



Universiteit  
Leiden  
The Netherlands

## **New fluorescent platinum (II) complexes containing anthracene derivatives as a carrier ligand : synthesis, characterization and in vitro studies**

Marqués Gallego, P.

### **Citation**

Marqués Gallego, P. (2009, September 17). *New fluorescent platinum (II) complexes containing anthracene derivatives as a carrier ligand : synthesis, characterization and in vitro studies*. Retrieved from <https://hdl.handle.net/1887/13999>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/13999>

**Note:** To cite this publication please use the final published version (if applicable).

**New fluorescent platinum(II) complexes containing anthracene  
derivatives as a carrier ligand**

Synthesis, characterization and *in vitro* studies

PROEFSCHRIFT

ter verkrijging van de graad van Doctor aan de Universiteit Leiden,

op gezag van Rector Magnificus prof.mr. P.F. van der Heijden,

volgens besluit van het College voor Promoties

te verdedigen op donderdag 17 september 2009

klokke 15.00 uur

door

**Patricia Marqués Gallego**

geboren te Madrid in 1978

**Promotiecomissie**

**Promotor** Prof. Dr. J. Reedijk

**Overige leden** Prof. Dr. U. Jaehde (Universität Bonn, Germany)  
Prof. Dr. H. J. Tanke (Universiteit Leiden, Nederland)  
Dr. D. de Vos (Teva/Pharmachemie BV, Haarlem, Nederland)  
Dr. E. Bouwman (Universiteit Leiden, Nederland)  
Prof. Dr. J. Brouwer (Universiteit Leiden, Nederland)

For the publication of this thesis, financial support by Teva/Pharmachemie B.V. (Haarlem) is gratefully acknowledged.

Printed by Wöhrmann Print Service, Zutphen 2009



# Table of contents

<b>List of abbreviations</b>	<b>5</b>
<b>Chapter 1.</b> General introduction	7
<i>Part I Platinum(II) compounds containing 9-anthryl pyridyl enones as a carrier ligand</i>	
<b>Chapter 2.</b> New fluorescent platinum(II) compounds containing 9-anthryl pyridyl enone as a carrier ligand	37
<b>Chapter 3.</b> New fluorescent platinum(II) compounds containing 9-anthryl pyridyl enone as a carrier ligand. <i>In vitro</i> studies in the A2780 ovarian carcinoma cell line	63
<b>Chapter 4.</b> Relevance of a leaving group for antitumor activity of new platinum(II) compounds containing E-1-(9-anthryl)-3-(2-pyridyl)-2-propenone, A9pyp, as a carrier ligand	81
<i>Part II A new platinum(II) compound containing N,N'-bis(anthracen-9-ylmethyl)propane-1,3-diamine as a carrier ligand</i>	
<b>Chapter 5.</b> A new fluorescent platinum(II) compound containing N,N'-bis(anthracen-9-ylmethyl)propane-1,3-diamine (bapda) as a carrier ligand: Synthesis and characterization	107
<b>Chapter 6.</b> A new fluorescent platinum(II) compound containing N,N'-bis(anthracen-9-ylmethyl)propane-1,3-diamine (bapda) as a carrier ligand: <i>In vitro</i> cytotoxicity and cellular processing in the A2780 ovarian carcinoma cell line	123
<b>Chapter 7.</b> <i>In vitro</i> studies towards the understanding of the cellular processing of <i>cis</i> -[Pt(bapda)Cl <sub>2</sub> ]	145
<b>Chapter 8.</b> Summary, general conclusions and future perspectives	173
<b>Samenvatting</b>	183
<b>Curriculum Vitae</b>	189
<b>List of publications</b>	190
<b>Acknowledgements</b>	191

## List of abbreviations

A2780	human ovarian carcinoma cell line
A2780R	cisplatin-resistant human ovarian carcinoma cell line
A498	renal cancer cell line
A9opy	E-2-[1-(9-anthryl)-3-oxo-3-prop-2-enylpyridine]
A9pyp	E-1-[9-anthryl)-3-(2-pyridyl)-2-propenone]
Anal.	Elemental analysis
ATP	Adenosinetriphosphate
BAF A <sub>1</sub>	Bafilomicyn A <sub>1</sub>
BAPDA	N,N'-bis(anthracen-9-ylmethyl)propane-1,3-diamine
BER	base-excision repair
cbdca	1,1-cyclobutylidicarboxylic acid
COSY	correlation spectroscopy
DCM	Dichloromethane
DMF	N,N'-dimethylformamide
DMSO, dmsO	dimethylsulfoxide (solvent), (ligand)
DMEM	Dulbecco's modified Eagle's medium
DNA	deoxyribonucleic acid
eap	N,N'-diethyl-2,4-pentanediamine
EC <sub>50</sub>	drug concentration that produces 50% of the maximum possible response
Na <sub>2</sub> H <sub>2</sub> edta	Ethylenediamine tetraacetic acid disodium salt
ESI-MS	Electrospray mass spectroscopy
9-EtG	9-ethylguanine
EVSA-T	a breast cancer cell line
FAAS	Flameless Atomic Absorption Spectroscopy
FCS	Fetal calf serum
GSH	glutathione
GS-X pump	glutathione S-conjugate export pump
H226	a non-small lung cancer cell line
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HMG	High Mobility Group proteins
IC <sub>50</sub>	concentration of a compound that induces 50% growth inhibition in cells compared to untreated cells
ICP-OES	Inductively Coupled Plasma Optical Emission Spectrometer

IGROV	an ovarian cancer cell
IR	infrared
L-BSO	L-buthionine-S,R-sulfoximide
M19	a melanoma cell line
MCF-7	a breast cancer cell line
MeOH	Methanol
MMR	mismatch repair mechanism
MRP	multi-drug resistance protein
MT	metallothioneins
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide
m/z	mass to charge ratio
NER	nucleotide excision repair
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
PBS	phosphate buffered saline
RPMI	Roswell Park Memorial Institute medium
RF	resistance factor
RNA	ribonucleic acid
SDS	Sodium dodecyl sulfate
SRB	sulforhodamine B
THF	Tetrahydrofuran
Tris	2-amino-2-(hydroxymethyl)propane-1,3-diol
UV	Ultra-Violet
VEGF	vascular endothelial growth factor
WIDR	a colon cancer cell line