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ABSTRACT

Drug use is prevalent in prisons with drugs associated with depressant effects found to be more prevalent than stimulants. Synthetic cathinones (SCats; often sold as "bath salts", "ecstasy", "molly", and "monkey dust") are the second largest category of new psychoactive substances (NPS) currently monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and are commonly used as substitutes for regulated stimulants, such as amphetamine, cocaine, and MDMA. *N,N*-dimethylpentylone (also known as dimethylpentylone, dipentylone, and bk-DMBDP) was detected for the first time in the Scottish prisons in seven powder samples seized between January and July 2023. Samples were analyzed using gas chromatography-mass spectrometry (GC-MS), ultra-high performance liquid chromatography-quadrupole time of flight mass spectrometry (UPLC-QToF-MS), and nuclear magnetic resonance imaging (NMR). Dimethylpentylone was detected alongside other drugs in four samples, including the novel benzodiazepine desalkylgidazepam (bromonordiazepam) and the synthetic cannabinoid receptor agonists (SCRAs) MDMB-INACA and MDMB-4en-PINACA.

1. Introduction

Drug use is prevalent within prisons and is commonly associated with increased violence, as well as adverse post-imprisonment outcomes, such as lower rates of employment [1–3]. Drugs with depressant effects, such as heroin, sedatives, and cannabis, are more prevalent in prisons because they help prisoners cope with the stressful prison environment by reducing insomnia and helping time pass more quickly. In contrast, stimulants are more prevalent in the general population because they have functions advantageous to socializing, such as keeping people awake (inducing insomnia) [3–10].

Synthetic cathinones (SCats) are synthetic stimulants derived from the β-ketoamphetamine cathinone, an alkaloid naturally occurring in khat. They are generally used as substitutes for regulated stimulants, such as amphetamine, cocaine, and 3,4-methylenedioxymethamphetamine (MDMA) [11] and have been sold under a variety of names associated with stimulants, including "bath salts", "ecstasy", "molly", and "monkey dust" [1]. The SCats are usually snorted or swallowed in powder or crystal form, but can also be smoked, injected, or consumed by other means [12,13].

SCats represent the second largest category of new psychoactive substances (NPS) currently monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Despite similar chemical structures, SCat derivatives can differ considerably in potency and selectivity for target proteins as well as their mechanisms of action [14]. Unfortunately, comprehensive information on the pharmacological properties and toxicology is not available for most SCats, but incidents of poisoning with and without fatalities underline the severe health risks that can occur following SCat consumption [14–20]. Toxicity is usually associated with a sympathomimetic toxidrome, which may manifest in an increase in body temperature, blood pressure, and heart rate; agitation; seizures; and hallucinations [21]. These effects are primarily mediated by inhibiting dopamine, noradrenaline and serotonin reuptake transporters, or inducing neurotransmitter release, leading to increased postsynaptic transmitter concentrations [15,22,23].

Although numbers of new SCats that emerged in Europe showed a declining trend in recent years, some large seizures of 3-

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chloromethcathinone (3-CMC) and 3-methylmethcathinone (3-MMC), for example, suggest that some compounds might play an eminent role on the market [11]. Since the international control of eutylone in 2021, *N,N*-dimethylpentylone (1-(1,3-benzodioxol-5-yl)-2-(dimethylamino) pentan-1-one; also known as dimethylpentylone, dipentylone, and bk-DMBDP) has been increasingly detected worldwide [15]. The chemical structure of dimethylpentylone is provided in Fig. 1. Dimethylpentylone detections have been reported in the United States in post-mortem toxicology samples [24,25] and a syringe exchange [26], in Spain in wastewater [27,28], in Hong Kong in toxicology samples [29], in Australia in toxicology samples from patients presenting to emergency deparments [30], and in New Zealand in post-mortem toxicology samples [31].

This study reports the first detections of the SCat dimethylpentylone in samples seized from the Scottish prisons. Samples were analytically characterized using gas chromatography-mass spectrometry (GC-MS), ultra-high performance liquid chromatography-quadrupole time of flight mass spectrometry (UPLC-QToF-MS), and nuclear magnetic resonance (NMR) spectroscopy. To the best of the authors' knowledge, this is the first report in the scientific literature of detections of dimethylpentylone in the UK.

2. Materials and methods

2.1. Materials

LC-MS grade methanol, water, acetonitrile, and deuterated chloroform were purchased from Fisher Scientific, UK; bupivacaine and formic acid were obtained from Sigma-Aldrich (Poole, UK).

