Isotopic profiling of selected designer drugs for forensic intelligence purposes

A thesis submitted in fulfilment of the requirements for the Degree of

DOCTOR OF PHILOSOPHY

Thesis by published and unpublished work

Nicola Michelle Beckett

BSc. (Medicinal Chemistry)

M. D. (Forensics)

Institute for Glycomics, Gold Coast
School of Natural Sciences, Nathan
Griffith University

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Abstract

Driven by forensic intelligence, illicit drug chemical profiling via Gas Chromatography-Mass Spectrometry (GC-MS) remains the leading approach that forensic scientists and law enforcement agencies pursue in a bid to counteract the ever-increasing drug epidemic. An alternative approach for forensic drug investigations that delivers intelligence at a more specific level than that of chemical profiling is isotopic profiling via Isotope Ratio Mass Spectrometry (IRMS). The analysis of selected stable isotopes (\(^{18}\text{O}:{^{16}\text{O}}, ^{15}\text{N}:{^{14}\text{N}}, ^{13}\text{C}:{^{12}\text{C}}\) and \(^{2}\text{H}:{^{1}\text{H}}\), for example) that compose drug molecules has been suggested as a credible technique that can aid in forensic drug investigations. This research, consisting of four individual projects, was designed to investigate the potential of using isotopic profiling for source, synthetic procedure and batch linkage or discrimination of selected designer drugs/Novel Psychoactive Drugs (NPDs).

The overall aims of this research were to; (i) replicate the clandestine manufacture of selected synthetic designer drugs (piperazines and cathinones) to enable characterization of specific isotopic compositions indicative of the synthetic components of manufacture (precursors, intermediates and products); (ii) to investigate the use of IRMS as a potential profiling tool for the linking and/or discriminating of authentic designer drug batches; (iii) to generate isotopic profiles of selected designer drugs synthesized from differing sources of precursors, to investigate distinguishing characteristics between batches and identification of possible linkage relationships between precursors and corresponding products; (iv) to determine if isotopic profiling via IRMS is a valuable and reliable tool for the analysis of piperazine street samples (provided by Northern Territory Police) and ultimately whether it can be used to provide evidence of origin, synthetic procedure, production batch or chemical components.

The collective projects present preliminary analysis of \(\delta^{13}\text{C}\) and \(\delta^{15}\text{N}\) values in piperazine analogues; benzylpiperazine hydrochloride (BZP·HCl) and corresponding synthetic intermediate (piperazine·HCl),
trifluoromethylphenylpiperazine hydrochloride (TFMPP·HCl) and cathinone analogues; 4-methylmethcathinone hydrochloride (4MMC·HCl), methcathinone hydrochloride (MMC·HCl) and 3,4-methylenedioxy-N-methylcathinone hydrochloride (βK-MDMA·HCl). These NPDs were synthesized in-house following various clandestine methods adopted from the Internet. Different precursor sources and/or synthetic procedures were utilised and manipulated for each drug compound and comparison of the resulting isotopic profiles were evaluated.

**Individual projects**

**Project 1.** Synthetic procedure discrimination of clandestinely synthesized benzylpiperazine via $^{13}$C and $^{15}$N stable isotopes (Chapter 3).

**Project 2.** Precursor discrimination of the designer drug benzylpiperazine using $\delta^{13}$C and $\delta^{15}$N stable isotopes (Chapter 4).

**Project 3.** Isotopic profiling of seized benzylpiperazine and trifluoromethylphenylpiperazine tablets using $\delta^{13}$C and $\delta^{15}$N stable isotopes (Chapter 5).

**Project 4.** Isotopic profiling and source discrimination of popular cathinone analogues using $^{13}$C and $^{15}$N stable isotopes (Chapter 6).

Chapter 3 (Project 1) provides a preliminary investigation into the potential of using IRMS for discriminating batches of BZP·HCl manufactured from various clandestine synthetic procedures. Precursors (piperazine dihydrochloride (PD) and piperazine hexahydrate (PH)), intermediate (piperazine·HCl) and product (BZP·HCl) samples were analysed and their $^{13}$C:$^{12}$C and $^{15}$N:$^{14}$N stable isotope compositions determined. The data revealed clear discrimination between both intermediate and product batches manufactured from each of the synthetic procedures under investigation. Fractionation patterns were observed between precursor-intermediate, precursor-product and intermediate-product pairs that allowed identification of the particular method of synthesis. Project 1 served as a ‘proof of concept’ study revealing the applicability of IRMS analysis for
linkage/discrimination investigations relative to the compounds under examination in this PhD project.

