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Synthesis, full chemical characterisation and development of validated methods for the quantification of (±)-4′-methylmethcathinone (mephedrone): A new "legal high"

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ABSTRACT

The recent global increase in the abuse of 4′-methylmethcathinone and related compounds has developed a requirement for full chemical characterisation of these products. In this work we present full synthetic and chemical characterisation data and supplemental information for mephedrone synthesised as both the hydrobromide and hydrochloride salt. Additionally we report the first fully validated chromatographic methods for the detection and quantitative analysis of the substance both in its pure form and in the presence of a number of common adulterants used in illicit drug manufacture.

1. Introduction

In the last few years there has been a striking increase in the sale of "*legal highs*" [1]. These chemicals may be bought through the internet at low cost and are sometimes pure compounds which display highly similar chemical structures to existing and illegal drugs of abuse within the phenethylamine class.

(±)-4′-Methylmethcathinone or (±)-mephedrone (**3**) [2–11] is a synthetic β-ketoamphetamine that is structurally similar to methcathinone (**4**, R=Me), related to cathinone (**4**, R=H), a psychoactive compound found in Khat. (±)-Mephedrone has begun to recently emerge in drug seizures as its use as a "*legal high*" replacement for controlled stimulants including amphetamines such as methamphetamine (**5**) and MDMA (**6**) has increased (Scheme 1). (±)-Mephedrone is now a substance controlled by legislation in the United Kingdom, Germany, Norway, Sweden, The Netherlands, Finland, Romania, Republic of Ireland, Denmark, Canada and Israel. Since the legislative change a number of second-generation "*legal high*" products, which pertain to contain legal mephedrone substitutes, have become available – however many of these have been reported to contain structurally related cathinone derivatives that are themselves controlled substances [12].

The prevalence of these cathinone-derived "*legal high*" drugs has given rise to both legal and analytical challenges in the identification of these substances – thus the robust analytical profiling and the development of validated methods of testing are required. Though a number of groups have independently reported the synthesis [9,10] and selected analytical information (such as the NMR [9–11], MS [9–11] and IR [9,10]) for (±)-mephedrone – there has been no comprehensive analytical profiling or development of validated chromatographic methods for this substance. This paper seeks to address this by presenting the chemical synthesis, determination of key physicochemical parameters (Log *P*, pK_a) and full structural elucidation of two salt forms of (±)-4′-methylmethcathinone by NMR, IR, UV and MS. Additionally we report fully validated chromatographic methods (HPLC and GCMS) for the detection and quantitative analysis of the substance both in its pure form or in the presence of a number of common adulterants used in illicit drug manufacture.

2. Experimental

All reagents were of commercial quality (obtained from Sigma–Aldrich, Gillingham, UK or Alfa-Aesar, Heysham, UK) and used without further purification. Solvents were dried, where necessary, using standard procedures. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL AS-400 (400 MHz) instrument (JEOL, Tokyo, Japan). Infrared spectra were obtained in the range of

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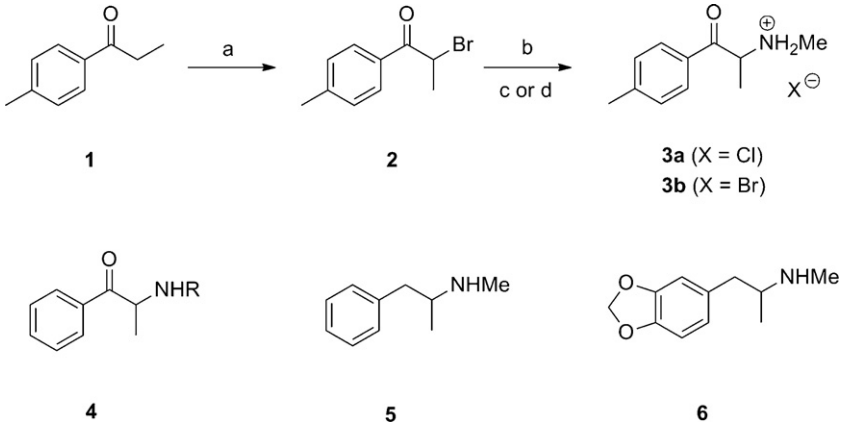


Scheme 1. *Reagents and Conditions*: (a) Br_2/HBr (48% in water)/CH_2Cl_2/rt/1h (99.6%); (b) $MeNH_2$.HCl/NEt_3/CH_2Cl_2/rt/24h; (c) HCl (3M in *n*-butanol)/^{i}PrOH/rt/1h (51.2% from **2**); (d) HBr (33% in AcOH)/AcOH/rt/1h (67.4% from **2**).

