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The Synthesis and Antimicrobial Activities of Some 1,4-Naphthoquinones (II)

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Abstract □ In order to evaluate the antimicrobial effect of 2,3-disubstituted-1,4-naphthoquinone derivatives we newly synthesized several 2-chloro and 2-bromo-3-(substituted)-1,4-naphthoquninones. Amination reaction of 2,3-dihalo-1,4-naphthoquinones with aryl and aliphatic amines in ethanol gave 2-halo-3-(N-alkyl or N-aryl)-1,4-naphthoquinone derivatives (**1a,b-10a,b**) in 60%-90% yield. These derivatives subjected to antibacterial and antifungal activities, *in vitro*, against *Bacillus subtilis ATCC 6633, Candida albicans 10231 and local, Pseudomonas aeruginosa NCTC10490, Staphylococcus aureus ATCC 6538p, Escherichia coli NIHJ, Aspergillus niger KCTC 1231, Tricophyton mentagrophytes KCTC 6085.* Among these derivatives, **1b**, **6b** and **7a** showed the potent antibacterial activities. **1b**, **8b** and **9b** have the antifungal activities. **1b** is most effective in preventing the growth of *Bacillus subtilis and Pseudomonas aeruginosa, Candida albicans, Aspergillus niger, Tricophyton mentagrophytes.* The several of these compounds demonstrated a broad spectrum of activities *in vitro.*

Keywords □ 2-chloro-and 2-bromo-3-(substituted)-1,4-naphthoquinone, aromatic and aliphatic amine, substitution, antifungal, antibacterial activities.

Some 1,4-naphthoquinone derivatives posess various biological activities[1-5]. Also 2,3-disubstituted-1,4-naphthoquinones have potent antibacterial[1,3-5], antifungal[1,8], anticoagulant[14,15], antimararial[5,16], cytotoxic and antineoplastic[6,7,9,10] activities. Many naphthoquinoid antibiotics such as rifamycin, tolypomycin, damavaricin and manumycin have 1,4-naphthoquinone ring as pharmacophore[2]. These derivatives were chosen since many compounds contained such 1,4-naphthoquinone systems displayed antibacterial, antineoplastic and antifungal activity[1,3-8]. Also the derivatives of 2-halo-1,4-naphthoquinone were capable of inhibiting the growth of the Gram posive, negative bacteria and fungi. 1,4-Naphthoquinones have function as bacterial growth inhibitors by functioning competitively in electron transport with the endogenous vitamin K or ubiquinone[5]. The mechanism of cytotoxicities of 1,4-naphthoquinone derivatives is due to inhibition of electron transfer in respiratory chain of mitochondria and the production of oxygen free semiquinone radical[7,9].

The antifungal activities may be increased by aliphatic and halogen side chain[3-5]. The 2-alkylamino groups were also introduced to a 1,4-naphthoquinone ring, together with other halogen functional group (**1a,b-10a,b**). For the continuous study on biological activities of 2-halo-3-substituted-1,4-naphthoquinones, a number of 1,4-naphthoquinone were synthesized to determine their growth inhibitory activities against bacteria and fungi.

The 2-halo-3-substituted-1,4-naphthoquinone derivatives (**1a,b-10a,b**) were prepared respectively by treatment of 2,3-dichloro- and 2,3-dibromo-1,4-naphthoquinone with the appropriate amine in ethanol[11-13] (Scheme 1). The antimicrobial effect, MIC of the compounds was determined by the standard two-fold agar dilution method[1]. The following microbial strains were used as target organisms: *Bacillus subtilis ATCC 6633, Candida albicans ATCC 10231 and local, Pseudomonas aeruginosa NCTC 10490, Sta-*

phylococcus aureus ATCC 6538p, Escherichia coli NIHJ, Aspergillus niger KCTC 1231, Tricophyton metagrophytes KCTC 6085.

EXPERIMENTAL SECTION

Reagent

1,4-Naphthoquinons, 2,3-dichloro-1,4-naphthoquinone and amines were obtained from Aldrich Chemical Company, ethanol and bromine from Shinyo Pure Chemicals Co. Mueller-Hinton broth and Sabouraud Agar were purchased from Difco.

