Chemical analysis of four capsules containing the controlled substance analogues 4-methylmethcathinone, 2-fluoromethamphetamine, α-phthalimidopropiophenone and N-ethylcathinone

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ABSTRACT

In August 2007, four capsules containing white powders, said to have originated from an Israel-based Internet company “Neorganics”, were anonymously delivered to the Royal Adelaide Hospital, South Australia. The capsules were analysed and the active components were identified including 4-methylmethcathinone, 2-fluoromethamphetamine, α-phthalimidopropiophenone and N-ethylcathinone, all of which were unlisted within South Australian controlled substance regulations. We examined the relevant scientific literature surrounding these chemicals and present both GCMS and NMR data for 4-methylmethcathinone and α-phthalimidopropiophenone, which have previously received little attention. We also present the vapour- and condensed-phase infrared spectra (IR) of 4-methylmethcathinone as these have also not been reported in the literature previously. We discuss the issues surrounding whether these chemicals can be classified as controlled substance analogues and the likely impact this could have on prosecutions of individuals distributing these products.

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1. Introduction

New pharmacologically active chemicals are often created when a structural or functional group is added to or deleted from a chemical with demonstrated pharmacological activity. New or novel chemicals with central nervous system (CNS) activity are known to consumers as “research chemicals” [1] and in the popular media as “designer drugs” [2]. Continued recent reporting, within the scientific literature, of seizures and of use of these types of chemicals [1,3–13] and rising discussion on Internet drug discussion forums [14], indicates that some manufacturers and consumers continue to experiment with these so-called research chemicals.

As there are a vast number of potentially active compounds, it is generally not feasible for controlled substance legislation to list each and every chemical variant explicitly. This is particularly problematic when there is no documented evidence of pharmacological activity or previous abuse. This lack of legislative control provides entrepreneurial individuals and companies with the opportunity to attempt to exploit or circumvent legislation and create pharmacologically active chemicals that are not explicitly controlled, and in some instances, market them as ‘legal’ alternatives.

The use of research chemicals within the illicit drug market, while generally infrequent, can rise sharply, as consumers are intrigued to experiment with them. However, the persistence of research chemicals in the market is usually brief [3]. Altering controlled substance legislation to include these new chemicals, as they emerge, can be a lengthy process, and in some instances, only occurs after problematic use has subsided [3]. Further complicating attempts to legally control the proliferation of these chemicals, the virtual anonymity and global reach of the Internet allow distribution of these products to an international market, despite, in most instances, differing legislation between the countries of the source company and distribution point.

In some jurisdictions analogue legislation exists to allow these new variants to be legally categorised as controlled substance analogues. This enables law enforcement agencies to attempt to restrict their distribution when they are not explicitly listed. In
South Australia (SA), under the Controlled Substances Act 1984, a “controlled substance analogue” is defined as a chemical with a similar chemical structure or similar pharmacological effects to a listed controlled substance [15]. However, expert testimony from a forensic chemist alone in classifying a chemical as a controlled substance analogue using structural similarity can be subjectively countered depending on the degree of differentiation from the explicitly listed controlled substance.

In this manuscript, we report the results obtained from chemical analysis of four capsules, delivered to the Royal Adelaide Hospital and said to have originated from an Israel-based Internet company, “Neorganics”. Neorganics distributed their product to an international market however, no description of the exact constituents of any of these products was offered on their website. Based on comments posted on the Internet drug discussion forum “Bluelight” [14], consumers perceived these products to be both “safe” and “legal”.

Capsule 1 was pale yellow and its appearance was consistent with the product marketed by Neorganics as “Spirit”. It contained 4-methylmethcathinone (1). Capsule 2 was white and its appearance was consistent with the product marketed by Neorganics as “Sub Coca 2”. It contained α-pthalimidopropiophenone (2) and 2-fluoromethamphetamine (3). Capsule 3 was green and white and capsule 4 was blue and white and their appearances were consistent with the products marketed by Neorganics as “Neo-dove” and “Sub Coca”, respectively. Both of these capsules contained caffeine, 4-methylmethcathinone, N-ethylcathinone (4) and α-pthalimidopropiophenone.

Evidence, in the literature, of previously documented abuse for each of these chemicals (excluding caffeine) was sought and, where applicable, is presented. GCMS and NMR data for (1) and (2) were not identified in the literature and as such we have included them below to assist with identification should they be detected in other jurisdictions. In addition, we have provided vapour- and condensed-phase infrared spectra (IR) for (1) which were also not located in the literature. Finally, we examine whether these chemicals would satisfy the legal definition of an analogue in South Australia and explore potential challenges for a forensic chemist in classifying these chemicals as controlled substance analogues.

