Reporting the novel synthetic cathinone 5-PPDI through its analytical characterization by mass spectrometry and nuclear magnetic resonance

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Abstract
Purpose In this work, the identification and characterization of the novel synthetic cathinone 5-PPDI found in a suspect drug sample were performed.

Methods The suspect sample was analyzed by gas chromatography–mass spectrometry (GC–MS), Fourier-transformed infrared (FTIR) spectroscopy, ultra-high performance liquid chromatography–high-resolution mass spectrometry (HRMS) and nuclear magnetic resonance (NMR) spectroscopy.

Results The fragmentation observed in GC–MS and the identification of functional groups by FTIR was not enough for compound identification. After an exhaustive analysis of the accurate-mass fragmentation observed in HRMS, the compound was tentatively identified as the novel cathinone 5-PPDI. Finally, five different NMR experiments were used for the unequivocal identification and complete characterization of the compound. In addition, the origin of this cathinone was investigated in depth.

Conclusions The analytical data provided in this work will be useful for the identification of 5-PPDI by forensic laboratories. In addition, the origin of this cathinone has been investigated, which could be of interest for the identification of future synthetic cathinones prepared following the similar synthesis route.

Keywords 5-PPDI · Synthetic cathinones · 1-(2,3-Dihydro-1H-inden-5-yl)-2-(pyrrolidin-1-yl)butan-1-one · High-resolution mass spectrometry · NMR spectroscopy · FTIR spectroscopy

Introduction
According to the last report from the European Monitoring Centre for Drug and Drug Addiction (EMCDDA), 14 novel cathinones were reported in the European Union in 2016. Synthetic cathinones represent the second largest novel psychoactive substance (NPS) class, with 118 compounds currently being monitored by EMCDDA. These compounds were the most commonly seized NPS in 2015, representing the third part of the total number of seizures [1]. Of these, many are pyrovalerone analogs; they are cathinones that contain the pyrrolidine moiety (42 substances) [1]. The compound reported in this paper, 5-PPDI, newly appeared as a new pyrovalerone analog that produces effects in humans and is not controlled. It is the indane analog of α-PBP, a drug that is currently controlled in the USA, China, and other countries [2, 3]. It is likely that it shares the same synthetic route, albeit with different precursors, as other pyrovalerone derivatives (α-bromination of the pentan-1-one precursor to form the 2-bromopentan-1-one intermediate, and reaction with pyrrolidine to yield the substance), and; therefore, the synthesis is easy to carry out by a facility that has the means to manufacture α-PVP [4].
Monitoring and identification of NPS is still handicapped due to this wide range of structures along with their high turnout rate. For this reason, it is essential to keep developing analytical approaches for their characterization [5–7].

The most commonly used analytical techniques in toxicological routine laboratories are Fourier-transformed infrared (FTIR) spectroscopy and gas chromatography–mass spectrometry (GC–MS), with the predominating ionization source being electron ionization (EI) [8]. FTIR is especially useful for NPS analysis when attenuated total reflectance (ATR) is used, allowing a direct analysis with a small amount of recoverable sample. The use of ATR-FTIR has recently demonstrated its potential for direct classification of NPS in seizures through the use of multivariate discriminant analysis, allowing compound identification with a cost-effective and rapid analysis (2 min per sample) [9, 10]. Nevertheless, this methodology can only be applied if the compound spectrum has been previously acquired, which limits its suitability for monitoring emerging NPS. GC–MS is probably the most frequently used instrumental technique in the field of toxicology, where its applicability for cathinone derivative analysis has been widely reported [11–14]. Although GC–MS provides a way to quickly identify a compound by the use of EI spectrum libraries, the frequent emergence of novel cathinone derivatives proves a serious drawback. First of all, most of the novel cathinones that have been detected recently are not listed in spectral libraries. Additionally, these cathinone derivatives tend to produce very similar (or identical) fragmentation patterns, and the identification of the molecular ion is commonly difficult due to the high fragmentation produced by an EI source [13].

Recent studies dealing with the analysis of synthetic cathinones have been carried out by ultra-high performance liquid chromatography (UHPLC) coupled to high-resolution mass spectrometry (HRMS), using electrospray ionization (ESI) interface as the ionization source. These studies have demonstrated the potential of this technique for cathinone derivative identification in legal high samples, usually employing a hybrid quadrupole time-of-flight (QTOF) mass analyzer [15, 16]. The QTOF instrument allows for a tentative compound identification even without the use of reference standards. Moreover, the applicability of the “non-target” approach for unknown compounds present in these samples has also been demonstrated [17].