Apparatus

All melting points were measured in open capillary tubes with Buchi SMP-20 model and are uncorrected.

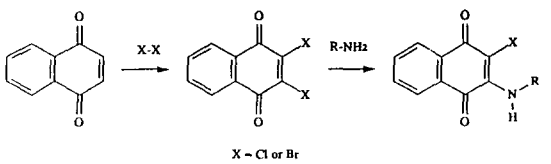
The reaction was checked on TLC that was performed on precoated silica gel (60G 254, Merck, chloroform for solvent, 30% H_2SO_4 vanillin solution). IR spectra were taken from Alphaceenteauri FT-IR spectrometer in nujol or with KBr pellet. ^{1}H-NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on Varian Model T-69A spectrometer (60 MHz), and chemical shifts are given in δ ppm with TMS as standard. UV spectrophotometer from Shimadzu UV-120-02 was used. The microoraganisms were incubated in shaking water bath from Thomastat T-22S, Thomas Kagaku Co.

Synthesis of 2,3-dibromo-1,4-naphthoquinone

1,4-Naphthoquinone (10.0g) was dissolved in 200 m*l* of glacial acetic acid, 40g of fused sodium acetate and 8.0 m*l* of bromine added, the mixture was allowed to stand for 24 hours at room temperature and then poured into 800 m*l* of water. The precipitate was collected, dried and recrystallized twice from ethanol or glacial acetic acid. The weight of product, mp. 215-217℃, was 13.28g (66%). (Lit[11,12], mp. 216-218℃).

General procedure for synthesis of 2-halo-3-(N-aryl or alkylamino)-1,4-naphthoquinone

A mixture of 2.27g (10 mmol) of 2,3-dihalo-1,4-naphthoquinone and amine (11 mmol) in 100 m*l* of ethanol was refluxed stirring for 4-5 hr. After the mixture was kept overnight in the refrigerator, or poured into 150 m*l* ice water, the precipitate was collected by filtration. It was dissolved in 100 m*l* of hot ethanol and was filtered. And after the mixture cooled, the precipitated compound was filtered, washed with cold ethanol and dried. It was purified by repeated crystallization with methanol to provide the corresponding 2,3-disubstituted-1,4-naphthoquinone[11-13,18-20] (Scheme 1).



Scheme 1

The amines used as reactants were 2-amino-5-methylpyridine, 4-aminopyridine, 4-ethylaniline, 4-chloroaniline, piperidine, 4-methylpiperidine, 1-(2-hydroxylethyl)piperazine, 2-methylaziridine, ethylamine and 2-hydroxyethylamine.

Synthesis of 2-chloro-3-(N-alkyl or N-arylamino)-1,4-naphthoquinones

1a-10a were prepared by the previous method[11-13]. A solution of the amine (10 mmol) was added to a solution of 2,3-dichloro-1,4-naphthoquinone in ethanol and the mixture was refluxed for 4-5 hr. After cooling, the separated crystalline product was washed with alcohol and recrystallized from a suitable solvent.

Also 2-bromo-3-(N-alkyl or N-arylamino)-1,4-naphthoquinones (**1b-10b**) were prepared in a similar manner to that described upper.

A mixture of 2.7g (10 mmol) of 2,3-dibromo-1,4-naphthoquinone, amines (10 mm*l*) in ethanol or glacial acetic acid was refluxed for 4-5 hr. After cooling, the product was recrystallized (Scheme 1).

2-chloro-3-(N-2-amino-5-methylpyridino)-1,4-naphthoquinone, 1a

mp.: 195-197℃ (red yellow plate 76%); IR (KBr, cm $^{-1}$): 3220 (s, NH), 3025, 1680 (s, C=O), 1640, 1515, 880, 810; ^{1}H-NMR ($CDCl_3$/DMSO-d_6); δ ppm=1.59 (1H, NH), 1.9 (3H, s, CH_3), 7.3-7.8 (4H, m, aromatic), 8.1-8.4 (3H, m, pyridine ring).

