NORCANTHARIDIN ANALOGUES: PP1 AND PP2A INHIBITION AND POTENTIAL THERAPEUTIC DEVELOPMENT

by

Benjamin Sauer

BSc (Hons)

A thesis submitted in partial fulfilment
of the requirements for the degree of

Doctorate of Philosophy (Chemistry)

University of Newcastle

Submitted July 2009

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I hereby certify that the work embodied in this Thesis contains four published papers of which I am a joint author. A copy of each of the papers is attached in the Appendices.

Benjamin Sauer

ACKNOWLEDGMENTS

Firstly I would like to thank my supervisor Professor Adam McCluskey for your support, encouragement, understanding, and most importantly, your persistence. Without your faith this thesis would not have been possible.

Thanks to the Medicinal Chemistry Group at the University of Newcastle, for teaching me many valuable skills, both chemistry and life related, which helped me acquire the knowledge and maturity which will be with me for many years to come. Timothy Hill and Cecilia Walkom particularly come to mind.

Thanks to the staff at the Department of Medical Oncology of the Mater Hospital, namely Jannette Sakoff and Jayne Gilbert, for screening all of my compounds.

Thanks to my friends, who helped, or at times maybe hindered my studies, but kept me sane throughout. A warm thank you goes out to the staff at Jurox Pty Ltd, who have also largely developed my chemistry skills and introduced me to the pharmaceutical industry.

And a big thanks goes out to my family; Carol, Rudi and Rebecca for putting up with my prolonged student life. And last but definitely not least, my life partner Lyndal and son Alex, thanks for your patients, tolerance and help with my busy schedule.

TABLE OF CONTENTS

Publications arising from this works:

LIST OF FIGURES

LIST OF TABLES

LIST OF TABLES (Continued)

ABBREVIATIONS

Abbreviations	
AIDS	Acquired Immunodeficiency Syndrome
ATP	Adenosine Triphosphate
cdk	cyclin dependant kinases
DCM	Dichloromethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
EIMS	Electron Impact Mass Spectra
EPI	Endogenous Protein Inhibitor
ESIMS	Electrospray Ionisation Mass Spectra
GCMS	Gas Chromatograph Mass Spectrometer
GI_{50}	Inhibition Concentration 50; drug concentration required to inhibit cell growth by 50% relative to untreated control
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromotography
IC_{50}	Inhibition Concentration 50; drug concentration required to inhibit enzyme function by 50%
IR	Infrared
MSD	Mass Selective Detector
NMR	Nuclear Magnetic Resonance
OA	Okadaic Acid
PK	Protein Kinase
PP	Protein Phosphatase
PP1	Protein Phosphatase 1
PP2A	Protein Phosphatase 2A
PPM	Protein Phosphatase Magnesium
PPP	Phosphor-Protein Phosphatases
pRb	Retinoblastoma
PTP	Protein Tyrosine Phosphatase
SAR	Structure Activity Relationship
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TS	Total Synthesis
TSG	Tumour Suppressor Genes

ABSTRACT

This study described in this work examines the potential for derivatives of the potent PP1 (IC_{50} 9.0 µM) and PP2A (IC_{50} 3.0µM) inhibitor, norcantharidin, the demethylated cantharidin analogue, and their protein phosphatase inhibition, namely PP1 and PP2A and their cytotoxicity across a range of human cancer cell lines.

A variety of derivatives were examined, paying particular attention to modifications to the anhydride moiety. These included a series of ring opened and ring closed cantharimides, a series of α-hydroxylactams, a series of lactone analogues and derivatives, and a series of heteroatom substituted analogues.

Of the analogues developed, the ring opened and ring closed cantharimides displayed moderate to excellent activity, in cases, an improvement over the lead compound norcantharidin was observed. The ring closed dodecyl-linked bis-analogue (**63**) was the most potent analogue displaying µM potent cytoxicities against all the cell lines examined. Of the ring opened analogues, the morpholino analogues proved most active.