Publications


Cell proliferation inhibition and antitumor activity of novel alkyl series of diorganotin(IV) compounds

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ABSTRACT: Diorganotin(IV) compounds, $R_2SnCl_2$, are often tetrahedral, and structurally resemble the active platinum compounds, i.e. cisplatin, and consequently a large number of such complexes have been tested for antitumor activity. A structural correlation with biological activity for diorganotin(IV) complexes has shown that active species are associated with complexes having Sn–N bonds longer than 2.39 Å which in turn determines the formation of a tin–DNA complex. In view of these, a series of diorganotin(IV) dichloride complexes of $N_2$-pyridylmethylcyclohexylamine (nitrogen-chelating ligand) has been synthesized and characterized on the basis of IR, NMR, and $^{119}$Sn-Mossbauer studies. In the present study, an attempt was made to determine the comparative antiproliferative and antitumor effect of diorganotin(IV) complexes with different alkyl groups $[Me_2SnCl_2L_1$ (OTC-1), Et$SnCl_2L_1$ (OTC-2) and $Bu_2SnCl_2L_1$ (OTC-3)]. The present study in human lymphocytes demonstrated that these diorganotin(IV) complexes could block the cell cycle progression and induce sister chromatid exchanges (SCEs) significantly, however, with respect to the induction of chromosome aberrations (CAs) it was very mild. Both the levels of p53 and p16 proteins were raised after diorganotin(IV) treatment and such induction was maximum in the OTC-3 treated samples. The antitumor activity was determined in accordance with the US National Cancer Institute (NCI) standard protocol for primary screening in Dalton’s lymphoma that was maintained by serial intraperitoneal transplantation. The T/C (treated/control) value was increased (186% with OTC-3) when diorganotin(IV) was given after transplantation. The data suggest that the OTC-3 has better antiproliferative and antitumor activity and endogenous glutathione level has no influence on the effect of OTC-3. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS: diorganotin(IV); antiproliferative; antitumor; DNA damage

Introduction

After the discovery of the antiproliferative and antitumor activity of cisplatin, i.e. cis-diammine dichloroplatinum (II) several groups started to investigate the possible therapeutic applications of metal-based drugs, often organometallic compounds, and more particularly organotin(IV) compounds (Loecher and Einhorn, 1984; Pellerito and Nagy, 2002; Gielen and Tiekink, 2005). The organotin(IV) compounds that were first tested were those that were available or easily synthesized, such as tri- or diorganotin(IV) halides. It was reported that diorganotin(IV) oxides and hydroxides, which either contain a tin–oxygen bond or are capable of forming such a bond upon hydrolysis, have antitumor potential (Crowe, 1987; Gielen et al., 1995).

Diorganotin(IV) compounds, $R_2SnCl_2$, are often tetrahedral, and when appropriate nitrogen-chelating ligands are coordinated to the central metal, octahedral complexes $R_2SnCl_2L_2$ (where $L_2$ is bidentate ligand) are obtained (Crowe et al., 1984a). These complexes structurally resemble the active platinum compounds, i.e. cisplatin and carboplatin, and consequently a large number of such complexes have been tested for antitumor activity. Three primary factors are involved in the structure–activity relationship for organotin(IV) derivatives $R_2SnL_2$; the nature of the organic group $R$, of halide or pseudohalide $X$, and of donor ligand $L$. Examination of the structures of organotin(IV) compounds containing a N-donor atom when tested for antitumor activity revealed that in the active Sn complexes the average Sn–N bond lengths were $>2.39$ Å, whereas the inactive complexes had Sn–N bonds $<2.39$ Å. This implies that presussociation of the ligand may be an important step in the mode of action of these complexes, while the coordinated ligand may favor transport of the active species to the site of action in the
p53-dependent antiproliferative and antitumor effect of novel alkyl series of diorganotin(IV) compounds

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Summary Purpose: A series of diorganotin(IV) dichloride complexes of N-(2-pyridylmethylene)arylamine (nitrogen-chelating ligands) have been synthesized and characterized. The present study was carried out to investigate the comparative anti-proliferative and anti-tumor effect of Me₂SnCl₂·L₁ (OTC-1), Et₂SnCl₂·L₂ (OTC-2) and nBu₂SnCl·L₂ (OTC-3) in combination with X-rays (1.5 Gy). Method: The cytotoxicity of these diorganotin(IV) compounds was studied in human peripheral lymphocytes and the antitumor activity was assessed in Dalton's lymphoma cells. The involvement of proteins that regulate cell cycle and apoptosis was investigated to elucidate the mechanism of their action. Results: 5 mg kg⁻¹ of OTC-3 showed better antiproliferative and antitumor activity than OTC-1 and OTC-2, both as alone or in combination with X-rays. The maximum enhancement of exchange aberrations and the level of p53 and p16 proteins were observed in the OTC-3 treated samples. Upregulated expression of p53 caused a significant down-regulated transcriptionally repression of Survivin in OTC-3 treated human lymphocytes. Conclusion: It could be possible that after treatment with either OTC-3 alone or in combination with X-rays the Dalton's lymphoma cells may die apoptotically after inducing initial delay in cell cycle and thereby survivability of mouse bearing Dalton's Lymphoma cells was increased significantly.

Keywords Diorganotin(IV) · Antiproliferation · Anti-tumor · Apoptosis

Introduction

The biological activity of organotin(IV) compounds is well known owing to their practical applications as fungicides, bactericides, biocides and pesticides [1, 2]. However, one of the fields that have been more studied and reviewed is the activity of such compounds against cancer [1, 3]. The organotin(IV) compounds that were first tested were those that were available or easily synthesized, like tri- or diorganotin(IV) oxides and hydroxides, which either contain tin-oxygen bond or are capable of forming such a bond upon hydrolysis, have antitumor potential [4, 5]. Diorganotin(IV) compounds, R₂SnCl₂ are often tetrahedral, and when appropriate nitrogen-chelating ligands are co-ordinated to the central metal, octahedral complexes R₃SnCl₂·L (L=bidentate ligand) are obtained [6]. Diorganotin(IV) compounds structurally resemble the active platinum compounds, i.e. cisplatin and carboplatin, and consequently a large number of such complexes have been tested for antitumor activity. Three primary factors are involved in the structure–activity relationship for organotin(IV) derivatives R₃SnX₄·n(L)₂, the nature of the organic group R, of halide or pseudohalide X, and of donor ligand L. Examination of the structures of organotin(IV) comcompound...