Synthetic Approaches to 3-Amino-1,4-naphthoquinone-2-carboxylic Acid Derivatives and Photochemical Synthesis of Novel 1,4,5,10-Tetrahydro-5,10-dioxo-2*H*-naphth[2,3-*d*][1,3]oxazine Derivatives

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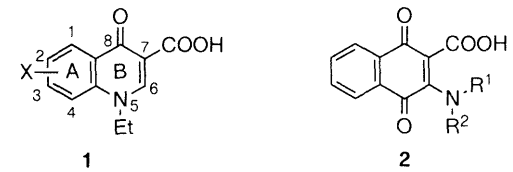
Synthesis of 3-alkylamino-1,4-naphthoquinone-2-carboxylic acid (2) was attempted. Although 3-(1-piperidinyl)-1,4-naphthoquinone-2-carboxylic acid (2a) was not obtained, probably because of its instability, the esters (18a, b) of 2a could be prepared. 2-Alkylamino-3-hydroxymethyl-1,4-naphthoquinones (9a—g) were photochemically cyclized to the 1,4,5,10-tetrahydro-5,10-2*H*-naphth[2,3-*d*][1,3]oxazines (19a—g), containing a novel heterocyclic ring system in moderate yields. Anti-bacterial activity of the prepared compounds was weak or insignificant.

Keywords naphthoquinone; 1,4-quinolonecarboxylic acid; photochemical reaction; cyclization; oxidation; oxazine

5,8-Dihydro-8-oxo-1,3-dioxolo[4,5-*g*]quinoline-7-carboxylic acid derivatives (**1**) are well known as anti-bacterial agents,[1] but the appearance of the quinolone-resistant bacteria has made it necessary to modify the molecular structures with the aim of finding new effective agents.[2] We planned to synthesise 3-amino-1,4-naphthoquinone-2-carboxylic acid derivatives (**2**). In the structure of **2**, the nitrogen atom has been removed from the B ring of **1**, but the biological activity of **2** is not expected to be greatly altered because the electronic effect of the enaminoketone structure of **1** seems to be similar to that of **2**. This paper deals with attempts for the synthesis of **2** and the unexpected finding of a new photochemical cyclization of an intermediate 2-hydroxymethyl-3-amino-1,4-naphthoquinones to novel 1,4,5,10-tetrahydro-5,10-dioxo-2*H*-naphth[2,3-*d*][1,3]oxazine derivatives (**19**).



1 (X = 3-CH_3, 3-Cl, 2,3-OCH_2CH_2O-, *etc.*) **2**

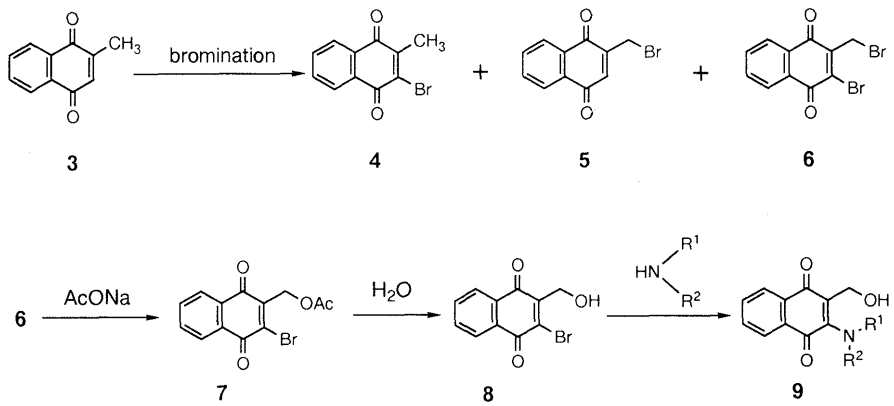
Fig. 1

Bromination of commercially available 2-methyl-1,4-naphthoquinone (vitamin K_3; **3**) was first examined under various reaction conditions by using bromine, *N*-bromosuccinimide (NBS) and pyridinium hydrobromide perbromide (PHPB) as brominating agents. The results are shown in Table I. The best yield (92.2%) of the dibromide (**6**)[3] was obtained in run 5; in other runs the monobromides (**4**[4] or **5**[3]) were also obtained in various yields. The dibromide (**6**) was treated with sodium acetate in various solvents. Although the best yield (80.3%) of the acetoxymethyl-1,4-naphthoquinone (**7**) was obtained

TABLE I. Bromination of Vitamin K_3 (**3**)

Run	Brominating agent	Solvent	Temp. (°C)	Time	Yield (%)[a] 4 : 5 : 6
1	Br_2 (2.0 eq)	AcOH	r.t.	24 h	77.6 : 0 : 0
2	NBS (2.1 eq)	CCl_4[b]	77	24 h	0 : 53.8 : 0[c]
3	NBS (3.0 eq)	Ac_2O[b]	120	80 min	0 : 45.1 : 36.3
4	PHPB (2.1 eq)	AcOH	70	30 min	54.3 : 0 : 33.1
5	PHPB (2.1 eq)	AcOH	70	80 min	0 : 0 : 92.2

a) Isolated yield. *b*) In the presence of azoisobutyronitrile (AIBN). *c*) The starting material (**3**) was recovered (34.8% yield). r.t. = room temperature.



3 **4** **5** **6**

6 → **7** → **8** → **9**

Chart 1

when dimethyl sulfoxide (DMSO) was used as the solvent (Table II, run 4), a dark pigment and several by-products were formed in the reaction mixture. So we adopted the reaction condition of run 2 (80 °C in acetic acid–chloroform; yield, 74.9%) for the routine preparation of **7**. The ester **7** was hydrolyzed to the alcohol (**8**) by refluxing in a trifluoroacetic acid–water system. Treatment of the alcohol (**8**) with pyrrolidine in dichloromethane gave the 2-aminonaphthoquinone (**9a**) in 74.7% yield. Table III shows the results of the amination under various reaction conditions and aminating agent. Although cyclic secondary amines (runs 1—4; not run 5) and aliphatic primary amines (runs 11, 12) gave good results, secondary amines (runs 7—9; except run 6), and an aromatic primary amine (run 13) were almost ineffective.

