
| | |
|---|----|
| Chapter 1. Introduction | 1 |
| 1.1. Basic concepts on photochemistry | 3 |
| 1.1.1. Photoinduced energy transfer..... | 6 |
| 1.1.2. Photoinduced electron transfer..... | 7 |
| 1.2. Cancer treatments nowadays | 8 |
| 1.3. Nanomedicine | 12 |
| 1.3.1. Viral nanoparticles..... | 12 |
| 1.3.2. Organic nanoparticles..... | 13 |
| 1.3.2.1. Drug conjugates..... | 13 |
| 1.3.2.2. Lipid-based nanocarriers..... | 13 |
| 1.3.2.3. Polymer-based nanocarriers..... | 14 |
| 1.3.3. Inorganic Nanoparticles..... | 14 |
| 1.4. Upconversion nanoparticles | 15 |
| 1.4.1. Upconversion process..... | 16 |
| 1.4.1.1. Excited-state absorption (ESA)..... | 17 |
| 1.4.1.2. Energy transfer upconversion (ETU)..... | 18 |
| 1.4.1.3. Photon avalanche (PA)..... | 18 |
| 1.4.2. UCNP composition..... | 20 |
| 1.4.3. UCNP synthesis..... | 22 |
| 1.4.3.1. Coprecipitation..... | 22 |
| 1.4.3.2. Thermal decomposition..... | 22 |
| 1.4.3.3. Hydro(solvo)thermal..... | 23 |
| 1.4.3.3.1. Ostwald-ripening..... | 23 |
| 1.4.4. UCNP biomedical applications..... | 24 |
| 1.4.4.1. Bioimage..... | 24 |
| 1.4.4.2. Biosensing and bioassay..... | 25 |
| 1.4.4.3. Therapy..... | 26 |
| 1.5. Drugs for photosensitized reactions | 26 |
| 1.5.1. Photosensitization mechanism..... | 27 |
| 1.5.2. Light..... | 27 |
| 1.5.3. Fluoroquinolones..... | 29 |
| 1.5.3.1. Fluoroquinolones' mechanism of action..... | 31 |
| 1.5.3.2. Fluoroquinolones' photogenotoxicity | 32 |

| | |
|---|-----------|
| 1.6. Photosensitized release..... | 32 |
| 1.6.1. Loaded drugs..... | 33 |
| 1.6.2. Conjugated drugs..... | 34 |
| 1.6.2.1. Coumarin-4-ylmethyl groups..... | 35 |
| 1.6.2.2. <i>Orto</i> -Nitrobenzyl groups | 37 |
| 1.7. References..... | 38 |
| | |
| Chapter 2. General objectives..... | 53 |
| | |
| Chapter 3. Chemical tuning for potential antitumor fluoroquinolones..... | 57 |
| 3.1. Introduction..... | 59 |
| 3.2. Results and discussion..... | 62 |
| 3.2.1. Absorption spectra of fluoroquinolones 1 and 2..... | 62 |
| 3.2.2. Emission measurements of fluoroquinolones 1 and 2... | 63 |
| 3.2.3. Laser flash photolysis studies (LFP) of fluoroquinolones 1 and 2..... | 64 |
| 3.2.4. Photodegradation studies..... | 68 |
| 3.2.5. Phototoxic properties..... | 69 |
| 3.3. Conclusion..... | 76 |
| 3.4. Experimental section..... | 77 |
| 3.4.1. Materials..... | 77 |
| 3.4.2. Synthesis of fluoroquinolones..... | 77 |
| 3.4.3. Emission measurements..... | 79 |
| 3.4.4. LFP measurements..... | 80 |
| 3.4.5. Irradiation procedures and equipment..... | 81 |
| 3.4.6. General procedure to identify photoproducts of 1 and 2 | 83 |
| 3.4.7. In Vitro 3T3 neutral red uptake (NRU) phototoxicity test. | 86 |
| 3.4.8. Cellular localization studies by confocal microscopy..... | 87 |
| 3.5. NMR Spectra..... | 87 |
| 3.3. References..... | 94 |

