

Contents

Contents	ix
Abbreviations	xiii
1 Introduction	1
1.1 Photosensitization by drugs	1
1.1.1 General photophysical concepts	1
1.1.2 Type I and Type II oxidation	5
1.2 Principles of drug phototoxicity	7
1.2.1 Phototoxicity of statin drugs	8
1.2.2 Phototoxicity of halogenated nonsteroidal antiinflammatory drugs	12
2 Aims	17
2.1 Aims	17
2.2 Objetivos	18
3 Phototoxicity of Rosuvastatin	19
3.1 Introduction	19
3.2 Results and discussion	21
3.2.1 Photophysics of rosuvastatin	21
3.2.2 Photophysics of the major rosuvastatin photoproduct	22
3.2.3 Interaction of ppRSV with biomolecules	26
3.3 Conclusion	29
3.4 Experimental part	30
3.4.1 Chemicals	30
3.4.2 Photochemical synthesis of ppRSV	30
3.4.3 LFP experiments	30
3.4.4 Singlet oxygen measurements	31
3.4.5 EPR trapping experiments	31
3.4.6 Tryptophan photodegradation	32

4	Phototoxicity of Itraconazole	33
4.1	Introduction	33
4.1.1	Itraconazole and its photoadverse effects	33
4.2	Results and discussion	35
4.2.1	Photophysical properties of itraconazole	35
4.2.2	Photochemistry of itraconazole	36
4.2.3	Type I photooxidation mediated by itraconazole	40
4.2.4	Dyads as biomodels	41
4.2.5	Photobinding of itraconazole to model biomolecules	42
4.3	Conclusions	46
4.4	Experimental part	46
4.4.1	Chemicals	46
4.4.2	Photolysis of 1	46
4.4.3	Isolation and identification of photoproducts 2-4	47
4.4.4	Synthesis of the model dyad 5	47
4.4.5	Isolation and identification of photoproduct 6	47
5	Photosensitization by Imatinib	49
5.1	Introduction	49
5.2	Results and discussion	51
5.2.1	Photogenotoxicity of imatinib and its substructures	51
5.2.2	Photophysical studies	51
5.3	Conclusions	57
5.4	Experimental part	57
5.4.1	Chemicals	57
5.4.2	Agarose gels	57
6	Limitations of TEMPO/EPR method	59
6.1	Introduction	59
6.2	Results and discussion	61
6.2.1	Determination of singlet oxygen quantum yield by TRNIR or TEMPO/EPR	61
6.2.2	Effect of added TEMP on singlet oxygen detection by TRNIR	61
6.2.3	Quenching of photosensitizer excited states by TEMP	62
6.2.4	Electron transfer oxidation of TEMP to TEMPO	65
6.2.5	The case of rose Bengal, an archetypal $^1\text{O}_2$ photosensitizer	65
6.3	Conclusion	67
6.4	Experimental part	67
6.4.1	Chemicals	67
6.4.2	Steady state fluorescence quenching	67
6.4.3	Fluorescence lifetimes	68
6.4.4	Singlet oxygen time-resolved near infrared (TRNIR) emission measurements	68
6.4.5	EPR trapping measurements	68
6.4.6	Photoinduced electron transfer	69

7	General experimental procedures	71
7.1	Photoreactors	71
7.2	UV-Vis absorption spectroscopy	71
7.3	Fluorescence and phosphorescence emissions	71
7.4	Laser flash photolysis (LFP)	72
7.5	Singlet oxygen measurements	72
7.5.1	ITQ (UPV-CSIC) system, used in chapter 3	72
7.5.2	ISOF-CNR system, used in chapter 6	73
7.6	NMR and HRMS spectroscopic characterization	73
8	Summaries	75
8.1	Summary	75
8.2	Resumen	78
8.3	Resum	81
9	General conclusions	85
A	appendix chapter 4	89
A.1	Itraconazole	89
A.2	Photoproduct 2	91
A.3	Photoproduct 3	92
A.4	Photoproduct 4	93
A.5	Model dyad 5	96
A.6	Model dyad 6	97
B	appendix chapter 5	101
B.1	2-phenylaminopyrimidine (1)	101
B.2	4-(Pyridin-2-yl)-2-aminopyrimidine (2)	102
B.3	N-(3-aminophenyl)benzamide (3)	104
C	appendix chapter 6	107
D	Publications	111
	Bibliography	111
	List of Figures	123
	List of Tables	129