Table II. Conversion of **6** to **7**

Run	AcONa (eq)	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]
1	1.05	AcOH–$CHCl_3$	80	5.0	19.5[b]
2	5.0	AcOH–$CHCl_3$	80	5.0	74.9
3	1.05	DMF	r.t.	2.0	35.5
4	1.05	DMSO	r.t.	2.0	80.3

a) Isolated yield. *b*) The starting material (**6**) was recovered (71.3% yield). r.t. = room temperature.

Table III. Conversion of **8** to **9**

Run	R^1	R^2	Solvent	Temp. (°C)	Time (h)	9	Yield (%)[a]
1	$-(CH_2)_4-$		CH_2Cl_2	r.t.	0.25	**9a**	74.7
2	$-C_2H_4OC_2H_4-$		CH_2Cl_2	r.t.	0.25	**9b**	71.0
3	$-(CH_2)_5-$		CH_2Cl_2	r.t.	0.25	**9c**	70.0
4	$-(CH_2)_6-$		CH_2Cl_2	r.t.	0.25	**9d**	69.4
5	$-C_2H_4N(Me)C_2H_4-$		CH_2Cl_2	r.t.	0.25	—	—[b]
6	Me	Me	CH_2Cl_2	r.t.	0.25	**9e**	75.3
7	Et	Et	CH_2Cl_2	r.t.	0.25	—	—[b]
8	*n*-Pr	*n*-Pr	CH_2Cl_2	r.t.	0.25	—	N.R.[c]
9	*n*-Pr	*n*-Pr	$CHCl_3$	61[d]	48	—	N.R.[c]
10	Ph	Me	$CHCl_3$	61[d]	48	—	N.R.[c]
11	Me	H	MeOH	r.t.	1	**9f**	41.4
12	*n*-Pr	H	MeOH	r.t.	1	**9g**	52.2
13	Ph	H	$CHCl_3$	61[d]	48	—	N.R.[c]

a) Isolated yield. *b*) A complex mixture was obtained. *c*) No reaction. *d*) At the boiling point of the solvent. r.t. = room temperature.

Oxidation of the hydroxymethyl group of **8** and **9a** to the corresponding carboxylic acid (**2**) was attempted by using several known oxidation procedures, but the attempts resulted in the recovery of the starting materials or formation of complex mixtures or phthalic acid (**12**) (Chart 2). So we tried the preparation of the aminoester (**16**) *via* the route shown in Chart 3. Methyl 3-hydroxy-1,4-naphthoquinone-2-carboxylate (**14**) was prepared in 31.8% yield from phenylacetyl chloride according to Soliman's procedure.[5] Direct amination of **14** with pyrrolidine resulted in almost complete recovery of **14**. Treatment of the ester (**14**) with diazomethane gave the methyl ether (**15**), which was then treated with pyrrolidine without isolation to give the corresponding aminoester (**16a**) in 32.2% yield. Amination of **14** with *N*-methylamine also gave **16b** in 31.1% yield.

In order to obtain the desired aminoacid (**2**), hydrolysis of **16a** under several conditions was examined. As summarized in Table IV, the products obtained were only the deaminated product (**14**) and/or the decarboxylated products (**17** and **18**[6]). Therefore, we abondoned this approach to **2**.

