	>100	12.5
5c	H	H	Cl	25.0	0.8	>100	6.3
8				100	25.0	50.0	50.0

6-Arylamino-7-chloro-5,8-quinazolinediones **3a-m** generally showed potent antifungal activities against all tested fungal species, and very potent activity especially against *C. tropicalis*. Actually, the activity of the quinones **3a-m** was superior or comparable to those of ketoconazole against all tested fungi. Most of compounds **3** completely inhibited the growth of all fungal species tested at the MIC level of 0.8-12.5 μg/mL. Also, 7-arylthio-5,8-quinazoline-diones **4a-c** generally showed the potent antifungal activity. Even, 6,7-bis-(arylthio)-5,8-quinazolinediones **5a-c** showed significant antifungal activity against, *C. albicans*, *C. tropicalis* and *A. niger* although they did not exhibit the activity against *C. krusei*.

In terms of the structure-activity relationship, the 6-arylamino-7-chloro-5,8-quinazolinedione series (**3**) showed, in general, more potent antifungal activity than 7-arylthio-5,8-quinazolinedione series **4** and 6,7-bis-(arylthio)-5,8-quinazolinediones series (**5**). The 6-arylamino-7-chloro-substituted compounds **3** exhibited the greatest activity, indicating a correlation that may offer insight into the mode of action of these compounds. The 6,7-bis-(arylthio)-moieties of compounds **5** partially improve their antifungal activity in comparison to the 6-arylamino-7-chloro-substituted compounds **3**.

In addition, the 7-methoxy-5,8-quinazolinedione (**8**) without an 6-arylamino group exhibited weak antifungal activity (Table II). Thus, 6-arylamino or 7-arylthio-moieties of compounds **3** and **4** improve the antifungal activity significantly. The structure-activity relationship may not exist between properties of substituents (R = F, Cl, Br, ..) for the 6-arylamino moieties of the compounds **3**.

The cytotoxic potential of compounds **3a-m** has also been determined in human cancer cells according to the NCI protocols (Skehan *et al.*, 1990) and reported (Park *et al.*, 2004). Observations from previously reported data, revealed that compounds **3i-m** among tested compounds **3** showed significant cytotoxic activity. Compounds **3a-h** did not show significant cytotoxic activity but showed selectivity, in that they possess potent antifungal activities without cytotoxicity in mammalian cells.

CONCLUSION

6-Arylamino-7-chloro-5,8-quinazolinediones **3** were synthesized by regioselective nucleophilic substitution of 6,7-chloro-5,8-quinazolinedione (**7**) with appropriate arylamines. In a similar manner, 7-arylthio-5,8-quinzolinediones **4** were synthesized by the nucleophilic substitution of 7-methoxy-5,8-quinazolinedione (**8**) with appropriate arylthiols. The 6,7-bis-(arylthio)-5,8-quinazolinediones **5** were synthesized by nucleophilic substitution on 6,7-chloro-5,8-quinazolinedione (**7**) with two equivalents of the arylthiols. Most of the substitutions went as expected and had overall high yields.

6-Arylamino-7-chloro-5,8-quinazolinediones **3** generally showed more potent antifungal activity than 7-arylthio-5,8-quinzolinediones **4** and 6,7-bis-(arylthio)-5,8-quinazolinedi-ones **5**. The results of this study suggest that 6-arylamino-7-chloro-5,8-quinazolinediones **3** would be potent antifungal agents. Further investigations of the 6-(substituted-phenoxy)-7-chloro-5,8-quinazolinedione and 7-(substituted-phenoxy)-5,8-quinazolinedione series for improving antifungal properties are in progress.

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