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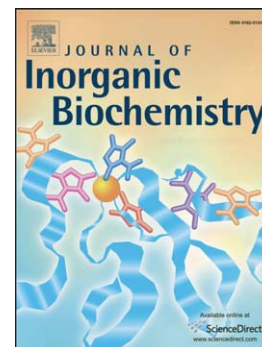
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## Insights Into Molecular Mechanism of Action of Salan Titanium(IV) Complex with *In vitro* and *In vivo* Anticancer Activity

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### Abstract

Titanium compounds, in particular, Ti(IV) based diaminobis(phenolato) "salan" complexes demonstrate high cytotoxicity toward a wide range of cancer cell lines *in vitro*, and still, very little is known on their mode of action. A representative salan Ti(IV) complex was tested both *in vitro* and *in vivo* on human HT-29 colorectal adenocarcinoma and A2780 ovarian carcinoma cells. Both cell lines were sensitive *in vitro* with A2780 demonstrating an enhanced rate of uptake and intracellular accumulation and thus an earlier response to the drug. HT-29 cells responded *in vivo* by impaired tumor development in nude mice. Both cell lines responded *in vitro* (but to a different extent) by upregulation of p53 with no apparent effect on p21 followed by cell cycle arrest, apoptosis and necrosis as demonstrated by sub-G1 cell accumulation and staining by Annexin-V and propidium iodide. Furthermore, time dependent activation of cysteine-aspartic proteases<sup>9</sup> (caspase<sup>9</sup>) as well as some minor activation of cysteine-aspartic proteases<sup>3</sup> (caspase<sup>3</sup>) support a direct effect on the apoptotic pathway. The differential response of the two cell lines to the salan titanium(IV) complex suggests that more than one pathway is involved in their growth regulation and thus could inhibit development of drug resistant variants.

**Keywords:** cytotoxicity mechanism, metallodrugs, cisplatin, *in vivo*, cell cycle, apoptosis

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