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(E)-6-(1-Alkyloxyiminoalkyl)-5,8-dimethoxy-1,4-naphthoquinones: Synthesis, Cytotoxic Activity and Antitumor Activity

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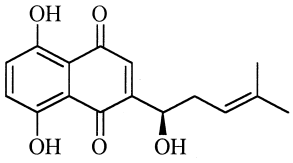
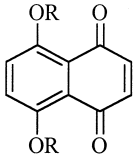
Abstract—All of 13 *(E)*-6-(1-alkyloxyiminomethyl)-5,8-dimethoxy-1,4-naphthoquinone derivatives synthesized showed high ED_{50} values, ranging from 0.1 to 0.3 μg/mL against L1210 cells. However, they were inactive on A549 cells. Nine compounds exhibited higher *T*/*C* (%) values (318–388%) than Adriamycin (*T*/*C*, 315%).

Naphthazarin (5,8-dihydroxy-1,4-naphthoquinone, **II**) is a structural component of some antitumor agents such as doxorubicin,[1] mitoxanthrone[2] and shikonin.[3] Shikonin (**I**) isolated from *Lithospermum erythrorhizon* showed antitumor activity in mice bearing S-180 cells.[4] In our recent studies, it was found that the biological activity of naphthazarin derivatives was dependent upon the electrophilicity of the quinone moiety.[5] **II** occurs in a resonance equilibrium state, so that its electron density is dispersed over the naphthazarin ring. In order to increase the relative electrophilicity in C-2 and C-3 of the quinonoid moiety, **II** was dimethylated to produce 5,8-dimethoxy-1,4-naphthoquinone (DMNQ, **III**), which was more vulnerable to nucleophiles. **III** was found to be less toxic and more active than **II**.[6]



I



II R = H

III R = CH_3

Based on these findings, **III** was modified to give a series of 2- or 6-substituted DMNQ analogues (**IV**–**VII**).[7,8] The order of increasing cytotoxicity was as follows; acyl-DMNQ derivatives (**IV**) > hydroxyiminoalkyl (**VI**) and propoxyiminoalkyl-DMNQ derivatives (**VII**) > azidoalkyl-DMNQ derivatives (**V**). More electrophilic acyl-DMNQ analogues possessed the highest activity. Despite moderate antiproliferative activity, 6-(1-propoxyiminoalkyl)-DMNQ derivatives (**VII**) displayed the highest antitumor activity in mice bearing S-180 cells.[9] The high activity of series **VII** is believed to be due to its enhanced water solubility and a retardation of first pass metabolism.[8]

The enhanced antitumor activity of 6-(1-propoxyiminoalkyl)-DMNQ derivatives prompted us to synthesize a series of 6-(1-alkoxyiminoalkyl)-DMNQ derivatives and analyze their structure–activity relationships. The 6-(1-alkoxyiminoalkyl)-DMNQ derivatives were tested for their cytotoxic activity on L1210 and A549 cells as well as their antitumor activity against mice bearing S-180 cells.

Two series of *(E)*-6-(1-alkyloxyiminomethyl)-DMNQ (**VIIa**–**g**, R_1 = H) and *(E)*-6-(1-alkyloxyiminoheptyl)-DMNQ (**VIIh**–**m**, R_1 = hexyl) derivatives were synthesized according to the method used for 6-(1-propoxyiminoalkyl)-DMNQ derivatives[8,10] as shown in Scheme 1. The reaction of acyl-1,4,5,8-tetramethoxynaphthalenes (TMN) with hydroxylamine produced *(E)*- and *(Z)*-isomers of the oxime (*E*-isomer: TMN standing *trans* to oximic OH). As an example, *(Z/E)*-isomers of 2-(1-hydroxyiminoheptyl)-TMN were produced at a ratio of 0.6:1. α-Methylene protons of *(Z/E)*-isomers appeared at 2.65 and 2.91 ppm, respectively, in the ^{1}H NMR spectrum, which is in agreement with the reported data.[11,12] Furthermore, it was found that the *(Z)*-isomer could not be readily alkylated under the conditions examined.