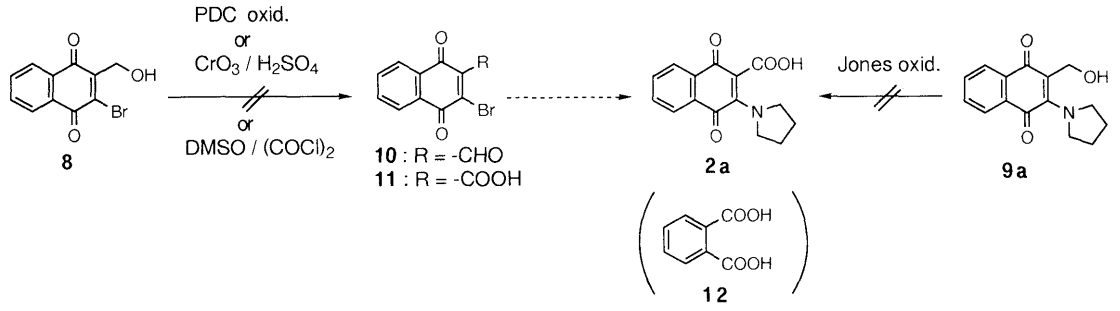


Chart 2

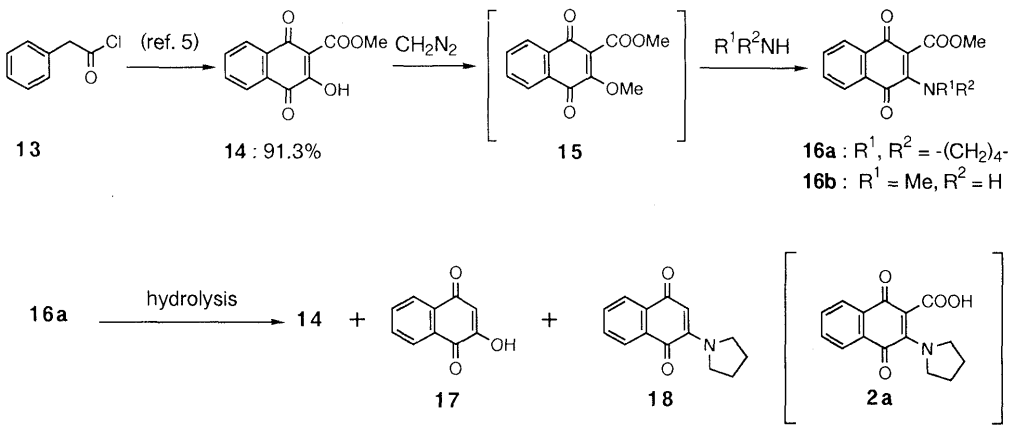


Chart 3

In the experiments for the preparation of the alcohols (**9**), we observed that during storage of a solution of **9a** in ethyl acetate a new spot gradually appeared in the thin-layer chromatogram (TLC), but the change hardly occurred in the dark. When a solution of **9a** in ethyl acetate was externally irradiated with a 500 W high-pressure mercury arc lamp in a quartz cell at room temperature, we isolated the oxazine compound (**19a**) in 35.3% yield. Its infrared (IR) spectrum showed the absence of the hydroxy group. Its mass spectrum (MS) and elemental micro-analysis data indicated the molecular formula $C_{15}H_{13}NO_3$, implying loss of two hydrogen atoms from **9a**. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **19a** showed a triplet signal (1H) due to the C-3a proton (>N-C<u>H</u>-O-) at δ 4.85 ppm and two doublet signals (1H each) due to the C-5 protons (=C-C<u>H</u>$_2$-O-) at δ 4.66 and 4.94 ppm. The ^{13}C-NMR spectrum of **19** showed the C-3a carbon signal at δ 89.5 ppm. These data support the illustrated structure of **19a**, which is a new and interesting heterocyclic ring system.

The present photochemical cyclization seems to be synthetically useful. In general, naphthoquinone derivatives show a variety of photochemical behaviors probably because the naphthoquinone nucleus itself has can act as a photo-sensitizer,[7] so the present cyclization seems not to be abnormal. Several photo-irradiation experiments were carried out in order to optimize the reaction condition, and the results are summarized in Table V. The yield of the product (**19a**) increased to about 70% either by the use of Pyrex cell as the reaction vessel or by addition of piperylene as a triplet excited state deactivator,[8] but simultaneous use of Pyrex cell and piperylene did not improve the yield of **19a**. The photochemical

TABLE IV. Hydrolysis of **16a**

Run	Reagent	Solvent	Temp. (°C)	Time (h)	Yield (%)[a] 14 : 17 : 18
1	1 N KOH	MeOH	r.t.	12	97.5 : 0 : 0
2	6 N NaOH	MeOH	100	7	0 : 71.8 : 0
3	2 N HCl	MeOH–H_2O	r.t.	7	85.3 : 0 : 0
4	2 N HCl	MeOH–H_2O	100	5	0 : 83.3 : 0
5	TMSI	CCl_4	50	12	0 : 0 : 57.2[b]
6	TMSCl/NaI	MeCN	80	7	0 : 0 : 30.8[c]
7	$AlCl_3$	EtSH	r.t.	3	0 : 0 : 63.2[d]

a) Isolated yield. *b*) The starting material (**16a**) was recovered (28.1% yield). *c*) The starting material (**16a**) was recovered (28.1% yield). *d*) The starting material (**16a**) was recovered (10.5% yield). r.t. = room temperature.

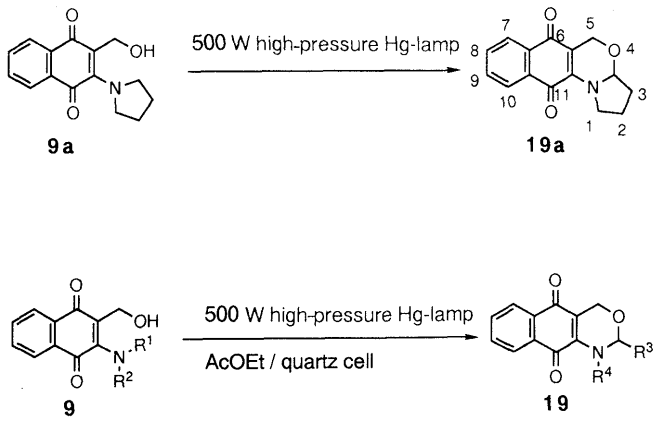


Chart 4

TABLE V. Conversion of **9a** to **19a**

Run	Solvent	Cell	Yield (%)[a]
1	AcOEt	Quartz	35.3
2	MeOH	Quartz	45.7
3	AcOEt	Pyrex	65.3
4	MeOH	Pyrex	71.8
5	AcOEt–piperylene[b]	Quartz	67.9
6	MeOH–piperylene	Quartz	69.2
7	AcOEt–piperylene	Pyrex	69.2
8	MeOH–piperylene	Pyrex	70.5

a) Isolated yield. *b*) 1,3-Pentadiene.

TABLE VI. Photochemical Conversion of **9** to **19** in MeOH (Pyrex Cell)

Run	Starting materials 9	R^1	R^2	Time (h)	Products 19	R^3	R^4	Yield (%)[a]
1	**9b**	$-C_2H_4OC_2H_4-$		4	**19b**	$-CH_2OC_2H_4-$		42.4
2	**9c**	$-(CH_2)_5-$		6	**19c**	$-(CH_2)_4-$		55.7
3	**9d**	$-(CH_2)_6-$		9	**19d**	$-(CH_2)_5-$		44.1
4	**9e**	Me	Me	3	**19e**	H	Me	69.8
5	**9f**	Me	H	12	**19f**	H	H	—[b]
6	**9g**	*n*-Pr	H	24	**19g**	Et	H	59.7

a) Isolated yield. *b*) A complex mixture was obtained.

