Synthesis of novel compounds based on reticuline scaffold for new drugs discovery

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Synthesis of Novel Compounds Based on the Reticuline Scaffold for New Drugs Discovery.

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

Doctor of Philosophy

From

University of Wollongong

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December, 2005
Declaration

I, Tam-Dan (Uta) Batenburg-Nguyen hereby declare that all materials presented in this thesis, submitted in the fulfillment of the requirements for the award of Doctor of Philosophy, in the Department of Chemistry, University of Wollongong, are exclusively of my own work. These materials have not been submitted for qualifications at any other academic institution, unless otherwise referenced or acknowledged.

Tam-Dan (Uta) Batenburg-Nguyen

December, 2005
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<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1, \alpha_2$ receptor</td>
<td>Alpha adrenoceptors</td>
</tr>
<tr>
<td>$A_1, A_{2A}, A_3$</td>
<td>Adenosine receptors</td>
</tr>
<tr>
<td>$\text{Ag}_2\text{CO}_3$</td>
<td>Silver carbonate</td>
</tr>
<tr>
<td>$\text{AgOAc}$</td>
<td>Silver acetate</td>
</tr>
<tr>
<td>$\text{AgOCOCF}_3$</td>
<td>Silver trifluoroacetate</td>
</tr>
<tr>
<td>$\text{Ag}_3\text{PO}_4$</td>
<td>Silver phosphate</td>
</tr>
<tr>
<td>APV</td>
<td>Amprenavir</td>
</tr>
<tr>
<td>ATPase</td>
<td>Adenosine 5'-Triphosphatase</td>
</tr>
<tr>
<td>AT1 receptor</td>
<td>Angiotensin receptor</td>
</tr>
<tr>
<td>AZT</td>
<td>Azidothymidine</td>
</tr>
<tr>
<td>$\beta_1$ receptor</td>
<td>Beta adrenoceptor</td>
</tr>
<tr>
<td>B2 receptor</td>
<td>Bradykinin receptor</td>
</tr>
<tr>
<td>BBI</td>
<td>Bisbenzylisoquinoline</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butoxycarbonyl group</td>
</tr>
<tr>
<td>$n$-BuLi</td>
<td>$n$-Butyl lithium</td>
</tr>
<tr>
<td>BZD receptor</td>
<td>Benzodiazepine receptor</td>
</tr>
<tr>
<td>CS</td>
<td>(S)-Canadine synthase</td>
</tr>
<tr>
<td>CC50</td>
<td>Cytotoxic concentration (the concentration that was required to reduce cell growth by 50 %)</td>
</tr>
<tr>
<td>CCK receptor</td>
<td>Cholecystokinin receptor</td>
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<td>CDCl3</td>
<td>Deuterochloroform</td>
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<td>CH$_3$CN</td>
<td>Acetonitrile</td>
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<td>CH$_3$OH</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<td>-----------</td>
</tr>
<tr>
<td>CI⁺</td>
<td>Chemical Ionisation</td>
</tr>
<tr>
<td>CM</td>
<td>Cross metathesis</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<tr>
<td>CXCR2, CCR1</td>
<td>Chemokine receptors</td>
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<tr>
<td>COR</td>
<td>Condeinone reductase</td>
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<td>CNMT</td>
<td>(S)-Coclaurine-(N)-methyltransferase</td>
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<tr>
<td>gCOSY</td>
<td>Correlated Spectroscopy</td>
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<tr>
<td>mCPBA</td>
<td>\textit{meta}-Chloroperoxybenzoic acid</td>
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<tr>
<td>CuI</td>
<td>Copper Iodide</td>
</tr>
<tr>
<td>CYP80P</td>
<td>Cytochrome (P_{450})-dependent hydroxylase</td>
</tr>
<tr>
<td>d</td>
<td>Days</td>
</tr>
<tr>
<td>D1, D2S receptors</td>
<td>Dopamine receptors</td>
</tr>
<tr>
<td>DA transporter</td>
<td>Dopamine transporter</td>
</tr>
<tr>
<td>DCC</td>
<td>Dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DDC</td>
<td>2,3'-Dideoxycytidine</td>
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<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>(N,N)-Dimethylformamide</td>
</tr>
<tr>
<td>DMG</td>
<td>(N,N)-Dimethylglycine</td>
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<tr>
<td>DOP receptor</td>
<td>Delta opiate receptor</td>
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<tr>
<td>DPPP</td>
<td>1,3-Bis(diphenylphosphino)propane</td>
</tr>
<tr>
<td>\textit{E. coli}</td>
<td>\textit{Escherichia coli}</td>
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<tr>
<td>EC(_{50})</td>
<td>Effective concentration (the concentration of an agonist that produces 50% of the maximum possible response for that agonist)</td>
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EDCI 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide

