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Analytical characterization of three cathinone derivatives, 4-MPD, 4F-PHP and bk-EPDP, purchased as bulk powder from online vendors

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Abstract

Novel emerging drugs of abuse, also referred as new psychoactive substances (NPS), constitute an ever-changing mixture of chemical compounds designed to circumvent legislative controls by means of chemical modifications of previously banned recreational drugs. One of such class, synthetic cathinones, namely β-keto derivatives of amphetamines, has been largely abused over the past decade. A number of new synthetic cathinones are detected each year, either in bulk powders/crystals or in biological matrices. It is therefore important to continuously monitor the supply of new synthetic derivatives and promptly report them. By using complementary analytical techniques (i.e. 1D and 2D NMR, FT-IR, GC-MS, HRMS and HPLC-UV), this study investigates the detection, identification and full characterization of 1-(4-methylphenyl)-2-(methylamino)-pentanone (4-methyl-pentedrone, 4-MPD), 1-(4-fluorophenyl)-2-(pyrrolidin-1-yl)-hexanone (4F-PHP) and 1-(1,3-benzodioxol-5-yl)-2-(ethylamino)-1-pentanone (bk-EPDP), three emerging cathinone derivatives.

Keyword: synthetic cathinones, new psychoactive substances, 4-MPD, 4F-PHP, bk-EPDP

Introduction

The emergence and propagation of new psychoactive substances (NPS), also known as 'legal highs' or 'designer drugs', is an expanding worldwide problem.[1, 2] Designed and synthesised to reproduce the effects of traditional illicit substances such as cannabis, stimulants and hallucinogens, they are widely available in many countries for purchase online.

Synthetic cathinones constitute a class of NPS which have had an increased demand over the past few years following the introduction of mephedrone to the illicit market. Like other NPS, to evade seizures under local drug legislations, various analogues of synthetic cathinones can be synthesised with modifications to circumvent the legal restrictions. New products are often purposely labelled with just the chemical abbreviation or, in some cases, marketed without any ingredient information or intentionally declared different from actual composition. Hence, effective and reliable analytical methods used to accurately identify the structure of new cathinone derivatives, together with constant monitoring of market availability are important. They serve as first step to identify new compounds which can then lead on to further studies of their health risks when consumed recreationally.[2] Data from different spectroscopic techniques coupled to mass spectrometry are often used in a complementary fashion in order to characterise and confirm unknown structures, particularly in cases where suitable reference material does not

exist or where the compounds are novel and unknown.[3-7] This approach of using uncorrelated analytical methods is recommend by the Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG).[8]

In this work, the detection and identification of three suspected samples containing cathinones were carried out (**1–3**, **Figure 1**). The samples were obtained from TICTAC Communications Ltd and were test purchased online from an overseas, open access website as NPS prior to the May 2016 Act. Based on their labels, these samples were assumed to belong to the cathinone drug class. However, their compositions and purity were indeterminate. The labels of each sample used were abbreviated as 4-MPD **(1)**, 4F-PHP **(2)** and bk-EPDP **(3)**. Analytical reports of compounds **1**-**3** have been recently reported to the European Monitoring Centre for Drugs and Drug Abuse (EMCDDA) early warning system (EWS) on new psychoactive substances, to the European Project Response [9-12], and to the Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG) [13]. Compound **1**, 1-(4-methylphenyl)-2-(methylamino)-pentanone (i.e. 4-methyl-pentedrone, 4-MPD), compound **2**, 1-(4-fluorophenyl)-2-(pyrrolidin-1-yl)-hexanone and compound **3**, 1-(1,3-benzodioxol-5-yl)-2-(ethylamino)-1-pentanone, have been recently reported by TICTAC Communications Ltd and King's College London to the UK Focal Point (the UK reporting agency for EWS) as compounds new to the UK.

