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The Synthesis of 6-(N-Arylamino)-7-Chloro-5,8-Quinolinedione Derivatives for Evaluation of Antifungal Activities

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A series of 6-(N-arylamino)-7-chloro-5,8-quinolinedione derivatives was newly synthesized for the evaluation of antifungal activities. 5-Amino-8-hydroxy-quinoline (II) was treated with $KClO_3$ in HCl to give 6,7-dichloro-5,8-quinolinediones (III). 6-(N-Arylamino)-7-chloro-5,8-quinolinediones **1-12** were prepared by regioselective nucleophilic substitution of III with arylamines. In the presence of $CeCl_3$, the N-arylamino groups were introduced at the 6-position of 5,8-quinolinedione ring by the regioselective substitution. These derivatives **1-12** were tested for antifungal and also antibacterial activities, *in vitro*, against *Candida albicans, Aspergillus niger, Tricophyton mentagrophytes, Bacillus subtilis, Pseudomonas aeruginosa, Staphylococcus aureus* and *Escherichia coli*. The MIC values were determined by the two-fold agar/streak dilution method. Newly obtained 6-(N-arylamino)-7-chloro-5,8-quinolinedione derivatives showed potent antifungal and antibacterial activities. Among these derivatives, **1**, **3**, **5**, **7**, **8** and **9** showed more potent antifungal activities than fluconazole and griseofulvin. Also most of derivatives were found to be more active than ampicillin against gram-positive bacteria. **1** and **7** showed the very potent antifungal activities. **1** was the most effective in preventing the growth of *Candida albicans, Aspergillus niger, Tricophyton mentagrophytes, Bacillus subtilis* and *Staphylococcus aureus* at MIC 1.6 μg/ml.

Key words: 6-(N-arylamino)-7-chloro-5,8-quinolinedione, MIC, antifungal, antibacterial activities

INTRODUCTION

Quinone derivatives such as quinolinedione, naphthoquinone, benzoquinone, p- and o-dihydroxyquinone possess various biological activities (Clark *et al.*, 1984, Lin *et al.*, 1991, Niels *et al.*, 1986, Ryu *et al.*, 1992, 1993, Take *et al.*, 1986, Wurm *et al.*, 1980). 5,8-Quinolinediones among the quinone derivatives have potent antifungal, antibacterial (Roberts *et al.*, 1978, Wagner *et al.*, 1962), antimalarial (Bowman *et al.*, 1973, Porter *et al.*, 1971) and antineoplastic (Inouye *et al.*, 1987, Yasuda *et al.*, 1987) acitivities. The 5,8-quinolinedione ring is the potent minimum pharmacophore of antitumor antibiotics such as streptonigrin and lavendamycin (Rao *et al.*, 1991, Inouye *et al.*, 1987). The streptonigrin and lavendamycin produce superoxide (Cadenas *et al.*, 1990) and inhibit reverse transcriptase of virus (Inouye *et al.*, 1987, Hafuri *et al.*, 1988) and have also potent activity against anaerobic bacteria that has not superoxide dismutase (Hassan *et al.*, 1977).

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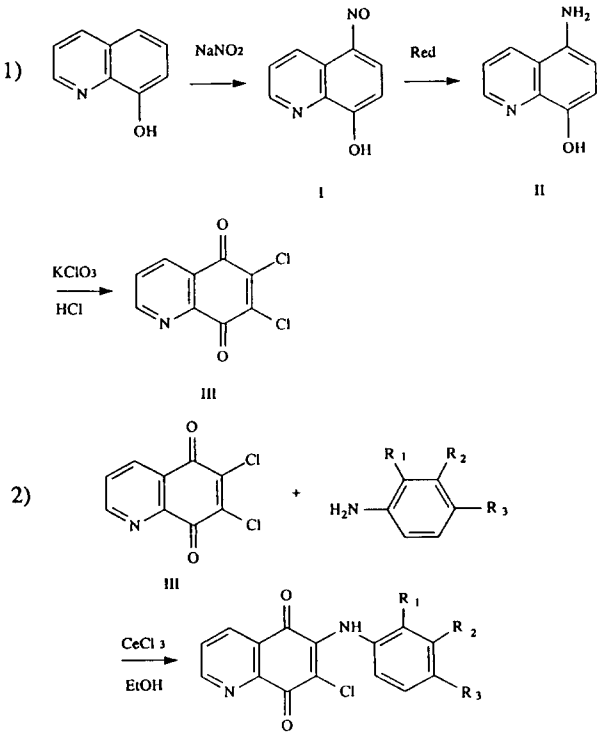
The mechanism of cytotoxicities of 5,8-quinolinedione derivatives is due to inhibition of electron transfer in respiratory chain of mitochondria and product of oxygen free semiquinone radical (Oyanagui *et al.*, 1989). As antimetabolites of coenzyme Q, the 6-(substituted)-7-chloro-5,8-quinolinediones inhibited mitochondrial Co-Q dependent succinoxidase and electron transfer in Plasmodium, that was correlated with *in vivo* antimalarial activity (Bowman *et al.*, 1973, Porter *et al.*, 1971).