2.1.1. Reference standards

Neat reference standards of dimethylpentylone (98.2 % purity) and desalkylgidazepam (bromonordiazepam; 98.8 % purity) were purchased from Chiron AS (Trondheim, Norway). A neat reference standard of MDMB-INACA ($\geq$ 98 % purity) was obtained from Cayman Chemical (Ann Arbor, MI, USA). MDMB-4en-PINACA (98.6 % purity) was synthesized and supplied by the Sutcliffe Group at Manchester Metropolitan University, Manchester, UK as described previously [32].

2.1.2. Seized samples

Samples included in this study were non-attributable samples seized by the Scottish Prison Service (SPS). Samples were individually sealed in labelled tamperproof evidence bags and, once deemed suitable for analysis, anonymized by SPS staff and delivered by Police Scotland to the Home Office licensed drug testing laboratory at LRCFS at the University of Dundee. Samples were analyzed upon delivery and within two months of the seizure date.

2.2. Methods

2.2.1. Gas chromatography-mass spectrometry (GC-MS)

All samples were powders. Approximately 10 mg of the powders were extracted in 1 mL of 0.25 mg/mL bupivacaine (internal standard) in methanol and sonicated (5 min) and the supernatants were qualitatively analyzed by GC-MS.

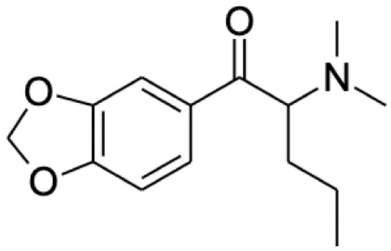

Fig. 1. Chemical structure of dimethylpentylone.

GC-MS analysis of sample extracts was performed using a 7820 A gas chromatograph coupled to a 5977E mass spectrometer (Agilent technologies, Santa Clara, CA, USA). Injection mode: 1 µL sample injection was used with a 20:1 split into a 4 mm internal diameter deactivated glass liner pre-packed with quartz wool, injection port temperature: 200°C, carrier gas: He, flow: 1 mL/min. Column: HP-5MS, 0.33 µm, 0.2 mm × 25 m (Agilent Technologies). GC oven: 80°C held for 3 min; 40°C/min to 300°C held for 6 min; total run time: 14.5 min; transfer line: 295°C. The mass spectrometer operated in electron ionization (EI) mode. Ionization conditions: 70 eV in full scan mode (50–550 amu), ion source: 230°C, quadrupole: 150°C.

The criteria for compound identification has been described previously for SCRAs and novel benzodiazepines [33–35]. Compound identification required comparison of the compound retention times and mass spectra in seized samples to that of a reference standard of known origin analyzed within 24 h of the seized samples under the same instrumental conditions. For positive identification, the GC-MS retention times from seized sample extracts had to be within 0.05 minutes of the retention time of the reference standard. In addition, a reverse match (Rmatch) factor from the SWGDRUG mass spectral library (version 3.12, released 16 January 2023), which measures the difference between the mass spectrum of the sample chromatographic peak to spectra held in the spectra library, was required to be greater than 850/1000 for positive identification.

For samples with a mixture of compounds, the percentage total peak area of each compound was determined by comparing the peak areas of each compound to the total peak area of all active components in the sample. The percentage peak area was then corrected to account for the difference in EI-MS detector response between each compound by analyzing a mixture of the reference materials of each drug at the same concentration (200 µg/mL) in MeOH on the GC-MS and calculating correction factors based on comparison of the peak areas of the reference materials. The correction factors applied for each compound can be found in the Supplementary Information (Table S1.1).

Since a reference standard was not originally available, the first two detections of dimethylpentylone were orthogonally confirmed by analysis with UPLC-QToF-MS and NMR with details described below. The remaining detections were confirmed by comparison with a certified reference standard as discussed above.

