# MACROMOLECULAR PLATINUM-BASED ANTICANCER AGENTS

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*Declaration*

*I declare that this thesis is my own, unaided work. It is being submitted for the degree of Doctor of Philosophy 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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## ABSTRACT

Platinum is nowadays one of the best and widely used antitumor agents in cancer chemotherapy. The numerous performances reported by many previous researchers for this metal in the fight against several malignancies led to the synthesis of many platinum complexes. However, the clinical responses related to these complexes led to the development of non-platinum compounds with metal ions which exhibit antitumor activity. Ferrocene is one of them, owing the high consideration *inter alia* to its environmental oxidoreductive behavior. Methotrexate is another clinically used anticancer drug worthy to be mentioned. With a structure very close to that of folic acid, differing from it by an amine function and a methyl group, respectively, instead of an hydrogen and an hydroxyl group on the folate, methotrexate has been considered as an antagonist of folic acid by its mechanism of action in the biological environment. It has, together with platinum and non-platinum complexes, shown notorious side-effects by fighting both normal and abnormal cells despite their antineoplastic potency. This is the reason why a drug delivery system is considered as a tool to improve metal complexes and other drugs selectivity for cancer cells. The strategy of enhancing the potency of non-polymeric chemically, physically, or biologically active compounds through the expediency of binding such compounds to a polymeric carrier has revolutioned numerous technologies. In the present thesis is demonstrated the synthesis of several water-soluble macromolecular drug carriers intended for biomedical applications, and the anchoring of platinum to ferrocene-containing antineoplastic agents on one side, then to methotrexate-containing antineoplastic agents on the other side, resulting in a co-conjugate or a conjugate bearing two different drugs on a single carrier. This multidrug anchoring offers the advantage to exploit the potency of two different drugs on a single polymeric structure, each drug having its own pharmacokinetic path. Platinum is the common drug, while ferrocene and

methotrexate are the various co-drugs. This order of having the platinum imparted to the polymeric carrier after the two drugs above mentioned were adopted in obedience to the strategy of having the most synthetically demanding drug incorporated in the carrier before the least one. Anchoring of the three drugs to polymeric structures was achieved in aqueous environment. Methotrexate (MTX) and ferrocene (Fc) binding were achieved *via* HBTU as coupling agent. In all cases, more or less, but very close to, 100% drug loading could be achieved under careful control of experimental conditions. The water-soluble polymeric carriers used are copolyaspartamides, prepared by an aminolytic ring-opening process of polysuccinimide, and copoly(amidoamines) obtained by Michael polyaddition of methylenebisacrylamide (MBA). These polymers were designed to bear amine, hydroxyl or carboxylic acid functional groups in their structure, either as part of the main chain or side chain. The functional groups herein mentioned are important for the coupling of the chemically modified drug species. Exploratory *in-vitro* biological studies are discussed, as the co-conjugation of the metallic antineoplastic drug, ferrocene and the antifolate methotrexate, each with the metallic drug platinum, is performed. The results of these preliminary tests show that polymer-drug conjugates and co-conjugates can play a role in future cancer therapy.

# DEDICATION

I dedicate this thesis to: my wife Lubuya Françoise Mwepu; my children Kalonji Henoc Mbombo Diainabo, Mwanza Grandie Diainabo, Mwadi Joyce Diainabo and Kapiamba Elie Diainabo; my mother Mwanza Tshibaya; my brothers Kabala Placide Jadika, Kapiamba ToTo, Mpunga Pierrot, Kalonji Timothée Mbombo and Tshibangu Jules; my sister Ntumba Therese and to all my family in law.

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## LIST OF ABREVIATIONS

| | |
|---|---|
| AEE | 2- (2-aminoethoxy) ethanol |
| AEM | 3- (2- aminoethyl) morpholine |
| APD | 3- amino 1, 2 propanediol |
| APM | 4- (3- aminopropyl) morpholine |
| Aspac | Aspartic acid |
| CoPAs | Copopyaspartamide |
| DCC | Dicyclohexylcarbodiimide |
| DEEA | Diethylaminoethylamine |
| API | Aminopropyl imidazole |
| DEP | Diethylaminopropylamine |
| DET | Diethylenetriamine |
| DMEA | Dimethylaminoethylamine |
| DMF | Dimethylformamide |
| DMSO | Dimethylsulfoxyde |

| | |
|---|---|
| EA | Ethanolamine |
| EDA | Ethylenediamine |
| EDDA | 2, 2’ – (ethylenedioxy) diethylamine |
| EPR | Enhanced permeability retention |
| FA | Folic acid |
| FAO | Food and agricultural organization |
| FRC | Folate reduced carrier |
| HBTU | 2- (1H-benzotriazol- 1 – yl) – 1, 1, 3, 3 – Tetramethyluroniumhexafluorophosphate |
| HMP | Hexamethylphosphoramide |
| HSU | N- hydroxysuccinimide |
| Inh | Inherent |
| MBA | Metylenebisacrylamide |
| MDR | Multi- drug resistance |
| MTX | Methotrexate |
| NMP | N- Methylpyrrolidone |
| NMR | Nuclear magnetic resonance |
| Copaa | copoly (amidoamine) |
| PAAs | Poly(amidoamines) |
| PABA | Paraaminobenzoic acid |

| | |
|---|---|
| PAs | Polyaspartamide |
| PASA | Paraminosalicylic acid |
| PDA | 1, 3 –propylenediamine |
| PEG | Poly (ethyleneglycol) |
| PSI | Polysuccinimide |
| RNA | Ribonucleic acid |
| RT | Room temperature |
| TEA | Triethylamine |
| TRIA | 4, 7, 10 – trioxa- 1, 13 - tridecanediamine |