When no reference standard is available, the use of UHPLC–HRMS is not enough for compound identification, and thus, additional spectroscopic techniques must be used. Nuclear magnetic resonance (NMR) spectroscopy is one of the most useful techniques for structural elucidation (including synthetic cathinones), allowing the differentiation of the substitutional isomerism without the use of reference standards [18–20]. Thus, the combination of UHPLC–HRMS and NMR allows the identification and complete characterization of unknown (or unreported) NPS [17, 21–24].

In this work, an unknown white powder (suspected to contain a synthetic cathinone) was received in our laboratory. After analysis by GC–MS and ATR-FTIR, the compound could not be identified. Analysis by UHPLC–HRMS allowed a tentative compound identification of the unreported synthetic cathinone 1-(2,3-dihydro-1H-inden-5-yl)-2-(pyrrolidin-1-yl)butan-1-one, sold on several webpages as 5-PPDI. The analysis of this cathinone by NMR in combination with HRMS data provided enough information for the unequivocal compound identification.

Materials and methods

Drug sample

The suspect sample was submitted by an anonymous user to Energy Control’s drop-in service for its analysis. Additional information about the Energy Control can be seen elsewhere [25].

Reagents and chemicals

For GC–MS analysis, GC-grade n-hexane and GC-grade acetone were purchased from Scharlau (Scharlab, Barcelona, Spain). For UHPLC–HRMS analysis, HPLC-grade water was obtained by purifying demineralized water using a Milli-Q system from Millipore (Bedford, MA, USA). HPLC-grade methanol, HPLC-grade acetonitrile, formic acid, acetone, and sodium hydroxide (NaOH) were acquired from Scharlau. Leucine enkephalin was purchased from Sigma-Aldrich (St. Louis, MO, USA). For NMR analysis, deuterated chloroform (CDCl3) was purchased from Sigma-Aldrich. For FTIR analysis, potassium bromide (KBr) was purchased from Scharlau.

Sample treatment

For FTIR analysis, the sample was directly analyzed by ATR-FTIR spectroscopy.

For GC–MS analysis, 10 mg of sample were extracted with 1 mL of acetone in an ultrasonic bath for 15 min. After centrifugation, the supernatant was five thousand-fold diluted with GC-grade n-hexane, and 1 µL of the extract was injected into the GC–MS system.

For UHPLC–HRMS analysis, 10 mg of sample were extracted with 1 mL of acetone in an ultrasonic bath for 15 min. After centrifugation, the supernatant was ten thousand-fold diluted with HPLC-grade water, and 20 µL of the extract was injected in the UHPLC–HRMS system.
For NMR analysis, approximately 15 mg of sample was dissolved in 0.6 mL of CDCl₃.

**Instrumentation**

For FTIR analysis, a Jasco FT/IR-6200 FTIR spectrometer (Jasco Inc., Easton, MD, USA) equipped with a Specac Silver Gate ATR accessory (Specac, Orpington, UK) was used. Data acquisition was performed at 23 °C between 4000 and 400 cm⁻¹, with a resolution of 4 cm⁻¹ and performing 32 acquisitions.

For GC–MS analysis, an Agilent 6890 N gas chromatograph (Agilent Technologies, Santa Clara, CA, USA) equipped with an Agilent 7683 autosampler (Agilent Technologies) was coupled to a Quattro Micro GC triple quadrupole mass spectrometer (Micromass, Boston, MA, USA) using an EI interface. The injector and the interface were operated at 250 °C. A 1-µL aliquot of sample was injected in splitless mode using deactivated liners into a 30 m x 0.25 mm i.d., 0.25 µm film thickness DB-5MS column (Agilent Technologies). Helium (99.999%; Praxair, Valencia, Spain) was used as carrier gas at a flow rate of 1 mL/min. The oven temperature was initially maintained at 90 °C for 1 min and programmed to reach 300 °C at 20 °C/min. It was finally maintained at 300 °C for 1.5 min (total run time, 13 min). The mass spectrometer was operated in EI mode at 70 eV. MS system worked in scan acquisition mode, acquiring from m/z 50 to 400. Analytical data were acquired and processed using MassLynx data station operation software (version 4.0; Waters, Mildford, MA, USA).

