Structural studies on the interaction between a B-DNA duplex and Pt-based compounds

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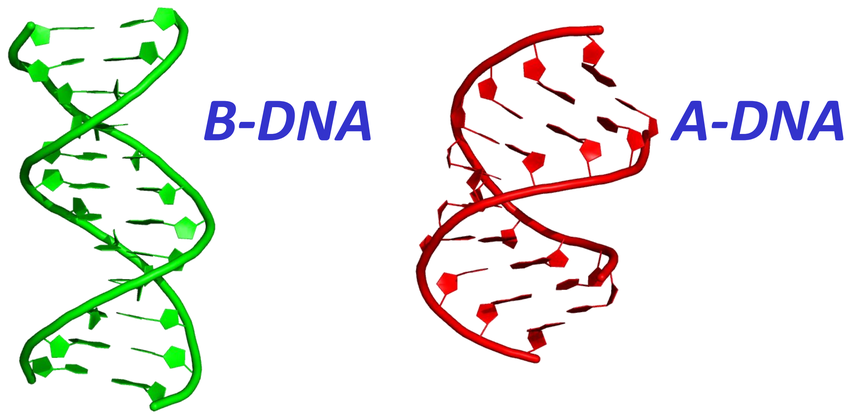
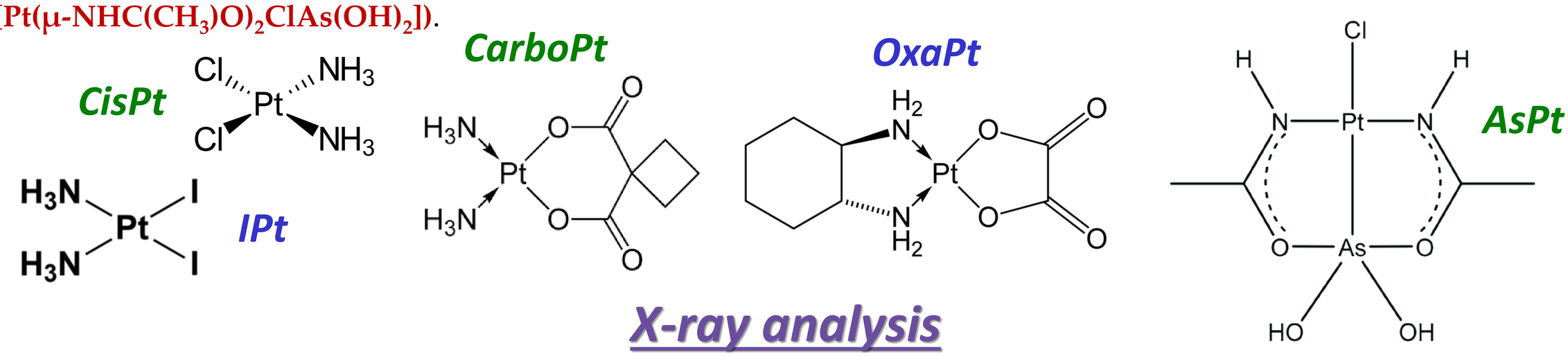
Background

Metal-based therapy remains a highly utilized and effective option in the ***treatment of many types of cancer***. However, due to the persistence of ***severe side effects and the increase of resistance events***, new metal-based chemotherapeutics that could overcome these limitations are required. In this context, the investigation of the mode of action of these metal compounds by a detailed analysis of their ***interaction with nucleic acids*** or proteins is necessary and could benefit the design of new powerful antitumor drugs.



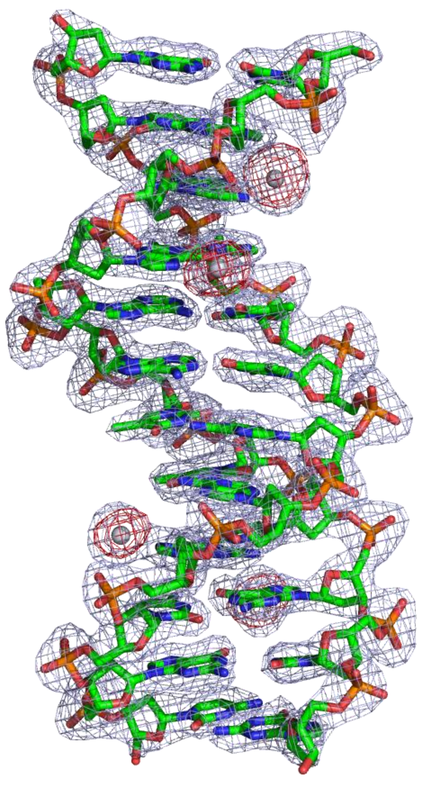
The most effective and extensively studied ***inorganic antitumor drug***, which is able to interfere with DNA replication and transcription, is ***cisplatin*** (**[*cis*-Pt(NH_3)$_2$Cl$_2$]**). The first crystal structure of an adduct formed upon interaction of cisplatin with a ***B-DNA double helix*** (the ***dodecamer CGCGAATTCGCG***) was solved by Dickerson in 1984. Cisplatin binds to the duplex via ***ligation to the N7 position of the major groove guanines*** that are characterized by a conformational mobility.

Our study is focused on a comprehensive analysis of the interaction of B-DNA with ***cisplatin (CisPt)***, ***the iodinated derivative of cisplatin*** (**IPt, [cis-Pt(NH_3)$_2$I$_2$]**), ***carboplatin (carboPt)***, ***oxaliplatin (OxaPt)***, and ***arsenoplatin-1*** (**AsPt, [Pt(μ-NHC(CH_3)O)$_2$ClAs(OH)$_2$]**).



X-ray analysis

CisPt-DNA adduct



$2F_o$-F_c map - 1 σ
Anomalous map - 3 σ

Experiments: native DNA (***CGCGAATTCGCG)*** crystals were equilibrated with solid Pt-based compound for few days. Data collection were performed at Elettra Sincrotrone Trieste and the European Synchrotron Radiation Facility (ESRF).

Results: The binding of platin to the selected B-DNA double helix involves ligation to the ***N7 position*** of a number of guanines that depends on the metal compound, which seems also able to select the specific interacting guanine (see Table).

Metal Compound	Interacting residues (strand A)	Interacting residues (strand B)	Structure resolution
CisPt	Gua4, Gua10	Gua16, Gua22	2.31 Å
IPt	Gua4, Gua10	Gua14, Gua16, Gua22	2.50 Å
CarboPt	Gua10	Gua22	1.85 Å
OxaPt	-	Gua14	1.69 Å
AsPt	Gua2	Gua14	2.51 Å

Crystallographic results suggest that **IPt** is the most ***reactive*** Pt-based compound towards the examined DNA model.

Future studies

CD and ***UV-Vis*** analyses will be performed in order to study ***in solution*** the effects of the five Pt-compounds on the ***folding*** and ***stability*** of the selected B-DNA sequence.
The ***mode-of-action*** of the Pt-compounds will be also investigated by a comprehensive ***mass spectrometry*** study.
The effects of these Pt-based compounds on ***A-DNA double helix*** will also examined.

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