2-bromo-3-(N-2-amino-5-methylpyridino)-1,4-naphthoquinone, 1b

mp.: 225-230℃ (brown yellow plate 66%); IR (KBr, cm $^{-1}$): 3220 (s, NH), 3025, 1675 (S, C=O), 1640, 1580, 1270, 880, 800, 700; ^{1}H-NMR (DMSO-

d_6); δ ppm=2.29 (1H, NH), 1.9 (3H, s, CH_3), 7.3-7.9 (4H, m, aromatic), 8.1-8.4 (3H, m, pyridine ring).

2-chloro-3-(N-4-aminopyridino)-1,4-naphthoquinone, 2a

mp.: 276-279℃ (red plate 85%); IR (KBr, cm^{-1}); 3215 (s, NH), 3020, 1670 (s, C=O), 1640, 1520, 870, 800; ^{1}H-NMR ($CDCl_3$/DMSO-d_6); δ ppm=1.7 (1H, NH), (3H, s, CH_3) 7.4-7.8 (4H, m, aromatic), 8.2-8.5 (4H, m, pyridine ring).

2-bromo-3-(N-4-aminopyridine)-1,4-naphthoquinone, 2b

mp.: 295-297℃ (red plate 64%); IR (KBr, cm^{-1}); 3220 (s, NH), 3030, 1685 (s, C=O), 1625, 1570, 1240, 870, 800, 700; ^{1}H-NMR (DMSO-d_6); δ ppm=2.1 (1 H, NH), 7.2-7.6 (4H, m, aromatic), 8.2-8.6 (3H, m, pyridine ring).

2-chloro-3-(N-4-ethylanilnino)-1,4-naphthoquinone, 3a

mp.: 274-276℃ (dark red plate 92%); IR (KBr, cm^{-1}); 3230 (s, NH), 3050, 2955, 1680 (s, C=O), 1640, 1515, 880, 710; ^{1}H-NMR ($CDCl_3$/DMSO-d_6); δ ppm=1.9 (1H, NH), 1.15 (3H, t, CH_3, J=7.3 Hz), 2.3 (2H, q, CH_2, J=7.3 Hz).

2-bromo-3-(N-4-ethylanilino)-1,4-naphthoquinone, 3b

mp.: 172-176℃ (red yellow plate 72%); IR (KBr, cm^{-1}); 3230 (s, NH), 3060, 2950, 1670 (s, C=O), 1630, 1520, 860, 715; ^{1}H-NMR ($CDCl_3$/DMSO-d_6); δ ppm=1.8 (1H, NH), 1.1 (3H, t, CH_3, J=7.4 Hz), 2.2 (2H, q, CH_2, J=7.4 Hz).

2-chloro-3-(N-4-chloroanilnino)-1,4-naphthoquinone, 4a

mp.: 223-225℃ (red needle 85%); IR (KBr, cm^{-1}); 3240 (s, NH), 3040, 1680 (s, C=O), 1650, 1570, 1240, 850, 710; ^{1}H-NMR ($CDCl_3$); δ ppm=2.21 (1H, NH), 7.0-8.4 (8, m, 2 aromatic ring).

2-bromo-3-(N-4-chloroanilino)-1,4-naphthoquinone, 4b

mp.: 223-225℃ (red yellow plate 75%, Lit.[12]).; IR (KBr, cm^{-1}); 3240 (s, NH), 3040, 1680 (s, C=O), 1650, 1240, 850, 710; ^{1}H-NMR ($CDCl_3$); δ ppm=2.21 (1H, NH), 7.0-8.4 (8, m, 2 aromatic ring).

2-chloro-3-(N-piperidino)-1,4-naphthoquinone, 5a

mp.: 92-94℃ (yellow brown powder 94% Lit.[13]).; IR (KBr, cm^{-1}); 3230 (s, NH), 3050, 2945, 1670 (s, C=O), 1640, 1515, 1450;^{1}H-NMR ($CDCl_3$-/DMSO-d $_6$); δ ppm=1.7 (1H, NH), 1.4-2.3 (5H, m, piperidine ring) 7.22-7.6 (4H, m, aromatic).