2. Materials and methods

Four capsules were anonymously delivered to the Royal Adelaide Hospital and submitted to Forensic Science SA for analysis.

2.1. Sample preparation

2.1.1. GCMS analysis

A small quantity of the powder within each capsule was extracted into a range of solvents (ethanol, 0.004N HCl solution and, after prior basification with ammonium hydroxide solution, isooctane and dichloromethane (DCM)). 1 μL of each extract was injected into the GC. 20 μL of pentfluoropropionic anhydride (PFPA) was added directly to each basic extract and allowed to react for 10 min prior to quenching the reaction by the addition of 50 μL of water. 1 μL of each extract was injected into the GC.

Electron impact mass spectra were obtained using an Agilent 6890N gas chromatograph fitted with a 5973 Selective Detector. The extracted components were separated using a HP-1 capillary column (15 m × 0.25 mm × 0.25 μm) with helium carrier gas at constant flow of 58 cm s⁻¹ and a split ratio of 50:1. The injector was heated to 300 °C and the temperature program of the oven commenced at 90 °C for 3 min, ramped at 45 °C/min until reaching a temperature of 300 °C, at which the temperature remained for 1 min. The mass spectra were collected after a 1.0 min solvent delay using a 70 eV ionisation voltage with a 40–450 C0 Cz2 Cz0 − phthalimidopropiophenone was obtained from Oakwood Products, Inc., 1741 Old Dunbar Road, West Columbia SC 29172, USA.

3.3. Synthesis of 4-methylmethcathinone

3.1. α-Bromination

To a flask containing 1.0 g of 4-methylpropiophenone (6.7 mmol) in 22 mL of glacial acetic acid was added to 1.1 g of bromine (6.8 mmol) dropwise and stirred for an hour. The reaction mixture was then poured into cold water and the 4-methyl-2-bromopropiophenone oil layer was removed. The oil layer was then washed with a sodium carbonate solution. The 4-methyl-2-bromopropiophenone crystallised out at 0 °C and was recrystallised from ether [16].

3.2. 4-Methylmethcathinone

1.0 g of the 4-methyl-2-bromopropiophenone (4.4 mmol) was dissolved in 30 mL of CH2Cl2 and added dropwise over an hour to a stirred solution of 0.3 g of methylamine hydrochloride (4.4 mmol) and 1.0 g of triethylamine (9 mmol) in 50 mL of CH2Cl2. After the addition was complete the mixture was stirred at room temperature for 4 h. 100 mL of aqueous HCl was added and the aqueous layer was removed and washed with 40 mL of CH2Cl2. The aqueous layer was made alkaline with a solution of NaOH and the amine was extracted into 2 × 50 mL of CH2Cl2. The CH2Cl2 was evaporated under vacuum and the resultant oil was dissolved in anhydrous ether. HCl gas was bubbled through the ether to produce the 4-methylmethcathinone hydrochloride. The hydrochloride salt was recrystallised from iPrOH. The yield of 4-methylmethcathinone hydrochloride was approximately 30% [17].
4. Results

4-Methylmethcathinone (1)

Fig. 1 shows the electron impact mass spectrum of 4-methylmethcathinone. The molecular ion at 177 m/z is barely visible. A characteristic of N-methyl phenethylamine mass spectra is a base peak at 58 m/z, caused by the formation of the immonium ion via the amine-initiated alpha-cleavage of the benzylic bond. The major fragmentation of methcathinones has been described previously [18] and is initiated from cleavage of the β-ketone moiety. For 4-methylmethcathinone, the 4-methylbenzoyl cation at m/z 119 is formed, which subsequently loses CO to form the methylphenyl cation with m/z 91. The loss of acetylene from the methylphenyl cation produces the m/z 65 ion.

The minor ion observed at m/z 162 is caused by amine-initiated alpha-cleavage resulting in loss of the α-methyl. Other minor ions observed at m/z 56 and m/z 42 are the results of secondary decomposition of the immonium ion, caused by the loss of H₂ and CH₄ respectively.

The mass spectral information for the pentafluoropropionic anhydride (PFPA) derivatised sample is shown in Fig. 2. The mass fragmentation pattern includes the molecular ion at m/z 323, the pentafluoropropionyl immonium ion fragment at m/z 204 and the rearrangement decomposition of the 204 ion to form the ion at m/z 160.