4000–400 cm^{-1} using a ThermoScientific Nicolet iS10ATR-FTIR instrument (ThermoScientific, Rochester, USA). Mass spectra were recorded on a ThermoScientific LTQ ORBITRAP mass spectrometer (ThermoScientific, Rochester, USA) using electrospray ionisation. Ultraviolet spectra were obtained using a Unicam 300 UV spectrophotometer (ThermoScientific, Rochester, USA). Thin-Layer Chromatography (TLC) was carried out on aluminium-backed SiO_2 plates (Merck, Darmstadt, Germany) and spots visualised using ultra-violet light (254 nm). Microanalysis was carried out in the Department of Pure and Applied Chemistry using a PerkinElmer 2400 Series II elemental analyser (PerkinElmer, San Jose, USA). Melting points were determined either using a Gallenkamp melting point apparatus (Gallenkamp-Sanyo, UK) (**2**) or by differential scanning calorimetry DSC; Netzsch STA449C, Netzsch-Gerätebau, Wolverhampton, UK (**3a** and **3b**). Optical rotation values $[\alpha]_D^{22}$ (10^{-1} deg cm^2 g^{-1}) were performed on a Bellingham & Stanley ADP-220 polarimeter (Bellingham & Stanley, Tunbridge Wells, UK). Log *P* and pK_a values were determined on a Sirius T3 instrument (Sirius Analytical Instruments, Forest Row, UK). Calculated Log *P* and pK_a values were determined using Pipeline Pilot software, Vers. 7.5 (Accelrys, San Diego, USA).

2.1. Synthesis of (±)-4′-methyl-2-bromopropiophenone (**2**) [13,14]

The title compound was prepared using the method reported by Kalendra et al. [13] with the following modifications: To a solution of 4-methylpropiophenone (**1**, 14.8 g, 100 mmol) in dichloromethane (50 mL) was added one drop of hydrobromic acid (48% aqueous solution) and one drop of bromine. The mixture was stirred at room temperature until the bromine colour was discharged (*circa.* 30 s) and additional bromine (5.1 mL, 100 mmol total including the original drop) was introduced dropwise with stirring. The mixture was stirred for 1 h and then concentrated *in vacuo* to reveal a dark orange oil which solidified on standing. The crude product was recrystallised from diethyl ether to give (±)-4′-methyl-2-bromopropiophenone (22.6 g, 99.6%) as colourless prisms. Mpt. (Et_2O) 76–77 °C (lit. [14] 75–77 °C); R_f [SiO_2, EtOAc:*n*-hexane (1:3)] = 0.79; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$) δ = 7.91 (2H, d, *J* = 8.3 Hz, AA′BB′), 7.27 (2H, d, *J* = 8.3 Hz, AA′BB′), 5.28 (1H, q, *J* = 7.0 Hz, **CH**(Br)CH_3), 2.42 (3H, s, Ar**CH_3**) and 1.86 ppm (3H, d, *J* = 7.0 Hz, CH(Br)**CH_3**); ^{13}C NMR (400 MHz, 23 °C, $CDCl_3$) δ = 193.1 (C=O), 144.8 (ArC), 131.6 (ArC), 129.5 (2× ArCH), 129.1 (2× ArCH), 41.6 (**CH**(Br)CH_3), 21.8 ($ArCH_3$) and 20.3 ppm (CH(Br)**CH_3**); GCMS (EI, 70 eV): t_R = 5.09 min; *m*/*z* = 225.5 (5, $[MBr^{79}]^+$), 227.5 (5, $[MBr^{81}]^+$), 118.3 (100), 108.4 (12), 90.5 (85) and 64.5 (70%). The bromide was used in the subsequent steps without further purification.

