DOCTORAL THESIS

The application of iridium(III) complexes in luminescent sensing and theranostics

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Abstract

The development of transition metal complex-based luminescent probes and theranostic have recently aroused tremendous interest for labelling and detecting environmental contaminants and cellular biomarkers, particularly in the use of real-time diagnosis and treatment of disease. Reasons behind include the unique photophysical properties of transition metal complexes, particularly in the properties of their long-lived and environmentally sensitive emission, which can be easily fine-tuned via the modification of the metal center and auxiliary ligand of the metal complex to achieve the desired emissive characteristics.

In Chapter 2, a series of luminescent iridium(III) complexes were introduced and their synthesis and evaluation on their ability to interact with hydroxide (OH^-) ion in semi-aqueous media at ambient temperature were discussed. Upon addition of OH^- ion, a nucleophilic aromatic substitution reaction takes place at the bromine groups of the N^N ligand of iridium(III) complex **2.1**, resulting in the generation of product with a yellow-green luminescence. Complex **2.1** showed a 35-fold enhancement in emission signal at pH 14 when compared to neutral pH, and the detection limit for OH^- ions was found to be 4.96 μM. Complex **2.1** exhibited high sensitivity and selectivity, long-lived luminescence and impressive stability. Additionally, practical application of complex **2.1** was demonstrated to be able to detect OH^- ions in simulated wastewater.

In Chapter 3, a series of luminescent iridium(III) complexes were introduced and their design and evaluation on their affinity to detect oxalyl chloride ($(COCl)_2$) at ambient temperature were discussed. In the presence of $(COCl)_2$, a double amidation reaction takes place at the diamino functionality of complex **3.1**, leading to the switching-on of a long-lived red luminescence with 9-fold enhancement in emission signal. Complex **3.1** exhibited high sensitivity and selectivity and the detection limit for $(COCl)_2$ was found to be 32 nM. Additionally, complex **3.1** can be used to detect $(COCl)_2$ using a simple smartphone, which allows the detection to be a real-time one.

In Chapter 4, a dual–functional luminescent probe and inhibitor was designed for the in–situ monitoring of neuraminidase (NA) using a structure–based molecular design strategy. The candidate iridium(III) complexes **4.1a**–**4.1d** were synthesized by grafting an oseltamivir moiety as a binding unit onto signaling iridium(III) precursors, generating probes that allowed for the simultaneous inhibition and sensing of NA. Complexes **4.1a**–**4.1d** showed strong yellow or red luminescence in aqueous buffer containing 0.5% acetonitrile in response to NA. In particular, complex **4.1d** exhibited enhanced inhibition against NA compared to the FDA–approved antiviral drug, oseltamivir. Moreover, complex **4.1d** also displayed a long–lived lifetime, large Stokes shift, and high quantum yield, allowing its luminescence output to be distinguished in the presence of an interfering auto-fluorescent background. We have successfully developed the first dual–functional molecule **4.1d** for the in–situ inhibition and detection of NA, which provides the possibility for the in–field simultaneous therapy and monitoring of influenza infection.

In Chapter 5, a general strategy was introduced for the development of a long–lifetime iridium(III) theranostic by grafting a well–known inhibitor as a "binding unit" onto an iridium(III) complex precursor as a "signaling unit". To further optimize their emissive properties, the effect of imaging behavior was explored by incorporating different substituents onto the parental "signaling unit". This design concept was validated by a series of tailored iridium(III) theranostic **5.2a**–**5.2h** for the visualization and inhibition of EGFR in living cancer cells. By comprehensively assessing the theranostic potency of **5.2a**–**5.2h** in both *in vitro* and *in cellulo* contexts, probe **5.2f** containing electron–donating methoxy groups on the "signaling unit" was discovered to be the most promising candidate theranostic with desirable photophysical/chemical properties. Probe **5.2f** selectively bound to EGFR *in vitro* and *in cellulo*, enabling it to selectively discriminate living EGFR–overexpressing cancer cells from normal cells that express low levels of EGFR with an "always–on" luminescence signal output. In particular, its long–lived lifetime enabled its luminescence signal to be readily distinguished from the interfering

fluorescence of organic dyes by using time–resolved technique. Complex **5.2f** simultaneously visualized and inhibited EGFR in a dose–dependent manner, leading to a reduction in the phosphorylation of downstream proteins ERK and MEK, and inhibition of the activity of downstream transcription factor AP1. Notably, complex **5.2f** is comparable to the parental EGFR inhibitor **5.1b**, in terms of both inhibitory activity against EGFR and cytotoxicity against EGFR–overexpressing cancer cells. This tailored dual–functional iridium(III) theranostic toolkit provides an alternative strategy for the real–time and personalized diagnosis and treatment of cancers.

Chapter 6 discusses the challenges and future inspirations for the development of iridium(III) complex-based luminescent probes and theranostic.

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