UHPLC–HRMS analysis was performed using an ACQUITY UHPLC system (Waters) coupled to a XEVO G2 QTOF hybrid QTOF mass spectrometer (Waters Micromass, Manchester, UK) with an orthogonal Z-spray ESI interface operating in positive ionization mode. The chromatographic separation was performed using a CORTECS C18 (Waters) analytical column (100 × 2.1 mm i.d., 2.7 µm particle size; Waters) at a flow rate of 0.3 mL/min. The column temperature was set to 40 °C. The mobile phases used were 0.01% formic acid in water (A) and 0.01% formic acid in methanol (B). The mobile phase gradient was performed as follows: 10% B at 0 min, linearly increased to 90% B over 14 min, 90% B at 16 min, and finally 10% B at 18 min in order to return to initial conditions. The injection volume was 20 µL. Nitrogen (Praxair) was used as desolvation and nebulizing gas. The desolvation gas flow was set at 1000 L/h. The TOF resolution was ~20,000 at full width at half maximum at m/z 556. The range acquired by the MS system was m/z 50–1000. A capillary voltage 0.7 kV and a cone voltage 20 V were used during all the chromatographic runs. Argon (99.995%) (Praxair) was used as a collision gas. The interface temperature was set to 650 °C and the source temperature to 120 °C. For MS² experiments, two acquisition functions with different collision energies were created. The low energy function used a collision energy of 4 eV in order to obtain information about the protonated molecule and adducts (if present), while the high energy function applied a collision energy ramp from 15 to 40 eV, in order to promote fragmentation of the compounds. Calibration of the mass-axis was performed daily from m/z 50 to 1000 using 0.05 M NaOH/5% formic acid (1:1, v/v), diluted 25-fold with acetonitrile/H₂O mixture (80:20, v/v). For accurate mass measurement, a 2 µg/mL leucine enkephalin solution in acetonitrile/H₂O with 0.1% formic acid (50:50, v/v) was used as lock-mass, and pumped at a flow rate of 20 µL/min. The leucine enkephalin protonated molecule (m/z 556.2771) was used for recalibrating the mass axis and ensuring an accurate mass during all the chromatographic run. UHPLC–HRMS data were acquired in continuum mode using MassLynx data station operation software (version 4.1; Waters) and processed with the UNIFI scientific information system (version 1.8; Waters).

NMR analyses were performed using a Bruker Ascend 400 MHz spectrometer equipped with a SampleCase autosampler (Bruker, Ettlingen, Germany), performing data acquisition at 303 K using CDCl₃. The residual solvents signals at δ = 7.24 ppm for ¹H (CHCl₃) and at δ = 77.23 ppm for ¹³C (CDCl₃) were used as internal references. Characterization of the compound was performed using five gradient-enhanced experiments: ¹H NMR, ¹³C NMR, correlated spectroscopy (COSY), heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond correlation (HMBC). NMR experimental data were collected using the Bruker Icon NMR 5.0.5 software (Bruker). The Mestrelab Nova program was used for raw data processing (Mestrelab Research, Santiago de Compostela, Spain).

**Results and discussion**

**Infrared spectroscopy and gas chromatography–mass spectrometry**

Preliminary analyses were performed by ATR-FTIR and GC–MS. In the case of FTIR analysis, no spectra databases were available at our laboratory, and therefore only functional groups could be identified. No significant information could be obtained, and only aliphatic (<3000 cm⁻¹) and aromatic (>3000 cm⁻¹) C–H stretching signals, and a carbonyl stretching signal (1675 cm⁻¹) were present in the FTIR spectrum. The FTIR spectrum and the identification of the observed bands can be found in supplementary material Fig. S1.

Analysis by GC–MS revealed the presence of only one organic compound, detectable by this equipment, which presented a chromatographic peak at 9.45 min. When the
mass spectrum of this chromatographic peak was extracted (Fig. 1), no matches were obtained after applying the spectra libraries available at the laboratory (NIST, Cayman Chemical, and a home-made library). The fragmentation spectrum showed only an intense fragment ion at \( m/z \) 112. No information about the molecular ion could be obtained from the EI spectrum.

The combination of the information provided by FTIR and GC–MS was not enough for compound identification, requiring analysis by HRMS (and NMR) for compound identification.

