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Experimental and theoretical study of possible correlation between the electrochemistry of canthin-6-one and the anti-proliferative activity against human cancer stem cells

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ABSTRACT

This work presents an approach to study the performance of novel targets able to overcome cancer stem cell chemoresistance, based on the voltammetric data for microparticulate films of natural or synthetic alkaloids from the canthin-6-one series. A comparison of this voltammetric technique with conventional solution phase electrochemistry suggests the differences in the anti-proliferative activity of canthin-6-ones could be tentatively correlated to their different capacity to generate semiquinone radical anions. These data also match theoretical calculations.

1. Introduction

Bioassay guided investigations of the active components of plants used in traditional medicine have led to the discovery of many new chemotherapeutic agents in the fight against cancer [1]. Several plants belonging to the Rutaceae family have been studied for their antitumoral properties [2], and isolated compounds from their extracts have been shown to induce an inhibition of cancer cell proliferation *in vitro* [3]. Canthinones are a subclass of β-carboline alkaloids that possess an additional D-ring, having a characteristic tetracyclic core with a particular naphthyridone motif (cycles C and D, Scheme 1). Their cytotoxic and anti-tumor properties are due to their ability to inhibit critical processes in the cell [4,5]. In this context, we have previously studied the effect of the *Zanthoxylum chiloperone* var. *angustifolium* stem bark extract and its major components e.g., canthin-6-one (**L1**), 5-methoxycanthin-6-one (**L2**), canthin-6-one *N*-oxide (**L3**) and synthetic derivates of canthin-6-one (**L1**): 4,5-dihydro-canthin-6-one (**L4**) and benzo [4,5]canthin-6-one (**L5**) (see Scheme 1) on glioblastoma cancer stem cells (using the TG1 cell line) using the WST-1 assay (Water Soluble Tetrazolium salt, a cell proliferation reagent) [6]. The WST-1 assay revealed that some molecules have anti-proliferative activity (**L1 and L2**) while others are not bioactive (**L3**–**L5**) against TG1 cells (see Ref. [6] and Table 1).

The development of methods that allow for correlations between chemical structure and anti-proliferation activity is extremely important. Solution-phase electrochemistry has been applied to this purpose [7–9]. In particular, redox potentials for different compounds in solution have been correlated with anti-proliferative activity [10–13]. In the current report, the voltammetry of immobilized particles (VIMP), a solid-state electrochemical technique developed by Scholz et al. [14,15] was used to elucidate possible correlations between electrochemical behavior

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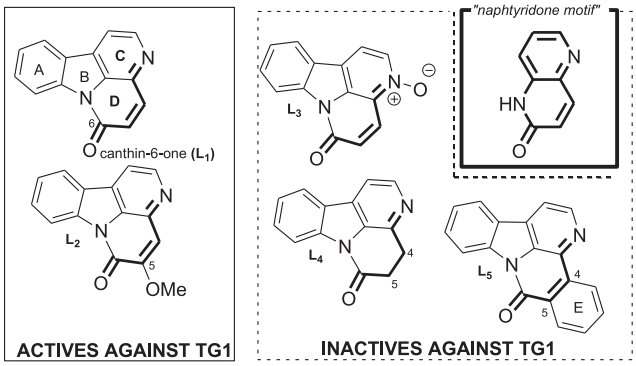


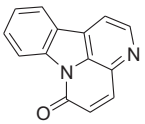
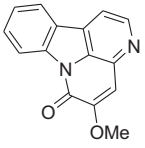
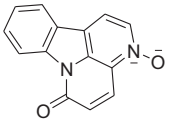
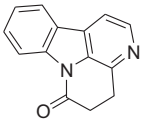
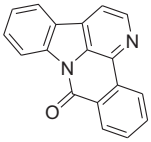
Scheme 1. Chemical structures of compounds **L1**–**L5**.

and anti-cancer activity. Several canthin-6-one alkaloids where tested against cancer stem cells. VIMP proved an excellent technique for this type of screening because of its high sensitivity and because solid-state electrochemical processes allow for the testing of reactions that are inhibited in solution or obscured by fast electrochemical processes in conventional solution electrochemistry. It should be emphasized, however, that anti-proliferative activity results from a complex range of biological factors that include cell membrane penetration and protein binding. Possible correlations found with VIMP may therefore be an oversimplification. Nonetheless, VIMP has been used for testing the anti-oxidative capacity of samples from dry extracts of fruits and vegetables [16,17] and the anti-malarial activity of drugs acting via the hemozoin mechanism [18].

2. Results and discussion

Electrochemical experiments in aqueous solution were confined to the 0.10–0.80 mM range because of the low solubility of the **L** compounds in neutral and alkaline media. In acidic media, all compounds display a similar CV response consisting of an apparently irreversible reduction peak at ca. −0.70 V preceded by a weak shoulder, attributable to a typical adsorption pre-peak [19,20]. In neutral and alkaline media, the voltammograms for **L1** and **L2** exhibit a prominent cathodic peak at ca. −0.90 V preceded by a pronounced adsorptive shoulder whereas, as can be seen in Fig. 1, compounds **L3**–**L5** produced weaker signals. As a result of adsorption complications, satisfactory controlled potential electrolysis experiments were performed only in acidic media. For solutions of **L1** and **L2** in 1.0 M HCl these experiments yielded a unique product identified as the respective 4,5-dihydrocanthin-6-one hydrochloride (identification was based on ^{1}H NMR data; Supplementary material). The double bond 4,5 of the naphthyridone motif was reduced (Fig. 1). Electrolysis of **L1** and **L2** in neutral and alkaline media yielded a compound without the naphthyridone motif, as denoted by the decrease in the carbonyl FTIR band at 1650 cm^{-1} coupled with a concomitant increase of the alcohol −OH band at 3500 cm^{-1} (Supplementary material). The reduction in neutral media yielded a mixture of products, as clearly suggested by ATR-FTIR spectra recorded at different times during the electrolysis. Between 10 and 20 min one product displaying the OH bending band at 1330 cm^{-1} and C–O band at 1190 cm^{-1} appeared, while at longer electrolysis times (20–45 min), this compound was progressively replaced by a second product only retaining the C–N bands at 1312 and 1305 cm^{-1} (Supplementary material).

Table 1
Illustration of possible correlation between cyclic voltammetric signals (potential scan rate 20 mV s^{-1}) and anti-proliferative activity against cancer stem cells measured by WST assay [6] for canthin 6-one alkaloids.

Compounds		Reported viability (% of control)[a] [6]	Qualitative evaluation of antiproliferative activity	Ep/V (vs. Ag/AgCl) phosphate buffer	Ep/V (vs. Ag/AgCl)0.10 M NaOH
L1		40%	Active	−0.85, −0.98 (**path II**)	−1.00, −1.20 (**path II**)
L2		60%	Active	−0.85, −0.95 (**path II**)	−1.20 (**path II**)
L3		100%	Inactive	−1.25 (**path III**)	None
L4		90%	Inactive	−1.25 (**path III**)	None
L5		120%	Inactive (proliferative activity)	−1.25 (**path III**)	None

[a] Viability (% of control) of glioblastoma cancer stem cells (TG1) treated with 300 μM of compounds **L1**–**L5** for 24 h, measured by WST assay [6].