Project 2, presented in Chapter 4, is the isotopic profiling of BZP·HCl products and synthetic intermediates (piperazine·HCl) synthesized in-house from three different precursor sources, following a clandestine procedure adapted from the Internet. The $\delta^{13}$C and $\delta^{15}$N data revealed that discrimination and correct grouping of all the intermediates was apparent. However, discrimination of the product samples was not clear-cut and was complicated by fractionation encountered as a result of the synthetic procedure (synthesis of the intermediate and precipitation of the product (Scheme 1.1, Chapter 1)). Project 2 highlighted that fractionation (kinetic and thermodynamic) can introduce isotopic variation in the resulting products (within source batches), which was predominantly observed for $^{15}$N. The method of precipitation (addition of hydrochloric acid (HCl) saturated ethanol (EtOH) to the reaction mixture), common in clandestine settings, proved a significant source of fractionation due to the inability to tightly control the concentration of protons available for precipitation of the BZP. In a clandestine manufacturing context, where synthetic procedures are not tightly controlled, consideration must be given when analysing samples of this nature using IRMS.

In Chapter 5 (Project 3), the applicability of IRMS analysis for providing information relating to the ‘production batch’ of seized piperazine containing tablets provided by the Northern Territory (NT) Police was examined. The tablets, containing BZP·HCl and TFMPP·HCl were seized on two separate occasions from within the NT region and upon chemical analysis (GC-MS) provided no further information relative to the two cases. The analogues were isolated from the tablets and upon $^{13}$C:$^{12}$C and $^{15}$N:$^{14}$N examination, two possible scenarios regarding potential linkage between the cases were formulated. Having conducted isotopic analysis of these seized tablets, vital ‘production batch’ information was obtained allowing possible scenarios relative to linking/discriminating the two cases, that was unattainable via conventional chemical analysis.
Chapter 6 (Project 4) investigates the isotopic discrimination of selected cathinone analogues synthesized in-house from two different precursor supplier sources. The analogues 4MMC·HCl, MMC·HCl and βk-MMC·HCl were synthesized following sub-optimal procedures adapted from the literature (which are likely conducted in a clandestine environment), thus resulting in incomplete synthesis, variable yields (20-30%) and consequentially significant $^{13}\text{C}$ and $^{15}\text{N}$ fractionation. However, discrimination of the different sources for the respective analogue pairs was achieved for all of the analogues based on the $\delta^{15}\text{N}$ isotopic data. Interestingly, the $\delta^{13}\text{C}$ data revealed significant fractionation for each analogue, but provided minimal discriminating ability overall. Similar to Project 2, Project 4 $^{15}\text{N}$ fractionation was evident as a result of the synthetic procedure, $N$-alkylation of the precursor (propiophenone derivative), and precipitation of the product. This study highlighted that although incomplete synthesis of the cathinone products and significant fractionation as a result of the synthetic procedure were apparent, IRMS analysis was still able to provide discrimination of the different source groups via $^{13}\text{C}:{^{12}\text{C}}$ and $^{15}\text{N}:{^{14}\text{N}}$ stable isotopes abundances.

The $\delta^{13}\text{C}$ and $\delta^{15}\text{N}$ data obtained from the respective IRMS studies presented in this thesis clearly show promising linkage or discriminative potential relative to the respective source, production batch or synthetic method under examination. Certain precursor-product relationships were identified, discrimination of different drug batches was apparent, fractionation patterns and occurrences were identified and potential causes of fractionation were revealed. The controlled piperazine studies (Projects 1 and 2) established the foundation, reliability and confidence in this profiling technique and resultantly, isotopic profiling was successfully conducted on unauthentic (seized) piperazine samples (Project 3).

By exploring the potential of IRMS as an investigative tool for forensic drug intelligence purposes, this PhD project provides an extension to the science behind isotopic analysis of illicit drugs and contributes novel findings relative to isotopic investigation of selected NPDs. Additionally, it highlights an alternative
or ultimately a complimentary profiling technique for forensic personnel or laboratories to consider for investigative analysis and thus aims to improve our ability to harness the rapidly growing NPD epidemic.
Keywords

Cathinones, Designer drugs, Forensic chemistry, Forensic intelligence, Illicit drugs, Isotopes, Isotopic profiling, Isotope ratio mass spectrometry, Piperazines.
Statement of Original Authorship

The work contained in this thesis has not been previously submitted to meet requirements for an award at this or any other higher education Institution. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person, except where due reference is made.