In previous paper (Ryu *et al.*, 1992, 1993), quinone derivatives were tested for antifungal activities. For the continuous study on antifungal activities of quinones, a number of 6-(N-arylamino)-7-chloro-5,8-quinolinediones were synthesized to determine their growth inhibitory activities against fungi and bacteria. Following the observation that certain 6- or 7-chloro-5,8-quinolinediones have specially antifungal and antibacterial activities (Roberts *et al.*, 1978, Wagner *et al.*, 1962), a series of 7-chloro-5,8-quinolinediones was extended further by the preparation of other types of derivatives. The potentiating effect on antifungal activities may be increased by N-arylamino chain attached to the 6-po-



Schem 1. Synthesis of 6-(N-arylamino)-7-chloro-5,8-quinolinedione.

sition of 5,8-quinolinediones (Wagner *et al.*, 1962). The N-arylamino chains were also introduced to a 5,8-quinolinedione ring, together with other 7-chloro group.

The 6-(N-arylamino)-7-chloro-5,8-quinolinedione derivatives **1-12** were prepared selectively by nucleophilic substitution of 6,7-dichloro-5,8-quinolinedione with the arylamines in the presence of CeCl3 (Pratt *et al.*, 1962) (Scheme I).

The derivatives **1-12** were tested for their growth inhibitory activities against fungi and bacteria. The MIC values were determined by the standard two-fold agar dilution/streak method (Mcginnis *et al.*, 1990, Ryu *et al.*, 1992, 1993).

MATERIALS AND METHODS

Material and Apparatus

8-Hydroxyquinoline and arylamines were obtained from Aldrich Chemical Company, ethanol and bromine from Shinyo Pure Chemicals Co. Mueller-Hinton broth, Sabouraud Agar and Brain Heart Infusion (BHI) broth were purchased from Difco. Other chemicals such as DMSO, fluconazole, griseofulvin and ampicillin were reagent grade commercially available.

All melting points were measured in open capillary tubes with Thomas Hoover Capillary Apparatus Model and were uncorrected.

The extent of reaction was checked on TLC that was performed on precoated silica gel (60G 254, Merck); $CHCl_3$ for solvent; detected by heating at 110℃ after spraying 30% H_2SO_4 vanillin solution.

IR spectra were taken from Brucker IR spectrometer with KBr pellet. ^{1}H-NMR spectra were recorded in DMSO-d_6 on Perkin Elmer Model 1420 spectrometer (80 MHz), and chemical shifts are given in ppm with TMS as standard. UV spectrophotometer from Shimadzu UV-120-02 was used.

The microorganisms were incubated in shaking water bath from Vision Scientific Co.

Synthesis of 5-nitroso-8-hydroxyquinoline hydrochloride (I)

To a solution of 8-hydroxyquinoline (58 g, 0.40 mol) in water (200 ml), C-HCl (74 ml) and ice (200 g) was added a solution of $NaNO_2$ (30 g) in water (100 ml) in portions with vigorous shaking over 1 hr at 0 to 4℃. The mixture was allowed to stand overnight at 0℃ before the product was filtered off and I (61 g, 95%) was obtained.

Synthesis of 5-amino-8-hydroxyquinoline sulfate (II)

I (40 g, 0.25 mol) was dissolved in water (160 ml) and 5N-NaOH solution (269 ml). When the solution was warmed to 40℃ and treated with $Na_2S_2O_4$ (95 g), the temperature rose spontaneously to 75-80℃. The orange solution was allowed to cool slowly about 50℃; 12N-H_2SO_4 (250 ml) was then added and the solution was maintained with stirring for 2 hr. The resulting precipitate of II was filtered off after the mixture had been cooled in an ice-bath and II was obtained (34 g, 69%).

