

MACROMOLECULAR DERIVATIVES OF METHOTREXATE AND FERROCENE AS POTENTIAL PRODRUGS IN CANCER CHEMOTHERAPY

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A dissertation submitted to the Faculty of Science, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree of Master of Science.

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DECLARATION

I declare that this dissertation is my own, unaided work. It is 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 _____, 2010

ABSTRACT

Cancerous diseases present a formidable health problem worldwide. While the chemotherapy of cancer, in conjunction with other treatment modalities, has reached a significant level of maturity, efficacious use of such agents is still restricted by numerous pharmacological deficiencies, such as poor solubility, short serum circulation lifetimes, and low bioavailability resulting from lack of affinity to cancer tissue and inadequate mechanisms of cell entry. More critically still, most drugs suffer from toxic side effects and a risk of drug resistance. In an attempt to enhance the therapeutic effectiveness of carcinostatic drugs, the concept of anchoring bioactive agents to polymeric carriers has proved to be a promising approach to overcome these deficiencies and was the main aim of this project.

Water-soluble, biodegradable macromolecular carriers used were *polyaspartamides*, prepared by an aminolytic ring-opening process of polysuccinimide; *polyamides* obtained by ester-amine base-catalyzed polyaddition; and *polyamidoamines* prepared by Michael-type addition polymerization. The drug-anchoring potential of carrier polymers was demonstrated by the coupling of methotrexate (MTX), ferrocene and platinum drug models.

MTX was linked to carrier *via* polymer attached amine by N-acylation of linear amine-functionalized polyaspartamide carriers with the acid group from methotrexate. Acylation was brought about by mediation of HBTU coupling agent. The resulting MTX content of the conjugates was in the range of 10-19% by mass.

In the present dissertation, series of water-soluble ferrocene conjugates were synthesized as for MTX by N-acylation of linear amine-functionalized polyaspartamide carriers with 4-ferrocenylbutanoic acid. Acylation was brought about again by mediation of HBTU coupling agent. The resulting iron content of the conjugates was in the range of 6-13% by mass.

Polymer-attached dihydroxylato-type ligands were used to anchor the platinum drug to the polymeric carriers. The platinum content of the conjugates was in the range of 6-8% by mass.

A member of selected conjugates was submitted to the Department of Immunology, University of Pretoria, and to the School of Pharmacy, University of California, Los Angeles, CA, for biomedical activity assessment.

In order to demonstrate the multidrug-binding capacity of the polyaspartamide-type carriers, ferrocene was co-conjugated to selected polymeric conjugates containing MTX or folic acid. The latter was used to ensure target-specific drug delivery.

DEDICATION

This dissertation is dedicated to my father for his prayers and constant support throughout my studies.

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TABLE OF CONTENTS

Declaration	ii
Abstract	iii
Dedication	v
Acknowledgements	vi
Table of contents	vii
List of Figures	x
List of Schemes	xi
List of Tables	xiii
List of Abbreviations	xv
Chapter 1: Introduction	1
1.1 What is cancer	1
1.2 Cancer problems	1
1.3 Aims of the project	3
Chapter 2: Literature review	
2.1 Causes of cancer	5
2.1.1 Carcinogens	5
2.1.2 Age	5
2.1.3 Genetic make up	6
2.1.4 The immune system	6
2.1.5 Diet	6
2.1.6 Day to day environment	7
2.1.7 Viruses	7
2.1.8 The many or other causes of cancer	7
2.2 Cancer treatments	7
2.2.1 Surgery	7
2.2.2 Radiation therapy	8

2.2.3 Targeted therapies	9
2.2.4 Immunotherapy	9
2.2.5 Chemotherapeutic treatment of cancer	10
2.2.5.1 Drug carriers	14
2.2.5.2 Polymer as drug carrier	14
2.2.5.2.1 Natural polymers as drug carriers	15
2.2.5.2.2 Synthetic polymers as drug carriers	15
2.3 The polymer-drug Anchoring strategy	15
2.4 The bioactive agents	19
2.4.1 Methotrexate	19
2.4.2 Ferrocene	22
2.4.3 Platinum compounds	24
Chapter 3: Results and discussion	
3.1 Synthesis of carrier polymers	26
3.1.1 Polyaspartamides	28
3.1.1.1 Poly-DL-succinimide	29
3.1.1.2 Poly α , β -DL-aspartamides	29
3.1.2 Other polyamides	49
3.1.3 Polyamidoamines	54
3.1.3.1 Polyaddition reaction of methylenebisacrylamide with primary monoamines and primary diamines	55
3.2 Polymer-drug conjugation	61
3.2.1 Polymer-Methotrexate conjugation	61
3.2.1.1 Polymer-Folic acid conjugation	61
3.2.1.2 Polymer-MTX conjugation	61
3.2.2 Polymer-Ferrocene conjugation	71
3.2.3 Polymer-Platinum conjugation	76
3.2.4 Polymer-multidrug conjugation	80
3.3 Biomedical testing	85

