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2005

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

Tam-Dan Batenburg-Nguyen  
*University of Wollongong*, tam@uow.edu.au

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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**



**Tam-Dan (Uta) Batenburg-Nguyen**

B. Adv. Med Chem (Hons)

Department of Chemistry

University of Wollongong

Wollongong, Australia

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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## List of Abbreviations.

|                                                   |                                                                                             |
|---------------------------------------------------|---------------------------------------------------------------------------------------------|
| $\alpha_1, \alpha_2$ receptor                     | Alpha adrenoceptors                                                                         |
| A <sub>1</sub> , A <sub>2A</sub> , A <sub>3</sub> | Adenosine receptors                                                                         |
| Ag <sub>2</sub> CO <sub>3</sub>                   | Silver carbonate                                                                            |
| AgOAc                                             | Silver acetate                                                                              |
| AgOCOCF <sub>3</sub>                              | Silver trifluoroacetate                                                                     |
| Ag <sub>3</sub> PO <sub>4</sub>                   | Silver phosphate                                                                            |
| APV                                               | Amprenavir                                                                                  |
| ATPase                                            | Adenosine 5'-Triphosphatase                                                                 |
| AT <sub>1</sub> receptor                          | Angiotensin receptor                                                                        |
| AZT                                               | Azidothymidine                                                                              |
| $\beta_1$ receptor                                | Beta adrenoceptor                                                                           |
| B <sub>2</sub> receptor                           | Bradykinin receptor                                                                         |
| BBi                                               | Bisbenzylisoquinoline                                                                       |
| Boc                                               | <i>tert</i> -Butoxycarbonyl group                                                           |
| <i>n</i> -BuLi                                    | <i>n</i> -Butyl lithium                                                                     |
| BZD receptor                                      | Benzodiazepine receptor                                                                     |
| CS                                                | ( <i>S</i> )-Canadine synthase                                                              |
| CC <sub>50</sub>                                  | Cytotoxic concentration (the concentration that was required to reduce cell growth by 50 %) |
| CCK receptor                                      | Cholecystokinin receptor                                                                    |
| CDCl <sub>3</sub>                                 | Deuteriochloroform                                                                          |
| CH <sub>3</sub> CN                                | Acetonitrile                                                                                |
| CH <sub>3</sub> OH                                | Methanol                                                                                    |

|                   |                                                                                                                                |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------|
| CI <sup>+</sup>   | Chemical Ionisation                                                                                                            |
| CM                | Cross metathesis                                                                                                               |
| CNS               | Central Nervous System                                                                                                         |
| CXCR2, CCR1       | Chemokine receptors                                                                                                            |
| COR               | Condeinone reductase                                                                                                           |
| CNMT              | ( <i>S</i> )-Coclaurine- <i>N</i> -methyltransferase                                                                           |
| gCOSY             | Correlated Spectroscopy                                                                                                        |
| <i>m</i> CPBA     | <i>meta</i> -Chloroperoxybenzoic acid                                                                                          |
| CuI               | Copper Iodide                                                                                                                  |
| CYP80P            | Cytochrome P <sub>450</sub> -dependent hydroxylase                                                                             |
| d                 | Days                                                                                                                           |
| D1, D2S receptors | Dopamine receptors                                                                                                             |
| DA transporter    | Dopamine transporter                                                                                                           |
| DCC               | Dicyclohexylcarbodiimide                                                                                                       |
| DCM               | Dichloromethane                                                                                                                |
| DDC               | 2,3'- Dideoxycytidine                                                                                                          |
| DMAP              | 4-Dimethylaminopyridine                                                                                                        |
| DMF               | <i>N,N</i> -Dimethylformamide                                                                                                  |
| DMG               | <i>N,N</i> -Dimethylglycine                                                                                                    |
| DOP receptor      | Delta opiate receptor                                                                                                          |
| DPPP              | 1,3-Bis(diphenylphosphino)propane                                                                                              |
| <i>E. coli</i>    | <i>Escherichia coli</i>                                                                                                        |
| EC <sub>50</sub>  | Effective concentration (the concentration of an agonist that produces 50 % of the maximum possible response for that agonist) |