Synthesis of 6,7-dichloro-5,8-quinolinedione (III)

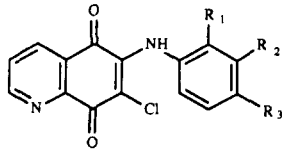
$KClO_3$ (5.5 g) was added over 40 min to a mixture of II (9 g, 0.35 mol) in C-HCl (69 ml) at 60℃ and was heated at 50-60℃ for 30 min. The mixture was poured into ice water (500 ml). The precipitate was filtered and recrystallized twice from BuOH.

6,7-Dichloro-5,8-quinolinedione (III) (7.5 g, 90%, mp. 221-222℃) was obtained (Schelhammer *et al.*, 1959, mp. 220-222℃).

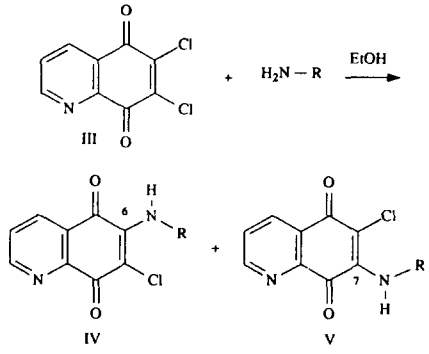
General procedure for synthesis of 6-(N-Arylamino)-7-chloro-5,8-quinolinedione

A mixture of III (2.27 g, 0.01 mol) and arylamine (0.011 mol) in EtOH (100 ml) was refluxed for 4-5 hr. After the mixture was kept overnight in the refrigerator or was poured into ice water (150 ml), the precipitate was collected by filtration. It was dissolved in hot EtOH and was recrystalized at room temperature. And the recrystallized compound corresponding 6-(N-

Table I. The Structure and Physical Data of 6-(N-arylamino)-7-chloro-5,8-quinolinedione derivatives



Comp. No.	N-Arylamino	R_1	R_2	R_3	mp. ℃	Yield %	Color & Appearance
1	(3,4-difluoro-phenyl)amino	H	F	F	192-193	82	purple, needle
2	(3-cyano-phenyl)amino	H	CN	H	256-258	80	violet, fine plate
3	(4-iodo-phenyl)amino	H	H	I	214-218	77	violet, fine plate
4	[(4-bromo(2-trifluoromethyl)phenyl]amino	CF_3	H	Br	225-227	81	orange, plate
5	(3,4-dichloro-phenyl)amino	H	Cl	Cl	216-218	94	purple, plate
6	(2,4-difluoro-phenyl)amino	F	H	F	195-197	83	red, plate
7	(2,4-dibromo-phenyl)amino	Br	H	Br	240-245	79	black, fine plate
8	(2,4-dichloro-phenyl)amino	Cl	H	Cl	246-249	82	violet, needle
9	(3-chloro-4-methyl-phenyl)amino	H	Cl	CH_3	226-228	85	orange, needle
10	(4-chloro-3-nitro-phenyl)amino	H	NO_2	Cl	255-257	90	red, fine plate
11	(4-Hydroxy-phenyl)amino	H	H	OH	238-240	94	drak brown, plate
12	(3-methyl-4-bromo-phenyl)amino	H	CH_3	Br	213-216	89	purple, amorphous



Scheme 2. Substitution in the absence of $CeCl_3$.

arylamino)-7-chloro-5,8-quinolinedione was filtered, washed with cold EtOH and dried (Scheme 2, Table I and II).

The used arylamines as reactants were 3,4-difluoroaniline, 3-cyanoaniline, 4-bromo-2-trifluoromethylaniline, 4-iodoaniline, 3,4-dichloroaniline, 2,4-difluoroaniline, 2, 4-dibromoaniline, 2,4-dichloroaniline, 3-chloro-4-methylaniline, 4-chloro-3-nitroaniline, 3-aminoacetophenone, 4-bromo-3-methylaniline.

Antimicrobial activities of 6-(N-arylamino)-7-chloro-5, 8-quinolinedione

The antimicrobial effect of the compounds **1-12** was determined standard twofold agar dilution/streak method (Mcginnis *et al.*, 1990, Ryu *et al.*, 1992, 1993). The MIC (*Minimal Inhibitory Concentration*) of **1-12** was determined by judging visually the microbial growth in the series of test agar plates.