The 1H and 13C NMR spectra of 4-methylmethcathinone are shown in Fig. 3. The exact position of the methyl group attached to the phenyl ring was verified to be in the 4-position as a result of the 1H coupling pattern of two doublets seen at 7.86 and 7.35 ppm respectively.

\[ \text{H} \ (600 \text{ MHz, CD}_2\text{Cl}_2): \delta 7.86 \ (2H, \text{d, } J = 8.1 \text{ Hz, H}_2^0), \ 7.35 \ (2H, \text{d, } J = 8.1 \text{ Hz, H}_3^0), \ 4.81 \ (1H, \text{q, } J = 7.2 \text{ Hz, H}_2), \ 2.74 \ (3H, \text{ s, N–Me}), \ 2.44 \ (3H, \text{ s, Ar–Me}), \ 1.74 \ (3H, \text{ d, } J = 7.2 \text{ Hz, H}_3). \]

\[ \text{C} \ (150 \text{ MHz, CD}_2\text{Cl}_2/\text{CDCl}_3): 194.9 \ (\text{C}_1), \ 147.1 \ (\text{C}_4^0), \ 130.8 \ (\text{C}_1^0), \ 130.6 \ (\text{C}_3^0), \ 129.5 \ (\text{C}_2^0), \ 60.0 \ (\text{C}_2), \ 32.5 \ (\text{N–CH}_3), \ 22.4 \ (\text{Ar–Me}), \ 17.3 \ (\text{C}_3). \]

Fig. 1. Electron impact mass spectrum for 4-methylmethcathinone.

Fig. 2. Electron impact mass spectrum for PFPA derivatised 4-methylmethcathinone.
Note solvent resonances at $^1$H 5.25 ppm and $^{13}$C 53, 77 ppm respectively. The large broad resonance at 115 ppm is background and is due to the NMR probe.

It is apparent from a direct comparison between the IR data from the synthesised standard and the suspected 4-methylmethcathinone extracted from the capsules (Appendix A) that these compounds are identical. It has been demonstrated that ATR-FTIR and GC-IRD can discriminate between the structural isomers of a series of compounds related to methcathinone [13,19]. From both the vapour phase IR and ATR-FTIR definite similarities between the suspected 4-methylmethcathinone extracted from the capsules and the standard are apparent. It is therefore plausible that these two IR techniques could be used to identify the different regioisomers of 4-methylmethcathinone (Figs. 4 and 5).

**α-Phthalimidopropiophenone(2)**

![Image of α-Phthalimidopropiophenone](image)

Fig. 6 shows the electron impact mass spectrum of α-phthalimidopropiophenone (PAPP). The molecular ion at $m/z$ 279 is clearly visible. The formation of the immonium ion via the amine-initiated alpha-cleavage of the benzylic bond results in the base peak at 174. Cleavage of the β-ketone moiety produces the benzoyl cation at $m/z$ 105, which subsequently loses CO to form the phenyl cation with $m/z$ 77. The loss of acetylene from the phenyl cation is responsible for the $m/z$ 51 fragment. It is proposed that ions at $m/z$ 130 and $m/z$ 147 result from a two-step fragmentation initiated by a McLafferty rearrangement via a radical cation on the phthalidimido oxygen followed by subsequent loss of a hydroxyl radical. A scheme for this proposed fragmentation is outlined at Scheme 1.

In the case of PAPP the $^1$H and $^{13}$C NMR spectra are shown in Fig. 7. The aromatic proton resonances are overlapping to a certain degree even at 600 MHz and resulted in the need for 2D COSY and HMQC spectra to confirm the identity of PAPP. In addition two carbonyl resonances where observed in the $^{13}$C spectrum, when combined with MS results, allowed the phthalimide fragment to be identified within the molecule.

$^1$H NMR (600 MHz); δ 7.84–7.80 (4H, m, H$_2$0, H$_3$0), 7.72–7.69 (2H, m, H$_4$0), 7.49 (1H, tot, J = 7.4, 1.3 Hz, H$_4$), 7.40 (2H, tot, J = 7.4, 1.6 Hz, H$_3$), 5.66 (1H, q, J = 7.1 Hz, H$_2$), 1.73 (3H, d, J = 7.1 Hz, H$_3$).

