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Thesis abstract

Chemical syntheses, biophysical characterisation and biological investigations of multifunctional anticancer platinum(IV) coordination complexes

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Cancer kills. It costs many lives. Fortunately, multiple preventative treatment options are available in the clinic. Standard intravenous chemotherapy is the most accepted treatment regimen, which has a reputation as oncology's workhorse. The square planar platinum(II) coordination complexes, cisplatin, oxaliplatin and carboplatin are a clinically renowned class of drugs administered in chemotherapy. Their potency is elicited through covalently binding to deoxyribonucleic acid, which results in crosslinks that activate programmed cell death. Despite their success in treating multiple cancer types, these platinum(II) drugs also exhibit disadvantageous pharmacokinetic and pharmacological effects that greatly impact patient care.

The design of multifunctional platinum(IV) coordination complexes as chemotherapeutic prodrugs is a key research focus in cancer drug design and discovery. This synthetic strategy is working to overcome the clinical challenges associated with platinum(II) drugs. One desirable feature of platinum(IV) complexes is their six-coordinate octahedral geometry, in which two axial coordination sites are synthetically accessible for coordinating bioactive and non-bioactive moieties (or ligands) that can regulate the overall pharmacokinetic and pharmacological properties of the complexes. Axial ligands come in a variety of structural forms and typically with distinct functional groups that can improve the physicochemical properties of the complexes such as aqueous solubility, stability, lipophilicity, rate of reduction, bioavailability and more. Additionally, ligands also carry their own therapeutic properties that can contribute to enhancing the overall anticancer effects of the complexes. Platinum(IV) complexes are also kinetically stable. By adapting to this synthetic strategy, it is possible to create drug prototypes that are effective, well-tolerated and suitable for oral administration. Having chemotherapeutics that can be taken orally and without or with reduced dose-limiting side effects will greatly improve cancer treatment experience.

In this work, multiple platinum(IV) complexes incorporating a distinct selection of bioactive ligands were synthesised. A series of biophysical characterisation techniques, including but not limited to, high-performance liquid chromatography, nuclear magnetic resonance spectroscopy, ultraviolet-visible spectroscopy, circular dichroism spectroscopy, high-resolution electrospray ionisation spectrometry, infrared spectroscopy and elemental microanalysis were utilised to evaluate the purity and confirm the chemical structures of

the platinum(IV) complexes. The resultant and pure platinum(IV) complexes were screened against twelve human cell lines including, HT29 colon, U87 glioblastoma, MCF-7 breast, A2780 ovarian, H460 lung, A431 skin, Du145 prostate, BE2-C neuroblastoma, SJ-G2 glioblastoma, MIA pancreas, the cisplatin-resistant ADDP ovarian variant, and the non-tumour derived MCF10A breast line. Remarkably, their anticancer potential proved to be significantly better than cisplatin, oxaliplatin and carboplatin in most of the cell lines evaluated. Most importantly, the studied platinum(IV) complexes also proved to be potent in the cisplatin-resistant ADDP ovarian variant cell line in comparison to all other cell line populations, indicating that they are not susceptible to the drug resistance mechanisms induced by standard clinical treatment with cisplatin. The results obtained in this work are instrumental in advancing our understanding of cancer treatment. The platinum(IV) prodrugs investigated in this work will allow us to work toward innovative drug design approaches for the treatment of multiple cancers, especially those that are highly aggressive and difficult to treat. This evolving approach to platinum(IV) complexes, as supported by evidence in the literature, has the potential to transform standard chemotherapeutic regimens. Improved knowledge in this research area may alleviate the burden of cancer, giving hope to cancer victims and their families.

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