Experimental

Reagents and Samples

Methanol, acetonitrile, water, formic acid (FA) and trifluoroacetic acid (TFA), HPLC grade, dimethyl sulfoxide-*d*6 and isotopic purity 99.9 atom %D were purchased from Sigma-Aldrich (Dorset, UK). Methanol (LC-MS grade), t-butyl-methyl-ether (TBME), tripelennamine, quinolone were from Sigma-Aldrich (Dorset, UK). Deuterium oxide, isotopic purity 99.8 atom %D, was purchased from Fluorochem LTD (Derbyshire, UK). Three unknown street samples were received from TICTAC Communications Ltd (London, UK). The samples were test purchased as NPS from an overseas, open access website. Samples were kept in a locked cabinet at room temperature.

Sample Preparation

Stock solutions 1 mg/mL of each sample were prepared in methanol, and then samples were filtered with polypropylene (PP) syringe filters (pore size 0.2 µm). Stock solutions were stored at -20 ^{o}C.

Sample preparations for HPLC-DAD analysis were prepared at concentration of 0.1 mg/mL with HPLC mobile phase (50:50 (v/v) water:acetonitrile containing 0.1% TFA). PP syringe filters, pore size 0.2 µm, were used to filter the samples before injecting them into the HPLC instrument.

Sample preparations for the HRMS analysis were prepared at the concentration of 1µg/mL in a 50:50 (v/v) water:methanol containing 0.1% FA. PP syringe filters, pore size 0.2 µm, were used to filter samples prior to MS analysis.

Samples for NMR spectroscopy analysis were dissolved in deuterated solvents. Solutions were filtered through PP syringe filters.

Sample preparation for GC-MS analysis was 1 mL of methanol added to 1.5 mL polypropylene tubes (Appleton Woods, Birmingham, UK) containing approximately 100 mg powder which was then vortexed for at least 30 minutes before being centrifuged at 6,030 g for 1

minute. An aliquot of 10 µL was diluted with 1 mL of TBME, containing 100 µg/mL each of quinoline and tripelennamine as the internal standards.

Analytical Instrument Conditions

HPLC-DAD: a HP 1050 series was used equipped with a quaternary pump, an auto-sampler, *a* diode array detector (DAD) and a Kontron DEG 104 degasser. Agilent ChemStation software was used to control the equipment. A C8 kinetex® column 100×2.1 mm i.d., particle size 5 µm was purchased from Phenomenex Inc. HPLC mobile phases A and B consisted of 0.1% v/v TFA in water and acetonitrile, respectively. The gradient was 0% B ramping to 90% B within 20 minute. The flow rate was set at 0.2 mL/min and the injection volume was 5 µL.

HRMS: a Thermo Scientific™ Exactive™ Plus EMR mass spectrometer was employed with flow-injection-analysis mode (a zero dead volume connector replaced the HPLC column) at 0.2mL/min using 50% B: 50% A where A is water in 0.3% FA and B is acetonitrile in 0.3%FA.

NMR spectroscopy: a Bruker Avance DRX 400 MHz NMR spectrometer was used employing solvent residual peaks as internal standards.

GC-MS: the samples were qualitatively analysed using an Agilent 7890A GC with 5975C VL MSD (Santa Clara, California, USA) equipped with a split-splitless injector and an HP5-MS column (30 m length, 0.25 mm internal diameter, 0.25 µm film thickness) and running on Agilent ChemStation software. 1 µL of the extract was injected using 5:1 split ratio. The column was held at 80°C for 4 minutes and then ramped up at 40°C/min to 290°C and held to a total run time of 19.25 minutes. A mass range of m/z 40 to 400 was scanned.

FT-IR: all powders were analysed on the Bruker Alpha (Platinum ATR; Coventry, UK) IR instrument that uses a diamond to achieve attenuated total reflection (ATR) as the mode of action. A spatula tip of powdered sample was directly loaded onto the FTIR instrument for analysis following a background scan.

Results and discussion

Classifying samples as the cathinone drug class

The chemical structures of the three synthetic cathinones are presented in **Figure 1**. Following analytical investigation via GC-MS, FT-IR, tandem MS and NMR we concluded that full structural elucidation of these compounds was not previously reported in any scientific paper to the best of our knowledge.

FIGURE 1 ABOUT HERE

Figure 1. Chemical structures of the cathinones detected in the analysed samples.