TABLE VII. Antifungal and Antibacterial Activity of the Prepared Compounds (MIC: μg/ml)

	9a	**9e**	**16a**	**19a**	**19b**	**19c**	**19e**	MCZ[a]	NA[b]
C. albicans IFO 1385[c]	>100	>100	>100	>100	>100	>50	100	25	—
C. albicans 200/175[c]	>100	>100	>100	>100	100	>50	25	>100	—
S. cerevisiae ATCC 9763[c]	>100	100	>100	50	12.5	50	25	1.56	—
C. neoformans IFM 40092[c]	>100	>100	>100	>100	>100	>50	100	12.5	—
A. fumigatus IFM 4942[c]	>100	>100	>100	>100	50	>50	50	12.5	—
M. canis IFM 40767[c]	>100	—	>100	25	—	—	25	≤0.78	—
S. aureus FDA 209P[d]	>100	100	>100	25	50	100	25	—	25
S. pyogenes IID S-23[d]	>100	50	>100	50	50	50	50	—	—
E. coli NIHJ JC-2[e]	>100	>100	>100	>100	>100	>100	>100	—	6.25
K. pneumoniae NCTC 9632[e]	>100	>100	>100	>100	>100	>100	>100	—	3.13
S. marcescens IFO 12648[e]	>100	>100	>100	>100	>100	>100	>100	—	1.56
P. aeruginosa E-2[e]	>100	>100	>100	>100	>100	>100	>100	—	100

a) Miconazole. *b*) Nalidixic acid. *c*) Fungi. *d*) Bacteria (gram positive). *e*) Bacteria (gram negative).

cyclization under the best reaction condition of run 4 as in Table V was applied to **9b—g**, and the results are summarized in Table VI. The yields of **19b—e** and **19g** were moderate.

Unfortunately, the anti-bacterial activities of these compounds were weak or insignificant as shown in Table VII.

Experimental

All melting points are uncorrected. IR spectra were taken with a Shimadzu IR-435 spectrometer. ^{1}H-NMR and ^{13}C-NMR were obtained on Varian XL-300 and/or JEOL EX-270 spectrometers and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. Abbreviations of ^{1}H-NMR signal patterns are as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Low-resolution MS (LRMS) and high-resolution MS (HRMS) were obtained on a Hitachi M-80 spectrometer. All solvents were removed under reduced pressure in the usual work-up procedure. Unless otherwise stated, anhydrous sodium sulfate was used as a drying agent. Silica gel (Merck Art. 7734) was used in column chromatography and silica gel (Silica gel 60PF$_{254}$, Nacalai Tesque Ltd.) was used in preparative thin-layer chromatography (PTLC).

Bromination of Vitamin K$_3$ a) Bromination by Bromine: A solution of Br_2 (0.52 ml, 10 mmol) in AcOH (2 ml) was added over 10 min at 0 °C to a stirred mixture of **3** (861 mg, 5 mmol), AcONa (1.64 g, 20 mmol) and AcOH (10 ml), then the reaction mixture was stirred at room temperature for 24 h. The whole was poured into ice water (50 ml), and the precipitates (**4**) were collected by filtration, washed with water, dried, and recrystallized from methanol to give pale yellow needles. Yield 974 mg (77.6%), mp 150.9—151.8 °C (lit.[4] mp 151—152 °C). IR ($CHCl_3$): 1661 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 2.40 (s, 3H, –C$\underline{H}_3$), 7.70—7.77 (m, 2H, Ar-H), 8.10—8.18 (m, 2H, Ar-H).

b) Bromination by NBS in CCl_4: A solution of **3** (344 mg, 2 mmol), NBS (748 mg, 4.2 mmol), AIBN (33 mg, 0.2 mmol) in CCl_4 (30 ml) was refluxed for 24 h, then the precipitates were filtered off. The solvent of the filtrate was evaporated off and the residue was chromatographed (solvent, C_6H_6). The solvent of the main fraction was evaporated off and the crystalline residue was recrystallized from methanol to give **5** as yellow needles. Yield 270 mg (53.8%), mp 94.2—96.2 °C (lit.[3] mp 94—96 °C). IR ($CHCl_3$): 1660 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 4.40 (s, 2H, –C$\underline{H}_2$Br), 7.10 (s, 1H, C^3-H), 7.70—7.85 (m, 2H, C^6-H and C^7-H), 7.95—8.20 (m, 2H, C^5-H and C^8-H).

c) Bromination by NBS in Ac_2O: The reaction was carried out in the same manner as b) except for the use of Ac_2O (8 ml) instead of CCl_4 and a reaction temperature of 120 °C (80 min). Chromatography of the crude product gave **5** (226 mg, 45.1%) and **6** (240 mg, 36.3%). **6**: Yellow needles from 2-propanol, mp 118.0—119.0 °C (lit.[3] mp 118—120 °C). IR ($CHCl_3$): 1675 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 4.63 (s, 2H, –C$\underline{H}_2$Br), 7.77—7.84 (m, 2H, C^6-H and C^7-H), 8.17—8.21 (m, 2H, C^5-H and C^8-H). LRMS *m/z*: 328 (M$^+$).

d) Bromination by PHPB in AcOH: The reaction was carried out in the same manner as b) except for the use of **3** (2.58 g, 15 mmol), PHPB (10.07 g, 31.5 mmol) instead of NBS, AcOH (45 ml) instead of CCl_4, and a reaction temperature of 70 °C (80 min). The reaction mixture was cooled to room temperature, then poured into ice-water (300 ml). Precipitated crude product was collected by filtration, washed with water, dried and recrystallized from 2-propanol to give **6** (4.56 g, 92.2%).

2-Acetoxymethyl-3-bromo-1,4-naphthoquinone (7) A mixture of **6** (1.65 g, 5 mmol), AcONa (2.05 g, 25 mmol) and AcOH–$CHCl_3$ (2:1, 45 ml) was refluxed at 70 °C for 6 h. The solvent mixture was evaporated off, and water (150 ml) was added to the residue. The product was extracted with AcOEt (100 ml × 3) and dried. After evaporation of the solvent, the crude product was purified by column chromatography (CH_2Cl_2 : hexane = 1 : 2). Evaporation of the main fraction gave a crystalline residue, which was recrystallized from hexane to give yellow needles. Yield 1.16 g (74.9%), mp 99.0—101.0 °C. IR ($CHCl_3$): 1735 (>C=O), 1673 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 2.11 (s, 3H, –COC$\underline{H}_3$)), 5.27 (s, 2H, –C$\underline{H}_2$O–), 7.78—7.82 (m, 2H, C^6-H and C^7-H), 8.12—8.17 (m, 2H, C^5-H and C^8-H). *Anal.* Calcd for $C_{13}H_9BrO_4$: C, 50.51; H, 2.93. Found: C, 50.39; H, 2.88.