2-bromo-3-(N-piperidino)-1,4-naphthoquinone, 5b

mp.: 82-84℃ (brown powder74%, Lit.[13]).; IR (KBr, cm^{-1}); 3300 (s, NH), 3040, 2950, 1680 (s, C=O), 1640, 1525, 1460; ^{1}H-NMR ($CDCl_3$/DMSO-d_6); δ ppm=1.6 (1H, NH), 1.4-2.2 (5H, m, piperidine ring), 7.2-7.7 (4H, m, aromatic).

2-chloro-3-(N-4-methylpiperidino)-1,4-naphthoquinone, 6a

mp.: 92-94℃ (red yellow powder 94% Lit.[2]).; IR (KBr, cm^{-1}); 3230 (s, NH), 3050, 2945, 1670 (s, C=O), 1640, 1515, 1450; ^{1}H-NMR ($CDCl_3$/DMSO-d_6); δ ppm=1.6 (1H, NH), 1.2 (3H, s, CH_3), 1.4-2.2 (4H, m, piperidine ring), 7.2-7.7 (4H, m, aromatic).

2-bromo-3-(N-4-methylpiperidino)-1,4-naphthoquinone, 6b

mp.: 193-1955℃ (yellow powder 84%, Lit.[12]).; IR (KBr, cm^{-1}); 3300 (s, NH), 3040, 2950, 1680 (s, C=O), 1640, 15255, 1460; ^{1}H-NMR ($CDCl_3$/DMSO-d_6); δ ppm=1.6 (1H, NH), 1.2 (3H, s, CH_3), 1.4-2.2 (4H, m, piperidine ring), 7.2-7.7 (4H, m, aromatic).

2-chloro-3-[N-1-(2-hydroxyethyl)piperizino]-1,4-naphthoquinone, 7a

mp.: 238-240℃ (red plate 93%); IR (KBr, cm^{-1}); 3390 (s, OH), 3260 (s, NH), 3065, 2940, 1685 (s, C=O), 1645, 1535, 1465; ^{1}H-NMR ($CDCl_3$); δ ppm=1.7 (1H, NH), 2.4 (2H, t, N-CH_2, J=7.1 Hz), 2.1-2.4 (4H, m, piperizine ring), 4.4 (2H, t, O-CH_2, J=7.1 Hz), 7.2-7.7 (4H, m, aromatic).

2-bromo-3-[N-1-(2-hydroxyethyl)piperizino]-1,4-naphthoquinone, 7b

mp.: 185-188℃ (red yellow plate 84%); IR (KBr, cm^{-1}); 3410 (s, OH), 3300 (s, NH), 3040, 2950, 1680 (s, C=O), 1640, 1525, 1460; ^{1}H-NMR ($CDCl_3$); δ ppm=1.7 (1H, NH), 2.5 (2H, t, N-CH_2, J=7.2 Hz), 2.1-2.4 (4H, m, piperizine ring), 4.4 (2H, t, O-CH_2, J=7.2 Hz), 7.2-7.7 (4H, m, aromatic).

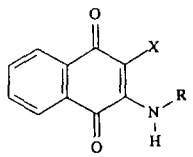
2-chloro-3-(N-2-methylaziridino)-1,4-naphthoquinone, 8a

mp.: 82-84℃ (red powder 94%); IR (KBr, cm^{-1}); 3300 (s, NH), 3070, 2965, 16855 (s, C=O), 1645, 1500, 1450; ^{1}H-NMR ($CDCl_3$); δ ppm=1.4 (3H, d, CH_3, J=7.0 Hz), 1.9 (1H, NH), 2.4-2.6 (3H, m, aziridine ring), 7.2-7.7 (4H, m, aromatic).