The suspected samples were initially screened via FT-IR for the presence of synthetic cathinones, rather than other chemical types of legal highs such as tryptamines, synthetic cannabinoids, phenylethylamines or piperazines. For the cathinone drug class, the functional groups of cathinone is displayed in a spectra as the carbonyl stretching conjugated with phenyl group showing the characteristic absorption at 1700-1680 cm^{-1}. The broad spectrum from 3100-2200 cm^{-1} can be defined as the C-H stretching and the absorption from the amine salt if present in this form.[14] Thus, considering the FTIR spectrum of the three samples (Supporting

Information, Section S2), the cathinones characteristics were shown very clearly. IR spectra of the three emerging cathinones **1**-**3** appear identical to the ones illustrated in recent analytical reports. [9-13]

HPLC-DAD analysis

Reverse phase liquid chromatography with a C8 column was chosen to separate the cathinone component from any other impurities; the use of multiple wavelengths in the UV region allowed for any UV-absorbing impurity (typical of most NPS) to be examined. Five wavelengths in a range of 214 – 281 nm were set for detecting samples. With the same analytical conditions, samples were eluted at retention times ranging from 12.5 to15.1 minutes. There were no distinct impurity peaks in the chromatograms at any wavelengths operated, thus, samples were considered to be pure in terms of NPS content. HPLC-DAD chromatograms of all the samples are illustrated in Figure S5-1 (Supporting Information).

GC-EI-MS analysis

The total ion current (TIC) chromatogram of all samples showed some very minor impurities and also the sharp and distinct main peak of the suspected cathinones. The EI mass spectrum of the main peak showed an immonium ion as the dominant base peak for all samples (see supporting information, Section S1). GC-MS spectra were in agreement with those recently reported by Cayman Chemical [15-17].

NMR Analysis

Table 1 presents a summary of NMR spectroscopic results, including skeleton connectivity evidences obtained from HSQC, HMBC and COSY analyses (see also section S3, supporting information) of the three new cathinones. Beside us having reported NMR data for such new cathinones to the EMCDDA EWS, few other analytical reports have recently appear, illustrating the ^{1}H and ^{13}C NMR of compounds **2**-**3** [10-12], as well as bidimensional NMR spectra for compound **6**. No NMR data for compound **1** was however reported, nor any bidimensional spectra for compound **2**, which are presented in this work. In addition, to further complement the analytical properties of the new cathinone derivatives, we also present DEPT experiments of these derivatives.

TABLE 1

HRMS

The chemical structures identified by NMR analysis were further consolidated using HRMS (**Table 2**). The exact masses of all the compounds match the predicted theoretical values with errors being less than 3 ppm.

TABLE 2

FIGURE 2 ABOUT HERE

Figure 2. COSY and HMBC correlations: (a) compound **1**; (b) compound **2;** and (c) compound **3.**

Identification of 1-(4-methylphenyl)-2-(methylamino)-pentanone (compound 1):

Based on the structural elucidation using the NMR technique, compound **1** was identified as 1-(4-methylphenyl)-2-(methylamino)-pentanone (4-methyl-pentedrone). In the aromatic region of the ^{1}H NMR, the splitting pattern shows the characteristic pattern of para-substituent benzene rings (i.e. 'roof effect'). From the ^{1}H spectrum, there were eight types of H-signal. The 2D NMR data revealed that the substituent at the alpha carbon position was an *n*-propyl group. The ^{1}H splitting pattern, HSQC and the chemical shift of carbons at the benzene skeleton confirmed the presence of methyl group substituent in para-position. **Figure 2a** illustrates the HSQC, COSY and HMBC correlations of compound **1**'s structure. 4-methyl-pentedrone can be classified as an *N*-monoalkyl cathinone. Pozo *et al.* [18] have described the ESI fragmentation mechanism of the N-containing drugs (mephedrone) where the rearrangement might occur via formation of an indole ring if the loss of an amine group could not be found. In our work, the proposed mechanism shows that distinct product ions (fragments a-g, Figure S4-4) can be produced via an indole ring formation or an alkyl side chain loss fragmentation pathway. Indeed, *in-house* analysis of a deuterated standard of the synthetic cathinone mephedrone indicated that the indole ring pathway is preferred (Figure S4-2). This is in agreement with the findings of Pozo *et al*.[18] The base peak, with *m/z* 145.0885, derives from the loss of water, followed by propyl radical loss at the alpha carbon. Other product ions, such as the loss of ethane or propane at *m/z* 158.0963 and 144.0806, were also detected. An alkyl loss at N-position was finally observed at *m/z* 130.0650. The two proposed fragmentation pathways of compound **1** are shown in Figure S4-4 (Supporting Information). The molecular structure of compound **1** was also confirmed by the GC-EI-MS spectrum. As can be seen in Table S1 and Figure S1-1, the data revealed the base peak of compound **1** having *m/z* = 86.2, which conforms to the m/z value of the proposed immonium ion of compound **1** ($C_5H_{12}N^+$).