3-Bromo-2-hydroxymethyl-1,4-naphthoquinone (8) A solution of **7** (1.55 g, 5 mmol) and CF_3COOH–H_2O (3 : 1, 32 ml) was refluxed at 100 °C for 1 h and cooled to room temperature. The mixture was poured into ice-water (100 ml), and the precipitated crystals were filtered, washed with water, dried and recrystallized from AcOEt–hexane to give yellow needles. Yield 1.03 g (76.8%), mp 144.0—145.0 °C. IR ($CHCl_3$): 3500 (–OH), 1697, 1656 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 2.90—3.05 (br, 1H, –O$\underline{H}$), 4.89 (s, 2H, –C$\underline{H}_2$O–), 7.70—7.85 (m, 2H, C^6-H and C^7-H), 8.10—8.25 (m, 2H, C^5-H and C^8-H). *Anal.* Calcd for $C_{11}H_7BrO_3$: C, 49.47; H, 2.64. Found: C, 49.81; H, 2.67.

General Procedure for the Synthesis of 2-*N*-Alkylamino-3-hydroxymethyl-1,4-naphthoquinones; Synthesis of 3-Hydroxymethyl-2-(1-pyrrolidinyl)-1,4-naphthoquinone (9a) as a Typical Example Pyrrolidine (88 μl, 1.05 mmol) was added dropwise at room temperature to a stirred solution of **8** (134 mg, 0.5 mmol) in CH_2Cl_2 (5 ml). Stirring was continued for 15 min, then 10% Na_2CO_3 (10 ml) was added, and the product was extracted with CH_2Cl_2 (10 ml × 3). The organic layer was dried and evaporated.

The residue was purified by PTLC (solvent, AcOEt). The solvent of the main fraction was evaporated off to give a crystalline residue, which was recrystallized from AcOEt–hexane to give red needles. Yield 96 mg (74.7%), mp 115.0—117.0 °C. IR ($CHCl_3$): 3420 (–OH), 1675, 1609 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.91—1.96 (m, 4H, –C$\underline{H}_2$(C$\underline{H}_2$)$_2$C$\underline{H}_2$–), 3.25—3.35 (br, 1H, –O$\underline{H}$), 3.89—3.93 (m, 4H, –CH$_2$NC$\underline{H}_2$–), 4.63 (s, 2H, –C$\underline{H}_2$O–), 7.57 (td, 1H, C^6-H or C^7-H, J=7.5, 1.4 Hz), 7.67 (td, 1H, C^7-H or C^6-H, J=7.5, 1.4 Hz), 7.87 (dd, 1H, C^5-H or C^8-H, J=7.5, 1.4 Hz), 8.02 (dd, 1H, C^8-H or C^5-H, J=7.5, 1.4 Hz). LRMS *m/z*: 257 (M$^+$). *Anal.* Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.00; H, 5.93; N, 5.19.

9b: Obtained by the similar manner as that used for **9a** except for use of morpholine instead of pyrrolidine. Yield 97 mg (71.0%). Red needles from AcOEt–hexane, mp 137.0—138.9 °C. IR ($CHCl_3$): 3420 (–OH), 1665, 1617 (>C=O) cm^1. ^{1}H-NMR ($CDCl_3$, 300 MHz): 2.90—3.10 (br, 1H, –O$\underline{H}$), 3.63—3.66 (m, 4H, –C$\underline{H}_2$NC$\underline{H}_2$–), 3.84—3.87 (m, 4H, –C$\underline{H}_2$OC$\underline{H}_2$–), 4.58 (s, 2H, –C$\underline{H}_2$O–), 7.66—7.73 (m, 2H, C^6-H and C^7-H), 8.00 (dd, 1H, C^5-H or C^8-H, J=7.4, 1.7 Hz), 8.05 (dd, 1H, C^8-H or C^5-H, J=7.4, 1.7 Hz). *Anal.* Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.56; H, 5.52; N, 5.31.

9c: Obtained in the same manner as described for **9a** except for the use of piperidine instead of pyrrolidine. Yield 95 mg (70.0%). Red needles from AcOEt–hexane, mp 97.4—98.6 °C. IR ($CHCl_3$): 3420 (–OH), 1664, 1614 (>C=O) cm^1. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.73—1.78 (m, 6H, methylene protons), 3.40 (br, 1H, -O$\underline{H}$), 3.50—3.55 (m, 4H, –C$\underline{H}_2$NC$\underline{H}_2$–), 4.58 (s, 2H, –C$\underline{H}_2$O–), 7.63—7.64 (td, 1H, C^6-H or C^7-H, J=7.4, 1.7 Hz), 7.68 (td, 1H, C^7-H or C^6-H, J=7.4, 1.7 Hz), 7.99 (dd, 1H, C^5-H or C^8-H, J=7.4, 1.7 Hz), 8.03 (dd, 1H, C^8-H or C^5-H, J=7.4, 1.7 Hz). *Anal.* Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.53; H, 6.33; N, 4.95.

9d: Obtained by the same manner as described for **9a** except for the use of homopiperidine instead of pyrrolidine. Yield 99 mg (69.4%). Red needles from Et_2O, mp 96.9—100.2 °C. IR ($CHCl_3$): 3400 (–OH), 1665, 1608 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.65—1.69 (m, 4H, methylene protons), 1.82—1.85 (m, 4H, methylene protons), 3.35—3.45 (br, 1H, -O$\underline{H}$), 3.69 (t, 4H, -C$\underline{H}_2$NC$\underline{H}_2$-, J=5.7 Hz), 4.60 (s, 2H, –C$\underline{H}_2$O–), 7.61 (td, 1H, C^6-H or C^7-H, J=7.4, 1.6 Hz), 7.67 (td, 1H, C^7-H or C^6-H, J=7.4, 1.6 Hz), 7.93 (dd, 1H, C^5-H or C^8-H, J=7.4 and 1.6 Hz), 8.02 (dd, 1H, C^8-H or C^5-H, J= 7.4, 1.6 Hz). *Anal.* Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.64; H, 6.57; N, 5.16.