*E. faecalis* Enterococcus faecalis

EFV Efavirenz

EIr Electron impact

ESMS Electrospray mass spectrometry

ESi+ Electrospray (positive ion mode)

ETr receptor Endothelin receptor

Et3N Triethylamine

EtOAc Ethyl acetate

GFP Green fluorescent protein

GABA receptor Gamma-aminobutyric acid receptor

GAL2 receptor Galanin receptor

h Hour

H1, H2 receptors Histamine receptors

HBr Hydrogen bromide

HCl Hydrochloric acid

HIV Human Immunodeficiency Virus

HOAc Acetic acid

HOBt 1-Hydroxy-1H-benzotriazole

HRMS High resolution mass spectrometry

gHMBC Heteronuclear Multiple Quantum Correlation

gHSQC Heteronuclear Single Quantum Correlation

5HT receptors 5-Hydroxytryptamine, serotonin receptors

HIV-tat Human Immunodeficiency Virus-transactivator
IC$_{50}$  Inhibitory concentration (the concentration required to inhibit cell growth by 50 %)

K$_2$CO$_3$  Potassium carbonate

KF  Potassium fluoride

K$_2$OsO$_4$.2H$_2$O  Potassium osmate-dihydrate

KOP receptor  Kappa opiate receptor

LiAlH$_4$  Lithium aluminium hydride

μM  Micromolar

M$_2$, M$_3$ receptors  Muscarinic receptors

MDR  Multiple-Drug Resistance

min  Minutes

ML$_1$ receptor  Melatonin receptor

MOP receptor  Mu opiate receptor

MRSA  Methicillin-resistant Staphylococcus aureus

NADPH  Nicotinamide adenine dinucleotide phosphate

NaHCO$_3$  Sodium bicarbonate

NaBH$_4$  Sodium borohydride

NaCNBH$_3$  Sodium cyanoborohydride

Na$_2$EDTA  Disodium ethylenediaminetetraacetic acid

NaIO$_4$  Sodium metaperiodate

nM  Nanomolar

NaOH  Sodium hydroxide

NaOAc  Sodium acetate

NE receptor  Norepinephrine receptor

NH$_3$  Ammonia
<table>
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<th>Abbreviation</th>
<th>Definition</th>
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<td>NIS</td>
<td><em>N</em>-Iodosuccinimide</td>
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<tr>
<td>NK&lt;sub&gt;3&lt;/sub&gt; receptor</td>
<td>Neurokinin receptor</td>
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<tr>
<td>NMO</td>
<td><em>N</em>-Methylmorpholine <em>N</em>-oxide</td>
</tr>
<tr>
<td>NMP</td>
<td><em>N</em>-Methyl-2-pyrrolidinone</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>NT&lt;sub&gt;1&lt;/sub&gt; receptor</td>
<td>Neurotensin receptor</td>
</tr>
<tr>
<td>NVP</td>
<td>Nevirapine</td>
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<td>6OMT</td>
<td>(S)-Norcoclaurine-6-<em>O</em>-methyltransferase</td>
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<tr>
<td>4′OMT</td>
<td>4′-<em>O</em>-Methyltransferase</td>
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<td>ORL&lt;sub&gt;1&lt;/sub&gt; receptor</td>
<td>Opiate receptor-like receptor</td>
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<td><em>P</em>. <em>aeruginosa</em></td>
<td><em>Pseudomonas aeruginosa</em></td>
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<td>Pet. Spirit</td>
<td>Petroleum Spirit</td>
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<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Palladium acetate</td>
</tr>
<tr>
<td>Pd/C</td>
<td>Palladium on activated carbon</td>
</tr>
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<td>PdCl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Palladium chloride</td>
</tr>
<tr>
<td>PGP</td>
<td>P-Glycoprotein</td>
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<td>PPh&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Triphenylphosphine</td>
</tr>
<tr>
<td>PRD</td>
<td>Pharmaceutical Research and Development</td>
</tr>
<tr>
<td>PTLC</td>
<td>Preparative thin layer chromatography</td>
</tr>
<tr>
<td>RCM</td>
<td>Ring closing metathesis</td>
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<tr>
<td>R&lt;sub&gt;f&lt;/sub&gt;</td>
<td>Retention factor</td>
</tr>
<tr>
<td>RISC</td>
<td>RNA-induced silencing complex</td>
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<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>RNAi</td>
<td>Ribonucleic acid interference</td>
</tr>
<tr>
<td>hpRNAs</td>
<td>Hair-pin ribonucleic acid</td>
