New Ti(IV) metal complexes of salan ligands as anti-cancer agents (Yissum)

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New family of cytotoxic complexes with potentially less side effects

Categories	Oncology/cancer, Drug discovery, Apoptosis
Development Stage	Established in vitro; currently undergoing in vivo and mechanistic studies
Patent Status	A provisional patent application has been filed
Market	In 2006, cytotoxics of the platinum family, which include cisplatin, carboplatin and oxaliplatin, contributed around $3.5 billion (17%) of global cytostatics sales

Highlights

- Metal based anti-tumor therapeutics cisplatin and carboplatin are two of the most widely prescribed anticancer agents.
- However, there is a finite number of tumors that can be treated with cisplatin and it causes extreme toxic effects such as neurotoxicity, nephrotoxicity and others.
- Ti(IV) complexes with various cyclopentadienide or diketonato ligands demonstrate cytotoxic activity towards cisplatin-resistant and -sensitive cells with substantially reduced and mostly reversible side effects.
- However, the currently known compounds display rapid hydrolysis in aqueous environment to give a mixture of unidentified products. The final decomposition product, titanium dioxide, is inert and often used in food and cosmetics as a whitening pigment.
- There is a need for Ti(IV) complexes with better suited and rationally designed stabilizing ligands that demonstrate enhanced hydrolytic stability and improved anti-tumor properties.
- Salans are well known diamine bis(phenolato) compounds which have been used as chelating ligands for a wide variety of transition metals for various applications.

Our Innovation

New family of Ti(IV) salan complexes as a new family of highly cytotoxic compounds designed to include a single highly electron-donating chelating ligand to afford octahedral TiIV complexes of relatively high hydrolytic stability, with the aim of retaining ligand binding throughout the biological activity for achieving controlled processes and allowing mechanistic evaluation.

Key Features

- Cytotoxicity greater than that of Cp2TiCl2, (bzac)2Ti(OiPr)2 and cisplatin towards colon, ovarian, melanoma, leukaemia, breast and other cells.
- Particularly slow hydrolysis and defined hydrolytic process; the labile isopropoxo ligands hydrolyze within weeks in 1/9 water/THF solutions and the resulting salan-bound cluster does not further hydrolyze for days.
- A correlation is observed between the hydrolytic behavior and cytotoxicity, both features are tenable by structural modifications on the ligands.
- Some mechanistic insights include clear participation of the ligand-bound species in activity, identification of the cellular target as chiral (presumed to be DNA), and more.

Development Milestones

Seeking funding for ongoing research and collaboration with pharmaceutical companies to establish in vivo toxicity and activity and develop products

The Opportunity

- Opportunity to develop cure for a wide range of cancer types using a biologically-friendly metal core that causes reduced side effects
- All the cell lines of the seven tested so far show response to these compounds

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