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Cytotoxicity of lapachol, β-lapachone and related synthetic 1,4-naphthoquinones against oesophageal cancer cells

Suthananda N. Sunassee [a,*], Clinton G.L. Veale [a], Nelusha Shunmoogam-Gounden [b], Omalaja Osoniyi [b], Denver T. Hendricks [b], Mino R. Caira [c], Jo-Anne de la Mare [d], Adrienne L. Edkins [d], Antônio V. Pinto [e], Eufrânio N. da Silva Júnior [f], Michael T. Davies-Coleman [a]

[a] Department of Chemistry, Rhodes University, Grahamstown 6140, South Africa
[b] Division of Medical Biochemistry, University of Cape Town, Medical School, Anzio Road, Observatory, Cape Town 7925, South Africa
[c] Department of Chemistry, University of Cape Town, Rondebosch, South Africa
[d] Biomedical Biotechnology Research Unit, Department of Biochemistry, Microbiology and Biotechnology, Rhodes University, Grahamstown 6140, South Africa
[e] Natural Products Research Nucleus, Federal University of Rio de Janeiro, P.O. Box 69035, 21944-971 Rio de Janeiro, RJ, Brazil
[f] Institute of Exact Sciences, Department of Chemistry, Federal University of Minas Gerais, 31270-901 Belo Horizonte, MG, Brazil

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ABSTRACT

Naphthoquinones have been found to have a wide range of biological activities, including cytotoxicity to cancer cells. The secondary metabolites lapachol, α- and β-lapachone and a series of 25 related synthetic 1,4-naphthoquinones were screened against the oesophageal cancer cell line (WHCO1). Most of the compounds exhibited enhanced cytotoxicity (IC_{50} 1.6–11.7 μM) compared to the current drug of choice cisplatin (IC_{50} – 14.5 μM). This study also established that the two new synthetic halogenated compounds **12a** and **16a** (IC_{50} – 3.0 and 7.3 μM) and the previously reported compound **11a** (IC_{50} – 3.9 μM), were non-toxic to NIH3T3 normal fibroblast cells. Cell death of oesophageal cancer cells by processes involving PARP cleavage caused by **11a** was shown to be associated with elevated c-Jun levels, suggesting a role for this pathway in the mechanism of action of this cohort of naphthoquinone compounds.

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1. Introduction

Quinones, including 1,4-naphthoquinones, are ubiquitous in nature [1,2] and several well-known anticancer drugs used to treat solid tumours (*e.g.* doxorubicin, mitomycin and mitoxantrone) possess a quinonoid structure [3,4]. These compounds have also been identified as privileged structures due to their biological activities and structural properties [5] that have been linked to the stimulation of oxidative stress and alkylation of cellular nucleophiles in cancer cells [6].

Squamous cell oesophageal cancer (SCOC) is the second most common form of cancer reported in poor rural and peri-urban populations in South Africa, with residents of Soweto near Johannesburg having a five-fold increased chance of developing this form of cancer when compared with the global average for the incidence of SCOC [7]. The poor remission rates (20–30%) in early diagnosed cases, albeit current chemotherapeutic interventions using cisplatin and 5-fluorouracil [8], prompted an ongoing programme in South Africa aimed at the discovery of new natural product-derived compounds exhibiting potential anti-oesophageal cancer activity [9,10].

Recently, we have been attracted to the activity of the naturally occurring 1,4-naphthoquinone lapachol (**1**, Fig. 1), originally isolated from the wood of several Brazilian tree species of the family Bignoniaceae [11]. Lapachol has a well-documented history of cancer cell cytotoxicity [11], including activity against squamous cell carcinomas [12]. The closely related secondary metabolite β-lapachone (**2**, Fig. 1) has recently been shown to exhibit exploitable activity against various cancer molecular targets [13–16] and is currently in phase II clinical trials in the USA for the treatment of advanced solid tumours [17]. Although compound **1** has been licensed in Brazil for general clinical practice as a carcinostatic drug [18], and several studies pertaining to its anticancer properties have been reported [4], there remains some dissension over the effectiveness of **1** as an anticancer drug *per se* due to the

* Corresponding author. Present address: Molecular Targets Laboratory, Center for Cancer Research, Frederick National Laboratory for Cancer Research, Bldg 562, Rm 201, Frederick, MD 21702, United States. Tel.: +1 301 846 7413; fax: +1 301 846 6851.
E-mail address: snsunassee@gmail.com (S.N. Sunassee).

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