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Thesis abstract

Investigating novel platinum(II) and (IV) complexes with cyclometallated ligands, pyridine derivatives and peptide targeting as potential anticancer agents

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Abstract of a thesis submitted to Western Sydney University

Cancer takes a huge toll on our society and platinum anticancer drugs are on the frontlines, treating up to 50% of cancer patients worldwide. Currently, these treatments consist of Cisplatin and its derivatives, which have been approved globally since 1978. Although these complexes are efficient cell killers, they are not targeted to cancer and cause severe dose-limiting side effects and are often administered alongside a cocktail of other drugs to alleviate some of these symptoms. Additionally, these complexes are not equally effective in all types of cancer. In fact, some cells are inherently resistant to this mechanism of action and others quickly acquire resistance. To combat these shortfalls scientists have been developing new anticancer agents with alternative mechanisms of action. These unconventional platinum complexes have different Structure Activity Relationships (SARs) and many are active in Cisplatin-resistant cells and are not cross-resistant.

This thesis focuses on 56MESS and its derivatives. These unconventional complexes are formulated with one bidentate polypyridyl ligand (which is a phenanthroline or bipyridine derivative) and a bidentate ancillary ligand (which is usually diaminocyclohexane). These complexes are well known for their cytotoxicity which is 100 times that of Cisplatin. The primary objective of this thesis is to develop new unconventional platinum anticancer complexes with unique biophysical properties and can provide insights into the SAR of these types of complexes. The four main biophysical properties desired were, quadruplex DNA (QDNA) binding, fluorescence, increased platinum(IV) stability and active targeting. These objectives were achieved using unique combinations of ligands, where the polypyridyl ligand was substituted for a cyclometallated ligand or a pyridine derivative. These complexes showed remarkable fluorescent properties, stability and DNA binding properties as well as having good cytotoxic profiles. Additionally, active targeting of 56MESS was explored, and new biological techniques were investigated to find effective techniques for the preliminary assessment of anticancer prodrugs. The complexes synthesised have been separated into four main chapters that have been reported in four publications and an additional chapter that focused on active targeting and cell culture work.

The first project develops QDNA stabilising cyclometallated complexes, designed with one cyclometallated ligand and one polypyridyl, phenanthroline-based ligand to achieve a large positively charged surface area to stack onto QDNA. Several of these complexes were significantly more cytotoxic

than Cisplatin in all cell lines tested and had good to moderate selectivity indices, 1.7–4.5 in MCF10A/MCF-7. The fluorescence explored was found to have relatively high emission quantum yields (up to 0.064) and emission occurred outside cellular autofluorescence, meaning their fluorescence is ideal for *in vitro* analysis. The second project investigates the use of cyclometallated ligands that are close relatives of the typical ligands used in 56MESS and its derivatives, looking at the utility of the stabilising effect of cyclometallation as well as the fluorescence it produces. This group of complexes was found to have a similar cytotoxic profile to Cisplatin, and all had very high selectivity indexes compared to previous Pt(II) complexes. They were determined to have a good affinity to calf thymus DNA (ctDNA), and their fluorescence was successfully utilised in benchtop binding experiments. The next project looks at oxidising these cyclometallated complexes and how their platinum(IV) derivatives differ from Pt(IV)56MESS, again investigating the utility of the stabilising effect of cyclometallation and changes to fluorescence upon oxidation. The cyclometallation had an extreme stabilising effect increasing the reduction half-life by 30-fold. These platinum(IV) complexes also saw improved cytotoxicity compared to previous 56MESS-type complexes. The fourth chapter investigates imidazole and pyridine derivatives as alternative polypyridyl ligands in the 56MESS formula, looking at changes in their DNA binding and cytotoxicity. These complexes were determined to have good DNA binding properties and had a similar average cytotoxicity to Cisplatin but had remarkable variation within different cell lines suggesting they may have some inherent selectivity. The final chapter starts to investigate the use of prostate membrane antigen (PSMA) targeting ligand DCL in targeting Pt(IV)56MESS and offers new perspectives on the utility of MTT assays in assessing prodrugs.

For each novel complex, the synthetic strategy has been developed to produce good yields and high purity (>95%). Each was assessed using high-performance liquid chromatography (HPLC) for purity, and a combination of nuclear magnetic resonance spectroscopy (NMR), ultraviolet (UV) and circular dichroism (CD) spectroscopy and electrospray ionisation mass spectrometry (ESI–MS) to confirm structure and basic chemical properties. In addition, the lipophilicity of each complex was calculated using HPLC techniques, and fluorescence parameters and quantum yields were determined for all fluorescent complexes. To assess the biological activity of these complexes their cytotoxicity was determined against a panel of cancer cell lines and their DNA binding was investigated using a variety of techniques including DNA melting and fluorescent displacement experiments. For the platinum(IV) complexes additional reduction half-life experiments were undertaken.

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