Identification of 1-(4-fluorophenyl)-2-(pyrrolidin-1-yl)-hexanone (compound 2):

Complete elucidation has shown that this compound is 1-(4-fluorophenyl)-2-(pyrrolidin-1-yl)-hexanone. The ^{19}F spectrum shows a distinct peak at the chemical shift = -102.9 ppm (see supplementary information, Figure S3-13). The fluorine atom may influence ^{1}H and ^{13}C spectra of compound **2,** resulting in the ^{13}C chemical shift of the benzene ring downfield (**Table 1**). The ^{1}H spectrum, at the aromatic region, shows doublet of doublets peaks at δ 8.21 and 7.47 resulting from four and three bonds couplings by the F atom. Thus, compound **2** is an aromatic fluorine-containing atom placed in para position. The ^{1}H NMR spectrum also shows the overlapped peaks between the hydrogen atoms from the methylene groups at the five-membered ring (position 3″and 4″) and the hydrogen atoms from the long chain alkyl group (position 3) (**Table 1**). However, from HSQC, these protons can be differentiated as the spectrum reveals they are attached to the different carbon atoms. Hence, the six protons that appeared can be classified into two types, firstly, two protons of the butyl group at the alpha carbon side chain (-C$\underline{H}_2$-CH_2-CH_2-CH_3, position 3). Secondly, four protons of the pyrrolidine ring (position 3″and 4″). At position 4

and 5 in the ^{1}H spectrum, the protons are also overlapped with each other. From 2D NMR data and the ^{13}C chemical shift, these protons can be classified as the members of a butyl group but are different in the attached carbon (-CH_2-C<u>H</u>$_2$-C<u>H</u>$_2$-CH_3). **Figure 2b** shows COSY and HMBC correlations of compound **2**'s structure. The fragmentation pathway of compound **2** is shown in Figure S4-6 (Supporting Information). A loss of the pyrrolidine ring is a favourable pathway for this type of cathinones. Thus, the distinct fragment observed in the ESI-HRMS/MS were *m/z* = 109.0447 (Figure S4-6, fragment a). The cleavage between the alpha carbon and the carbonyl carbon producing an immonium ion or a benzoyl cation (Figure S4-6, fragments d and b) has also been detected. The immonium ion (140.1432) is identical to the based peak obtained from GC-EI-MS spectrum (Table S1).

Identification of 1-(1,3-benzodioxol-5-yl)-2-(ethylamino)-1-pentanone (compound 3):

