Studies on BODIPY-Platinum(II/IV) Conjugates for Cellular Imaging and Photodynamic Therapy

Cancer emerges from the abnormal proliferation of aberrant cells. Amidst a multitude of treatment options, chemotherapy is widely used as a viable methodology. Despite its widespread use, it is encumbered with significant limitations due to drug related side-effects. Consequently, in recent times, photodynamic therapy (PDT) and photoactivated chemotherapy (PACT) have emerged as highly promising alternatives to traditional chemotherapy. This work aims to conceive and synthesize new platinum(II/IV) complexes using ligands as multifunctional agents for effective phototherapy and photochemotherapy applications. In the initial phase, a series of mono-functional platinum(II) complexes [Pt($\mathbf{L}^{1\text{-}3}$)Cl]Cl (**1**-**3**) were synthesized having BODIPY (boron-dipicolylamine)-tagged dipicolylamine (dpa) ligands ($\mathbf{L}^{2}$ and $\mathbf{L}^{3}$) as green and red light emitting photosensitizers along with a benzyl derivative of dpa ($\mathbf{L}^{1}$). These mono-functional complexes exhibit remarkable affinity for DNA binding, as evidenced from a study employing the model nucleobase 9-EtG, while also displaying the ability to generate singlet oxygen upon photoactivation of the BODIPY photosensitizer. In subsequent investigations, we synthesized a novel platinum(IV)-BODIPY conjugate, named **Oxoplatin-B** (**4**), derived from cisplatin. The prodrug exhibited photo-induced ligand release, accompanied by the simultaneous formation of the cisplatin core through a two-electron Pt(IV)-Pt(II) reduction process. Encouraged from the results obtained with the green light Pt(IV) prodrug, we embarked on investigating the possibilities of a clinically applicable platinum(IV) prodrug with the formulation [Pt$(NH_3)_2Cl_2$(OH)($\mathbf{L}^{6}$)], having a red light active BODIPY ligand (H$\mathbf{L}^{6}$). Upon red light irradiation, the complex exhibited significant PDT activity with sub-micromolar IC_{50} values in cancer cells such as HeLa and MCF-7. Moving forward, we introduced a novel prodrug (**7**) formulation that combines a platinum(IV) core with a bioactive biotin (vitamin B7) moiety, covalently linked to a PEGylated BODIPY ligand (H$\mathbf{L}^{7}$) designed to respond to red light stimulation and for enhanced bioavailability. Notably, the complex displays remarkable stability in solution in dark, but rapidly activates upon red light exposure without any need for external reducing agents. Finally, we made a comprehensive study on the synthesis and characterization of a hetero-bimetallic conjugate (**9**). This conjugate presents a dual-action Pt(IV) complex with a chemo-active unit and a BODIPY-Ru(II)-bisterpyridine dyad complex as a visible light photosensitizer. This prodrug induced significant photocytotoxicity with remarkably high phototherapeutic index (PI) value of >4545 in A549 cancer cells. The findings of this work pave the way for innovative approaches in the design and development of new generation of platinum(II/IV) complexes having BODIPY-based photosensitizers, offering exciting prospects in PDT and cellular imaging applications.

References: Bera, A. and Chakravarty, A. R. *et al. Dalton Trans.*, **2022**, *51*, 3925-3936; *J. Inorg. Biochem.*, **2021**, *223*, 111526; *RSC Med. Chem.***, 2022,** *13***,** 1526-1539; "Biotin and boron-dipyrromethene tagged platinum(IV) prodrug for cellular imaging and mito-targeted photocytotoxicity in red light" (submitted for publication); "A heterobimetallic BODIPY-Ru(II)-Pt(IV) prodrug, functionalized with biotin for cell imaging and targeted photodynamic therapy"(*Manuscript under preparation*).