

DECLARATION

I declare that this dissertation is my own unaided work. It is being submitted for the degree of Master of Science, in the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination in any other University.

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_____ day of _____, 2008.

ABSTRACT

The application of inorganic chemistry to medicine is a rapidly developing field, and novel therapeutic and diagnostic metal complexes are now having an impact on medical practice. The family of platinum-containing medicinal agents used for the chemotherapy of malignancies ranks among the most potent types of anticancer drug in present use. While highly potent against many cancers, *cisplatin* like other anticancer drugs suffers from virtually all of the clinical limitations observed with metal-free antitumor agents in current clinical use, most notably toxic side effects and a propensity for eliciting drug resistance in the cancerous cell. In an effort to increase the effectiveness of chemotherapy, one of the techniques in, use involves the binding of, the monomeric anticancer drug systems to water-soluble, biocompatible and biodegradable polymeric carriers. The interest in, and use of, polymers as drug delivery systems has received considerable attention worldwide; and this technique was utilized in this project.

In the present project monomers bearing suitable side groups (aspartic and glycolic acid) for platinum drug anchoring in a chelating form were synthesized. These monomers were incorporated into the polymer backbone as side chain units. Functionalized polyaspartamides and polyamidoamines were water-soluble carriers used in this project, and they were obtained by condensation and Michael addition polymerization. Leaving group ligands (dicarboxylato, carboxylatohydroxylato, and dihydroxylato) were used to anchor the platinum drug to the polymer backbone. The platinum content of conjugates was in the range of 0.92 % - 18.15 %.

A certain number of the resulting conjugates were bio-evaluated *in vitro* for their antiproliferative activities against the HeLa, Colo 320 DM and MCF 7 human cancer cell lines, while the corresponding carriers were *in vitro*

tested for toxicity against resting and stimulated human lymphocyte cell lines. For 50 % cell growth inhibition, concentrations varying from 0.000044 to 9 µg/mL Pt for conjugates and 4 to >50 µg/mL for carriers were reported.

DEDICATION

This dissertation is dedicated to my parents for their constant support throughout my studies.

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TABLE OF CONTENTS

Declaration	i
Abstract	ii
Dedication	iv
Acknowledgements	v
Table of contents	vi
List of Figures	ix
List of Tables	x
List of Schemes	xii
List of Abbreviations	xiv
Chapter 1: Introduction	1
1.1 Cancer overview	1
1.2 Aims of the study	3
Chapter 2: Literature Review	5
2.1 Chemotherapeutic Treatment of Cancer	5
2.2 Polymer-Drug Conjugation Concept	8
2.2.1 Natural Polymers	9
2.2.2 Synthetic Polymers	11
2.3 The drug Model	15
2.3.1 History of Platinum in Medicine	15
2.3.2 Chemistry	17

2.3.2.1 Covalent Bond Character	17
2.3.2.2 Displacement Reactions	18
2.3.2.3 Reactions in Water and Biologic Fluids	18
2.3.2.4 Reaction with DNA	19
2.3.2.5 Toxicity of Cisplatin	20
Chapter 3: Results and discussion	22
3.1 Synthesis of Monomers	22
3.1.1 Synthesis of amine-functionalized aspartic acid derivatives	22
3.1.2 Synthesis of amine-functionalized glycolic acid derivatives	24
3.2 Synthesis of Macromolecular Carriers	27
3.2.1 Polyaspartamides	28
3.2.1.1 Poly-DL-succinimide	28
3.2.1.2 Poly- α,β -DL-aspartamides	29
3.2.2 Polyamidoamines	44
3.2.2.1 Polyaddition reaction of methylenebisacrylamide with primary amines	45
3.3 Polymer-Platinum Anchoring	53
3.3.1 Polymer-Platinum Anchoring via Dihydroxylato Ligand	56
3.3.2 Polymer-Platinum Anchoring via Dicarboxylato Ligand	61
3.3.3 Polymer-Platinum Anchoring via carboxylatohydroxylato Ligand	64
3.4 Bio-evaluation in cell culture tests: Preliminary results	67
Chapter 4: Experimental	70
4.1 General Procedures	70
4.2 Solvents and Reagents	71

4.3 Experimental procedures	71
4.3.1 Preparation of Monomers	71
4.3.2 Preparation of polymeric carriers	74
4.3.2.1 <i>Poly-DL-succinimide (PSI) 2</i>	74
4.3.2.2 <i>Synthesis of poly-α,β-DL-aspartamides</i>	74
4.3.2.3 <i>Synthesis of Polyamidoamines</i>	82
4.3.3 Preparation of polymeric platinum conjugates	87
4.3.3.1 <i>Preparation of DACH-Pt</i>	87
4.3.3.2 <i>Polyaspartamides-platinum anchoring</i>	87
4.3.3.3 <i>Polyamidoamines-platinum anchoring</i>	93
Chapter 5: Conclusion	96
References	98
Appendix	105

LIST OF FIGURES

Figure 2.1: General structure of a macromolecular carrier as proposed by Ringsdorf

Figure 2.2: Flow chart describing drug conjugate pharmacokinetics

Figure 2.3: *Cisplatin, carboplatin, nedaplatin and oxaliplatin*

Figure 2.4: *cis*- and *trans*- Platin (II) Isomers

Figure 2.5: Aquation and hydrolysis equilibria of *cisplatin*

Figure 2.6: General crosslinked forms of DNA from reaction with *cisplatin*.