2.2. Synthesis of (±)-4′-methylmethcathinone hydrochloride [(±)-mephedrone hydrochloride] (**3a**) [9,10]

The title compound was prepared using the method reported by Camilleri et al. [9] with the following modifications: to a suspension of (±)-4′-methyl-2-bromopropiophenone (4.54 g, 20 mmol) and methylamine hydrochloride (1.35 g, 20 mmol) in dichloromethane (40 mL) was added triethylamine (5.58 mL, 40 mmol). The mixture was stirred at room temperature overnight and then acidified (pH ~ 1) with 6 M hydrochloric acid (50 mL). The aqueous layer was washed with dichloromethane (3 × 50 mL), basified (pH ~ 10) with 5 M sodium hydroxide (*circa.* 100 mL) and then re-extracted with dichloromethane (3 × 50 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo* to give a viscous yellow oil. The oil was dissolved in isopropanol (4 mL), treated with hydrochloric acid (3 M solution in butanol, 10 mL) and stirred at room temperature for 1 h. The mixture was diluted with diethyl ether (150 mL) and stirred to reveal a pale yellow solid (*circa.* 30 min). The crude product was filtered, washed with diethyl ether and recrystallised from acetone to give (±)-4′-methylmethcathinone hydrochloride (1.09 g, 51.2% from **2**) as a colourless powder. Mpt. (acetone) 251.18 °C; R_f [SiO_2, EtOAc:*n*-hexane (1:3)] = 0.11; $[\alpha]_D^{22}$ = 0 (*c* = 0.5 g/100 mL in MeOH); found: C, 61.61; H, 7.35; N, 6.17. $C_{11}H_{16}ClNO$ requires C, 61.82; H, 7.55 and N, 6.55%; UV (EtOH): λ_{max} = 259.5 nm (*A* = 0.735, *c* = 9.95 × 10^{-4} g/100 mL); IR (ATR–FTIR): 2717.5 (NH_2^+), 1689.5 (C=O), 1606.3 cm^{-1} (C=C); ^{1}H NMR (400 MHz, 60 °C, d_6-DMSO) δ = 9.35 (2H, br s, CH(**NH_2^+**CH_3)CH_3); 7.96 (2H, d, *J* = 8.3 Hz, AA′BB′), 7.41 (2H, d, *J* = 8.3 Hz, AA′BB′), 5.08 (1H, q, *J* = 7.2 Hz, **CH**($NH_2^+$$CH_3$)$CH_3$), 2.59 (3H, s, CH($NH_2^+$**$CH_3$**)$CH_3$), 2.41 (3H, s, Ar**$CH_3$**) and 1.46 ppm (3H, d, *J* = 7.2 Hz, CH($NH_2^+$$CH_3$)**$CH_3$**); ^{13}C NMR (400 MHz, 60 °C, d_6-DMSO) δ = 195.8 (C=O, C1), 145.5 (ArC, C4′), 130.4 (ArC, C1′), 129.7 (2× ArCH, C3′/C5′), 128.9 (2× ArCH, C2′/C6′), 58.1 (**CH**CH_3, C2), 30.6 (NCH_3,), 21.2 ($ArCH_3$, C7′) and 15.5 ppm (CH**CH_3**, C3); LRMS (ESI+, 70 eV): *m*/*z* = 178 (6%, $[M+H]^+$), 160 (47), 145 (100), 130 (7), 119 (16) and 91 (5); HRMS (ESI+, 70 eV) calculated for [M+H] $C_{11}H_{16}NO$: 178.1226, found: 178.1226.