| | |
|--|------------|
| Chapter 4. Effects of fluoroquinolones structural modifications on their photosensitizing properties..... | 99 |
| 4.1. Introduction..... | 101 |
| 4.2. Results and discussion..... | 103 |
| 4.2.1. Study of the interactions between FQ and biomolecules using emission measurements..... | 103 |
| 4.2.2. Reactivity of FQ aryl cations with HSA..... | 112 |
| 4.2.3. Covalent binding of FQ to HSA..... | 114 |
| 4.2.4. Phototoxic properties of FQs..... | 116 |
| 4.3. Conclusion..... | 119 |
| 4.4. Experimental section..... | 119 |
| 4.4.1. Materials..... | 119 |
| 4.4.2. Synthesis of FQs..... | 119 |
| 4.4.3. Absorption and emission measurements..... | 120 |
| 4.4.4. Fluoroquinolone fluorescence quenching by DNA..... | 120 |
| 4.4.5. Fluorescence quenching of fluoroquinolones by albumin | 121 |
| 4.4.6. Albumin fluorescence quenching by fluoroquinolones.... | 121 |
| 4.4.7. Laser flash photolysis experiments..... | 122 |
| 4.4.8. Analysis of the covalent binding of fluoroquinolones to HSA induced by light..... | 123 |
| 4.4.9. <i>In Vitro</i> 3T3 neutral red uptake (NRU) phototoxicity test. | 124 |
| 4.5. References..... | 125 |
| | |
| Chapter 5. Studies of fluoroquinolone derivatives as alkylating bombs..... | 131 |
| 5.1. Introduction..... | 133 |
| 5.2. Results and discussion..... | 135 |
| 5.2.1. Synthesis and characterization of upconversion nanoparticles (UCNP)..... | 135 |
| 5.2.2. Photolysis of 1 in aqueous solutions with nanosystem NaYF ₄ :Yb(20%)Tm (0.5%) @NaYF ₄ @1-SA | 140 |
| 5.2.3. Cell viability assay of NaYF ₄ : Yb/Tm@NaYF ₄ @1-SA | 141 |
| 5.3. Conclusions..... | 142 |

| | |
|---|------------|
| 5.4. Experimental section..... | 143 |
| 5.4.1. Materials..... | 143 |
| 5.4.2. Synthesis of 1-Methyl-7-dimethylamino-6,8-difluoro-1,4-dihydro-3-quinolinecarboxylic acid (1)..... | 143 |
| 5.4.3. Instrumentation..... | 143 |
| 5.4.4. Synthesis of NaYF ₄ : Yb/Tm (20%, 0.5%) | 144 |
| 5.4.5. Synthesis of NaYF ₄ : Yb/Tm (20%, 0.5%)@ NaYF ₄ | 144 |
| 5.4.6. Synthesis of NaYF ₄ : Yb/Tm (20%, 0.5%)@ NaYF ₄ @1-SA.. | 145 |
| 5.4.7 Irradiation of nanosystem NaYF ₄ : Yb/Tm (20%, 0.5%)@NaYF ₄ @1-SA..... | 146 |
| 5.4.8. In Vitro HELA phototoxicity test..... | 146 |
| 5.5. References..... | 147 |
| | |
| Chapter 6. Photochemistry of photoactivable 7-Aminocoumarin derivatives..... | 153 |
| 6.1. Introduction..... | 155 |
| 6.2. Results and discussion..... | 158 |
| 6.2.1. Photolysis of COU-DCO and COU-PHA..... | 158 |
| 6.2.2. Photophysical Properties of COU-DCO and COU-PHA..... | 164 |
| 6.2.2.1. Emission Properties of COU-DCO and COU-PHA..... | 165 |
| 6.2.2.2. Femtosecond transient absorption spectroscopy of COU-DCO and COU-PHA..... | 168 |
| 6.2.2.3. Nanosecond laser flash photolysis experiments using COU-DCO and COU-PHA..... | 174 |
| 6.3. Conclusions..... | 180 |
| 6.4. Experimental section..... | 180 |
| 6.4.1. Materials..... | 180 |
| 6.4.2. Synthesis of COU, COU-DCO and COU-PHA..... | 181 |
| 6.4.3. Photolysis studies with COU-DCO and COU-PHA..... | 186 |
| 6.4.4. Laser flash photolysis experiments..... | 186 |
| 6.5. NMR Spectra..... | 187 |
| 6.6. References..... | 192 |