9e: Obtained by the same manner as described for **9a** except for the use of *N*,*N*-dimethylamine (50% in water, 0.30 ml, 3 mmol) instead of pyrrolidine. Yield 87 mg (75.3%). Red needles from AcOEt–hexane, mp 95.1—96.7 °C. IR ($CHCl_3$): 3380 (–OH), 1664, 1615 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 2.70—2.90 (br, 1H, –O$\underline{H}$), 3.28 (s, 6H, >NC$\underline{H}_3$), 4.61 (s, 2H, –C$\underline{H}_2$O–), 7.65 (td, 1H, C^6-H or C^7-H, J=7.4, 1.7 Hz), 7.66 (td, 1H, C^7-H or C^6-H, J=7.4, 1.7 Hz), 7.95 (dd, 1H, C^5-H or C^8-H, J=7.4, 1.7 Hz), 8.03 (dd, 1H, C^8-H or C^5-H, J=7.4, 1.7 Hz). *Anal.* Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.33; H, 5.59; N, 5.54.

9f: Obtained by the same manner as described for **9a** except for the use of **8** (267 mg, 1.0 mmol), MeOH (15 ml) instead of CH_2Cl_2, and *N*-methylamine (30% in MeOH, 1.0 ml, 8.7 mmol) instead of pyrrolidine. Yield 90 mg (40.4%). Red needles from AcOEt–hexane, mp 262.6—263.4 °C. IR ($CHCl_3$): 3440 (–OH), 3360 (>NH), 1672, 1604 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 2.54—2.64 (br, 1H, –O$\underline{H}$), 3.36 (d, 3H, >NC$\underline{H}_3$, J=5.9 Hz), 4.78 (s, 2H, –C$\underline{H}_2$O–), 6.20—6.40 (br, 1H, >N$\underline{H}$),

7.60 (td, 1H, C^6-H or C^7-H, J=7.6, 1.3 Hz), 7.72 (td, 1H, C^7-H or C^6-H, J=7.6, 1.3 Hz), 7.72 (d, 1H, C^5-H or C^8-H, J=7.6 Hz), 8.10 (d, 1H, C^8-H or C^5-H, J=7.6 Hz). *Anal.* Calcd for $C_{12}H_{11}NO_3 \cdot 1/4H_2O$: C, 65.00; H, 5.23; N, 6.32. Found: C, 64.84; H, 5.23; N, 6.09.

9g: Obtained by the same manner as described for **9f** except for the use of propylamine (0.173 ml, 2.1 mmol) instead of *N*-methylamine. Yield 128 mg (52.2%). Red needles from AcOEt–hexane, mp 95.9—96.4 °C. IR ($CHCl_3$): 3470 (–OH), 3328 (>NH), 1671, 1602 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 1.05 (t, 3H, $-CH_3$, J=7.3 Hz), 1.61—1.81 (m, 2H, $-CH_2CH_3$), 2.54—2.62 (br, 1H, –OH), 3.62 (q, 2H, $>NCH_2$, J=6.9 Hz), 4.73 (s, 2H, $-CH_2O-$), 6.00—6.36 (br, 1H, >NH), 7.60 (td, 1H, C^6-H or C^7-H, J=7.6, 1.3 Hz), 7.72 (td, 1H, C^7-H or C^6-H, J=7.6, 1.3 Hz), 8.02 (dd, 1H, C^5-H or C^8-H, J=7.6, 1.3 Hz), 8.10 (dd, 1H, C^8-H or C^5-H, J=7.6, 1.3 Hz). *Anal.* Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.35; H, 6.50; N, 5.67.

Methyl 1,4-Dihydro-1,4-dioxo-3-(1-pyrrolidinyl)-2-naphthoate (16a) An excess of an ethereal solution of CH_2N_2 (3 ml) was added to a solution of **14**[5] (232 mg, 1.0 mmol) in methanol (5 ml), and the mixture was stirred for 0.5 h. The solvents were evaporated off, and pyrrolidine (0.25 ml, 3.0 mmol) was added to a solution of the residue in methanol (5 ml). The mixture was refluxed at 80 °C for 15 min. The residue, obtained by removal of the solvent, was purified by PTLC (solvent, AcOEt). Evaporation of the solvent of the main fraction gave a crystalline residue, which was recrystallized from hexane to give orange needles. Yield 92 mg (32.2%), mp 146.8—148.2 °C. IR ($CHCl_3$): 1712 (>C=O), 1677, 1615 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 1.77—1.97 (m, 4H, $-CH_2(CH_2)_2CH_2-$), 3.58–3.75 (m, 4H, $-CH_2NCH_2-$), 3.85 (s, 3H, $-COOCH_3$), 7.53 (t, 1H, C^6-H or C^7-H, J=7.6 Hz), 7.63 (t, 1H, C^7-H or C^6-H, J=7.6 Hz), 7.87 (d, 1H, C^8-H or C^5-H, J=7.6 Hz), 7.99 (d, 1H, C^8-H or C^5-H, J=7.6 Hz). *Anal.* Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.13; H, 5.19; N, 4.90.