2.2.2. UPLC-QToF-MS

Confirmatory analysis was performed with dilutions of the sample extracts (1:100 v:v) and analyzed using UPLC-QToF-MS. The UPLC-QToF-MS analysis was performed using an Acquity UPLC instrument with a binary pump, autosampler held at 4°C, vacuum degasser, and a column oven held at 30°C coupled to a Xevo QToF-MS (Waters Corporation, Milford, MA, USA). The mobile phases used were (A) LC-MS grade water with 0.1 % formic acid and (B) acetonitrile with 0.1 % formic acid. The gradient used was 50:50 A:B from 0.0 to 4.0 min, 25:75 A:B from 4.0 to 5.0 min, 5:95 A:B from 5.0 to 5.99 min, and 50:50 A:B from 6.0 to 7.0 min. The flow rate was 0.5 mL/min and 2 µL of sample was injected onto a BEH C_{18} 50 × 2.1 mm, 1.7 mm particle size column (Waters Corporation). The QToF was operated in positive ionization mode with a source temperature of 120°C, a desolvation temperature at 500°C, and a capillary voltage at 2.25 kV. ToF-MS analysis for the high-resolution determination of molecular mass was carried out with a collision energy at 6 V. MS^e acquisition was carried out using collision energies ranging from 0 to 40 V. After the QToF-MS and MS^e data were processed, accurate parent ion fragmentation spectra were obtained using MS/MS data acquisition of selected parent ion accurate mass data using collision energies between 10 and 30 V.

2.2.3. NMR

The first two detections of dimethylpentylone were also confirmed by NMR analysis performed using a Bruker AVANCE III HD 500 MHz

spectrometer (Bruker, Billerica, MA, USA) running under TopSpin v.3.2.5 and equipped with a QCI-F cryo-probe (^{1}H, ^{13}C, and ^{15}N) at a sample compartment temperature of 20ºC. Samples were extracted in deuterated chloroform using ultrasonication (5 min), filtered, and transferred into a 5 mm NMR tube. Two seized powders (samples 1 and 2) and the dimethylpentylone reference standard were characterized by one-dimensional ^{1}H and ^{13}C, as well as two-dimensional ^{1}H/^{1}H COSY, ^{1}H/^{13}C HSQC, ^{1}H/^{13}C HMBC, and ^{1}H/^{15}N HMBC experiments.

3. Results and discussion

On the GC-MS, dimethylpentylone eluted at 5.228 mins and had a mass of *m/z* 249. There was one major mass fragment of *m/z* 100, which constitutes the (dimethylamino)-butene, the structure of which can be found in the Supplementary Information (Figure S3.2). On the UPLC-QToF-MS, dimethylpentylone eluted at 2.55 mins and had an exact mass of *m/z* 250.1438 $[M + H]^{+}$. There were four major mass fragments in the MS/MS spectrum, including *m/z* 100.1139, constituting the (dimethylamino)-butene; *m/z* 135.0457, constituting the 1,3-benzodioxolylmethyl; *m/z* 149.0252, constituting the 1,3-benzodioxolylmethylcarbonyl; and *m/z* 175.0775, constituting the 1,2-benzenediol-5-penta-1,5-diene. The structures of all the mass fragments can be found in the Supplementary Information (Figure S3.3). These mass fragments are similar to those reported previously in Tang et al.; however, they also reported two additional mass fragments at *m/z* 58.0655 and 205.0863 that were not found in this study [36].

The NMR data showed consistency between the dimethylpentylone reference standard and the two seized samples (Samples 1 and 2) indicating the protonated salt form of dimethylpentylone was present in both samples. Unknown contaminations, which were not characterized by NMR spectroscopy, were present in both samples along with the organic solvent acetone. Chemical shifts of dimethylpentylone and 1D and 2D NMR spectra of the dimethylpentylone reference standard can be found in the Supplementary Information (Figures S5.1-13). For comparison, stacked ^{1}H and ^{13}C spectra of the dimethylpentylone reference standard and samples 1 and 2 seized from the prisons are shown in the Supplementary Information (Figures S6.1-2). 2D NMR spectra for two samples from prisons were acquired but are not shown here.

Out of 274 seizures received for analysis that were seized between 30th January and 14th July 2023 from 13 of the 17 Scottish prisons, dimethylpentylone was detected in seven samples from three seizures from three different prisons. The details of the samples are shown in Table 1 and the complete analytical details can be found in the Supplementary Information. The prison establishments where these samples were seized are presented as an ID number to protect confidentiality. Five of the samples (3A–3E) were detected in the same seizure, where each sample was analyzed individually due to being in different paper or plastic wraps, examples of which can be seen in Fig. 2b-c. All samples were detected as powders, five were white and two were yellow.

Table 1
Samples seized from the Scottish prisons found to contain dimethylpentylone. The prison establishments are presented as an ID number to protect confidentiality. The percentage peak area was corrected for the difference in EI-MS detector response between each compound as described above in Section 2.2.1.