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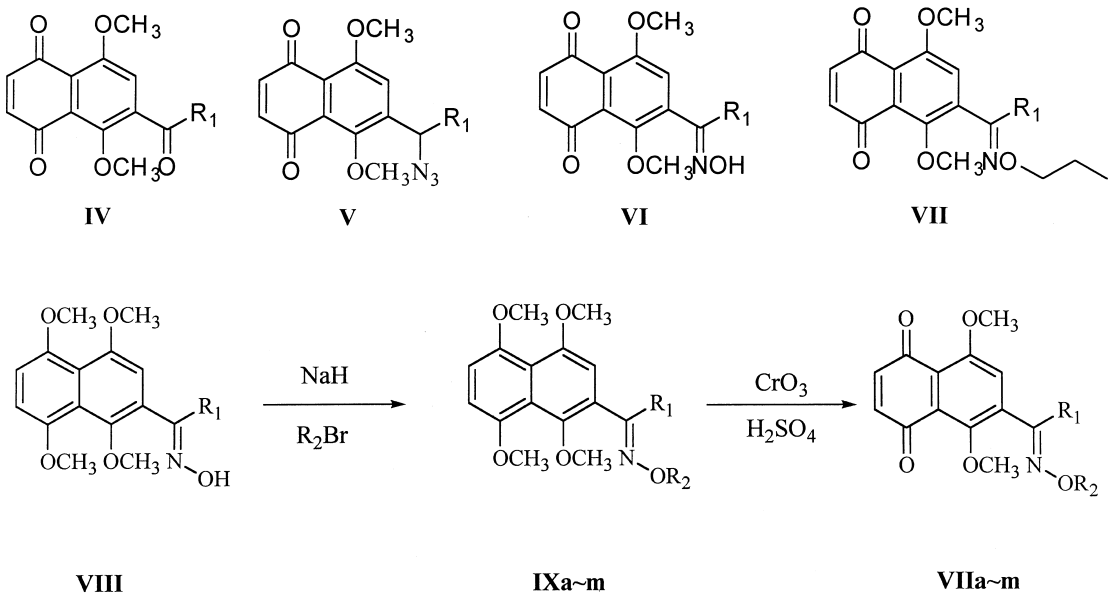


Scheme 1. Synthesis of *(E)*-6-(1-alkyloxyiminoalkyl)-5,8-dimethoxy-1,4-naphthoquinone derivatives. R_1 = H and hexyl; R_2 = methyl, propyl, pentyl, heptyl, nonyl and dodecyl.

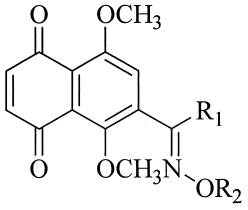
Alkylation of the *(E)*-oximes (**VIII**) with sodium hydride and the corresponding alkylhalide in THF gave *(E)*-6-(1-alkyloxyiminoalkyl)-1,4,5,8-tetramethoxynaphthalenes (**IXa–m**) at a yield of 75–91%. Jones oxidation of *(E)*-6-(1-alkyloxyiminoalkyl)-1,4,5,8-tetramethoxynaphthalenes (**IXa–m**) yielded *(E)*-6-(1-alkyloxyiminoalkyl)-DMNQ derivatives (**VIIa–m**) at yields varying from 26 to 85%.

Biological activities of the synthesized compounds are shown in Table 1 and Figure 1. Antiproliferative activities of all compounds were cell-specific and showed strong effects on L1210 cells (ED_{50}, 0.107–1.145 μg/mL), but they were inactive on A549 cells (ED_{50} >10 μg/mL). No difference in antitumor activity was apparent between the **VIIa–g** and **VIIh–m** series. The antiproliferative activity seemed to be independent of the size of R_2 in both series; *(E)*-6-(1-methyloxyiminoheptyl)-DMNQ (ED_{50}, 0.192 μg/mL) versus *(E)*-6-(1-dodecyloxyiminoheptyl)-DMNQ (ED_{50}, 0.193 μg/mL).

Among the 13 compounds tested, nine DMNQ derivatives had higher *T*/*C* values than Adriamycin (*T*/*C*, 315%). ED_{50} and *T*/*C* values did not correlate with each other. Both series seemed to have an optimal range in terms of R_2 for antitumor activity. This optimal range of R_2 was determined to be pentyl to nonyl (*T*/*C*, 388–355%) in the **Xa** series, and propyl to heptyl group (*T*/*C*, 369–375%) in the **VIIa–m** series. Compounds with shorter R_2 might be more vulnerable to the first pass metabolism in liver and be readily metabolized. Thus, their bioavailability is presumed to be poorer.

