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Correlation between reduction potentials and inhibitory effects on Epstein–Barr virus activation of poly-substituted anthraquinones

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Abstract

As a continuation of our studies using natural and synthetic products as cancer chemopreventive agents, we examined the reduction potentials of some poly-substituted anthraquinones in phosphate buffer at pH 7.2 by means of cyclic voltammetry. A definite correlation has been found between the reduction potentials and the inhibitory effects of the poly-substituted anthraquinones on Epstein–Barr virus early antigen activation. It has been further shown that the correlation can be enhanced by introducing log *P* as an additional parameter.

Keywords: Epstein–Barr virus; Anthraquinone; Reduction potential; Cyclic voltammetry

1. Introduction

Quinones (anthraquinones, naphthoquinones, and heteronaphthoquinones) being widely distributed in nature, are important naturally occurring pigments and known to demonstrate various physiological activities as antibiotics and anti-cancer agents. It has already been shown in previous papers that a number of naphthoquinones had been investigated in vitro anti-tumor promoting activity by determining the inhibitory effects on Epstein–Barr virus early antigen (EBV-EA) activation induced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) in Raji cells [1,2]. We have also found inhibitory activities of the mono- and di-substituted anthraquinones and bianthraquinones on EBV-EA activation, and have studied their connections with the electronic properties of the anthraquinones [3,4].

In studies of the structure–activity relationships for drugs, the standard redox potential is an important parameter to determine the physiological activities. We employed cyclic voltammetry to determine

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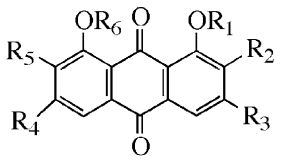

	R_1	R_2	R_3	R_4	R_5	R_6
1	H	H	CH_3	H	H	H
2	H	H	CH_3	OH	H	H
3	CH_3	OH	CH_3	H	H	H
4	CH_3	OH	CH_3	OCH_3	OCH_3	CH_3
5	CH_3	H	CH_3	OCH_3	OCH_3	H
6	CH_3	OH	CH_3	OH	OCH_3	H
7	CH_3	OH	CH_3	OH	OCH_3	H
8	H	H	H	CH_3	H	CH_3
9	H	CH_3	H	OCH_3	OH	CH_3
10	H	H	CH_2OH	H	H	H

Fig. 1. Structures of anthraquinones.

the standard redox potentials of 9 anthraquinones, 9 naphthoquinones, and 19 azaanthraquinones at physiological pH 7.2, and found definite correlations between the standard redox potentials and the inhibitory effects (log IC_{50}) on EBV-EA activation [5–8].

In the present study, we report the reduction potentials of 16 poly-substituted anthraquinones (Figs. 1 and 2) and the structure–activity relationship between their inhibitory effects and reduction potentials. Furthermore, we have calculated some electronic properties of the anthraquinones by the PM3 method using the CAChe MOPAC program [9], showing that the total energy could be used as another useful parameter to characterize the inhibitory effect on EBV-EA activation. It has also been found that the logarithm of the octanol–water partition coefficient (log *P*) [10] of the anthraquinones is one of the useful parameters for investigating their structure–activity relationship.

2. Material and methods

2.1. Reagents and materials

Chrysophanol (**1**), emodin (**2**), obtusifolin (**3**), chryso-obtusin (**4**), obtusin (**5**), aurantio-obtusin (**6**), questin (**7**), and 1-hydroxy-8-methoxy-6-methylanthraquinone (**8**) were isolated from the seed of *Cassia obtusifolia* L. [11] and 1,7-dihydroxy-6,8-dimethoxy-2-methylanthraquinone (**9**) from *Galium spurium var. echinospermon* Hayek [12]. Aloe-emodin (**10**) was isolated from the leaves of *Aloe ferox* Miller [13], and cassiamin C (**11**), cassiamin A (**12**), cassiamin B (**13**), 1,1′,3,8,8′-pentahydroxy-3′,6-dimethyl-[2,2′-bianthracene]-9,9′,10,10′-tetrone (**14**) from *Cassia siamea* [14]. 1,1′,8,8′-tetrahydroxy-3,3′-dihydroxymethyl-[2,2′-bianthracene]-9,9′,10,10′-tetrone (**15**) and 1,1′,3′,8,8′-pentahydroxy-3-hydroxymethyl-6′-methyl[2,2′-bianthracene]-9,9′,10,10′-tetrone (**16**)