2.3. Synthesis of (±)-4′-methylmethcathinone hydrobromide [(±)-mephedrone hydrobromide] (**3b**)

The title compound was prepared using an analogous method for (**3a**) with the following modifications: The yellow oil, (±)-4′-methylmethcathinone, was dissolved in glacial acetic acid

(2 mL), treated with hydrobromic acid (33% solution in acetic acid, 5 mL) and stirred at room temperature for 1 h. The mixture was diluted with diethyl ether (100 mL) and stirred to reveal a pale beige solid (*circa*. 30 min). The crude product was filtered, washed with diethyl ether and recrystallised from acetone to give (±)-4′-methylmethcathinone hydrobromide (1.74 g, 67.4% from **2**) as an off-white powder. Mpt. (acetone) 205.25 °C; R_f [SiO_2, EtOAc:*n*-hexane (1:3)] = 0.10; $[\alpha]_D^{22} = 0$ (c = 0.5 g/100 mL in MeOH); found: C, 50.87; H, 6.16; N, 5.32. $C_{11}H_{16}BrNO$ requires C, 51.18; H, 6.25 and N, 5.43%; UV (EtOH): λ_{max} = 257.5 nm (A = 0.665, $c = 1.105 \times 10^{-3}$ g/100 mL); IR (ATR–FTIR): 2738.5 (NH_2^+), 1682.8 (C=O) and 1604.4 cm^{-1} (C=C); ^{1}H NMR (400 MHz, 60 °C, d_6-DMSO) δ = 8.95 (2H, br s, CH(**NH_2**$^+$$CH_3$)$CH_3$); 7.94 (2H, d, J = 8.2 Hz, AA′BB′), 7.43 (2H, d, J = 8.2 Hz, AA′BB′), 5.14 (1H, q, J = 7.2 Hz, **CH**($NH_2^+CH_3$)CH_3), 2.64 (3H, s, CH(NH_2^+**CH_3**)CH_3), 2.43 (3H, s, Ar**CH_3**) and 1.46 ppm (3H, d, J = 7.2 Hz, CH($NH_2^+CH_3$)**CH_3**); ^{13}C NMR (400 MHz, 60 °C, d_6-DMSO) δ = 195.5 (C=O, C1), 145.2 (ArC, C4′), 130.2 (ArC, C1′), 129.4 (2× ArCH, C3′/C5′), 128.6 (2× ArCH, C2′/C6′), 58.1 (**CH**CH_3, C2), 30.5 (NCH_3,), 20.9 ($ArCH_3$, C7′) and 15.1 ppm (CH**CH_3**, C3); LRMS (ESI+, 70 eV): m/z = 178 (4%, $[M+H]^+$), 160 (46), 145 (100), 130 (5), 119 (16) and 91 (5); HRMS (ESI+, 70 eV) calculated for [M+H] $C_{11}H_{16}NO$: 178.1226, found: 178.1226.

2.4. High performance liquid chromatography (HPLC)

Reverse phase high-performance liquid chromatography was performed with an integrated Agilent HP Series 1100 Liquid Chromatograph (Agilent Technologies, Wokingham, UK) fitted with an in-line degasser, 100-place autoinjector and single channel, tunable UV absorbance detector (258 nm, for the pure substances) or a PDA-UV absorbance detector (for the adulterants method). Data analysis was carried out using ChemStation for LC (Ver. 10.02) software (Agilent Technologies, Wokingham, UK). The flow rate was 0.8 mL min^{-1} with an injection volume of 10 μL. Six replicate injections of each calibration standard were performed. The stationary phase (ACE 3C_{18}, 150 mm × 4.6 mm i.d., 3 μm particle size) used in the study was obtained from HiChrom Limited (Reading, UK). The column was fitted with a guard cartridge (ACE 3C_{18}) and maintained at an isothermal temperature of 22 °C with an Agilent HP Series 1100 column oven with a programmable controller (Agilent Technologies, Wokingham, UK).

Preparation of aqueous ammonium formate buffer (pH 3.5 ± 0.02): 1.30 g ammonium formate was dissolved in 1.8 L ultra-pure deionised water and the pH of the solution adjusted by dropwise addition of formic acid (98–100%) to pH 3.5 (±0.02). The mixture was transferred to a 2 L clear glass volumetric flask and diluted to volume with ultra-pure deionised water. The mobile phases used in this study were prepared by separately mixing volumes of the 10 mM formate buffer and organic modifier in the appropriate proportions denoted in the Section 3. Prior to use, all mobile phases were vacuum filtered through a 0.45 mm pore filter paper and degassed, using an ultrasonic bath, for 10 min at 25 °C.