In the determination of antifungal activities, the following fungal strains were used as target microorganisms: *Candida albicans* ATCC 10231 & local, *Aspergillus niger* KCTC 1231, *Tricophyton mentagrophytes* KCTC 6085. Also the following bacterial strains were used as target organisms in the determination of antibacterial activities: *Bacillus subtilis* ATCC 6633, *Pseudomonas aeruginosa* NCTC 10490, *Staphylococcus aureus* ATCC 6538p & *Methicillin resistant Staphylcoccus aureus, Escherichia coli* NIHJ.

Prior to determination of antifungal activity, the strains of fungi were cultured in Sabouraud agar at 30℃ for 3-7 days, whereas the strains of bacteria were cultured in BHI broth at 37℃ for 20 hr, and subcultured again for 6 hr. The number of cells were adjusted with sterile saline or the sterile BHI broth to 2×10^5 microorganisms and then used for the tests.

Test compounds (4 mg) were dissolved in 2 ml of DMSO and subjected to twofold step dilution of the solution (0.05 ml). Then that was added to the melted Sabouraud agar for fungi or Mueller-Hinton agar for bacteria over a final concentration range of 0.8 to 100 μg/ml. A 3 μl of fungal or bacterial inocula containing about 2×10^5 microorganisms was incubated by making a 2 cm long streak with loop on solidified agar plates. And all the plates were incubated at 30 or 37℃ for appropriate periods of time that sufficed to show clearly visible growth of colonies on drug-free control plates. The MIC was defined as the lowest concentration of drug at which there was no visible colonial growth. Fluconazole, griseofulvin and ampicillin as antifungal and antibacterial standard substance were used (Table III and IV).

RESULTS AND DISCUSSION

Chemistry

Table II. The Spectral Data of 6-(N-arylamino)-7-chloro-5,8-quinolinedione derivatives

Comp. No.	Spectral data; ^{1}H-NMR (DMSO-d_6, δ ppm), IR (ν_{max} KBr, cm^{-1})
1	IR; 3210 (s, NH), 3020, 1680 (s, C=O), 1600, 1570, 1500, 1310, 1210, 840. NMR; 7.2 (3H, m, benzene ring), 7.8-9.0 (3H, C_5H_3N), 9.4 (1H, NH).
2	IR; 3300 (s, NH), 3040, 2240 (s, C≡N), 1670(s, C=O), 1600, 1580, 1380, 1270, 800. NMR; 7.4-7.6 (4H, m, benzene ring), 7.8-9.0 (3H, C_5H_3N), 9.5 (1H, NH).
3	IR; 3220 (s, NH), 3040, 1680 (s, C=O), 1600, 1580, 1355. NMR; 7.0-7.7 (4H, m, benzene ring), 7.8-9.0 (3H, C_5H_3N), 9.4 (1H, NH).
4	IR; 3220 (s, NH), 3010, 1680 (s, C=O), 1575, 1510, 1310, 1140. NMR; 7.2-7.7 (3H, m, benzene ring), 7.8-9.0 (3H, C_5H_3N), 9.5 (1H, NH).
5	IR; 3210 (s, NH), 3040, 1675 (s, C=O), 1600, 1580, 1310, 1020, 840. NMR; 7.1-7.6 (3H, m, benzene ring), 7.8-9.0 (3H, C_5H_3N), 9.4 (1H, NH).
6	IR; 3220 (s, NH), 3040, 1680 (s, C=O), 1600, 1570, 1500, 1310, 1140, 850. NMR; 7.2-7.8 (3H, m, benzene ring), 7.8-9.0 (3H, C_5H_3N), 9.2 (1H, NH).
7	IR; 3340 (s, NH), 3040, 1675 (s, C=O), 1600, 1575, 1365, 1280, 870, 800. NMR; 7.2-7.8 (3H, m, benzene ring), 7.8-9.0 (3H, C_5H_3N), 9.2 (1H, NH).
8	IR; 3340 (s, NH), 3030, 1670 (s, C=O), 1600, 1380, 1270, 1140, 860, 800. NMR; 7.4 (3H, m, benzene ring), 7.8-8.4 (3H, C_5H_3N), 9.2 (1H, NH).
9	IR; 3320 (s, NH), 3040, 1660 (s, C=O), 1650, 1570, 1240, 850, 710. NMR; 4.3 (3H, -CH_3), 7.2 (3H, m, benzene ring), 7.8-9.0 (3H, C_5H_3N), 9.3 (1H, NH).
10	IR; 3200 (s, NH), 3040, 1655 (s, C=O), 1585, 1560, 1290, 855. NMR; 7.4-7.8 (3H, m, benzene ring), 7.8-9.0 (3H, C_5H_3N), 9.8 (1H, NH).
11	IR; 3240 (s, NH), 3040, 1680 (s, C=O), 1650, 1570, 1240, 850, 710. NMR; 7.0 (4H, m, benzene ring), 7.8-9.0 (3H, C_5H_3N), 9.2 (1H, OH), 9.4 (1H, NH).
12	IR; 3220 (s, NH), 3010, 1680 (s, C=O), 1600, 1560, 1300, 1030. NMR; 4.5 (3H, -CH_3), 7.0-7.8 (3H, m, benzene ring), 7.8-9.0 (3H, C_5H_3N), 9.4 (1H, NH).