$^{13}$C NMR (150 MHz); δ 196.12 (C1), 167.44 (C1’), 135.18 (C1’), 134.16 (C4’), 133.03 (C4’), 131.73 (C2’), 128.69 (C3’), 127.99 (C2’), 123.49 (C3’), 50.87 (C2’), 14.89 (C3’).
Many fluoroamphetamine, including 2-fluoromethamphetamine, have been characterised by both GCMS and NMR\[6,20\]. Previous reporting has demonstrated that each of the three possible fluoromethamphetamine regioisomers has different retention times \[20\] however, it has been reported that there is only a slight difference between the retention times of 3- and 4-fluoroamphetamine \[6\]. The Kovats retention index of 2-fluoromethamphetamine shows baseline separation from the other two regioisomers \[6\]. Initially, without a reference standard or NMR, this compound was suspected to be 4-fluoromethamphetamine and reported to consumers as such through the hastily prepared posting of a preliminary report on the Internet-based drug discussion forum “Bluelight” \[14\]. Subsequently, 2-fluoromethamphetamine and 4-fluoromethamphetamine standards were obtained and a retention time match and resolution from 4-fluoromethamphetamine (2.62 min) confirmed 2-fluoromethamphetamine (2.56 min) within the capsule.

**2-fluoromethamphetamine (3)**

![Image of 2-fluoromethamphetamine](image1)

Many fluoroamphetamine, including 2-fluoromethamphetamine, have been characterised by both GCMS and NMR \[6,20\].

**N-Ethylcathinone (4)**

![Image of N-Ethylcathinone](image2)

Initially, the mass spectrum of N-ethylcathinone was incorrectly assigned as N,N-dimethylcathinone and again, reported as such to consumers through the preliminary report. Subsequent
derivatisation using PFPA produced a small derivative peak that confirmed a secondary, rather than tertiary, amine. Dal Cason [11] provides both GCMS and NMR data about both ethylcathinone and dimethylcathinone.

5. Discussion

At the time the “Neorganics” products were received, 4-
methylmethcathinone, known to consumers as 4-M MCAT or 4-MMC had barely received mention on Internet discussion boards or the scientific literature. However, it was recently associated with a fatal overdose in Sweden [21].

Almost nothing has been previously reported about seizures of α-phthalimidopropiophenone, however, several similarly nitrogen protected propiophenones have been illicitly produced [5]. Fluoroamphetamines are not new to the scientific literature and several varieties have been seized in Europe [6] and Japan [22]. Recent seizures of N,N-dimethylcathinone (metamfepramone) in the US have raised awareness amongst law enforcement about the potential abuse of N-ethylcathinone [11].

Excluding caffeine, at the time these capsules were received, it is unlikely that any of the chemicals would be explicitly listed in most jurisdictional controlled substance legislation. Provided analogue legislation is available, local law enforcement agencies may request expert testimony from a forensic chemist to classify each chemical as an analogue, allowing prosecution of individuals supplying these products. It is interesting to note that, at the time these capsules were received, all of these chemicals were uncontrolled in Israel and analogue legislation does not exist [23].

In SA, each chemical could conceivably be considered as a structural analogue of a controlled substance. It may be challenging to demonstrate that α-phthalimidopropiophenone has “α
substantially similar chemical structure" to cathinone due to the structurally large phthalimide group attached at the nitrogen atom. Previous examination of the metabolism of a similarly nitrogen protected and assumed amphetamine-like propiophenone, α-pyrrolidinopropiophenone revealed that in vivo hydroxylation of the pyrrolidine ring with subsequent dehydrogenation to the corresponding lactam followed by double dealkylation of the pyrrolidine ring forms the primary amine, cathinone [24]. With this in mind, the forensic chemist may feel more comfortable when attempting to justify structural similarity of α-phthalimidopropiophenone to the controlled substance cathinone. The phthalimidide group simply acts as a stabiliser for cathinone, possibly increasing its ability to be stored stably.

6. Conclusions

We describe four research chemicals, two of which have received little previous attention in the scientific literature. We include analytical data for two of the chemicals that may assist forensic chemists in their identification. The four chemicals discussed are not listed as controlled substances locally and would require expert testimony classifying them as controlled substance analogues to attempt to restrict their distribution. We have included justification as to why these chemicals should be considered as analogues of controlled substances in SA.

Acknowledgements

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Appendix A. Summary of IR data for 4-methylmethcathinone

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Fig. 7. ¹H and ¹³C NMR spectra for α-phthalimidopropiophenone.
Appendix A (Continued)

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