Calibration standards (pure substances): 2.0 mg (±)-mephedrone was weighed accurately into a 100 mL clear glass volumetric flask and diluted to volume with mobile phase to give a solution containing 20.0 μg mL^{-1} (±)-mephedrone. This solution was then further diluted with mobile phase to give calibration standards containing 10.0 μg mL^{-1}, 5.0 μg mL^{-1}, 2.5 μg mL^{-1}, 1 μg mL^{-1} and 0.5 μg mL^{-1} (±)-mephedrone. Calibration standards ranging from 0.5 μg mL^{-1} to 10.0 μg mL^{-1} of (±)-mephedrone containing 2.5 μg mL^{-1} of nicotinamide as internal standard were prepared in mobile phase using an analogous procedure.

Calibration standards (adulterants study): 10.0 mg of each component (paracetamol, caffeine, methylone, lidocaine, mephedrone, ketamine, diamorphine, benzocaine, sucrose, mannitol and lactose) was weighed accurately into a 100 mL clear glass volumetric flask and diluted to volume with mobile phase to give a solution containing each component at 100.0 μg mL^{-1}. This solution was then further diluted with mobile phase (and the appropriate amount of IS added) to give calibration standards containing 25.0 μg mL^{-1}, 20.0 μg mL^{-1}, 10.0 μg mL^{-1}, 5.0 μg mL^{-1}, 2.5 μg mL^{-1}, 1 μg mL^{-1} and 0.5 μg mL^{-1} of each component (containing 2.5 μg mL^{-1} nicotinamide in each case).

2.5. Gas chromatography–mass spectrometry (GC–MS)

GC–MS analysis was performed using an Agilent 6850 GC and a VS 975C mass selective detector (MSD) (Agilent Technologies, Wokingham, UK). The mass spectrometer was operated in the electron ionization mode at 70 eV. Separation was achieved with a capillary column (HP5 MS, 30 m × 0.25 mm i.d., 0.25 μm) with helium as the carrier gas at a constant flow rate of 1.0 mL min^{-1}. The oven temperature programme started at 140 °C for 1 min, was increased to 280 °C at a rate of 12.5 °C min^{-1}, and then held at 280 °C for 12.5 min. A 1 μL aliquot of (±)-mephedrone (1 mg mL^{-1} in methanol) was injected in the split (50:1) mode with a purge time of 1 min. The injector and the GC interface temperatures were maintained at 280 °C and 230 °C, respectively. Mass spectra were obtained in the full scan mode (50–550 amu). Chromatographic separation was monitored in SIM mode. Calibration standards ranging from 0.001 mg mL^{-1} to 1 mg mL^{-1} of (±)-mephedrone and including 1 mg mL^{-1} of eicosane as internal standard were prepared in methanol.

2.6. Supplementary information

The supplementary information relating to this work contains all spectral data for the synthesized compounds (**2**), (**3a**) and (**3b**).

3. Results and discussion

Samples of (±)-mephedrone were prepared as both the hydrochloride (**3a**) and hydrobromide (**3b**) salts. The synthesis of the two racemic target compounds was achieved using a modification of the method reported by Camilleri et al. from (±)-4′-methyl-2-bromopropiophenone (**2**) in 51.2% and 67.4% yield, respectively (Scheme 1) [9]. Both compounds were obtained as stable, colourless to off-white powders after recrystallisation from acetone and exhibited an optical rotation $[\alpha]_D^{22}$ of 0 (c = 0.5 g/100 mL, MeOH). The purity of the samples was confirmed by elemental analysis. Analysis of (**3a**) revealed 61.61% (C), 7.35% (H) and 6.17% (N) which corresponded very closely for the theoretical percentage for the hydrochloride salt of 61.82% (C), 7.55% (H) and 6.55% (N). Similarly the hydrobromide salt (**3b**) gave 50.87% (C), 6.16% (H) and 5.32% (N) which was in agreement with its expected elemental composition (51.18% (C), 6.25% (H) and 5.43% (N)). The melting points for (**3a**) and (**3b**) were determined by differential scanning calorimetry (DSC) and gave sharp melting points at 251.18 °C and 205.25 °C, respectively. Though Gibbons et al. predicted selected molecular properties (including pK_a and Log P) for (±)-mephedrone using Vega ZZ and ChemSilico modelling packages – no experimental values have, to date, been determined [11]. The pK_a values and Log P values (**3a**, pK_a = 8.69; Log P = 1.96; **3b**, pK_a = 8.69; Log P = 1.97) were determined for each salt form using a Sirius T3 instrument and are in good agreement with our calculated values (pK_a = 7.64; Log P = 2.01 as determined by the Pipeline Pilot, Accelerys, Vers. 7.5).