The proton NMR spectrum of this compound shows the pattern of one doublet of doublets and two doublets peaks in the aromatic area derived from three different types of protons (position 6', 2', 5'), as well as an acetal proton (-O-CH_2-O-) signal at 6.09 ppm, which can confirm the existence of 3,4-methylenedioxy substituent group on the benzene ring. Other evidence such as the chemical shift of the acetal carbon at 102.6 ppm was observed (position 8') in the ^{13}C spectrum. Ten types of protons were found in this compound's ^{1}H spectrum. The 2D NMR (**Figure 2c**) revealed that the substituent at the alpha carbon position was an *n*-propyl moiety. The complete elucidation has shown this compound to be 1-(1,3-benzodioxol-5-yl)-2-(ethylamino)-1-pentanone (bk-EPDP). Bk-EPDP (compound **3**) can be classified as 3,4-methylenedioxy and *N*-monoalkylcathinone. The possible fragmentations of this kind of cathinone were the loss of water, the loss of CH_2O from the 3,4-methylenedioxy group, CO loss that followed water loss and the loss of methyl radical.[19, 20] For the *N*-monoalkyl cathinone subclass, we detected the fragments resulting from the loss of amine groups at m/z 135.0438 and 149.0231 (**Figure 3a**, peak d, e). However, the rearrangement via an indole ring may also be found. Based on the proposed fragmentation pathways of 4-MPD and deuterated mephedrone (Supporting Information), the proposed fragmentation pathway of compound **3,** presented in **Figure 3b,** occurs via indole-ring formation. The product ion spectrum of compound **3** shows several fragment ions since, apart from the carbonyl side chain fragmentation, the molecule can also experience the loss of CH_2O from 3,4-methylenedioxy group. The EI-MS of compound **3** shows the immonium ion at the *m/z* 100.2 (Table S1) as the base peak, obtained from the dissociation between the alpha and beta carbon bond. Furthermore, the characteristic peaks in GC-EI-MS spectra suggest the presence of 3,4-methylenedioxy substituent benzene ring at *m/z* 121.1 and 149.1 were also identified (see supporting information, Figures S1-3).

FIGURE 3 ABOUT HERE

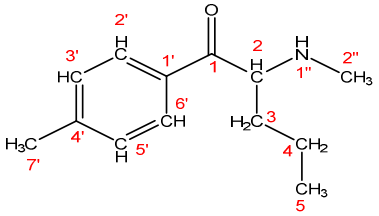
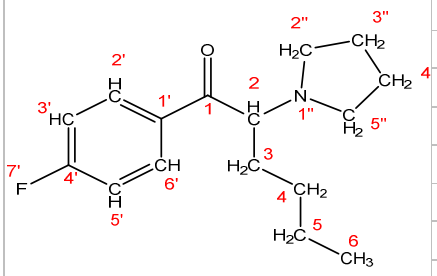
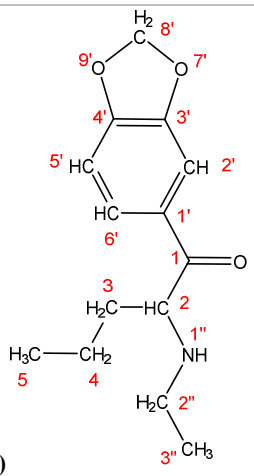
Figure 3. A) The product ion spectrum and B) the proposed fragmentation pathway of compound **3**

Conclusion

This work discloses the detection and structural identification of three emerging cathinone derivatives which were available on the web. While comparison of a reference material is desirable to confirm structural match, this is not always possible due to the lack of commercially available reference standards at the time of investigation. Chemical synthesis can be adopted to prepare in-house standards,[3, 4] however the use of multiple analytical tools can be a viable alternative to claim accurate structural elucidation. The purchased powders appeared highly pure, thus the characterised compounds could potentially be accepted as reference standards for routine tests by forensic laboratories. However, absolute quantitative analysis would need to be performed by means of e.g. accurate elemental analysis to establish the degree and amount of potential trace impurities and/or inorganic diluents.

No toxicological data are available for such novel compounds, which presents a potential risk to human health. Thus, the analytical data given here can assist clinical/forensic toxicology laboratories by helping identify these compounds in biological samples and bulk powders.