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<td>Abbreviation</td>
<td>Description</td>
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<td>-------------</td>
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<tr>
<td>siRNAs</td>
<td>Small interfering ribonucleic acid</td>
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<tr>
<td>RuCl$_3$.3H$_2$O</td>
<td>Ruthenium trichloride trihydrate</td>
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<tr>
<td>ROM</td>
<td>Ring opening metathesis</td>
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<td>RT</td>
<td>Room temperature</td>
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<td><em>S. aureus</em></td>
<td><em>Staphylococcus aureus</em></td>
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<td>SI</td>
<td>Selective Index (CC$<em>{50}$/EC$</em>{50}$)</td>
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<td>SMT</td>
<td>(S)-Scoulerine-9-O-methyltransferase</td>
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<td>SOCl$_2$</td>
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<td>SST receptor</td>
<td>Somatostatin receptor</td>
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<td>STOX</td>
<td>Tetrahydroberberine oxidase</td>
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<td>N-TFA</td>
<td>N-trifluoacetyl</td>
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<td>TFA</td>
<td>Trifluoroacetic acid</td>
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<td>THF</td>
<td>Tetrahydrofuran</td>
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<td>TLC</td>
<td>Thin layer chromatography</td>
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<td>Trimethylsilyl or tetramethylsilane (NMR)</td>
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<tr>
<td>Ts</td>
<td>$p$-Toluenesulfonyl</td>
</tr>
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<td>TsOH</td>
<td>$p$-Toluenesulfonic acid</td>
</tr>
<tr>
<td>V1a receptor</td>
<td>Vasopressin receptor</td>
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<td>VIP1 receptor</td>
<td>Human vasoactive intestinal peptide receptor</td>
</tr>
<tr>
<td>Y1, Y2 receptors</td>
<td>Hypothalamic neuropeptide receptors</td>
</tr>
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Abstract.

This thesis examines the synthesis of a library of benzyl- and bisbenzylisoquinolines (BBI) derivatives based on the reticuline motif. These compounds were assessed for their; i) cytotoxicity on 3 cancer cell lines, ii) activity on HIV-infected cells, iii) antibacterial activity, and iv) CNS receptor binding affinities.

Chapter 2 describes the employment of palladium-catalysed Stille, Heck and Sonogashira coupling reactions to synthesise a library of BBI derivatives. 2’-Vinyl- (67), 2’-allyl- (68) and 2’-iodo (58) derivatives of racemic, N-TFA protected, norlaudanosine were used as the key building blocks in this investigation. The key 2’-vinyl- and 2’-allyl-norlaudanosine derivatives 67 and 68, respectively were readily prepared from palladium-catalysed Stille coupling reactions of the 2’-iodonorlaudanosine derivative 58 and vinyl- or allyl-tributylstannane. The Heck coupling reactions between the 2’-vinyl-norlaudanosine derivative 67 and the 2’-iodonorlaudanosine derivative 58 gave not only the desired stilbene BBI derivative 65 but also the unexpected 1,1-disubstituted regioisomer 69. This unexpected regioisomer was a result of the electron rich nature of both stating materials that favoured a cationic palladium intermediate. The best Heck coupling reaction conditions involved the use of Pd(OAc)$_2$, DMG, NaOAc and NMP at 130 $^\circ$C. These conditions gave the highest yield and the best regioisomer selectively in favour of the BBI derivative 65. Fortunately these regioisomers were readily separated by triturating the product mixture with methanol. The Heck coupling reaction between the 2’-allylnorlaudanosine derivative 68 and the aryl iodide 58 successfully afforded the three carbon tethered BBI derivative 66 in moderate yield.