Table III. *In vitro* antifungal activities of 6-(N-arylamino)-7-chloro-5,8-quinolinedione derivatives MIC (μg/ml)

Comp. No.	*C. albicans*	*C. albicans* L.	*A. niger*	*T. mentagrophyte*
1	1.6	0.8	0.8	0.8
2	50.0	50.0	50.0	25.0
3	6.3	6.3	6.3	3.2
4	12.5	12.5	6.3	12.5
5	6.3	6.3	6.3	12.5
6	12.5	12.5	12.5	25.0
7	6.3	3.2	3.2	3.2
8	6.3	3.2	3.2	6.3
9	6.3	25.0	3.2	6.3
10	25.0	>100.0	12.5	100.0
11	100.0	>100.0	>100.0	100.0
12	12.5	12.5	12.5	12.5
Fluconazole	25.0	25.0	25.0	12.5
Griseofulvin	50.0	50.0	25.0	50.0

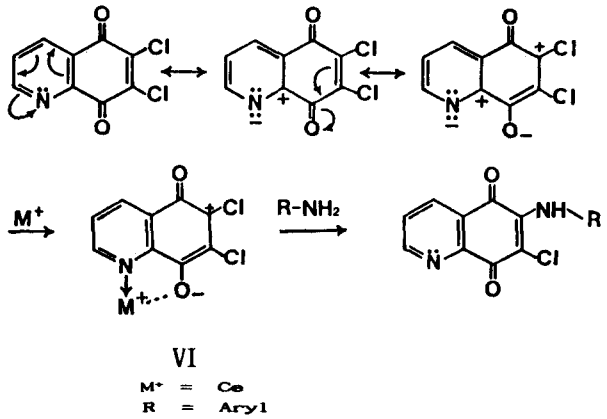
*MIC values were read after 3 days for *C. albicans*, *A. niger* and 7 days for *T. mentagrophte* at 30℃.
**Culture media tested was Sabouraud dextrose agar.
***Fungi tested; *Candida albicans* ATCC 10231 & *Candida albicans* local, *Aspergillus niger* KCTC 1231, *Tricophyton mentagrophytes* KCTC 6085.

The compounds **1-12** tested for antifungal and also antibacterial activities were prepared as shown in Table I. The 6,7-dichloro-5,8-quinolinedione (III) was prepared by the previously reported methods (Schelhammer *et al.*, 1959, Pratt *et al.*, 1962) (Scheme 1). The 6-(N-arylamino)-7-chloro-5,8-quinolinediones derivatives **1-12** were prepared selectively by nucleophilic substitution of 6,7-dichloro-5,8-quinolinedione with the appropriate arylamines in the presence of $CeCl_3$ (Scheme 1). While most of these reactions in the absence of $CeCl_3$ gave two isomers of 6-(N-arylamino)-7-chloro-5,8-quinolinedione (IV, 6-isomer) and 6-chloro-7-(N-arylamino)-5,8-quinolinedione (V, 7-isomer) (Scheme 2). But the 6-isomer (IV) which was substitutied at the

Table IV. *In vitro* antibacterial activities of 6-(N-arylamino)-7-chloro-5,8-quinolinedione derivatives MIC (μg/ml)