Nicola Beckett
October 2014
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### Abbreviations

<table>
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<tr>
<td>$^1$H NMR</td>
<td>$^1$H Nuclear Magnetic Resonance Spectroscopy</td>
</tr>
<tr>
<td>5HT</td>
<td>5-Hydroxytryptamine (serotonin)</td>
</tr>
<tr>
<td>$^{13}$C NMR</td>
<td>$^{13}$C Nuclear Magnetic Resonance Spectroscopy</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Alpha</td>
</tr>
<tr>
<td>AA</td>
<td>Alfa Aesar</td>
</tr>
<tr>
<td>APT</td>
<td>Attached proton test</td>
</tr>
<tr>
<td>aq</td>
<td>Aqueous</td>
</tr>
<tr>
<td>tert-BME</td>
<td>$t$-Butyl methyl ether</td>
</tr>
<tr>
<td>BZP</td>
<td>Benzylpiperazine</td>
</tr>
<tr>
<td>BZP·HCl</td>
<td>Benzylpiperazine hydrochloride</td>
</tr>
<tr>
<td>Ca$_2$SO$_4$</td>
<td>Calcium sulphate</td>
</tr>
<tr>
<td>CDCl$_3$</td>
<td>Deuterochloroform</td>
</tr>
<tr>
<td>CO$_2$</td>
<td>Carbon dioxide</td>
</tr>
<tr>
<td>$m$CPP</td>
<td>$m$-Chlorophenylpiperazine</td>
</tr>
<tr>
<td>D$_2$O</td>
<td>Deuterium oxide</td>
</tr>
<tr>
<td>DBZP</td>
<td>1,4-Dibenzylpiperazine</td>
</tr>
<tr>
<td>DBZP·HCl</td>
<td>1,4-Dibenzylpiperazine hydrochloride</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DI</td>
<td>De-ionised</td>
</tr>
<tr>
<td>EA</td>
<td>Elemental Analyser</td>
</tr>
<tr>
<td>Et$_3$N</td>
<td>Triethylamine</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>EtOH</td>
<td>Ethanol</td>
</tr>
<tr>
<td>GC</td>
<td>Gas Chromatography</td>
</tr>
<tr>
<td>GC-MS</td>
<td>Gas Chromatography-Mass Spectrometry</td>
</tr>
<tr>
<td>HCl</td>
<td>Hydrogen chloride</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Pressure Liquid Chromatography</td>
</tr>
<tr>
<td>IAEA</td>
<td>International Atomic Energy Agency</td>
</tr>
<tr>
<td>ICPAES</td>
<td>Inductively Coupled Plasma Atomic Emission Spectrometry</td>
</tr>
<tr>
<td>IRMS</td>
<td>Isotope Ratio Mass Spectrometry</td>
</tr>
<tr>
<td>k</td>
<td>Kappa</td>
</tr>
<tr>
<td>K$_2$CO$_3$</td>
<td>Potassium carbonate</td>
</tr>
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</table>
KIE  Kinetic Isotope Effect
KOH  Potassium hydroxide
LC   Liquid Chromatography
LC-MS Liquid Chromatography-Mass Spectrometry
LSD  d-Lysergic acid N,N-diethylamide
LSVEC Lithium carbonate
m/z  Mass to charge ratio
MA   Methamphetamine
MA-HCl Methamphetamine hydrochloride
M-CAT 4-Methylmethcathinone
MDMA 3,4-Methylenedioxymethamphetamine
βk-MDMA β-keto Methyleneedioxyamphetamine
MDMA-HCl 3,4-Methylenedioxymethamphetamine hydrochloride
βk-MDMA-HCl β-keto Methyleneedioxyamphetamine hydrochloride
MDMC 3,4-Methylenedioxymethy-N-cathinone
MDPV Methyleneedioxyprovalerone
MeOH Methanol
MeOPP para-Methoxyphenylpiperazine
MgSO₄ Magnesium sulphate
MMC Methcathinone
MMC·HCl Methcathinone hydrochloride
4MMC 4-Methylmethcathinone
4MMC·HCl 4-Methylmethcathinone hydrochloride
MP  MP Biomedical
MS  Mass Spectrometry
N₂  Nitrogen gas
Na₂SO₄ Sodium sulphate
NaHCO₃ Sodium hydrogen carbonate
NaOH Sodium hydroxide
NBS-19 National Bureau of Standards
NIST National Institute of Standards and Technology
NPD Novel Psychoactive Drug
P2P Phenyl-2-propanone
PD Piperazine dihydrochloride
<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>PH</td>
<td>Piperazine hexahydrate</td>
</tr>
<tr>
<td>RM</td>
<td>Reference material</td>
</tr>
<tr>
<td>SAT</td>
<td>Simulated Animal Tissue</td>
</tr>
<tr>
<td>SSA</td>
<td>Simulated Soil Aliquot</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic anhydride</td>
</tr>
<tr>
<td>TFMPP</td>
<td><em>meta</em>-Trifluoromethylphenylpiperazine</td>
</tr>
<tr>
<td>TFMPP·HCl</td>
<td><em>meta</em>-Trifluoromethylphenylpiperazine hydrochloride</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
<tr>
<td>UV</td>
<td>Ultra Violet</td>
</tr>
<tr>
<td>VPDB</td>
<td>Vienna PeeDee Belemnite</td>
</tr>
<tr>
<td>VSMOW</td>
<td>Vienna Standard Mean Ocean Water</td>
</tr>
<tr>
<td>VTF</td>
<td>Voltage-To-Frequency</td>
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“What is for you, will not pass you and what is meant to be, will be”