It was found, however, that these Heck coupling reaction conditions were only efficient with aryl iodide precursors. This was evident from the attempted
intramolecular Heck coupling reactions on the aryl bromide precursor 89, to give the macrocyclic BBI derivative 88. The optimised Heck coupling reaction conditions failed to produce the desired product, while more traditional Heck coupling conditions gave the required product in poor yield (15%).

The unsaturated BBI derivative 65 and its regioisomer 69 were subjected to hydrogenation conditions over Pd/C under a hydrogen atmosphere. However, the regioisomer 69 was found to be too sterically hindered and did not undergo the hydrogenation reaction, while derivative 65 encountered solubility problems and only rac-65 underwent the hydrogenation reaction to give rac-80, leaving the less soluble meso-65 intact. The compounds rac-80 and meso-65 were readily separated by column chromatography.

Chapter 2 also described the successful synthesis of the targeted acetylinic BBI derivative 63 via coupling of the 2’-ethynylbenzylisoquinoline derivative 84 with the aryl iodide 58, using a Pd/Cu catalysed Sonogashira coupling reaction, followed by N-TFA deprotection of the N-TFA 2’-ethynylbenzylisoquinoline derivative 83.

The synthesis of a library of 2’-arylvinyl- and 2’-arylallyl-benzylisoquinolines derivatives using the optimised Heck coupling reaction conditions developed in Chapter 2 is described in Chapter 3. This set of compounds included benzylisoquinolines having either an exocyclic N,N-dimethylamino (92-103) or N-acetamido (104-107) substituent. A third group of compounds (108-111) in this set had the exocyclic amino or amido group completely excluded. It was found that the Heck coupling reaction of the 2’-vinyllaudanosine derivative 67 and the aryl iodides 118, 119, 131 and 135 afforded only one regioisomer, unlike the Heck coupling between 67 and 58 in Chapter 2, which gave the two regioisomers 65 and 69. The Heck coupling reactions between the 2’-allyllaudanosine derivative 68 and the aryl iodides 118, 119, 131 and 135 gave two
regioisomers \textit{115a,b; 116a,b; 129a,b} and \textit{137a,b}, respectively, due to two possible sites of palladium hydride elimination.

In Chapter 4, the use of the ruthenium-catalysed CM and RCM reactions toward the successful synthesis of the four carbon tethered BBI derivatives, \textit{138-142}, in both unsaturated and saturated forms (\textit{via} hydrogenation reactions) was described. The synthesis of the analogous two and three carbon tethered BBI derivatives \textit{via} this method proved less efficient.

Chapter 5 reported the synthesis of a library of aminoalkyl benzylisoquinoline derivatives, incorporating both cyclic and acyclic amines (\textit{155-162}). These analogues were obtained by a simple reductive amination methodology involving the reaction of commercially available amines with the aldehydes \textit{186} and \textit{187}, which were generated from the 2’-vinyl- and 2’-allyllaudanosine derivatives \textit{67} and \textit{68}, respectively. The initially planned pathway to one of these aldehydes involved the rearrangement of the epoxide \textit{188}, however this epoxide was too unstable under the reaction conditions and readily underwent ring opening with \textit{m}-chlorobenzoic acid. An alternative pathway using oxidative cleavage of the diols \textit{190} and \textit{191}, which were generated from dihydroxylation of the 2’-vinyl- and 2’-allyllaudanosine derivatives, \textit{67} and \textit{68}, respectively, was found to be more successful for the synthesis of these aldehydes.

Chapter 5 also described the synthesis of an additional class of aminoalkyl benzylisoquinoline derivatives, \textit{163} and \textit{164}, containing a $\beta$-amino alcohol moiety. Retro-synthetic analysis showed two possible synthetic pathways which were either \textit{via} the ring opening of the cyclic sulfates \textit{195} and \textit{196} or \textit{via} the nucleophillic displacement of the tosylates \textit{197} and \textit{198} with an amine nucleophile. The latter pathway proved more successful and afforded the $\beta$-amino alcohol derivatives \textit{163} and \textit{164}, however, the yields of these reactions should be optimised in future studies.
The synthesis of the benzylisoquinoline derivatives containing a nine- and ten-membered heterocyclic ring, 165-167, was also described in Chapter 5. The synthesis of these analogues was initially attempted via the intramolecular reductive amination reaction between an aldehyde moiety at the C2’ position of 219 and its free isoquinoline amino group. However, the synthesis of the aldehyde moiety via the hydrolysis of its protected diacetal form was very difficult; therefore an alternative synthesis was developed. This method involved an intramolecular nucleophilic displacement of the chloride of the α-chloroacetamides 214 and 215 by the free isoquinoline amino moiety. This method successfully afforded the nine- and ten-membered ring benzylisoquinoline derivatives 165 and 167 in moderate yields (42-57 %). Lithium aluminium hydride reduction of 165 gave the corresponding cyclic diamino derivative 166 in high yield.