Comp. No.	*B. subtilis*	*S. aureus*	*MRS. aureus*	*E. coli*	*P. aeruginosa*
1	<0.8	0.8	6.3	100.0	100.0
2	3.2	3.2	12.5	>100.0	>100.0
3	3.2	3.2	3.2	>100.0	>100.0
4	<0.8	<0.8	<0.8	>100.0	>100.0
5	<0.8	<0.8	<0.8	>100.0	>100.0
6	1.6	3.2	3.2	>100.0	>100.0
7	<0.8	1.6	<0.8	>100.0	>100.0
8	1.6	1.6	1.6	>100.0	>100.0
9	3.2	3.2	3.2	>100.0	>100.0
10	6.3	6.3	3.2	>100.0	>100.0
11	50.0	25.0	100.0	>100.0	25.0
12	1.6	1.6	12.5	>100.0	100.0
Ampicillin	1.6	25.0	25.0	1.6	100.0

*MIC values were read after 20-22 hr of incubation at 37℃.
**Culture media tested was Mueller-Hinton agar.
***Bacteria tested; *Bacillus subtilis* ATCC 6633, *Staphylcoccus aureus* ATCC 6538p, *Methicillin resistant Staphylcoccus aureus*, *Escherichia coli* ATCC 10356, *Pseudomonas aeruginosa* NCTC 10490.



Scheme 3. The electron transfer mechanism of 6,7-dichloro-5,8-quinolinedione and regioselective substitution in the presence of $CeCl_3$.

6-position was formed exclusively in the presence of $CeCl_3$, suggesting that the $CeCl_3$ enhances the regioselective reactivity of the 6-position (Scheme 3). The regioselective substitution at the 6-position in the presence of $CeCl_3$ can be understood in terms of the 8-carbonyl group being bound to the β-position of the pyridine ring and hence more electron defiecient than 5-carbonyl group in α-position. The lower electron density is then transfered to the 6,7-double bond as shown and leads to electron deficiency and and observed preferential attack at the 6-position. The catalysis by the Ce^{3+} ion is understood as involving structure (VI) (Scheme 3).

Most of these reactions went as expected and were in 70-95% good yields.

Antifungal and antibacterial activities

These synthesized 5,8-quinolinedione derivatives **1**-**12** (Table I) were tested for determination of antifungal and antibacterial activities. The MIC values of these compounds were determined, *in vitro*, by the twofold agar dilution/streak method. The results are given in Table III and IV by comparison with those of fluconazole, griseofulvin and ampicillin. The control cultures showed no antimicrobial activities against all the strain of microorganisms.

As indicated in the Table III, **1**, **3**, **5**, **7**, **8** and **9** have potent antifungal activities with widely expanded spectra against fungi. **1** completely inhibited the fungal growth at 1.6 μg/ml against *Candida albicans*, *Aspergillus niger* and *Tricophyton mentagrophytes*. On the other hand, fluconazole inhibited the growth at 25 μg/ml against fungi respectively. In fact, activities of **1**, **3**, **4**, **5**, **7**, **8** and **9** were superior to that of fluconazole against many fungi.

Against gram-positive bacteria, such as *Bacillus subtilis* and *Staphylococcus aureus*, all the 5,8-quinolinedione derivatives displayed antibacterial activities comparable or slightly superior to that of ampicillin. Otherwise, all these compounds were found to be less active than ampicillin against gram-negative bacteria.

The compounds such as **1**, **5**, **7** and **8** containing (N-dihalo-phenyl)amino moiety exhibited increase of the potent antifungal activities. **1** with (3,4-difluorophenyl)-amino substituent exhibited more potent antimicrobial activities than **6** with (2,4-difluorophenyl)-amino group.

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REFERENCES CITED

Bowman, C. M., Porter, T. H., Skelton, F. S. and Folkers, K., 5,8-Quinolinequinone analogs which inhibit mitocondrial succinoxidase. *J. Med. Chem.*, 14, 206-209 (1973).

Clark, N. G., The fungicidal activity of substituted 1,4-naphthoquinones. *Pestic. Sci.*, 15, 235-40 (1984).

Cadenas, E. and Ernster, L., Effect of superoxide dismutase on the autoxidation of hydroquinones formed during DT-diaphorase catalysis and glutathione nucleophilic addition: Emerit, I., Packer, L. and Auclair, C. (Eds.), *Antioxidants in therapy and preventive medicine-Advances in experimental medicine and biology*, Vol. 264, Plenum, New York, 1990, pp. 37-44.

Hafuri, Y., Takemori, E., Oogose, K., Inouye, Y. and Nakamura, S., Mechanism of inhibition of reverse transcriptase by quinone antibiotics. *J. Antibiotics*, 41, 1471-1478 (1988).