Nanny xx
Publications and Communications

Refereed Publications


Conference Proceedings


20
Progress of research linking the scientific papers

The four papers presented as part of this thesis describe the topic of isotopic profiling of illicit drugs for forensic purposes. Combined, these papers demonstrate the potential of an emerging profiling technique, IRMS, in the field of forensic chemistry. Collectively, these papers enhance our scientific knowledge on the application of IRMS and describe novel research on the isotopic profiling of selected designer drugs. Additionally, this research augments the current literature pertaining to the ability of IRMS to discriminate and/or group illicit drugs sampled relative to their particular source, production batch and/or method of synthesis, thus reinforcing its powerful potential as an application for forensic intelligence purposes.
All papers included in this thesis are co-authored

Acknowledgment of Papers included in this thesis

Section 9.1 of the Griffith University Code for the Responsible Conduct of Research ("Criteria for Authorship"), in accordance with Section 5 of the Australian Code for the Responsible Conduct of Research, states:

To be named as an author, a researcher must have made a substantial scholarly contribution to the creative or scholarly work that constitutes the research output, and be able to take public responsibility for at least that part of the work they contributed. Attribution of authorship depends to some extent on the discipline and publisher policies, but in all cases, authorship must be based on substantial contributions in a combination of one or more of:

- conception and design of the research project
- analysis and interpretation of research data
- drafting or making significant parts of the creative or scholarly work or critically revising it so as to contribute significantly to the final output.

Section 9.3 of the Griffith University Code ("Responsibilities of Researchers"), in accordance with Section 5 of the Australian Code, states:

Researchers are expected to:

- offer authorship to all people, including research trainees, who meet the criteria for authorship listed above, but only those people.
- accept or decline offers of authorship promptly in writing.
- Include in the list of authors only those who have accepted authorship
- appoint one author to be the executive author to record authorship and manage correspondence about the work with the publisher and other interested parties
- acknowledge all those who have contributed to the research, facilities or materials but who do not qualify as authors, such as
research assistants, technical staff, and advisors on cultural or community knowledge. Obtain written consent to name individuals.

Included in the thesis are papers in Chapters 3, 4, 5 and 6, which are co-authored with other researchers. My contribution to each co-authored paper is outlined at the front of the relevant chapter. The bibliographic details for these papers including all authors are:

**Chapter 3: Synthetic method discrimination via isotope ratio mass spectrometry; piperazine analogues**

Title: Synthetic procedure discrimination of clandestinely synthesized benzylpiperazin via $^{13}\text{C}$ and $^{15}\text{N}$ stable isotopes.
Authors: N.M. Beckett, S.L. Cresswell, J.F. Carter, I.D. Grice
Journal: Journal of Forensic Sciences
Article type: Technical note
Manuscript number: FSI-S-14-01238
Submission date: 30 October 2015

**Chapter 4: Precursor discrimination via isotope ratio mass spectrometry**

Title: Precursor discrimination of designer drug benzylpiperazin using $\delta^{13}\text{C}$ and $\delta^{15}\text{N}$ stable isotopes.
Authors: N.M. Beckett, I.D. Grice, J.F. Carter, S.L. Cresswell
Journal: Science & Justice
Article type: Research paper
Publication date: 5 October 2014
Article URL: http://dx.doi.org/10.1016/j.scijus.2014.09.001
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**Chapter 5: Analysis of case material via isotope ratio mass spectrometry**

Title: Isotopic profiling of seized benzylpiperazin and trifluoromethylphenylpiperazin tablets using $\delta^{13}\text{C}$ and $\delta^{15}\text{N}$ stable isotopes.
Chapter 6: Precursor discrimination via isotope ratio mass spectrometry; c mothline analogues

Title: Isotopic profiling and source discrimination of popular cathinone analogues using $^{13}$C and $^{15}$N stable isotopes.

Authors: N.M. Beckett, I.D. Grice, S.L. Cresswell, J.F. Carter

Journal: Journal of Forensic Sciences

Article type: Research paper

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(Signed) ____________________________ (Date) 17/06/2015
Nicola Beckett

(Countersigned) ____________________________ (Date) 17/06/2015
Supervisor: Dr. I. Darren Grice

(Countersigned) ____________________________ (Date) 17/06/2015
Supervisor: Dr. Sarah L. Cresswell

(Countersigned) ____________________________ (Date) 17/06/2015
Associate Supervisor: Dr. James F. Carter