**High-resolution mass spectrometry**

The analysis by UHPLC–HRMS confirmed the high purity of the sample, and only a chromatographic peak was observed in the total ion current chromatogram. The low energy function spectrum of this chromatographic peak showed an ion at \( m/z \) 258.1845, corresponding to the protonated molecule of the compound (\( C_{17}H_{24}NO^+ \), -2.9 ppm) (Fig. 2a). The fragmentation observed in the high energy function spectrum suggested the compound to be a synthetic cathinone (Fig. 2b). The product ion 2 observed at \( m/z \) 187.1111 (\( C_{13}H_{15}O^+ \), -3.4 ppm) suggested the presence of a pyrrolidine moiety (neutral loss of \( C_2H_2N \), 71.0735 Da). This neutral loss has been described for several synthetic cathinones with a pyrrolidine moiety [15, 20, 22, 23]. The product ion 4 (at \( m/z \) 145.0642, \( C_{10}H_8O^+ \), -4.5 ppm) indicated that the alkyl chain in the \( \alpha \)-carbon of the cathinone should be an ethyl moiety. This fact was in accordance with product ion 1 at \( m/z \) 229.1448 (\( C_{15}H_{19}NO^+ \), -5.8 ppm), corresponding to a radical loss of 29.0391 Da (\( C_2H_5 \)). Finally, product ion 6 at \( m/z \) 117.0692 (\( C_9H_9^+ \), -5.8 ppm) was obtained after a CO loss (27.9949 Da) from product ion 4. The double bond equivalence for product ion 6 indicated the presence of five insaturations, four of them corresponding to the aromatic ring. The remaining one, and the presence of three carbon atoms, could be related to the presence of a 2,3-dihydroindene moiety.

Thus, a pyrrolidine, an ethyl and a 2,3-dihydroindene moieties would be the three parts of the cathinone structure, being proposed as \( 1\text{-}(2\text{-dihydro-1H-inden-5-yl})\text{-2-}(\text{pyrrolidin-1-yl})\text{butan-1-one} \). Searching for this systematic name on different websites which sell research chemicals, our putative cathinone was found under the name of 5-PPDI.

![Fig. 1](image-url) Electron ionization mass spectrum of a chromatographic peak at 9.54 min, corresponding to the unknown compound, obtained by gas chromatography–mass spectrometry

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To the best of our knowledge, this synthetic cathinone has not been reported yet.

Once the compound was tentatively identified as 5-PPDI, the fragmentation pathways for this synthetic cathinone were proposed. As shown in Fig. 3, all the observed product ions could be justified based on the structure of this cathinone. The base peak at \( m/z 112 \) observed in the EI mass spectrum (Fig. 1) corresponds to the product ion 7.

Nevertheless, the information obtained by HRMS allowed only a tentative identification. The complete characterization and unequivocal identification of the compound was performed by the combination of different NMR experiments.

**Nuclear magnetic resonance spectroscopy**

Figure 4 shows the \(^1\)H NMR and \(^{13}\)C NMR spectra for the tentatively identified 5-PPDI, and Table 1 presents signal assignment for \(^1\)H and \(^{13}\)C NMR signals.

For the \(^1\)H NMR spectrum, all the observed signals could be justified based on the structure of 5-PPDI without major problems. Nevertheless, some signals presented certain curiosities that should be discussed in more detail. Resonances of hydrogen atoms 4 and 5 presented broad signals, as usual in aliphatic rings with heteroatoms (for example, the pyrrolidine moiety) [20, 22, 23]. Methylene hydrogens signals which present resonance between \( \delta 1.75 \) and 2.25 presented as overlapping, making the assignation of these signals difficult. These signals were finally assigned after an accurate evaluation of the COSY and HSQC spectra, which can be found in supplementary material (Fig. S2). The study of HSQC spectra also allowed a direct assignation of \(^{13}\)C NMR signals.

The combination of the NMR experiments and the fragmentation observed in HRMS, allowed the complete characterization of the compound and thus, its identification. Nevertheless, in order to enhance the confidence of compound structure, an additional bidimensional NMR experiment was performed. Figure 5 shows the HMBC spectrum of 5-PPDI. The multiple bond correlations observed in this experiment confirmed the structure initially proposed. Thus,
the compound was unequivocally identified as the synthetic cathinone 5-PPDI.

**Reasons behind synthesizing 5-PPDI**

Structure-activity relationship (SAR) is very difficult to deduce from theoretical data. There is some available information on the SAR of amphetamines, but less for the SAR of synthetic cathinones.

Although SARs of amphetamines and synthetic cathinones are not the same, some inferences can be made from modifications in one family to the other. It has been shown that the phenyl ring in pyrovalerone derivatives can be substituted with a benzodioxole, and the compound will retain similar activity (α-PVP to MDPV, Fig. 6). Similarly, the benzodioxole moiety in MDA can be substituted with an indane and also will retain similar properties (MDA to 5-APDI). It is therefore a reasonable assumption that the benzodioxole and phenyl moieties are interchangeable in pyrovalerone derivatives and amphetamine analogs. Then, the benzodioxole could be replaced by an indane, substituting the phenyl moiety of α-PBP with an indane moiety which will yield to the active compound 5-PPDI. Replacing the phenyl moiety of α-PBP with a benzodioxole leads to MDPBP, a compound that is, at least, active; it is a logical next step to see if something similar happens with 5-PPDI (Fig. 6).