2-bromo-3-(N-2-methylaziridino)-1,4-naphthoquinone, 8b

mp.: 137-139℃ (black red powder 81%); IR (KBr, cm^{-1}); 3300 (s, NH), 3040, 2950, 1680 (s, C=O), 1640, 1525, 1460; ^{1}H-NMR ($CDCl_3$); δ ppm=1.3 (3H,

Table I. 2-Halo-3-(N-alkyl or N-arylamino)-1,4-naphthoquinones



No	X	No	X	R
1a	X=Cl,	**1ba**	X=Br	N-2-amino-5-methylpyridino
2a	X=Cl,	**2br**	X=Br	N-4-aminopyridino
3a	X=Cl,	**3b**	X=Br	N-4-ethylanilino
4a	X=Cl,	**4b**	X=Br	N-4-chloroanilino
5a	X=Cl,	**5b**	X=Br	N-piperidino
6a	X=Cl,	**6b**	X=Br	N-4-methylpiperidino
7a	X=Cl,	**7b**	X=Br	N-1-(2-hydroxyethyl) piperizino
8a	X=Cl,	**8b**	X=Br	N-2-methylaziridino
9a	X=Cl,	**9b**	X=Br	N-ethylamino
10a	X=Cl,	**10b**	X=Br	N-2-hydroxyethylamino

d, CH_3, J=7.0 Hz), 1.7 (1H, NH), 2.3-2.6 (3H, m, aziridine ring), 7.2-7.7 (4H, m, aromatic).

2-chloro-3-(N-ethylamino)-1,4-naphthoquinone, 8a

mp.: 133-134℃ (red plate 95% Lit.[20]).; IR (KBr, cm^{-1}); δ ppm=1.7 (1H, NH), 1.4 (3H, t, CH_3, J=7.3 Hz), 2.5 (2H, q, N-CH_2, J=7.3 Hz), 7.4-7.8 (4H, m, aromatic).

2-bromo-3-(N-ethylamino)-1,4-naphthoquinone, 8b

mp.: 115-1118℃ (red yellow powder 84%, Lit.[20]).; IR (KBr, cm^{-1}); 3300 (s, NH), 3040, 2950, 1680 (s, C=O), 1640, 1525, 1460; ^{1}H-NMR ($CDCl_3$); δ ppm=1.65 (1H, NH), 1.3 (3H, t, CH_3, J=7.3 Hz), 2.5 (2H, q, N-CH_2, J=7.3 Hz), 7.3-7.8 (4H, m, aromatic).

2-chloro-3-(N-2-hydroxyethylamino)-1,4-naphthoquinone, 10a

mp.: 128-130℃ (red powder 93% Lit.[2]).; IR (KBr, cm^{-1}); 3420 (s, OH), 3260 (s, NH), 3050, 2940, 1685 (s, C=O), 1645, 1535, 1465; ^{1}H-NMR ($CDCl_3$); δ ppm=1.7 (1H, NH), 2.6 (2H, t, N-CH_2, J=7.2 Hz), 2.0 (1H, s, OH), 4.3 (2H, t, O-CH_2, J=7.2 Hz), 7.2-7.7 (4H, m, aromatic).

2-bromo-3-(N-2-hydroxyethylamino)-1,4-naphthoquinone, 10b

mp.: 128-130℃ (red brown powder 84%, Lit.[2]).; IR (KBr, cm^{-1}); 3410 (s, OH), 3300 (s, NH), 3040, 2950, 1680 (s, C=O), 1640, 1525, 1460; ^{1}H-NMR ($CDCl_3$); δ ppm=1.57 (1H, NH), 2.5 (2H, t, N-CH_2, J=7.2 Hz), 2.1 (1H, s, OH), 4.4 (2H, t, O-CH_2, J=7.2 Hz), 7.2-7.7 (4H, m, aromatic).

Antimicrobial activities of 2,3-disubstituted-1,4-naphthoquinones

The antimicrobial effect of the compounds was determined by the standard two-fold agar dilution method[1]. The MIC (*Minimal Inhibitory Concentration*) of the compounds was determined by judging visually the microbial growth in the series of test agar plates.

Antibacterial activities

The following four bacterial strains were used as target organisms: *Bacillus subtilis ATCC 6633, Pseudomonas aeruginosa NCTC 10490, Staphylococcus aureus ATCC 6538p, Escherichia coli NIHJ.*

The 1,4-naphthoquinone derivatives under investigation were dissolved in water or acetone and filtered through bacterial membrane filter (0.45 μm).

Prior to testing, the strains of bacteria were cultured in liquid Mueller-Hinton broth at 37℃ for 24 hr, and subcultured again for 6 hr. The number of bacterial cell suspension was adjusted with the same sterile broth to 2×10^5 microorganisms and then used for the tests.

