

## 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 ( $\text{OH}^-$ ) ion in semi-aqueous media at ambient temperature were discussed. Upon addition of  $\text{OH}^-$  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  $\text{OH}^-$  ions was found to be 4.96  $\mu\text{M}$ . 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  $\text{OH}^-$  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 ( $(\text{COCl})_2$ ) at ambient temperature were discussed. In the presence of  $(\text{COCl})_2$ , 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  $(\text{COCl})_2$  was found to be 32 nM. Additionally, complex **3.1** can be used to detect  $(\text{COCl})_2$  using a simple smartphone, which allows the detection to be a real-time one.

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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 autofluorescent 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

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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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# Table of Contents

<b>Declaration</b>	<b>i</b>
<b>Abstract</b>	<b>ii</b>
<b>Acknowledgements</b>	<b>v</b>
<b>Table of Contents</b>	<b>vi</b>
<b>List of Tables</b>	<b>ix</b>
<b>List of Figures</b>	<b>x</b>
<b>List of Schemes</b>	<b>xvii</b>
<b>Abbreviations and symbols</b>	<b>xviii</b>
<b>Chapter 1 Introduction</b>	
1.1 Background	1
1.2 Conventional strategies for analyte detection	1
1.3 Transition metal complex as luminescent probes	2
1.4 Principle of transition metal complex based luminescent probes	5
1.5 Transition metal complex as dual-functional theranostic	7
1.6 Objective	10
1.7 Reference	10
<b>Chapter 2 A reaction-based luminescent switch-on sensor for the detection of OH<sup>-</sup> ion in simulated wastewater</b>	
2.1 Introduction	16
2.2 Results and discussion	17
2.2.1 Screening of iridium(III) complexes	17
2.2.2 Photophysical properties of complex <b>2.1</b>	19
2.2.3 OH <sup>-</sup> ion sensing	22
2.2.4 Application as a pH sensor in simulated water entity	31
2.3 Experimental section	32
2.3.1 Chemicals and materials	32
2.3.2 General Experiment	32
2.3.3 Synthesis of iridium(III) complexes	32
2.3.4 Photophysical measurement	35
2.3.5 Stability analysis of complex <b>2.1</b>	35
2.3.6 OH <sup>-</sup> detection	35
2.3.7 Solid phase-based detection	36
2.3.8 Application of complex <b>2.1</b> in simulated wastewater	36

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2.4 Conclusion	36
2.5 Reference	37
<b>Chapter 3 Real-time detection of oxalyl chloride based on a long-lived iridium(III) probe</b>	
3.1 Introduction	40
3.2 Results and discussion	41
3.2.1 Screening of iridium(III) complexes	41
3.2.2 Photophysical properties of complex <b>3.1</b>	45
3.2.3 (COCl) <sub>2</sub> sensing	48
3.2.4 Application as a portable probe based on smartphone	52
3.3 Experimental section	53
3.3.1 Chemicals and materials	53
3.3.2 General Experiment	54
3.3.3 Synthesis of iridium(III) complexes	54
3.3.4 Photophysical measurement	56
3.3.5 (COCl) <sub>2</sub> detection	56
3.4 Conclusion	57
3.5 Reference	58
<b>Chapter 4 A dual-functional molecular strategy for in-situ suppressing and visualizing of neuraminidase in aqueous solution using iridium(III) complexes</b>	
4.1 Introduction	61
4.2 Results and discussion	64
4.2.1 Synthesis of complexes <b>4.1–4.1d</b>	64
4.2.2 Inhibition activity of complexes <b>4.1–4.1d</b>	67
4.2.3 Photophysical properties of complexes <b>4.1–4.1d</b>	68
4.2.4 Response of complexes <b>4.1–4.1d</b> to neuraminidase	70
4.2.5 Complex <b>4.1d</b> as dual-functional probe and inhibitor against neuraminidase	72
4.3 Experimental section	75
4.3.1 Chemicals and materials	75
4.3.2 General experiment	76
4.3.3 Synthesis of complexes <b>4.11a–4.11d</b>	76
4.3.4 Synthesis of complexes <b>4.1a–4.1d</b>	77
4.3.5 Photophysical measurement	89
4.3.6 Inhibition assay of complexes <b>4.1a–4.1d</b>	90
4.3.7 Detection of neuraminidase using complexes <b>4.1a–4.1d</b> as probes	90
4.3.8 Dose-dependent assay using complex <b>4.1d</b> as an inhibitor	90

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4.3.9 Protein thermal shift assay	90
4.4 Conclusion	91
4.5 Reference	91
<b>Chapter 5 Structure–guided discovery of a luminescent theranostic toolkit for living cancer cells and the imaging behavior effect</b>	
5.1 Introduction	94
5.2 Results and discussion	99
5.2.1 Synthesis of complexes <b>5.2a–5.2h</b>	99
5.2.2 Inhibition activity of complexes <b>5.2a–5.2h</b>	100
5.2.3 Photophysical properties of complexes <b>5.2a–5.2h</b>	101
5.2.4 <i>In cellulo</i> response of complexes <b>5.2a–5.2h</b>	103
5.2.5 Complex <b>5.2f</b> as dual-functional theranostic	105
5.3 Experimental section	113
5.3.1 Chemicals and materials	113
5.3.2 General experiment	113
5.3.3 Synthesis of complexes <b>5.2a–5.2h</b>	114
5.3.4 Photophysical measurement	132
5.3.5 Time–resolved emission spectroscopy (TRES) measurement	133
5.3.6 Stability experiments	133
5.3.7 Cell cultures	134
5.3.8 MTT assay	134
5.3.9 Confocal imaging	134
5.3.10 Cellular thermal shift assay	135
5.3.11 Immunofluorescence	135
5.3.12 Western blotting	135
5.3.13 Knockdown assay	136
5.3.14 Luciferase reporter assay	136
5.3.15 EGFR kinase assay	136
5.4 Conclusion	137
5.5 Reference	138
<b>Chapter 6 Summary and outlook</b>	142
<b>Curriculum Vitae</b>	144