Sample ID	Prison ID	Date seized	Powder Color	Analysis Result	% Peak Area
1	3	30/01/2023	White	Dimethylpentylone Desalkylgidazepam	99.33 % 0.67 %
2	1	25/05/2023	White	Dimethylpentylone	-
3 A	6	14/07/2023	Yellow	Dimethylpentylone MDMB-INACA MDMB-4en-PINACA	13.66 % 72.35 % 13.99 %
3B			White	Dimethylpentylone MDMB-INACA	57.07 % 42.93 %
3 C			White	Dimethylpentylone	-
3D			Yellow	Dimethylpentylone MDMB-INACA MDMB-4en-PINACA	9.27 % 80.56 % 10.18 %
3E			White	Dimethylpentylone	-

Although there was one media report from 31st August 2022 of a detection of dimethylpentylone at the Creamfields North festival in Cheshire, England [37], to the best of the authors' knowledge, this is the first confirmed detection and report in the scientific literature of dimethylpentylone in the UK. There is limited information on the pharmacology and effects of dimethylpentylone but it has been described by people who use drugs as a low-potency stimulant [15]. In a study examining the behavioral effects of dimethylpentylone and three other novel SCats in rats, Gatch et al. found dimethylpentylone produced similar discriminative stimulus effects as methamphetamine and cocaine and therefore has abuse potential. However, its potency was low, requiring three to six times greater doses to elicit the same response as the other SCats tested [38]. Despite its reported low potency, the detection of dimethylpentylone in patients presenting to emergency departments with illicit drug-related toxicity [30] and post-mortem toxicology samples [24,25,31] demonstrates the severe health risks of dimethylpentylone consumption.

In four of the seven samples, dimethylpentylone was detected alongside other drugs: one had the novel benzodiazepine-type drug desalkylgidazepam (bromonordiazepam) and three contained SCRAs. Desalkylgidazepam was a minor component of the sample, accounting for less than 1 % of the active drug components in the sample based on the corrected percentage peak areas. Given the relatively small amount of desalkylgidazepam present in the sample and that novel benzodiazepine-type drugs are one of the most prevalent drug types detected in the Scottish prisons [35], this mixture may be due to cross contamination from prisoner handling; however, it is not possible to eliminate purposeful addition as a possible reason for its presence. Benzodiazepines have been found to be one of the most common drugs used with SCats, reportedly to counteract the adverse effects of SCats, such as anxiety and the excitatory effects [20,39–43]. Most reports of benzodiazepines found alongside SCats were from toxicological analysis [20,40,44–47], where the presence of the benzodiazepines may be due to their prescribed medical use as a common treatment for the symptoms of drug intoxication. Most studies reported the presence of prescription benzodiazepines, like diazepam [40,44–47], rather than novel benzodiazepine-type drugs that could only be present as a result of illicit use. In comparison, there have been very few reports of the mixture found in drug seizures [39], as was found in this study. To the best of the authors' knowledge, there have been no studies to date examining the effects of the combined illicit use of SCats and novel benzodiazepine-type drugs.

For the samples containing SCRAs, MDMB-INACA was present in all samples, comprising 42.93–80.56 % of the samples, and MDMB-4en-PINACA was also found in two samples, comprising 10.18 and 13.99 % of the samples. Dimethylpentylone comprised between 9.27 % and 57.07 % of the samples with SCRAs. Although these mixtures may also be due to cross-contamination, the relative amounts of the compounds present in these samples indicate more purposeful mixing. SCats have previously been detected alongside SCRAs in samples from the Scottish prisons, where the SCat 4 F-PHP (1-(4-fluorophenyl)-2-(pyrrolidin-1-yl)hexanone) was detected with the SCRA AMB-FUBINACA in infused papers from 2019 [33]; however, there have been very few other reports of SCat/SCRA mixtures in the literature. Between March 2017 and November 2018, the synthetic cathinone *N*-ethylpentylone was found in combination with SCRAs in the post-mortem urine of four prisoners from Florida [48]. In New Zealand in 2017, the SCat para-fluorophenylpiperazine (pFPP) was also found in 55 of 157 (35 %) samples of herbal material found to contain the SCRA AMB-FUBINACA [49]. Finally, there was a case report from 2016 of an attempted suicide with a mix of SCRAs (AB-CHMINACA and AB-FUBINACA) and SCats