Because 5-PPDI has not previously appeared in the literature and little is known about it, vendors tend to send it for free with other orders, or even to send a sample at no cost to the consumer in an attempt to get users to describe its effects and generate interest in the substance [26]. It appears that the compound is inactive at dosages similar to other pyrovalerone derivatives, and users tend to not push the dose above the one which they perceive as safe. Some users report light activity, especially with administration through vaporization of the compound, which is reported to be more potent than oral or nasal use. Reports are mixed however, likely due to factors such as purity, personal tolerance, route of administration, etc., leading to conflicting reports such as one user reporting 20 mg vaporized to be an active dose, and another reporting that 32 mg vaporized to yield no effects. It is also possible that some vendors claim to ship 5-PPDI, but in reality they ship other compounds, leading to the disparity in effects reported [27, 28].
Fig. 4 Nuclear magnetic resonance spectra of the unknown substance. a $^1$H spectrum, with proton-signal assignation based on the structure of 5-PPDI. b $^{13}$C spectrum, with carbon-signal assignation based on its structure.
Conclusions

This work presents the detection and characterization of the novel cathinone 1-(2,3-dihydro-1H-inden-5-yl)-2-(pyrrolidin-1-yl)butan-1-one, better known as 5-PPDI. The results obtained in this study remark the limitations of the routine analysis techniques used in forensic laboratories for NPS detection and identification. Thus, FTIR spectroscopy and GC–MS allow a rapid identification of the sample only if the corresponding spectrum has been previously recorded.

In this work, GC–MS revealed that the compound was highly pure, without any other organic compound being detected. Nevertheless, no matches were obtained for the acquired spectrum using commercial libraries, illustrating that this technique is not efficient for structure elucidation of unknown substances or unanalyzed compounds; therefore, advanced techniques are required for that aim.

The analysis by UHPLC–HRMS allowed a tentative identification of the compound, based on the accurate-mass fragmentation observed. Nevertheless, due to the lack of an analytical reference standard at the moment of developing this work, the compound could not be unequivocally identified based only on HRMS data. The use of different NMR experiments (1H, 13C, COSY, HSQC and HMBC) confirmed its structure, and after combining this information with that obtained by HRMS, the substance was unequivocally characterized as 5-PPDI.

The analytical data provided in this work will facilitate the detection and identification of this novel synthetic cathinone by forensic and toxicological laboratories, even if they use routine techniques.

Although this compound does not appear to be very potent, and it will be unlikely to see widespread use, it is interesting to consider that it was synthesized with a clear objective to produce a viable alternative to compounds like α-PBP. Its structure demonstrates some knowledge on pharmacology and SAR of synthetic cathinones, and contributes to clarifying the theory, by which manufacturers of NPS are proficient at finding alternatives to banned compounds. Such a theory casts a doubt on the efficacy of systematically scheduling NPS, because manufacturers have been able to provide alternatives that not only evade legislation, but also are usually active compounds.

Table 1 1H and 13C nuclear magnetic resonance (NMR) signal assignment

| Hydrogen δ (ppm) | Multiplicity | Carbon δ (ppm) |
|-------------------|--------------|---------------|
| 1                 | 0.94         | 10.88         |
| 2                 | 2.08, 2.29   | 25.27         |
| 3                 | 4.98         | 63.16         |
| 4                 | 2.75, 3.59, 3.71, 3.79 | 48.72, 52.88 |
| 5                 | 1.93, 2.08   | 23.92         |
| 6                 | –            | 196.43        |
| 7                 | –            | 153.16        |
| 8                 | 7.74         | 124.39        |
| 9                 | –            | 145.93        |
| 10                | 2.92         | 32.52, 33.21  |
| 11                | 2.08         | 24.44         |
| 12                | –            | 134.62        |
| 13                | 7.31         | 125.21        |
| 14                | 7.67         | 127.20        |

δ Chemical shift
a Multiplicity of these signals could not be established

Table 1 1H and 13C nuclear magnetic resonance (NMR) signal assignment
Fig. 5 Heteronuclear multiple bond correlation spectrum of the compound identified as 5-PPDI

Fig. 6 Structures of synthetic cathinones with moiety changes to 5-PPDI
Compliance with ethical standards

Conflict of interest There are no financial or other relations that could lead to a conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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