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Polymeric carriers in medicine

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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.

_____

Hembe Elie Mukaya

_____ 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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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	*trans*-1,2-diaminocyclohexanediaquaplatinum(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_3N	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