16b: Obtained in the same manner as described for the synthesis of **16a** except for the use of methylamine (30% methanolic solution, 0.35 ml, *ca.* 3 mmol). Orange plates, mp 206.1—208.4 °C. Yield 79 mg (31.1%). IR ($CHCl_3$): 3355 (>NH), 1724 (>C=O), 1677, 1610 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.05 (s, 3H, $>NCH_3$), 3.93 (s, 3H, $-COOCH_3$), 6.35—6.55 (br, 1H, $-NHCH_3$), 7.61—7.80 (m, 2H, C^6-H and C^7-H), 8.13—8.16 (m, 2H, C^5-H and C^8-H). HRMS *m/z*: Calcd for $C_{13}H_{11}NO_4$; 245.0690. Found; 245.0679. *Anal.* Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.62; H, 4.57; N, 5.51.

Reaction of 16a with 1 N KOH A mixture of **16a** (60 mg, 0.21 mmol), 1 N KOH (5 ml) and EtOH (2 ml) was stirred at room temperature for 12 h. After removal of the solvent by evaporation and addition of 10% HCl (5 ml) and water (5 ml) to the residue, the product was extracted with CH_2Cl_2 (10 ml × 3). The extract was dried, and the solvent was evaporated off. The residue was purified by PTLC (solvent, AcOEt). The residue, obtained by evaporation of the main fraction, was recrystallized from ether to give **14**. Yield, 47 mg (97.5%). The product was identical with **14** on the basis of IR and ^{1}H-NMR comparisons.

Reaction of 16a with Me_3SiI A mixture of **16a** (29 mg, 0.1 mmol), CCl_4 (5 ml) and Me_3SiI (15 μl, 0.1 mmol) was stirred at 50 °C for 12 h. Work-up similar to that used for the reaction of **16a** with 1 N KOH gave **16a** (8 mg, 28.1%) and **18**. **18**: yield, 13 mg (57.2%). Red needles from 2-propanol, mp 157.7—159.6 °C (lit.[6] mp 158—160 °C). IR ($CHCl_3$): 1672, 1614 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 1.97—2.02 (m, 4H, $-CH_2(CH_2)_2CH_2-$), 3.85—4.10 (m, 4H, $-CH_2NCH_2-$),5.74 (s, 1H, C^3-H), 7.59 (td, 1H, C^6-H or C^7-H, J=7.6, 1.3 Hz), 7.69 (td, 1H, C^6-H or C^7-H, J=7.6, 1.3 Hz), 8.01 (dd, 1H, C^5-H or C^8-H, J=7.6, 1.3 Hz), 8.07 (dd, 1H, C^8-H or C^5-H, J=7.6, 1.3 Hz).

Photochemical Reaction of 9; Irradiation of 9a as an Example a) In a Quartz Cell: A solution of **9a** (129 mg, 0.5 mmol) in AcOEt (20 ml) was placed in a quartz cell and irradiated at room temperature for 3 h by a 500 W high-pressure Hg-arc lamp (Taika Ind. Ltd.). After removal of the solvent by evaporation, the residue was purified by PTLC (solvent, AcOEt) to give a crystalline residue, which was recrystallized from AcOEt–hexane to give **19a** as red needles. Yield 45 mg (35.3%), mp 135.3—136.8 °C. IR ($CHCl_3$): 1669, 1616 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.93—2.31 (m, 4H, $-CH_2(CH_2)_2CH_2-$), 3.75–3.84 (m, 1H, $-CH_2NCH-$), 4.15—4.23 (m, 1H, $-CH_2NCH-$), 4.66 (d, 1H, $-CH_2O-$, J=16.7 Hz), 4.85 (t, 1H, $>NCH-O-$, J=5.6 Hz), 4.94 (d, 1H, $-CH_2O-$, J=16.7 Hz), 7.61 (td, 1H, C^6-H or C^7-H, J=7.5, 1.5 Hz), 7.69 (td, 1H, C^7-H or C^6-H, J=7.5, 1.5 Hz), 8.00 (dd, 1H, C^5-H or C^8-H, J=7.5, 1.5 Hz), 8.04 (dd, 1H, C^8-H or C^5-H, J=7.5, 1.5 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz): 23.00 and 30.43 ($-CH_2(CH_2)_2CH_2-$), 50.05 and 64.47 ($-CH_2O-$), 89.54 ($>NCHO-$), 115.17, 125.09, 125.88, 130.84, 131.82, 132.52, 133.81 (C-5a, C-6a, C-7—C-10 and C-10a), 144.00 (C-11a), 179.47 and 181.21 (C-6 and C-11). LRMS *m/z*: 255 (M^+). *Anal.* Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.28; H, 5.13; N, 5.43.

b) In a Pyrex Cell: A solution of **9a** (77 mg, 0.3 mmol) in MeOH (15 ml) was placed in a Pyrex cell and irradiated at room temperature for 3 h by a 500 W high-pressure Hg-arc lamp. Work-up similar to that described above gave 55 mg (71.8%) of **19a**.

19b: Obtained in the same manner as described under b) except for the use of **9b** instead of **9a**. Pale red needles from AcOEt–hexane. Yield 35 mg (42.4%). mp 169.8—173.2 °C. IR ($CHCl_3$): 1662, 1616 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.36 (ddd, 1H, $-NCH_2-$, J=3.3, 8.2, 12.8 Hz), 3.67 (dd, 1H, $>CHCH_2O-$, J=6.6, 11.7 Hz), 3.80—3.93 (m, 2H, $-CH_2CH_2O-$), 4.06 (dd, 1H, $>CHCH_2O-$, J=3.3, 11.7 Hz), 4.37—4.44 (m, 2H, $>NCH-O-$ and $>NCH_2-$), 4.64 (d, 1H, $ArCH_2O-$, J=17.0 Hz), 4.93 (d, 1H, $ArCH_2O-$, J=17.0 Hz), 7.65 (td, 1H, C^6-H or C^7-H, J=7.4, 1.6 Hz), 7.70 (td, 1H, C^7-H or C^6-H, J=7.4, 1.6 Hz), 8.00 (dd, 1H, C^5-H or C^8-H, J=7.4, 1.6 Hz), 8.03 (dd, 1H, C^8-H or C^5-H, J=7.4, 1.6 Hz). *Anal.* Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.19; H, 4.72; N, 5.17.