Figure 3.1: Models of platinum-conjugates *via* chelation

LIST OF TABLES

Table 3.1: ^1H NMR of **M2**, **M3a**, **M3b**, **M3c**, **M4a** and **M4b**

Table 3.2: Summary of experimental data for monomer **M2**, **M3a**, **M3b**, **M3c**, **M4a** and **M4b**

Table 3.3: Summary of experimental data polyaspartamide carriers bearing a dihydroxyl-functionalized side chain as the drug-anchoring site

Table 3.4: ^1H NMR of copolyaspartamides **3a(80)**, **3b(80)**, **3c(80)**, **3d(80)**, **3a(90)**, **3b(90)** and **3d(90)**

Table 3.5: Summary of experimental data polyaspartamide carriers bearing a dicarboxylato-terminated side chain as the drug binding site

Table 3.6: ^1H NMR of copolyaspartamides **4a(80)**, **4b(80)**, **4c(80)**, and **4b(90)**

Table 3.7: Summary of experimental data polyaspartamide carriers bearing a hydroxylatocarboxylato-terminated side chain as the drug binding site

Table 3.8: ^1H NMR of copolyaspartamides **5a(80)**, **5b(80)**, **5c(80)**, and **5a(90)**

Table 3.9: Preparative data of polyamidoamines **6a(80)** – **6b(50)** and **7a(80)** – **7a(50)**

Table 3.10: ^1H NMR of polyamidoamines **6a(80)** – **6b(50)** and **7a(80)** – **7a(50)**

Table 3.11: Preparative data of polyamidoamines **8a(80)**, **8b(80)**, **8a(90)** and **8b(90)**

Table 3.12: ^1H NMR of polyamidoamines **8a(80)**, **8b(80)**, **8a(90)** and **8b(90)**

Table 3.13: Preparative and analytical data of platinum-conjugates, Pt chelated *via* dihydroxylato ligand

Table 3.14: Preparative and analytical data of platinum-conjugates, Pt chelated *via* dicarboxylato ligand

Table 3.15: Preparative and analytical data of platinum-conjugates, Pt chelated *via* carboxylatohydroxylato ligand

Table 3.16: Antiproliferative activity of platinum conjugates and toxicity of carriers

LIST OF SCHEMES

Scheme 1: Synthesis of acryloylaspartic acid derivative **M2**

Scheme 2: Synthesis of macromonomers aspartic acid derivatives

Scheme 3: Synthesis of macromonomers glycolic acid derivatives

Scheme 4: Polycondensation of DL-aspartic acid

Scheme 5: Synthesis of poly- α,β -DL-aspartamide

Scheme 6: Aminolytic ring opening reaction in polysuccinimide

Scheme 7: Synthesis of APD-derived polyaspartamide carriers

Scheme 8: Synthesis of Dicarboxylato-functionalized polyaspartamide carriers

Scheme 9: Synthesis of Carboxylatohydroxylato-functionalized polyaspartamide carriers

Scheme 10: Synthesis of polyamidoamines **6a(80)**, **6b(80)**, **6a(50)** and **6b(50)**

Scheme 11: Synthesis of polyamidoamines **7a(80)**, **7b(80)** and **7a(50)**

Scheme 12: Synthesis of polyamidoamines **8a(80)**, **8b(80)**, **8a(90)** and **8b(90)**

Scheme 13: Synthesis of DACH-Pt as platination agent

Scheme 14: Synthesis of conjugates **3a(80)-Pt** – **3d(80)-Pt**

Scheme 15: Synthesis of conjugates **3a(90)-Pt** – **3d(90)-Pt**

Scheme 16: Synthesis of conjugates **6a(80)-Pt** and **6b(80)-Pt**

Scheme 17: Synthesis of conjugates **6a(50)-Pt** and **6b(50)-Pt**

Scheme 18: Synthesis of conjugates **4a(80)-Pt**, **4b(80)-Pt** and **4c(80)-Pt**

Scheme 19: Synthesis of conjugate **4b(90)-Pt**

Scheme 20: Synthesis of conjugates **8a(80)-Pt**, **8b(80)-Pt** and **8c(80)-Pt**

Scheme 21: Synthesis of conjugates **5a(80)-Pt**, **5b(80)-Pt** and **5c(80)-Pt**

Scheme 22: Synthesis of conjugate **5a(90)-Pt**

Scheme 23: Synthesis of conjugates **7a(80)-Pt** and **7b(80)-Pt**

LIST OF ABBREVIATIONS

Acraga	2-acrylamidoglycolic acid monohydrate
AEE	2-(2-aminoethoxy)ethanol
APD	3-Amino-1,2-propanediol
Asp	Aspartic acid
d	Day(s)
Dach-Pt	<i>trans</i> -1,2-diaminocyclohexanediaqua platinum(II) dinitrate
DCC	N,N'-dicyclohexylcarbodiimide
DEEA	2-(diethylamino)ethylamine
DMEA	2-(dimethylamino)ethylamine
DMF	N,N'-dimethylformamide
DMP	3-(dimethylamino)propylamine
DMSO	Dimethylsulfoxide
DNA	deoxyribonucleic acid
EA	Ethanolamine
EDDA	2,2'-(ethylenedioxy)-diethylamine
Et ₃ N	Triethylamine
M2	Acryloylaspartic acid
M2'	2-acrylamidoglycolic acid monohydrate
M3a	N-(4,8-diaza-octanoyl)aspartic acid
M3b	N-(4,7-diaza-6(5)-methyl-heptanoyl)-aspartic acid
M3c	N-(4,13-diaza-7,10-dioxa-tridecanoyl)aspartic acid

M4a	N-(4,8-diaza-octanoyl)amidoglycolic acid
M4b	N-(4,13-diaza-7,10-dioxa-tridecanoyl)amidoglycolic acid
MEA	2-(methoxy)ethylamine
NMR	Nuclear magnetic resonance
PDA	1,3-diaminopropane
1,2-PDA	1,2-diaminopropane
ppm	Parts per million
RT	Room temperature