Test components (1 mg) were dissolved in a minimum volume of ethanol or water and prepared for two-fold step dilution series of the solution (0.1 ml). That was then added to the incubated Mueller-Hinton agar which had about 2×10^5 microorganisms. The MIC was determined by judging visually the bacterial growth in the series of test agar plates. Ampicillin as antibacterial standard substance was used (Table II).

Antifungal activities

The antifungal effect of the compounds was determined by the standard two-fold agar dilution method. The following three fungal strains were used as target organisms: *Candida albicans ATCC 10231 and local, Aspergillus niger KCTC 1231, Tricophyton mentagrophytes KCTC 6085.*

Prior to determination of antifungal activity, the strains of fungi were cultured in Sabouraud agar at 30℃ for 3-7 days. The number of cell was ad-

Table II. Antibacterial and antifungal activities of 1,4-naphthoquninone derivatives

Compound	MIC (μg/ml)						
	B. subtillus	*S.aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*	*T. mentagrophytes*
1a	25	25.5	50	100	25	25	25
1b	6.3	100	25	6.3	6.3	6.3	6.3
2a	50	50	50	50	50	50	50
2b	100	100	100	100	>100	100	100
3a	25	50	25	50	25	25	25
3b	100	>100	100	100	50	50	50
4a	25	50	100	25	25	25	50
4b	50	100	100	50	50	50	50
5a	100	25	50	100	50	25	25
5b	50	100	50	50	25	25	25
6a	25	50	100	50	25	50	50
6b	50	100	100	25	12.5	12.5	12.5
7a	6.3	100	25	12.5	100	100	100
7b	12.5	25	25	50	50	100	100
8a	12.5	100	100	12.5	50	100	100
8b	12.5	6.3	100	50	12.5	12.5	50
9a	50	25	25	100	25	50	12.5
9b	100	>100	>100	100	12.5	25	12.5
10a	50	6.3	25	100	50	25	25
10b	50	100	100	50	50	50	50
Ampicillin	12.5	3.2	25	6.3	*	*	*
Griseofulvin	*	*	*	*	50	25	50

*not determined.

justed with the same sterile broth to 2×10^5 microorganisms and then used for the tests. Also *MIC* was prepared in a similar manner to that described on antibacterial activities). Griseofulvin as antifungal standard substance was used (Table II).

RESULTS AND DISCUSSION

Chemistry

The compounds **1-10** tested were prepared as shown in Table I. The 2,3-dihalo-1,4-naphthoquinone amines were prepared by the previously reported methods[11, 13,18-20] (Scheme 1). The 2-halo-3-substituted-1,4-naphthoquinone derivatives (**1-10**) were prepared respectively by treatment of 2,3-dichloro- and 2,3-dibromo-1,4-naphthoquinone with the appropriate amine in ethanol. These reactions went as expected and were in satisfactory yields.

Determination of antibacterial and antifungal activities

The minimal inhibitory concentrations of the antimicrobial compounds were determined *in vitro* by the two-fold broth dilution method. The result is given as MIC in Table II in comparison with those of ampicillin and griseofulvin. The control blank showed no antimicrobial agents against all the strain of microorganisms.

As indicated in the Table II, **1b** has potent activities with widely expanded spectra against Gram positive, negative bacteria and fungi. **1b** completely inhibited the bacterial growth at 6.25 μg/ml against *Bacillus substilis, Candida albicans, Pseudomonas aeruginosa, Aspergillus, niger, Tricophyton mentagrophytes.* On the other hand, ampicillin inhibited the growth at 12.5 and 6.35 μg/ml against bacteria, respectively.

Against bacteria, **1b, 7a** and **7b** displayed potent activities comparable or slightly inferior to that of ampicillin. In fact, **1b, 6b** and **9b** showed comparable activities or superior to that of griseofulvin against many fungi.

The derivatives such as **7a** and **7b** with 1-(2-hydroxyethyl)piperizino group exhibited increase of the potent activities against bacteria. **8a** and **8b** with 2-methylaziridyl substituent showed increase of the

potent activities against fungi.

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