Hassan, H. M. and Fridovich, I., Enzymatic defense against the toxicity of oxygen and of streptonigrin in *E. coli*. *J. Bacterol.*, 129(3), 1574-1579 (1977).

Hodnet, E .M., Wongweichintana, C., Dunn, W. and Marrs, M., Substituted 1,4-naphthoquinones vs. the ascitic sarcoma 180 of mice. *J. Med. Chem.*, 26, 570-574 (1983).

Inouye, Y., Take, Y., Keiko, O., Kobo, A. and Nakamura, S., The quinolinquione as the minimum entity for reverse transcriptase-inhibitory activity of streptonigrin. *J. Antibiotics*, 40, 105-109 (1987).

Lin, T. S., Zhu, L. Y., Xu, S. P., Divo, A. and Sartorelli, A., Synthesis and antimalarial activity of 2-aziridinyl- and 2,3-bis-(aziridinyl)-1,4-naphthoquinonyl sulfonate and acylate derivatives. *J. Med. Chem.*, 34, 1634-1639 (1991).

Mcginnis, M. R. and Rindali, M. G., Antifungal drug: Lorian, V. (Eds.), *Antibiotics in laboratory medicine*, 3rd ed., Williams and Wilkins, Baltimore, 1991, pp. 198-256.

Niels, J. and Wengel, A., Fungicidal activity of 2-(1-alkenyl)-3-hydroxy-1,4-naphthoquinones and related compounds. *Pestic. Sci.*, 17, 686-90 (1986).

Oyanagui, Y. (Eds.), *SOD and active oxygen modulators-pharmacology and clinical trials*, Nihon-Igakukan, Tokyo, Japan, 1989, pp. 389, 618, 670.

Porter, T. H., Skelton, F. S. and Folkers, K., Synthesis of 5,8-quinolinequinones as inhibitors of coenzyme Q and antimalarials. *J. Med. Chem.*, 14, 1029-1033 (1971).

Pratt, Y. T., Quinolinequinone VI-Reaction with aromatic amines. *J. Org. Chem.*, 27, 3905-3910 (1962).

Pratt, Y. T. and Drake, N. L., Synthesis of 6,7-dichloroquinoline-5,8-quinone. *J. Am. Chem. Soc.*, 82, 1155-1160 (1960).

Rao, K. V. and Beach, J. W., Synthesis and evaluation of some isoquinolin analogues-streptonigrin. *J. Med. Chem.*, 34, 1871-1879 (1991).

Roberts, H., Choo, W. M., Smith, S. C., Marzuki, S., Linnane, A. W., Porter, T. H. and Folkers, K., The site of inhibition of mitochondrial electron transfer by coenzyme Q analogs. *Arch. Biochem. Biophys.*, 191, 306-315 (1978).

Ryu, C. K., Ryu, J. C., Chung, C. Y. and Kim, D. H., Antimicrobial activities of 1,4-naphthoquinone derivatives. *Yakhak Hoeji*, 36(2), 110-114 (1992).

Ryu, C. K. and Kim, D. H., The synthesis and antimicrobial activities of 1,4-naphthoquinones (II). *Arch. Pharm. Res.*, 15(3), 263-268 (1992).

Ryu, C. K. and Kim, D. H., The some antimicrobial activities of 1,4-naphthoquinones (III). *Arch. Pharm. Res.*, 16(2), 161-163 (1993).

Schellhammer, C. W. and Petersen, S., Derivatives of 5,8-quinolinequinone. *Ann. der Chem.*, 624, 108-119 (1959).

Take, Y., Sawada, M., Kunai, H., Inouye, Y. and Nakamura, S., Role of the naphthoquinone moiety in the biological activities of sakyomicin A. *J. Antibiotics*, 39, 557-563 (1986).

Wagner, A., Beck, W. and Diskus, A., Fungicides, *Austrian patent*, 220, 425-426 (1962); *Chem. Abstract*, 57, 3420, 9823, 11160 (1962); 56, 4740 (1962).

Wurm, G., Geres, U. and Schmidt, H., Untersuchungen an 1,4-Naphthoquinonen. *D. Apotheker Zeitung*, 43, 2045-2051 (1980).

Yasuda, M. and Boger, D. L., Streptonigrin and lavandamycin partial structure. A probe for the minimum potent pharmacophore of the antitumor anitibiotics. *J. Heterocycl. Chem.*, 24, 1253-1260 (1987).