Chapter 4: Experimental	
4.1 General procedure	86
4.2 Reagents, Reactants and Solvents	86
4.3 Preparation of polymeric carriers	
4.3.1 Poly-DL-Succinimide (PSI) 2	87
4.3.2 Synthesis of poly- α,β -DL-aspartamides	87
4.3.3 Other polyamides	98
4.3.4 Polyamidoamines	99
4.4 Preparation of polymeric conjugates	103
4.4.1 Polymer-folic acid conjugates	103
4.4.2 Polymer-Methotrexate conjugates	108
4.4.3 Polymer-Ferrocene conjugates	109
4.4.3.1 Synthesis of ferrocenylbutanoic acid	109
4.4.3.2 Preparation of polymer-ferrocene conjugates	109
4.4.4 Polymer-platinum conjugates	114
4.4.4.1 Preparation of DACH-Pt	114
4.4.4.2 Polyamides-platinum anchoring	114
4.4.5 Polymer multidrug conjugates	115
Chapter 5: Summary and Conclusion	120
References	123
Appendix	128

LIST OF FIGURES

Figure2.1: General structure of a polymer carrier as proposed by Ringsdorf	17
Figure2.2: Structure of Methotrexate	21
Figure2.3: Mechanism of action of Methotrexate	22
Figure2.4: Cisplatin and other platinum analogues of clinical application	25
Figure 3.1: Structure of polyamide-type carrier	28
Figure 3.2: Structures showing resemblance of folic acid and MTX	66

LIST OF SCHEMES

Scheme 2.1: Polymer-drug conjugate as proposed by our group	18
Scheme 2.2: Reactions of ferrocene complex in biological environment	24
Scheme 1: Polycondensation of DL-aspartic acid	29
Scheme 2: Synthesis of Poly- α , β -DL-aspartamide	30
Scheme 3: Copolymer, Poly- α , β -DL-aspartamide	30
Scheme 4: Synthesis of Copolyaspartamides 4a to 4e	33
Scheme 5: Synthesis of Copolyaspartamides 5a to 5c	36
Scheme 6: Synthesis of Copolyaspartamides 6a to 6c	40
Scheme 7: Synthesis of Copolyaspartamide 7a to 7c	44
Scheme 8: Synthesis of Copolyaspartamides 8a to 8b	47
Scheme 9: Synthesis of Copolyamide 9a	51
Scheme 10: Synthesis of Copolyamide 9b	51
Scheme 11: Synthesis of Copolyamide 9c	52
Scheme 12: Synthesis of Copolyamide 9d	52
Scheme 13: Synthesis of Polyamidoamines 10-14	57
Scheme 14: Reaction for the synthesis of 4a(90)-FA, 4b(90)-FA, 5a(90)-FA, 5a(95)-FA, 4c(90)-FA and 4d(90)-FA	62
Scheme 15: Reaction for the synthesis of 6a-FA, 6b-FA, 6c-FA, 7a-FA, 7c-FA, 8a-FA and 8b-FA	63
Scheme 16: Reaction for the synthesis of 4a(90)-MTX, 4b(90)-MTX, 5a(90)-MTX, 5b(95)-MTX	67
Scheme 17: Reaction for the preparation of 4-ferrocenylbutanoic acid	72
Scheme 18: Reaction for the synthesis of 4a(90)-Fc to 4d(90)-Fc	72
Scheme 19: Reaction for the synthesis of 6a-Fc to 8b-Fc	73
Scheme 20: Reaction for the synthesis of dihydroxylato platinum conjugate 9a-Pt	77

