New tumor active compounds with multiple metal centers

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ABSTRACT

Platinum compounds with multiple metal centers provide a new class of tumor active compounds with different nature of binding with DNA and different spectrum of activity as compared to cisplatin. A notable example of a multicentered platinum compound is BBR3464 which has shown significant activity against both cisplatin-responsive and cisplatin-resistant cancer cell lines. BBR3464 consists of three *trans*-platinum units linked together by 1,6-diaminohexane chains. Only the two terminal platinum ions in BBR3464 undergo covalent binding with DNA whereas the central platinum ion undergoes only non-covalent interactions. We have designed a number of new multicentered compounds of the type Pt-M-Pt where M stands for Pt, Pd or other suitable metal ions that is linked to ammino and/or planaramine ligands such as 2-hydroxypyridine, 3-hydroxypyridine and 4-hydroxypyridine. The compounds have been synthesized using step-up method of synthesis and purified by repeated dissolution and precipitation. The activity of the compounds against human cancer cell lines have been determined by MTT reduction assay.

Compounds{*trans*-PtCl(NH_3)}$_2\mu$-{*trans*-Pd(NH_3)(2-hydroxypyridine)-($H_2N(CH_2)_6NH_2)_2$]Cl_4 (code named CH25), {*trans*-PtCl(NH_3)}$_2\mu$-{*trans*-Pt(NH_3)(2-hydroxypyridine)-($H_2N(CH_2)_6NH_2)_2$]Cl_4 (code named CH9) and [{*trans*-PtCl($NH_3)_2$}$_2\mu$-{*trans*-Pd$(NH_3)_2(H_2N(CH_2)_6NH_2)_2$]$Cl_4$ [code named DH6Cl] have been found to be significantly more active than cisplatin against the cell lines A2780, A2780^{cisR} and A2780^{ZD0473R}. All the compounds are believed to form a range of interstrand GG adducts with DNA as a result of which global changes in DNA conformation take place. CH25 and CH9 which has a 2-hydroxypyridine ligand attached to the central metal ion also undergo stacking interaction with nucleobases in DNA, which is believed to be responsible for pronounced DNA damage. The variations in activity of the compounds and their binding with DNA illustrate structure-activity relationship.