# Contents

1 Introduction ................................................................. 1

1.1 Inorganic Medicines ....................................................... 1

1.2 Lessons from Cisplatin and Its Derivatives ............................ 3

1.2.1 Overview of Platinum Drugs ........................................ 3

1.2.2 Anticancer Mechanism of Cisplatin ............................... 4

1.2.3 Transplatin and Its Anallogues ..................................... 9

1.2.4 Cisplatin Resistance and Side Effect Problems ................... 10

1.3 The Chemistry and Anticancer Properties of Gold .................... 11

1.3.1 The Chemical Properties of Gold Complexes [32] .............. 11

1.3.2 Gold Complexes Inhibit Thiol-Containing Enzyme Activities ................ 13

1.3.3 Current Status of Gold(I) Anticancer Agents ..................... 21

1.3.4 Current Status of Anticancer Gold(III) Complexes ............ 26

1.4 The Chemistry and Anticancer Properties of Platinum ............... 31

1.4.1 The Chemical Properties of Platinum Complexes ............... 31

1.4.2 Physiologically Stable Platinum(II) Complexes as Anticancer Agents 34

1.5 The Chemistry of N-Heterocyclic Carbene Ligands .................. 40

1.5.1 Electronic Properties of NHC Ligands ............................ 41

1.5.2 Steric Effects of NHC Ligands ..................................... 41

1.5.3 Synthesis of NHC Ligands [125] ................................. 42

1.5.4 Synthesis of Metal-NHC Complexes .............................. 43

1.6 Luminescent Properties of Platinum(II) and Gold(I)/(III) Complexes 45

1.7 Fluorescent Thiol Probes ............................................... 47

References ................................................................. 47
2 Experimental Section

2.1 Materials and Instrumentation

2.2 X-Ray Crystallography

2.2.1 Crystal Growth

2.2.2 Single Crystal Analysis

2.3 Stability Testing

2.3.1 UV–Vis Absorption Measurements

2.3.2 ESI-MS Measurements

2.3.3 $^1$H NMR Measurements

2.4 Emission Measurements

2.4.1 Emission Spectra Measurements

2.4.2 Emission Lifetime Measurements

2.5 Fluorescence Microscopy

2.6 Cell Culture and Cytotoxicity Studies

2.6.1 Cell Subculture

2.6.2 MTT Assay

2.7 Gel Mobility Shift Assay

2.8 Spectroscopic Binding Studies

2.8.1 Determination of DNA-Binding Constants

2.8.2 Binding with Proteins

2.9 Transfection

2.10 Western Blot

2.11 Inductively Coupled Plasma Mass Spectrometry

2.12 Tube Formation Assay

2.13 In Vivo Antitumor Study

References

3 Gold(III) Complexes Containing N-Heterocyclic Carbene Ligand Serve as Dual Fluorescent Thiol “Switch-On” Probe and Anticancer Agent

3.1 Introduction

3.2 Experimental Section

3.2.1 Materials and Instrumentation

3.2.2 Synthesis and Characterization of Gold Complexes

3.2.3 Reactions with GSH

3.2.4 Luminescent Properties of 3.9

3.2.5 Anticancer Properties

3.3 Results and Discussion

3.3.1 Synthesis and Characterization

3.3.2 Reactions with GSH

3.3.3 Emission Properties of 3.9 Toward Thiols

3.3.4 Anticancer Properties

3.4 Conclusion

References
4 A Binuclear Gold(I) Complex with Mixed Bridging Diphosphine and Bis(N-Heterocyclic Carbene) Ligands Shows Favorable Thiol Reactivity and Effectively Inhibits Tumor Growth and Angiogenesis In Vivo ........................................... 101
4.1 Introduction .......................................................... 101
4.2 Experimental Section .................................................. 102
  4.2.1 Materials and Instrumentation ...................................... 102
  4.2.2 Synthesis and Characterization of Complexes .................... 103
  4.2.3 Biological Application ........................................... 106
4.3 Results and Discussion ................................................ 112
  4.3.1 Synthesis and Characterization .................................... 112
  4.3.2 Stability Toward Blood Thiols and In Vitro Cytotoxicity ........ 112
  4.3.3 Inhibition of Thioredoxin Reductase .............................. 116
  4.3.4 Inhibition of Cancer Stem Cell Activity ......................... 119
  4.3.5 In Vivo Antitumor Activities .................................... 121
  4.3.6 Safety Pharmacology Study ....................................... 127
4.4 Conclusion .......................................................... 131
References .............................................................. 131

5 Luminescent Organoplatinum(II) Complexes Containing Bis(N-Heterocyclic Carbene) Ligands Selectively Target Endoplasmic Reticulum and Induce Potent Phototoxicity ........ 135
5.1 Introduction .......................................................... 135
5.2 Experimental Section .................................................. 136
  5.2.1 Materials and Methods ........................................... 136
  5.2.2 Experimental Procedure and Compound Characterization ....... 136
  5.2.3 Stability Toward Physiological Thiols ............................. 139
  5.2.4 Photo-physical Properties and Application in Protein Binding and Cell Imaging ......................... 140
  5.2.5 Anticancer Properties ............................................ 142
5.3 Results and Discussion ................................................ 144
  5.3.1 Synthesis of the Complexes ....................................... 144
  5.3.2 Stability Test ...................................................... 147
  5.3.3 Anticancer Properties ............................................ 153
  5.3.4 Phototoxicities .................................................... 158
5.4 Conclusion .......................................................... 159
References .............................................................. 161

6 Summary and Evaluation ................................................. 163
Anti-Cancer N-Heterocyclic Carbene Complexes of Gold(III), Gold(I) and Platinum(II)
Thiol "Switch-on" Fluorescent Probes, Thioredoxin Reductase Inhibitors and Endoplasmic Reticulum Targeting Agents
Zou, T.
2016, XIII, 164 p. 179 illus., 79 illus. in color., Hardcover