Scheme 21: Reaction for the synthesis of dihydroxylato platinum conjugate 9b-Pt	77
Scheme 22: Preparation of platination agent DACH-Pt aq	78
Scheme 23: Preparation of polyaspartamide MTX/Fc co-conjugates	81
Scheme 24 Preparation of polyaspartamide FA/Fc co-conjugates	82

LIST OF TABLES

Table 3.1: Summary of experimental data of Polyaspartamide carriers 4a to 4e	34
Table 3.2: ¹ H NMR data for Polyaspartamide carriers 4a to 4e	35
Table 3.3 Summary of experimental data of Polyaspartamide carriers 5a to 5c	38
Table 3.4: ¹ H NMR data for Polyaspartamide carriers 5a to 5c	39
Table 3.5 Summary of experimental data of Polyaspartamide carriers 6a to 6c	42
Table 3.6: ¹ H NMR data for Polyaspartamide carriers 6a to 6c	43
Table 3.7 Summary of experimental data of Polyaspartamide carriers 7a to 7c	45
Table 3.8: ¹ H NMR data for Polyaspartamide carriers 7a to 7c	46
Table 3.9 Summary of experimental data of Polyaspartamide carriers 8a to 8b	48
Table 3.10: ¹ H NMR data for Polyaspartamide carriers 8a and 8b	49
Table 3.11: Synthesis of Polyamides 9a-9d	53
Table 3.12: ¹ H NMR data for Polyamides 9a-9d	53
Table 3.13: Preparative data of Polyamidoamines 10 to 14	58
Table 3.14: ¹ H NMR data for Polyamidoamines 1a to 10a	59
Table 3.15: Summary of experimental data for folic acid conjugates (4a(90)-FA to 8b-FA)	64
Table 3.16: ¹ H NMR data and viscometric results for folic acid conjugates (4a(90)-FA to 8b-FA)	65
Table 3.17: Summary of experimental data for MTX conjugates (4a(90)-MTX to 5b(95)-MTX)	69
Table 3.18: ¹ H NMR data and viscometric results for MTX conjugates (4a(90)-MTX to 8b-MTX)	70
Table 3.19: Summary of experimental data for the conjugates 4a(90)-Fc to 8b-Fc	74
Table 3.20: ¹ H NMR data and viscometric results for the conjugates 4a(90)-Fc to 8b-Fc	75

Table 3.21: Summary of experimental conditions and analytical data for the dihydroxylato platinum conjugates 9a-Pt and 9b-Pt	79
Table 3.22: Summary of experimental data of Polyaspartamide co-conjugates	83
Table 3.23: ¹ H NMR data and viscometric results for co-conjugates	84

LIST OF ABBREVIATIONS

AEE	2-(2-Aminoethoxy)ethanol
AEM	4-(2-aminoethyl)morpholine
APM	4-(3-aminopropyl)morpholine
aq	aqueous
d	day(s)
DACH	1,2-diaminocyclohexane
DCC	N,N'-dicyclohexylcarbodiimide
DEEA	2-(diethylamino)ethylamine
DEP	3-(diethylamino)-1-propylamine
DET	diethylenetriamine
Detart	diethyl L-tartrate
DMEA	2-(dimethylamino)ethylamine
DMF	N,N-dimethylformamide
DMP	3-(dimethylamino)-1-propylamine
DMSO	dimethyl sulphoxide
DNA	deoxyribonucleic acid
EA	ethanolamine
EDDA	2,2-(ethylenedioxy)-diethylamine
FA	folic acid
Fc	ferrocenyl
η_{inh}	inherent viscosity
HBTU	2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium fluorophosphates
MBA	methylenebisacrylamide
MTX	methotrexate
Net ₃	triethylamine
NMR	nuclear magnetic resonance
PDA	1,3-propylenediamine
ppm	parts per million
PSI	poly(D,L-succinimide)

RNA ribonucleic acid

RT room temperature

TRIA 4,7,10-trioxa-1,13-tridecanediamine

SOLUMIX: mixture of (% w/w): Toluene (42.96%), m-xylene (14.39%), p-xylene (6.72%), o-xylene (6.39%), ethylbenzene (6.08%), heptane and isomers (10.01%), n-hexane (2.26%), hexane, mixture of isomers (1.60%), pentane (0.16%), isopentane and 2-methylbutane (0.12%).