|                           |                                               |
|---------------------------|-----------------------------------------------|
| EDCI                      | 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide |
| <i>E. faecalis</i>        | <i>Enterococcus faecalis</i>                  |
| EFV                       | Efavirenz                                     |
| EI <sup>+</sup>           | Electron impact                               |
| ESMS                      | Electrospray mass spectrometry                |
| ES <sup>+</sup>           | Electrospray (positive ion mode)              |
| ET <sub>A</sub> receptor  | Endothelin receptor                           |
| Et <sub>3</sub> N         | Triethylamine                                 |
| EtOAc                     | Ethyl acetate                                 |
| GFP                       | Green fluorescent protein                     |
| GABA receptor             | Gamma-amino butyric acid receptor             |
| GAL <sub>2</sub> 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 <sub>50</sub>                                   | Inhibitory concentration (the concentration required to inhibit cell growth by 50 %) |
| K <sub>2</sub> CO <sub>3</sub>                     | Potassium carbonate                                                                  |
| KF                                                 | Potassium fluoride                                                                   |
| K <sub>2</sub> OsO <sub>4</sub> ·2H <sub>2</sub> O | Potassium osmate-dihydrate                                                           |
| KOP receptor                                       | Kappa opiate receptor                                                                |
| LiAlH <sub>4</sub>                                 | Lithium aluminium hydride                                                            |
| μM                                                 | Micromolar                                                                           |
| M <sub>2</sub> , M <sub>3</sub> receptors          | Muscarinic receptors                                                                 |
| MDR                                                | Multiple-Drug Resistance                                                             |
| min                                                | Minutes                                                                              |
| ML <sub>1</sub> receptor                           | Melatonin receptor                                                                   |
| MOP receptor                                       | Mu opiate receptor                                                                   |
| MRSA                                               | Methicillin-resistant <i>Staphylococcus aureus</i>                                   |
| NADPH                                              | Nicotinamide adenine dinucleotide phosphate                                          |
| NaHCO <sub>3</sub>                                 | Sodium bicarbonate                                                                   |
| NaBH <sub>4</sub>                                  | Sodium borohydride                                                                   |
| NaCNBH <sub>3</sub>                                | Sodium cyanoborohydride                                                              |
| Na <sub>2</sub> EDTA                               | Disodium ethylenediaminetetraacetic acid                                             |
| NaIO <sub>4</sub>                                  | Sodium metaperiodate                                                                 |
| nM                                                 | Nanomolar                                                                            |
| NaOH                                               | Sodium hydroxide                                                                     |
| NaOAc                                              | Sodium acetate                                                                       |
| NE receptor                                        | Norepinephrine receptor                                                              |
| NH <sub>3</sub>                                    | Ammonia                                                                              |

|                          |                                                           |
|--------------------------|-----------------------------------------------------------|
| NIS                      | <i>N</i> -Iodosuccinimide                                 |
| NK <sub>3</sub> receptor | Neurokinin receptor                                       |
| NMO                      | <i>N</i> -Methylmorpholine <i>N</i> -oxide                |
| NMP                      | <i>N</i> -Methyl-2-pyrrolidinone                          |
| NMR                      | Nuclear magnetic resonance                                |
| NT1 receptor             | Neurotensin receptor                                      |
| NVP                      | Nevirapine                                                |
| 6OMT                     | ( <i>S</i> )-Norcoclaurine-6- <i>O</i> -methyltransferase |
| 4'OMT                    | 4'- <i>O</i> -Methyltransferase                           |
| ORL1 receptor            | Opiate receptor-like receptor                             |
| <i>P.aeruginosa</i>      | <i>Pseudomonas aeruginosa</i>                             |
| Pet. Spirit              | Petroleum Spirit                                          |
| Pd(OAc) <sub>2</sub>     | Palladium acetate                                         |
| Pd/C                     | Palladium on activated carbon                             |
| PdCl <sub>2</sub>        | Palladium chloride                                        |
| PGP                      | P-Glycoprotein                                            |
| PPh <sub>3</sub>         | Triphenylphosphine                                        |
| PRD                      | Pharmaceutical Research and Developement                  |
| PTLC                     | Preparative thin layer chromatography                     |
| RCM                      | Ring closing metathesis                                   |
| R <sub>f</sub>           | Retention factor                                          |
| RISC                     | RNA-induced silencing complex                             |
| RNA                      | Ribonucleic acid                                          |
| RNAi                     | Ribonucleic acid interference                             |
| hpRNAs                   | Hair-pin ribonucleic acid                                 |