Table 1. NMR data of the synthetic cathinones **1-3**

Sample	ID	^{1}H	^{13}C (DEPT)	Connectivity correlation	
		HSQC correlation, ppm		COSY	HMBC†
4-MPD (1) 	1	-	196.8	-	2', 6'
	2	5.10	63.5 (+)	3	3, 4, 2″
	3	1.94-2.01	32.0 (-)	2, 4	2, 5
	4	1.13-1.38	17.0 (-)	3, 5	2, 5
	5	0.82	12.8 (+)	4	3, 4
	1'	-	130.5	-	3', 5'
	2', 6'	7.91	129.0 (+)	3', 5', 7'	1, 3', 4', 5'
	3', 5'	7.43	129.8 (+)	2', 6', 7'	1', 2', 6', 7'
	4'	-	147.5	-	2', 6', 7'
	7'	2.43	20.9 (+)	2', 3', 5', 6'	, 3', 4',5'
	2″	2.75	31.7 (+)	-	2
4F-PHP (2) 	1	-	195.3	-	2, 3, 2', 6'
	2	5.66	67.4 (+)	3, 1″	1, 3, 4
	3 *	1.82-2.03	29.3 (-)	2, 4,5	1, 2, 4, 5
	4 **	0.96-1.28	25.8(-)	3, 5, 6	2, 3, 5, 6
	5 **	0.96-1.28	21.9 (-)	3, 4, 6	3, 4, 6
	6	0.72	13.5 (+)	4, 5	4, 5
	1'	-	131.3	-	2', 3', 5', 6'
	2', 6'	8.21	132.1, 132.2 (+)	3', 5'	1, 1', 3', 4', 5'
	3', 5'	7.47	116.4, 116.6 (+)	2', 6'	1', 2',4', 6'
	4'	-	164.7, 167.3	-	2',3', 5', 6'
	2″,5″	3.03-3.67	51.9, 53.7 (-)	1″, 3″, 4″	3″, 4″
	3″, 4″ *	1.82-2.03	22.9 (-)	2″, 5″	2″, 5″
	1″ (HCl salt)	10.81	-	2, 2″, 5″	-
bk-EPDP (3) 	1	-	195.0	-	2, 3, 2', 6'
	2	5.04	61.6 (+)	3	1, 3, 4, 2″
	3	1.92-1.98	32.5 (-)	2, 4	1, 2, 4, 5
	4 *	1.12-1.35	17.1 (-)	3, 5	2, 3, 5
	5	0.82	10.6 (+)	4	3, 4
	1'	-	127.6	-	2', 5 ', 6'
	2'	7.42	108.5 (+)	6'	1, 1', 3', 4', 6'
	3'	-	148.3	-	2', 5', 8'
	4'	-	153.6	-	2', 5', 6' ,8'
	5'	6.98	107.8 (+)	6'	1', 3', 4', 6'
	6'	7.66	126.5 (+)	2',5'	1, 2', 4', 5'
	8'	6.09	102.6 (-)	-	3', 4'
	2″	3.01-3.17	42.2 (-)	3″	2, 3″
	3″ *	1.12-1.35	12.9 (+)	2″	2″

*, ** = overlapped with each other in ^{1}H; + = DEPT positive signal; − = DEPT negative signal.
†the HMBC column lists either the C or the H(s) for the groups which show cross-peaks with the corresponding group (i.e. same row) in ID column

Table 2. HRMS analysis of cathinone samples.

Chemical formula of $[M+H]^+$	**Exact mass $[M+H]^+$**	**Accurate mass $[M+H]^+$**	**Mass error (ppm)**	**Observed fragment ions (m/z)**		
				Accurate mass	Exact mass	Mass error (ppm)
Compound **1** $C_{13}H_{20}NO^+$	206.1539	206.1537	-0.97	188.1431 158.0963 146.0963 145.0885 144.0806 131.0728 130.0650	188.1434 158.0964 146.0964 145.0886 144.0808 131.0730 130.0651	-1.59 -0.63 -0.68 -0.69 -1.39 -1.53 -0.77
Compound **2** $C_{16}H_{23}FNO^+$	264.1758	264.1752	-2.27	193.1022 140.1432 137.0396 123.0239 109.0447	193.1023 140.1434 137.0397 123.0241 109.0448	-0.52 -1.43 -0.73 -1.63 -0.92
Compound **3** $C_{14}H_{20}NO_3^+$	250.1438	250.1432	-2.40	232.1327 205.0855 202.1223 189.0781 174.0549 172.0756 160.0755 149.0231 135.0438	232.1332 205.0859 202.1226 189.0784 174.0550 172.0757 160.0757 149.0233 135.0441	-2.15 -1.95 -1.48 -1.59 -0.57 -0.58 -1.25 -1.34 -2.22

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