Some of the benzyl- and bis-benzylisoquinoline derivatives reported in Chapters 2-5 were sent for biological testing for their cytotoxicity on 3 cancer cell lines, activity on HIV-infected cells, their antibacterial activity and CNS receptor binding affinities. The BBI derivatives showed higher activity on cancer cell lines than the corresponding benzylisoquinoline derivatives. Various BBI and benzylisoquinoline derivatives have showed promising CNS-receptor binding affinities, especially for 5HT receptors and more prominently on the 5-HT_{1B}, 5-HT_{2A} and 5-HT_{7} receptors. At this stage, a clear structure-activity trend could not be discerned and the mode of action of these analogues was not clear. Further results on the awaiting analogues may help to develop pharmacophore models for CNS active compounds in the future, and eventually, allow the design and development of more selective and potent ligands.
Acknowledgement

“*The most perfect form of encouragement is the response that tells the other person that you care*”- Stephanie Dowrick.

Firstly, I would like to thank my supervisors Professor Stephen G. Pyne and Dr Alison Ung for their dedication and supervision over the past 5 years. Steve, you are an incredible person and I considered myself to be the luckiest student on earth to be under your supervision. You have an amazing knowledge of chemistry and your passion in this field is admirable. Your patience and dedication in putting in the extra effort to ensure that your students can receive the best attention and help possible, and to that, I am very grateful. Alison, I have always admired your work ethics, your discipline and great responsibility. You have taught me much more than just chemistry; I have acquired many skills needed to grow as a chemist by just observing your working attitudes and listening to your guidance. You are also a great friend and I would like to say a big “thank you” for being there for me.

“*The difficult situations give us an unparalleled chance to grow. You don’t need to seek them out; they will find you. Rise up to meet them.*”- Stephanie Dowrick.

I would like to thank the University of Wollongong for an APA scholarship, the Department of Chemistry and the academics for all their assistance, Johnson and Johnson Research Ltd for their funding and Wayne Gerlach for his help. I would like to thank all the technical staff for their marvellous support. Thanks to Sandra and especially Wilford for taking your time on the weekend to run NMR spectra for me. Thanks to Larry, Karin and Roger for running many of my mass specs, especially those bundles I handed to you toward the end.

“*Hang around people who love life. Sniff their armpits. Repeat their jokes. Live in their skin for a while.*”- Stephanie Dowrick.

I also like to thank my fellow students for making my four years such an enjoyable time. Steve Taylor, you are such a cool guy and you have also taught me a lot...
about discipline and good work ethics; and also thanks for keeping me on edge which gave me a driving force to work hard and keep up with you. Thanks to Joe Harley and Tim for all their help. Thanks to the blokes, Tien, Andrew, Karl, Theerapan, Thanapan and Chris for their friendship. Thanks to Nicole, Pitchaya, Tawesin for your friendship also. Minyan and Sarah, you guys are so nice and so pleasant to be with, thank you for taking the time to care for me and just being there.

“Listen to the teachings of your hearts. At the end of each day, find something to be thankful for. Give thanks. Sleep in peace.” - Stephanie Dowrick.

I would like to dedicate this thesis to my family, Mum and Unity. Thank you for your supports and encouragement over the past years. Thank you Mum, for those beautiful home cooked meals, and those nagging times of telling me to eat when I was too busy writing up. Thank you Mum for just being there. Thanks to Unity for just being a cool sister.

*It’s easy to be pleasant and gracious when things go our ways. The challenging of maturity is to be pleasant and gracious when things do not go our way.*” - Stephanie Dowrick.

Last but not least, thanks to my other half, Johana Muchiri Mbere, for all your support and patience during the past year. Juggling family, life, thesis, taekwondo, etc. won’t be the same without you! Thank you for being in my life and just being there.