|                                           |                                                        |
|-------------------------------------------|--------------------------------------------------------|
| siRNAs                                    | Small interfering ribonucleic acid                     |
| $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ | Ruthenium trichloride trihydrate                       |
| ROM                                       | Ring opening metathesis                                |
| RT                                        | Room temperature                                       |
| <i>S. aureus</i>                          | <i>Staphylococcus aureus</i>                           |
| SI                                        | Selective Index ( $\text{CC}_{50}/\text{EC}_{50}$ )    |
| SMT                                       | ( <i>S</i> )-Scoulerine-9- <i>O</i> -methyltransferase |
| $\text{SOCl}_2$                           | Thionyl chloride                                       |
| SST receptor                              | Somatostatin receptor                                  |
| STOX                                      | Tetrahydroberberine oxidase                            |
| <i>N</i> -TFA                             | <i>N</i> -trifluoroacetyl                              |
| TFA                                       | Trifluoroacetic acid                                   |
| THF                                       | Tetrahydrofuran                                        |
| TLC                                       | Thin layer chromatography                              |
| TMS                                       | Trimethylsilyl or tetramethylsilane (NMR)              |
| Ts                                        | <i>p</i> -Toluenesulfonyl                              |
| TsOH                                      | <i>p</i> -Toluenesulfonic acid                         |
| V1a receptor                              | Vasopressin receptor                                   |
| VIP1 receptor                             | Human vasoactive intestinal peptide receptor           |
| Y1, Y2 receptors                          | Hypothalamic neuropeptide receptors                    |

## 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 starting materials that favoured a cationic palladium intermediate. The best Heck coupling reaction conditions involved the use of Pd(OAc)<sub>2</sub>, DMG, NaOAc and NMP at 130 °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'-vinylaudanosine 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 **115a,b**; **116a,b**; **129a,b** and **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, **138-142**, in both unsaturated and saturated forms (*via* hydrogenation reactions) was described. The synthesis of the analogous two and three carbon tethered BBI derivatives *via* this method proved less efficient.

Chapter 5 reported the synthesis of a library of aminoalkyl benzyloquinoline derivatives, incorporating both cyclic and acyclic amines (**155-162**). These analogues were obtained by a simple reductive amination methodology involving the reaction of commercially available amines with the aldehydes **186** and **187**, which were generated from the 2'-vinyl- and 2'-allyllaudanosine derivatives **67** and **68**, respectively. The initially planned pathway to one of these aldehydes involved the rearrangement of the epoxide **188**, however this epoxide was too unstable under the reaction conditions and readily underwent ring opening with *m*-chlorobenzoic acid. An alternative pathway using oxidative cleavage of the diols **190** and **191**, which were generated from dihydroxylation of the 2'-vinyl- and 2'-allyllaudanosine derivatives, **67** and **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 benzyloquinoline derivatives, **163** and **164**, containing a  $\beta$ -amino alcohol moiety. Retro-synthetic analysis showed two possible synthetic pathways which were either *via* the ring opening of the cyclic sulfates **195** and **196** or *via* the nucleophilic displacement of the tosylates **197** and **198** with an amine nucleophile. The latter pathway proved more successful and afforded the  $\beta$ -amino alcohol derivatives **163** and **164**, however, the yields of these reactions should be optimised in future studies.

The synthesis of the benzyloisoquinoline 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  $\alpha$ -chloroacetamides **214** and **215** by the free isoquinoline amino moiety. This method successfully afforded the nine- and ten-membered ring benzyloisoquinoline 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-benzyloisoquinoline 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 benzyloisoquinoline derivatives. Various BBI and benzyloisoquinoline derivatives have showed promising CNS-receptor binding affinities, especially for 5HT receptors and more prominently on the 5-HT<sub>1B</sub>, 5-HT<sub>2A</sub> and 5-HT<sub>7</sub> 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.

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

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*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.*

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