19c: Obtained in the same manner as described under b) except for the use of **9c** instead of **9a**. Red crystals from AcOEt–hexane. Yield 45 mg (55.7%), mp 110.1—111.2 °C. IR ($CHCl_3$): 1664, 1611 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.56—2.11 (m, 6H, $-(CH_2)_3-$), 2.94—3.02 (m, 1H, $>NCH_2-$), 4.41—4.46 (m, 2H, $>NCH_2-$ and $>NCHO-$), 4.56 (d, 1H, $ArCH_2O-$, J=16.5 Hz), 4.92 (d, 1H, $ArCH_2O-$, J=16.5 Hz), 7.62 (td, 1H, C^6-H or C^7-H, J=7.4, 1.6 Hz), 7.67 (td, 1H, C^7-H or C^6-H, J=7.4, 1.6 Hz), 7.98 (dd, 1H, C^5-H or C^8-H, J=7.4, 1.6 Hz), 8.01 (dd, 1H, C^8-H or C^5-H, J=7.4, 1.6 Hz). *Anal.* Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.39; H, 5.59; N, 4.99.

19d: Obtained in the same manner as described under b) except for the use of **9d** instead of **9a**. Red needles from AcOEt–hexane. Yield, 37 mg (44.1%). mp 100.5—102.4 °C. IR ($CHCl_3$): 1662, 1615 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.55—2.16 (m, 8H, $-(CH_2)_4-$), 2.90—3.10 (m, 1H, $>NCH_2-$), 4.40—4.50 (m, 2H, $-NCH_2-$ and $>NCHO-$), 4.55 (d, 1H, $ArCH_2O-$, J=16.5 Hz), 4.92 (d, 1H, $=C-CH_2O-$, J=16.5 Hz), 7.57 (td, 1H, C^6-H or C^7-H, J=7.4, 1.6 Hz), 7.62 (td, 1H, C^7-H or C^6-H, J=7.4, 1.6 Hz), 7.93 (dd, 1H, C^5-H or C^8-H, J=7.4, 1.6 Hz), 7.96 (dd, 1H, C^6-H or C^7-H, J=7.4, 1.6 Hz). *Anal.* Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.77; H, 6.05; N, 4.87.

19e: Obtained in the same manner as described under b) except for the use of **9e** instead of **9a**. Red needles from AcOEt–hexane. Yield 48 mg (69.8%), mp 109.5—110.0 °C. IR ($CHCl_3$): 1666, 1615 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.36 (s, 3H, $>NCH_3$), 4.63 (s, 2H, $>NCH_2O-$), 4.75 (s, 2H, $ArCH_2O-$), 7.63 (td, 1H, C^6-H or C^7-H, J=7.3, 1.6 Hz), 7.67 (td, 1H, C^7-H or C^6-H, J=7.3, 1.6 Hz), 8.02 (dd, 1H, C^5-H or C^8-H), 8.03 (dd, 1H, C^8-H or C^5-H, J=7.3, 1.6 Hz). *Anal.* Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 67.86; H, 4.64; N, 5.55. LRMS *m/z*: 229 (M^+).

19g: Obtained in the same manner as described under b) except for the use of **9g** instead of **9a**. Red needles from Et_2O. Yield 44 mg (59.7%), mp 159.5—161.0 °C. IR ($CHCl_3$): 3390 (>NH), 1674, 1616 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 1.09 (t, 3H, $-CH_2CH_3$, J=7.4 Hz), 1.78—1.86 (m, 2H, $-CH_2CH_3$), 4.63—4.69 (m, 1H, $>NCHO-$), 4.61 (d, 1H, $ArCH_2O-$, J=16.5 Hz), 4.92 (d, 1H, $ArCH_2O-$, J=16.5 Hz), 5.79—5.87 (br, 1H, >NH–), 7.60 (td, 1H, C^6-H or C^7-H, J=7.6, 1.3 Hz), 7.70 (td, 1H, C^7-H or C^6-H, J=7.6, 1.3 Hz), 8.00 (dd, 1H, C^5-H or C^8-H, J=7.6, 1.3 Hz), 8.05 (dd, 1H, C^8-H or C^5-H, J=7.6, 1.3 Hz). *Anal.* Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.05; H, 5.50; N, 5.42. LRMS *m/z*: 243 (M^+).

Antimicrobial Activity The antibacterial and antifungal activities of the prepared compounds, listed in Table VII, were determined by the agar dilution method in Meuller Hinton agar (Difco) for bacteria and Sabouraud dextrose agar (SDA; 1% polypeptone, 2% dextrose, 1.5% agar, pH 5.8) for fungi. The tested compounds were dissolved in DMSO and diluted with DMSO to prepare serial two-fold dilutions in the range of 15.6 to 8000 μg/ml. The final concentration of DMSO in the medium was adjusted to 5% for bacteria and 2.5% for fungi. The tested organisms were grown at 37 °C for 18 h for bacteria in Meuller Hinton broth (Difco) or at 30 °C for 48 h for yeasts in Sabouraud dextrose broth. Spore suspensions of *Aspergillus* and *Microsporum*, which were grown at 30 °C for 5 to 10 d on SDA, were prepared by rubbing the surface of the medium with a platinum loop after addition of sterile

saline containing 0.1% (w/v) Tween 80. The agar plates containing two-fold dilutions of the compounds were spotted with one loopful of the cell suspensions (*ca.* 10^6 viable cells/ml each), and incubated at 37 °C for 18 h for bacteria or at 30 °C for 2 to 6 d for fungi according to the growth characteristics of the organisms being tested. Results with yeast were determined after 48 h of incubation; *Aspergillus* and *Microsporum* required up to 3 d and 6 d of incubation for production of mature colonies, respectively. Each plate was examined, and the minimum inhibitory concentrations (MICs) were determined as the lowest concentration of the compound able to inhibit growth. The results are listed in Table VII.

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