**ANTI-CANCER EFFECTS OF NAPHTHOQUINONE DERIVATIVES
TESTED BY A SCREENING WITH EHRLICH ASCITES
CELLS IN MICE***

In the previous study (Egashira *et al.*, 1959), the procedure and evaluation of results of an anti-cancer screening system, using ascitic and solid forms of the Ehrlich tumor cells, were standardized on the basis of observations on inoculated animals analyzed from several viewpoints.

Among various kinds of synthetic chemical compounds which had been tested through this screening system, naphthoquinone derivatives were selected to be described herein. There have been few reports concerning the anti-cancer effects of naphthoquinones. Miyaki *et al.* (1956) synthesized several arylthionaphthoquinones and examined them by a cytological method. Abe *et al.* (1959) reported the result of a cell agar plate screening of the above compounds. In the present report, the screening result of 44 new naphthoquinone derivatives including the above will be described.

Naphthoquinone derivatives tested were divided depending on their chemical structures into 4 groups: A) alkylthionaphthoquinones (9 compounds), B) arylthionaphthoquinones (17), C) halogenonaphthoquinones (12), and D) miscellaneous (6).

The standards for procedure and evaluation of results were as described and tabulated in the previous paper (Egashira *et al.*, 1959). If a drug showed any effect either in intraperitoneal (i.p.) or subcutaneous (s.c.) group, the test was repeated so far as the amount of drug was permitted. When one proved to be toxic in the standard dose of 1200 μ g, a smaller amount was tried repeatedly.

The results of screening of 44 naphthoquinones are summarized in Tables 1-4. Three compounds in group A (Table 1), 2-methylthio-, 2,3-dimethylthio-, and 2-methylthio-3-Br-naphthoquinones, were determined to be effective to some extent both in i.p. and s.c.; 7 in group B (Table 2), especially 2-(p-toluy)-thionaphthoquinone, and 5 in group C (Table 3), especially 2-Cl- and 2,3-Cl-types showed effectiveness only in i.p., concerning the increase in longevity and viability.

According to the result of primary screening stated above, some effective drugs were examined again, the administration being started 3 days, instead of 1 day, after tumor inoculation (the secondary screening). Some of them were proved still effective through the procedure. The result on 2,3-dimethylthionaphthoquinone is illustrated in Fig. 1.

In summary, totally 44 naphthoquinone derivatives were examined through a standardized screening system. Effective compounds belonged to thio-type and some relationship of the function to the chemical structure was suggested.

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Fig. 1. Results of 2,3-dimethylthionaphthoquinone administration into mice receiving i.p. 2×10^6 Ehrlich tumor cells. Administration started 24 hours and 3 days after inoculation in primary and secondary screening procedures, respectively.

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Table 1. Screening results on alkylthionaphthoquinones

Drug	Dose (per mouse per day)	Toxicity	Tumor type		
			Ascites		Solid
			Viability	Longevity increase effect	Tumor weight decrease effect
	μg	(1)	(2)	(3)	(4)
$\text{R}_2 : -\text{S}\cdot\text{CH}_3$	1200	10/10			
	200	0/10	4/5	+	$\pm$
	200	0/5			$\pm$
$-\text{S}\cdot\text{C}_2\text{H}_5$	1200	10/10			
	600	2/5			+
	400	0/5			$\pm$
	200	0/5			—
$-\text{S}_3\cdot\text{C}_3\text{H}_7$	1200	10/10			
	200	0/10	0/5	—	—
$-\text{S}\cdot\text{CH}_2\text{COOH}$	1200	10/10			
	200	0/5			—
$\text{R}_2 : -\text{S}\cdot\text{CH}_3$	1200	7/10	1/1	++	++
$\text{R}_3 : -\text{S}\cdot\text{CH}_3$	400	5/10	2/2	++	$\pm$
	200	1/10			+
	200	0/20	4/10	+	$\pm$
	200	0/20	9/10	++	$\pm$
$-\text{S}\cdot\text{CH}_3$ $-\text{Cl}$	1200	10/10			
	600	5/5			—
	200	0/5			
$-\text{S}\cdot\text{CH}_3$ $-\text{Br}$	1200	5/5			
	200	1/10	3/4	++	+
$-\text{S}\cdot\text{CH}_3$ $-\text{NH}-$	1200	0/10	0/5	$\pm$	—
	800	0/5			—
$-\text{S}\cdot\text{CH}_3$ $-\text{NH}\cdot\text{CH}_2-$	1200	0/10	0/5	—	—

(1) No. of deaths within 9 days/No. of mice used.

(2) No. of survivals after 30 days/that over 9 days.

(3) Evaluated by increase ratio of mean longevity to control.

(4) Evaluated by ratio of mean tumor weight to control.

