

Development of a dynamic receptor-based
pharmacophore model of *Plasmodium falciparum*
spermidine synthase for selective inhibitor
identification

by

Pieter Buys Burger

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Department of Biochemistry

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Declaration

I, Pieter Buys Burger declare that the thesis/dissertation, which I hereby submit for the degree *Philosophiae Doctor* at the University of Pretoria, is my own work and has not previously been submitted by me for a degree at this or any other tertiary institution.

Signature:

Date:

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List of Abbreviations

2AMCHA	<i>trans</i> -2-Aminomethyl-cyclohexylamine
4AMP	<i>trans</i> -4-Amino-1-methylpiperidine
4MCHA	<i>trans</i> -4-methylcyclohexylamine
ABNR	Adopted Basis Newton-Raphson
ACD	Available Chemical Directory
ACT	Artemisinin Combination Treatment
AdoDATO	S-adenosyl-1,8-diamino-3-thiooctane
AbeAdo	5'-{[(<i>Z</i>)-4-amino-2-butenyl]methylamino}-5'-deoxyadenosine
ADMET	Absorption, Distribution, Metabolism, Excretion and Toxicity
AdoMet	S-adenosylmethionine
AdoMetDC	S-Adenosylmethionine Decarboxylase
ADT	AutoDockTools
APA	3-aminooxy-1-aminopropane
APE	5-amino-1-pentene
dcAdoMet	S-adenosyl-5'-deoxy-(5')-3-methylthiopropylamine
CHARMM	Chemistry at HARvard Molecular Mechanics
cSAT	Spermine/Spermidine Acetyltransferase
CHA	cyclohexylamine
CSD	Cambridge Structural Database
DDT	Dichloro-Diphenyl-Trichloroethane
DFMO	D,L- α -difluoromethylornithine
DHFR	Dihydrofolate Reductase
DHPS	Dihydropteroate Synthase
DPM	Dynamic Receptor-Based Pharmacophore Model

eIF5A	Eukaryotic Translation Initiation Factor 5A
EV	Exclusion Volumes
GA	Genetic Algorithm
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
HBA	Hydrogen Bond Acceptor
HBD	Hydrogen Bond Donor
HDHC	2-(3H-imidazol-4-yl)-N-methylethanamine
HIV-1	Human Immunodeficiency Virus Type 1
HTS	High-Throughput Screening
HYD	Hydrophobic
IRS	Indoor Residual Spraying
ITN	Insecticide-Treated Bed Nets
MC	Monte Carlo
MD	Molecular Dynamics
MDR	Multi-Drug Resistant
MCS	Maximal Common Substructure
MIF	Molecular Interaction Field
MMV	Medicines for Malaria Venture
MTA	5'-methylthioadenosine
NAC	N-(3-aminopropyl)-cyclohexylamine
NACD	N-(3-aminopropyl)-trans-cyclohexane-1,4-diamine
NCI	National Cancer Institute
NI	Negative Ionizable
NMR	Nuclear Magnetic Resonance
ns	Nanosecond
ODC	Ornithine Decarboxylase
PAO	Polyamine Oxidase
PBC	Periodic Boundary Conditions
PfSpdSyn	<i>Plasmodium falciparum</i> Spermidine Synthase
PhF	Pharmacophore Features

PI	Positive Ionizable
PME	Particle Mesh Ewald
ps	Picosecond
PSI	Protein Structure Initiative
QSAR	Quantitative Structure Activity Relationship
RMS	Root Mean Square
RMSD	Root Mean Square Deviation
SAR	Structure Activity Relationship
SBDD	Structure-Based Drug Design
SCG	Structure Genomics Consortium
SpdSyn	Spermidine Synthase
SpmSyn	Spermine Synthase
STD	Saturation Transfer Difference
TDR	Special Program for Research and Training in Tropical Disease
UHBD	University of Houston Brownian Dynamics
WARN	World Antimalarial Resistance Network
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research
ZINC	Zinc - Is Not Commercial