MACROMOLECULAR 4-AMINOQUINOLINE COMPOUNDS AS POTENTIAL ANTIMALARIAL DRUGS

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A thesis submitted to the faculty of Science, University of the Witwatersrand, in fulfilment of the requirements for the degree of Doctor of Philosophy of Science.

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DECLARATION

I declare that the work presented in this thesis was carried out by me under the supervision of Prof. E. W. Neuse. It is being submitted in fulfilment for the degree of Doctor of Philosophy of Science in the University of Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree of examination in any other University.

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Aderibigbe, Blessing

_____day of _____, 2010

DEDICATION

This thesis is dedicated to the Almighty God, who made this programme a success.

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LIST OF ABBREVIATIONS

AEE- 2(2-aminoethoxy)ethanol

AEM- 4(2-aminoethyl)morpholine

AEP- 1(2-aminoethyl)piperazine

AGM- aminoglutethimide

APD- (±)-3-amino-1,2-propanediol

DCC- Dicyclohexylcarbodiimide

DCM- Dichloromethane

DDT- Dichlorodiphenyltrichloroethane

DEEA- 2-Diethylaminoethylamine

DEP-3-Diethylamino-1-propylamine

DET- Diethylenetriamine

DME- 2-Dimethylaminoethylamine

DMF- N,N-Dimethylformamide

DMP- 3-Dimethylamino-1-propylamine

DNA- Deoxyribonucleic acid

DOX- Doxorubicin (DOX)

DOXP- 1-Deoxy-D-xylulose-5-phosphate

EA- Ethanolamine

EDA- Ethylenediamine

EDDA- 2,2^{1}-(Ethylenedioxy)diethylamine

Et_2O- Diethyl ether

EtOAc- Ethyl acetate

FabI- Enoyl-acyl-carrier protein reductase

FabH- β-ketoacyl-acyl-carrier protein synthase

G6PD- Glucose-6-phosphate dehydrogenase

HBTU- 2-(1H-benzotriazol-1-ly)-1,1,3,3-tetramethyluronium

HPMA- *N*-(2-hydroxypropyl)metacrylate polymers

MBA- Methylenebisacrylamide

MRP- Multiple resistance associated proteins

NMR- Nuclear magnetic resonance

N,*N*-Diethyldiethylenetriamine

PDA- 1,3-Diaminopropane

PSI- Polysuccinimide

RNA- Ribonucleic acid

TEA- Triethylamine

TRIS- Tris(2-aminoethyl)amine

WHO- World Health Organization

ABSTRACT

4-Aminoquinolines have a long and successful history as antimalarials as they have provided a number of useful antimalarials. *P. falciparum,* a causative organism of the most deadly form of human malaria, is generally slow to develop resistance to these drugs. 4-Aminoquinoline derivatives appear to bind to nucleoproteins and interfere with protein synthesis in susceptible organisms; the drugs intercalate readily into double-stranded DNA and inhibit both DNA and RNA polymerase. In addition, 4-aminoquinolines are found to concentrate in parasites' digestive vacuoles, thereby increasing the pH of the vacuoles, and thus interfere with the parasites' ability to metabolize. 4-Aminoquinolines on the other hand have raised considerable interest because of their anti-carcinogenic properties and their ability to inhibit tumor development and presently are being used in combination therapy with anti-cancer drugs to inhibit development of drug resistance in cancer cells caused by anti-cancer drugs. 8-Aminoquinoline mechanism is quite different from that of 4-aminoquinoline in that the 8-aminoquinolines are converted in the liver to an active quinone metabolite creating oxygen free radicals that interfere with the plasmodial electron chain transport chain during respiration.

Anti-cancer drugs are often toxic when delivered straight, but the bioreversible drug conjugation of anticancer drugs to water-soluble macromolecular carriers has proved to enhance the therapeutic effectiveness of anticancer drugs. Following facilitated pharmacokinetics pathways, the conjugates, acting as prodrugs, will release the active drug species in the transformed target cells and their designs are geared towards reducing pharmacological barriers of toxicity, drug resistance and poor bioavailability encountered with currently used anti-cancer drugs. In order to demonstrate the multidrug binding capacity of polyaspartamide, the co-conjugation of 4- and 8-aminoquinoline derivatives with anti-cancer agents was achieved, and the co-conjugates are expected to serve as resistance-reducing agents.

This present project aimed at the anchoring of 4-aminoquinoline to various amine functionalized polymeric carriers, and selected macromolecular 4-aminoquinoline compounds were screened for *in vitro* antiplasmodial activity.

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