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# 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.



## 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

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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-phthalimidopropiophenone (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 "Neodove" and "Sub Coca", respectively. Both of these capsules contained caffeine, 4-methylmethcathinone, *N*-ethylcathinone (4) and α-phthalimidopropiophenone.

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 pentafluoropropionic 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 Mass 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 *m/z* scan range at 3.18 scan $s^{-1}$.

#### 2.1.2. Vapour phase infrared analysis

The vapour phase infrared spectrum was collected using an Agilent 6890 gas chromatograph equipped with a Bio Rad IRD II infrared detector. The carrier gas was helium at a flow rate of 2.2 mL/min; the column was a 30 m × 0.32 mm × 0.52 μm HP-5 capillary. The injector was set at a pulsed split of 24 psi for 2 min with a temperature of 280 °C. The initial column temperature was 100 °C for 2 min and then an increase of 20 °C/min to a maximum of 270 °C. The temperature of the flow cell and the light pipes in the infrared detector were set at 275 and 270 °C, respectively. The infrared spectrum was obtained from 4000 to 550 $cm^{-1}$.

#### 2.1.3. Condensed-phase infrared analysis

The 4-methylmethcathinone was purified from the capsule by base extraction into ether. The ether solution was then passed through a solid phase silica column using a diethyl ether/diisopropyl ether/diethylamine mixture in a ratio of 45/45/10. The fractions were collected and screened via GCMS. The mixture was then evaporated under vacuum, redissolved in ether and converted into the hydrochloride salt.

The Fourier Transform Infrared Analysis was collected using a Thermo Nicolet 5700 FTIR with an Attenuated Total Reflectance (ATR) attachment. The infrared spectrum was obtained from 4000 to 399 $cm^{-1}$.

#### 2.1.4. NMR analysis

4-Methylmethcathinone was isolated from the other components in capsule 1 using a basic extraction with concentrated ammonia solution into DCM and taken to dryness. This was reconstituted in deuterated DCM for NMR analysis.

α-Phthalimidopropiophenone was isolated from the other components in capsule 3 using a basic extraction with concentrated ammonia solution into dichloromethane, acidification of the aqueous layer with 5% hydrochloric acid solution and subsequent extraction into dichloromethane. This was reconstituted in deuterated chloroform for NMR analysis.

NMR spectra were acquired on a Bruker Avance III 600 MHz spectrometer operating at 600 MHz ($^{1}H$) and 150 MHz ($^{13}C$) using standard pulse sequences. Spectra were recorded at 293 K using $CDCl_2/CDCl_3$. Chemical shifts (δ) are reported as parts per million (ppm) with respect to residual $CHCl_3$ (7.27 ppm) or residual dichloromethane $CH_2Cl_2$ (5.35 ppm). Abbreviations used in assigning spectra include: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet, m, multiplet and tot, triplet of triplets. NMR data was assigned with the aid of homonuclear ($^{1}H$–$^{1}H$) correlation spectroscopy (COSY) and heteronuclear ($^{1}H$–$^{13}C$) correlation spectroscopy (HMQC and HMBC).

### 2.2. Reagents and standards

All reagents were commercially available and were used without further purification unless otherwise indicated.

Certified reference standards for 4-methylmethcathinone, 2-fluoromethamphetamine and *N*-ethylcathinone were obtained from National Measurement Institute, 1 Suakin Street, Pymble NSW 2073, Australia.

A reference standard for α-phthalimidopropiophenone was obtained from Oakwood Products, Inc., 1741 Old Dunbar Road, West Columbia SC 29172, USA.

## 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 $CH_2Cl_2$ 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 $CH_2Cl_2$. 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 $CH_2Cl_2$. The aqueous layer was made alkaline with a solution of NaOH and the amine was extracted into 2× 50 mL of $CH_2Cl_2$. The $CH_2Cl_2$ 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].