Table 2. Screening results on arylthionaphthoquinones

Drug	Dose (per mouse per day)	Toxicity	Tumor type		
			Ascites		Solid
			Viability	Longevity increase effect	Tumor weight decrease effect
	μg	(1) (2)	(3)	(4)	
$R_1: -\text{S}-\text{C}_6\text{H}_4-\text{CH}_3$	1200 1200	2/10 2/20	4/4 5/9	+	—
$-\text{S}-\text{C}_6\text{H}_4-\text{Cl}$	1000	2/10	1/4	+	—
$-\text{S}-\text{C}_6\text{H}_4-\text{NO}_2$	1200 700	0/10 0/5	0/5	+	—
$-\text{S}-\text{C}_6\text{H}_4-\text{NH}\cdot\text{CO}\cdot\text{CH}_3$	1200	2/10	4/5	++	—
$-\text{S}-\text{C}_6\text{H}_4-\text{COOH}$	1200 300	10/10 3/5			±
$-\text{S}\cdot\text{CH}_2-\text{C}_6\text{H}_5$	1200 1200	0/10 0/10	3/5 4/5	+	—
$R_1: -\text{S}-\text{C}_6\text{H}_5$	2400	1/5			—
$R_1: -\text{Br}$	1200	1/10	4/4	++	—
$-\text{S}-\text{C}_6\text{H}_5$	1200	1/10	0/5	—	—
$-\text{NH}_2$					
$-\text{S}-\text{C}_6\text{H}_4-\text{CH}_3$	1200	0/10	0/5	±	—
$-\text{Br}$	800	0/5			—
$-\text{S}-\text{C}_6\text{H}_4-\text{Cl}$	550	0/10	2/5	+	—
$-\text{Br}$	400	0/10	0/5	—	—
$-\text{S}-\text{C}_6\text{H}_4-\text{NH}\cdot\text{CO}\cdot\text{CH}_3$	1200	0/10	4/5	++	—
$-\text{Cl}$	400	0/10	4/5	++	—
$-\text{S}-\text{C}_6\text{H}_5$	1200	1/10			—
$-\text{S}-\text{C}_6\text{H}_5$	1200	0/10	0/5	—	—
$-\text{S}-\text{C}_6\text{H}_5$					
$-\text{S}-\text{C}_6\text{H}_4-\text{Cl}$	1200	0/10	0/5	—	—
$-\text{S}-\text{C}_6\text{H}_5$					
$-\text{S}-\text{C}_6\text{H}_5$	1200	1/10	0/5	—	—
CH_3					
$-\text{S}-\text{C}_6\text{H}_5$					
$-\text{S}-\text{C}_6\text{H}_4-\text{CH}_3$	1000	0/10	0/5	—	±
$-\text{S}-\text{C}_6\text{H}_4-\text{CH}_3$	1200	0/10	0/5	±	—
$-\text{S}-\text{C}_6\text{H}_4-\text{CH}_3$	600	0/5			—
$-\text{S}-\text{C}_6\text{H}_4-\text{CH}_3$	1200	0/5			—
$-\text{S}-\text{C}_6\text{H}_4-\text{Cl}$					

Cf. footnotes of Table 1.

Table 3. Screening results on halogenonaphthoquinones

Drugs	Dose (per mouse per day)	Toxicity	Tumor type		
			Ascites		Solid
			Viability	Longevity increase effect	Tumor weight decrease effect
	μg	(1)	(2)	(3)	(4)
R_2 : -Cl	1200	10/10			
	300	10/10			
	100	0/10	4/5	++	-
-Br	1200	10/10			
	300	2/5			+
R_2 : -Cl	1200	10/10			
R_3 : -Cl	600	10/10			
R_5 : -NH ₂	200	2/10	4/5	++	-
-Cl					
-Cl	1200	7/10	2/3	++	-
-NO ₂					
R_2 : -Br					
R_3 : -Br	1200	4/10	2/3	+	-
-Cl					
-NH ₂	1200	0/10	0/5	-	$\pm$
-Br	1200	5/5			
-NH $\cdot$ CO $\cdot$ CH ₃	400	3/10	3/4	+	-
-Cl					
-N(CH ₃) ₂	1200	4/10	1/1	++	-
-Cl					
-NH $\cdot$ CH $\begin{matrix} \text{CH}_3 \\ \text{C}_2\text{H}_5 \end{matrix}$	1200	0/10	0/5	-	-
-Cl					
-NH $\cdot$ (CH ₂) ₂ COOH	1200	0/10	0/5	-	-
-Cl					
-NH(CH ₂) ₃	1000	1/10	0/5	-	-
-Cl					
-NH-	1200	0/10	0/5	-	-

Cf. footnotes of Table 1.

Table 4. Screening results on miscellaneous naphthoquinones

Drug	Dose (per mouse per day)	Toxicity	Tumor type		
			Ascites		Solid
			Viability	Longevity increase effect	Tumor weight decrease effect
$R_2 : -NH_2$	1200 μg	(1) 0/10	(2) 1/5	(3) $\pm$	(4) —
$-NH-$	1200	0/10	0/5	—	$\pm$
	1200	0/5			—
$-NH-$	1200	0/10	0/5	—	—
$-NH-$	1200	0/5	1/5	—	
$NH \cdot CH_2-$	1200	0/10	0/5	—	—
$R_2 : -NO_2$					
$R_3 : -OH$	1200	0/10	0/5	—	—

Cf. footnotes of Table 1.