Synthesis and cytotoxicity evaluation of six new cis-[Pt(NH3)2(Guo/dGuo)X] (X = Cl, Br, I) platinum(II) complexes in three human cancer cell lines with varying cisplatin sensitivity

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Cancer still represents a serious threat to human health, due to the high pathogenicity, invasiveness and resistance to therapies. Cisplatin is the most widely used among metal-based chemotherapeutics and is used to treat a wide range of tumors. However, some tumor cells can develop resistance mechanisms over time, modifying the mechanisms that regulate apoptosis, thus making platinum-based ineffective. For this reason, the investigation of novel metal-based complexes has been an important focus in recent years, in order to synthesize new classes of anticancer agents with the final aim of exerting greater cytotoxicity and selectively against tumor cells. Among these, platinum(II) nucleoside compounds represent potential antimetabolites for antitumor therapy[1]. Complexes of the *cis*-$[Pt(NH_3)_2(Am)Cl]^+$ type (Am = heterocyclic amine based on pyridine, pyrimidine, purine, piperidine or saturated amine) have demonstrated high stability and solubility in aqueous media, and an interesting *in vitro* and *in vivo* antitumor potential against several tumors, including sarcoma and leukemia[2]. In this work we evaluate the cytotoxic activity of six complexes of the type *cis*-$[Pt(NH_3)_2(Am)X]^+$, where Am = guanosine (Guo, **a**) or 2'-deoxy-guanosine (d-Guo, **b**); X = Cl (**1**), Br (**2**), I (**3**), on three cell lines with different sensitivity to cisplatin: HeLa (cervical adenocarcinoma), ZL-34 (pleural mesothelioma) and MCF-7 (breast adenocarcinoma). The cell viability was evaluated by SRB assay after treatment with Pt(II) complexes at increasing concentrations from 24 to 72 h. Cisplatin demonstrates to be more effective on all the tested cell lines, while comparing the complexes among themselves cis-$[Pt(NH_3)_2(Guo)Br]^+$ (2a) and cis-$[Pt(NH_3)_2(dGuo)Br]^+$ (2b) have higher cytotoxic activity against the tested cell lines with respect to the chlorido (1a, 1b) and iodido (3a, 3b) analogs, particularly on cervical adenocarcinoma (HeLa) cells. This work demonstrates that $[Pt(NH_3)_2(Am)X]^+$ complexes induce cancer cell death, and their activity can be modulated by the halogen substitution.

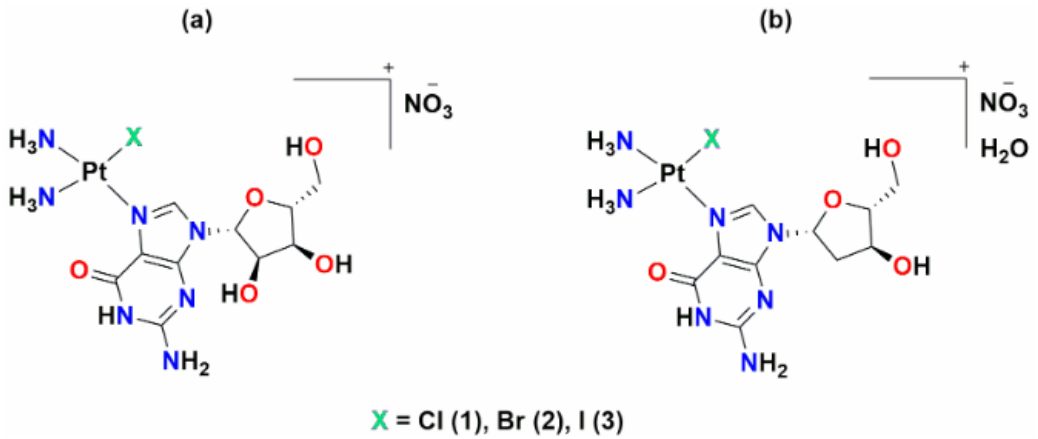

Figure 1: *Chemical structures of platinum(II) nucleoside monoadducts of the type (**a**) cis-[Pt(NH$_3$)$_2$(Guo)Cl]$^+$ (**1a, 2a, 3a**) and (**b**) cis-[Pt(NH$_3$)$_2$(dGuo)Cl]$^+$ (**1b, 2b, 3b**) complexes; X = Cl (**1**), Br (**2**) or I (**3**).*

References:

[1] F. De Castro, E. Stefàno, E. De Luca, M. Benedetti, F.P. Fanizzi, Pharmaceutics 2023, 15, 941.

[2] L.S. Hollis, A.R. Amundsen, E.W. Stern, Journal of Medicinal Chemistry 1989, 32, 128–136.