DOCTORAL THESIS

Synthesis, photophysical and biological studies of lanthanide complexes for photodynamic therapy

Zhou, Yan

Date of Award:
2017

ABSTRACT

Photodynamic therapy (PDT) is a promising therapeutic approach for cancer therapy, however, poor tumor selectivity and low penetration depth of light have always limited its function during medical treatment. The goal of my study was to develop a new generation of PDT agents to overcome the above restraints in current PDT cancer therapy. We have synthesized three series of porphyrinate lanthanide complexes to target cancer receptors $\alpha_v\beta_3$ integrin isoform for bladder cancer and phospholipid anionic membrane for lung and prostate cancers.

Prior to the PDT, we have also synthesized a series of water-soluble homoleptic lanthanides (Ln^{3+} = Gd, Er, and Yb) sandwich (DD) di-PEGylated porphyrin complexes. The Yb complex (**YbDD**) has shown the same NIR emission quantum yield as the highest record Yb complex in the literature (Yb-RhB), yet, the emission intensity is double compared to the Yb-N. This implies a new thinking about the quantity measurement for biological imaging. The brightness might be the prime factor for the development of luminescence *in vitro*/*in vivo* imaging agent rather than the emission quantum yield.

Table of Contents

Declaration ..... **i**

Abstract ..... **ii**

Acknowledgement ..... **iii**

Table of Contents ..... **v**

List of Schemes ..... **ix**

List of Figures ..... **x**

List of Tables ..... **xxi**

List of the Abbreviations and Symbols ..... **xxiii**

Chapter 1 Introduction **1**

1.1 Porphyrin 2

1.1.1 Porphyrin and its derivatives 2

1.1.2 Photophysical properties of porphyrin 6

1.1.3 Synthesis of porphyrin 11

1.2. Photodynamic therapy (PDT) 14

1.2.1 Photosensitizers 14

1.2.2 Singlet oxygen 18

1.2.3 Challenges of PDT 22

1.3 Porphyrinate lanthanide complexes 23

1.3.1 Lanthanide chemistry 23

1.3.2 Antenna effect of organic-lanthanide complexes system.....25

1.3.3 Porphyrinate lanthanide complexes.....26

1.3.3.1 Introduction.....26

1.3.3.2 Synthesis of porphyrinate lanthanide complexes.....31

1.4 Scopes of the study.....33

1.5 References.....35

Chapter 2 Cancer-Specific Multi-modal Imaging and anticancer agent -Photodynamic Therapy with Fluorescence and Magnetic Resonance Imaging with Porphyrin Lanthanide Complexes.....40

2.1 Introduction.....41

2.2 $\alpha_v\beta_3$-Isoform Specific Porphyrinate Lanthanide System for Highly Selective Bladder Cancer-Targeting Near-Infrared/Magnetic Resonance Imaging and Photodynamic Therapy.....43

2.2.1 $\alpha_v\beta_3$-Isoform Specific Ytterbium and Erbium Complexes Highly Specific for Bladder Cancer Imaging and Photodynamic Therapy.....45

2.2.1.1 Results and discussion.....45

2.2.1.1.1 Synthesis.....45

2.2.1.1.2 Photophysical properties.....47

2.2.1.1.3 *In vitro* imaging of **Ln-R$_n$** (Ln^{3+} = Yb and Er, n = 1-3).....53

2.2.1.1.4 Cellular uptake of **Ln-R$_n$** (Ln^{3+} = Yb and Er, n = 1-3).....56

2.2.1.1.5 *In vitro* dark and photocytotoxicity of **Ln-R$_n$** (Ln^{3+} = Yb and Er, n = 1-3).....58

2.2.2 $\alpha_v\beta_3$-Isoform Specific Gadolinium Complexes Highly Specific for Bladder Cancer Magnetic Resonance Imaging and Photodynamic Therapy 60
2.2.2.1 Results and discussion 60
2.2.2.1.1 Synthesis 60
2.2.2.1.2 Photophysical properties 62
2.2.2.1.3 *In vitro* imaging of **Gd-PEG-R$_n$** (n = 1-3) 70
2.2.2.1.4 *In vitro* dark and photocytotoxicity of **Gd-PEG-R$_n$** (n = 1-3) 72
2.2.2.1.5 T_1 relativity and *in vivo* MRI of the **Gd-PEG-R$_3$** 74
2.3 Porphyrin-based Gadolinium Complexes Targeting Anionic Phospholipid Membrane as Selective Bio-makers for Cancer Cells Imaging 77
2.3.1 Results and discussion 78
2.3.1.1 Synthesis 78
2.3.1.2 Photophysical properties 80
2.3.1.3 *In vitro* imaging of **Gd-P$_n$** (n = 1 and 2) 85
2.3.1.4 *In vitro* dark and photocytotoxicity of **Gd-P$_n$** (n = 1 and 2) 86
2.4 Conclusion 89
2.6 References 91

Chapter 3 Enhanced Near-Infrared Emission and Singlet Oxygen Generation from Lanthanide-Porphyrin Double-Decker Complexes in Aqueous Solutions 97

3.1 Introduction 98
3.2 Results and discussions 101

3.2.1 Synthesis and characterization 101

3.2.2 Photophysical properties 103

3.3 Conclusion 124

3.4 References 125

Chapter 4 Experimental 128

4.1 Synthesis and characterization 129

4.1.1 Experimental procedures of chapter 2 130

4.1.2 Experimental procedures of chapter 3 148

4.2 Photophysical measurement 152

4.2.1 Linear induced photophysical properties in chapter 2 and 3 152

4.3 *In vitro* and *in vivo* studies 154

4.4 MALDI-TOF mass and ^{1}H-NMR spectrrums of the intermediates and final products. 158

4.5 References 189