The survival ratio (SR), which is defined as the number of mice in a total of eight that survive for longer than 80 days after beginning of drug treatment, is an important parameter for antitumor activity (Fig. 1). Except *(E)*-6-(1-dodecyloxyiminomethyl)- and *(E)*-6-(1-nonyloxyiminoheptyl)-DMNQ, all other compounds showed a good SR. SR values correlated well with optimal *T*/*C* values. For the **VIIa–g** series, *(E)*-6-(1-pentyloxyiminomethyl)- (*T*/*C*, 388%), *(E)*-6-(1-heptyloxyiminomethyl)- (*T*/*C*, 355%) and *(E)*-6-(1-nonyloxyiminomethyl)-DMNQ

Table 1. Cytotoxic and antitumor activity of *(E)*-6-(1-alkyloxyiminoalkyl)-5,8-dimethoxy-1,4-naphthoquinones



VII

	R_1	R_2	ED_{50} (μg/mL) L1210	ED_{50} (μg/mL) A549	*T*/*C* (%)[a]	SR[b]
VIIa	H	Methyl	0.109	> 10	318	2
VIIb	H	Propyl	0.107	> 10	229	2
VIIc	H	Pentyl	0.175	> 10	388	5
VIId	H	Heptyl	0.213	> 10	355	5
VIIe	H	Nonyl	0.190	> 10	355	5
VIIf	H	Dodecyl	0.311	> 10	119	0
VIIg	H	Benzyl	0.264	> 10	331	4
VIIh	Hexyl	Methyl	0.192	> 10	323	5
VIIi	Hexyl	Propyl	0.166	> 10	369	5
VIIj	Hexyl	Pentyl	0.224	> 10	363	5
VIIk	Hexyl	Heptyl	0.162	> 10	375	5
VIIl	Hexyl	Nonyl	1.145	> 10	96	0
VIIm	Hexyl	Dodecyl	0.193	> 10	231	2
	Adriamycin		0.016	1.01	315	3

[a]Mice were injected via ip with 1×10^7 S-180 cells on day 0. Compounds were administered via ip on days 1, 2, 3, 4, 5, 6 and 7.
[b]SR: survival ratio; no. of mice surviving after 80 days among eight mice.

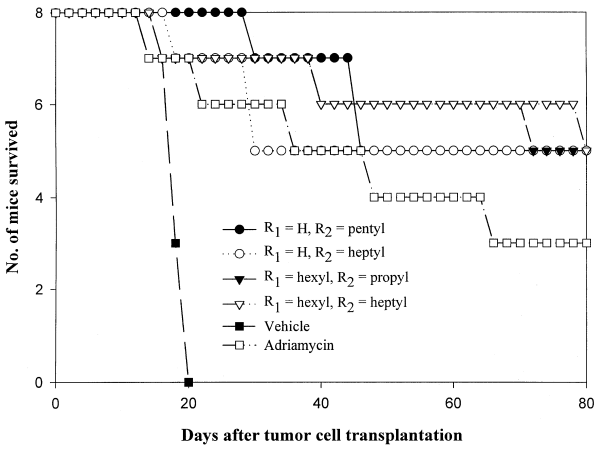


Figure 1. Effect of intraperitoneal administration of *(E)*-6-(1-propyloxyiminoalkyl)-5,8-dimethoxy-1,4-naphthoquinones on the life span of ICR mice bearing Sarcoma 180 cells (refer to the structures in Table 1).

(*T*/*C*, 355%) had SR values of 5. Likewise, for the heptyl-series, all compounds, except *(E)*-6-(1-nonyloxyiminoheptyl)- and *(E)*-6-(1-dodecyloxyiminoheptyl)-DMNQ, had the SR value 5.

In conclusion, the antitumor activities of *(E)*-6-(1-alkyloxyiminoalkyl)-DMNQ derivatives were found to be mainly dependent on the size of R_2, namely the alkyloxyimino group, and not on R_1. In any future work designed to synthesize a DMNQ with improved antitumor activity, further modification of R_2 is suggested.

Acknowledgements

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