| | |
|--|------------|
| Chapter 7. Developing biocompatible upconversion nanosystems for photocontrolled drug delivery using albumin complexed with coumarin derivatives..... | 197 |
| 7.1. Introduction..... | 199 |
| 7.2. Results and discussion..... | 201 |
| 7.3. Conclusions..... | 210 |
| 7.4. Experimental section..... | 211 |
| 7.4.1. Materials..... | 211 |
| 7.4.2. Experimental conditions for absorption and emission measurements..... | 211 |
| 7.4.3. Experimental and results of laser flash photolysis experiments..... | 212 |
| 7.4.4. Experimental for drug release studies..... | 213 |
| 7.4.4.1. Procedure for prodrug COU-CHB..... | 213 |
| 7.4.4.2. Procedure for nanosystem UCNP@PAA@HAS...COU-CHB..... | 214 |
| 7.4.5 Synthetic route and characterization of prodrug COU-CHB..... | 214 |
| 7.4.6 Synthetic route and additional results for obtaining NaYF ₄ : Yb/Er (18%, 2%) @PAA@HSA...COU-CHB nanosystem..... | 216 |
| 7.4.6.1. Synthesis of NaYF ₄ : Yb/ Er(18%, 2%)..... | 216 |
| 7.4.6.2. Surface modification of NaYF ₄ : Yb/Er (18%, 2%) with polyacrylic acid (PAA)..... | 218 |
| 7.4.6.3. Functionalization of NaYF ₄ : Yb/Er (18%, 2%)@PAA with Human Serum Albumin (HSA)..... | 219 |
| 7.4.6.4. Preparation of nanosystem NaYF ₄ : Yb/Er (18%, 2%) @PAA@HSA...COU-CHB..... | 219 |
| 7.4.6.5. Analysis of complexation between prodrug COU or COU-CHB and HSA..... | 220 |
| 7.5. NMR Spectra..... | 222 |
| 7.6. References..... | 224 |
| Chapter 8. Instrumentation..... | 229 |
| 8.1. General instrumentation..... | 231 |

| | |
|--|------------|
| 8.1.1. Nuclear magnetic resonance (NMR)..... | 231 |
| 8.1.2. Chromatography..... | 231 |
| 8.1.2.1. Thin-layer liquid chromatography (TLC)..... | 231 |
| 8.1.2.2. High performance liquid chromatography..... | 231 |
| 8.1.2.3. Ultra performance liquid chromatography tandem mass spectrometer (UPLC-MS/MS)..... | 231 |
| 8.2. Photochemical instrumentation..... | 232 |
| 8.2.1. UV-VIS absorption spectroscopy..... | 232 |
| 8.2.2. Time-resolved fluorescence spectroscopy..... | 232 |
| 8.2.3. Steady-state photolysis..... | 233 |
| 8.2.4. Laser flash photolysis spectroscopy (LFP)..... | 233 |
| 8.2.5. Femtosecond transient absorption spectroscopy..... | 233 |
| 8.2.6. Phosphorescence emission measurements..... | 235 |
| | |
| Chapter 9. General conclusions..... | 237 |
| | |
| Chapter 10. Summary-Resumen-Resum..... | 243 |
| 10.1. Summary..... | 245 |
| 10.2. Resumen..... | 248 |
| 10.3. Resum..... | 251 |
| | |
| Chapter 11. Scientific contribution..... | 255 |
| 11.1. Contribution to Congresses..... | 257 |
| 11.2. Publications..... | 258 |