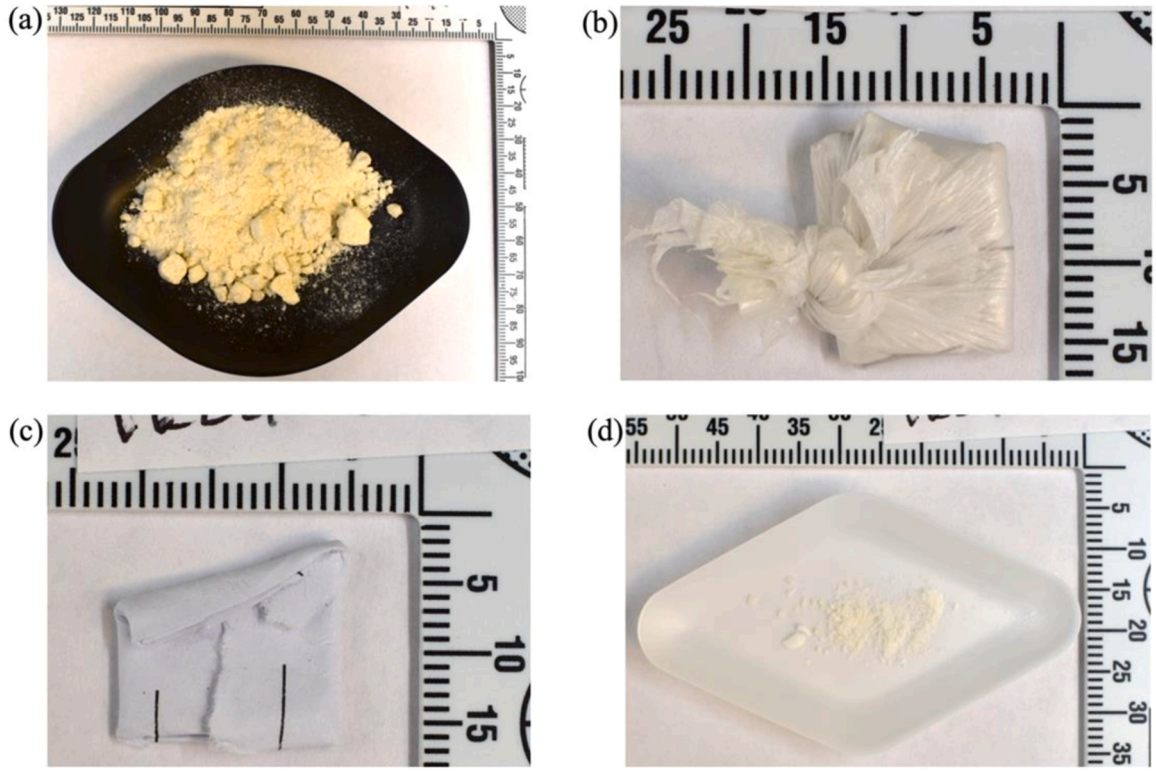

Fig. 2. Examples of samples seized from the Scottish prisons found to contain dimethylpentylone: (a) sample 1: 12.63 g of white powder seized on 30th January 2023 found positive for dimethylpentylone and desalkylgidazepam; (b) sample 3 A: knotted plastic bag containing a paper wrap with 14.7 mg yellow powder seized on 14th July 2023 and found positive for dimethylpentylone, MDMB-INACA, and MDMB-4en-PINACA; (c) sample 3 C: paper wrap containing 28.6 mg white powder (shown in d) seized 14th July 2023 and found positive for dimethylpentylone.

(α-PHP, α-PVP, and 4-CMC) [50]. The effects of the combined use of SCats and SCRAs are unknown [51].

4. Conclusion

Prison illicit drug markets are constantly evolving and the emergence of dimethylpentylone in the Scottish prisons is the latest example of the importance of near-real time laboratory testing programs for monitoring the ongoing changes in the prison drug markets. Following the detection of dimethylpentylone in mixtures with novel benzodiazepine-type drugs or SCRAs, research is required to determine the effects on people who use these new drug combinations.

CRediT authorship contribution statement

Olga Semenova: Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Caitlyn Norman:** Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Hannes Max Schwelm:** Writing – review & editing, Writing – original draft. **Niamh Nic Daéid:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Robert Reid:** Writing – review & editing, Methodology, Formal analysis. **Victoria Marland:** Writing – review & editing, Methodology, Formal analysis.

Declaration of Competing Interest

None

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.forsciint.2024.112145.

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