The ^{1}H NMR spectrum of the hydrochloride salt (**3a**) (obtained at 60 °C in d_6-DMSO,[1] Fig. 1) showed the characteristic AA′BB′

[1] The ^{1}H NMR spectra were recorded at 60 °C to ensure that the quartet at 5.08 ppm (which broadens and coalesces at ambient temperature) was fully

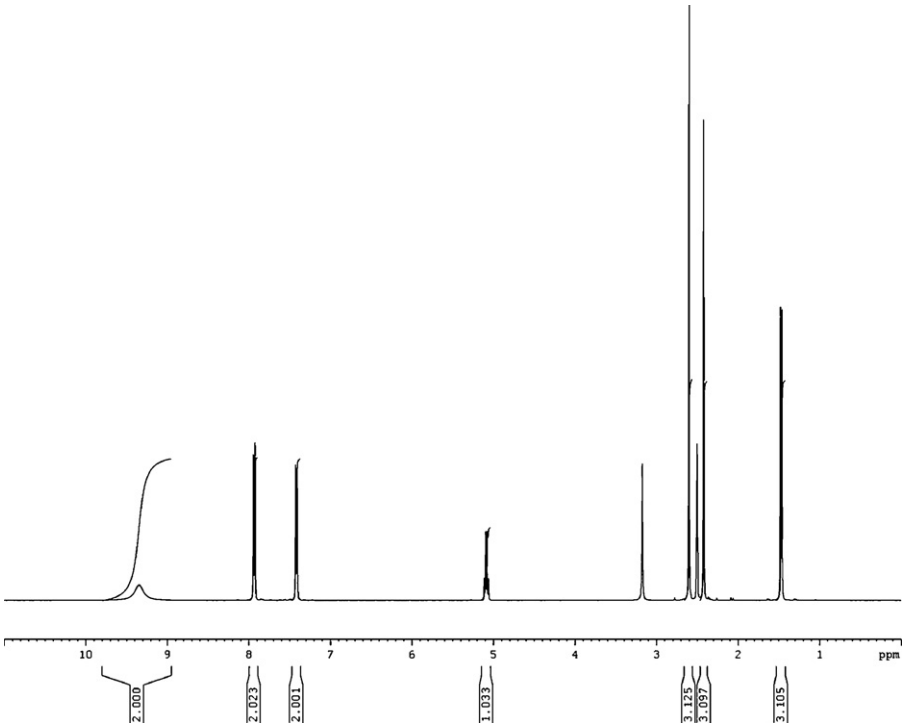


Fig. 1. ^{1}H NMR spectrum (400 MHz, d_6-DMSO, 60 °C) of (±)-mephedrone.HCl (**3a**).

aromatic system for a unsymmetrically *para*-disubstituted aromatic system (7.96 ppm, AA′BB′, 2H, J = 8.3 Hz; 7.41 ppm, AA′BB′, 2H, J = 8.3 Hz), a deshielded one-hydrogen quartet at 5.08 ppm (**CH**CH_3, J = 7.2 Hz), a deshielded three-hydrogen singlet at 2.59 ppm (NH**CH_3**), a slightly deshielded methyl singlet attributable to the methyl attached the aromatic ring (Ar**CH_3**, 2.41 ppm) and finally a methyl doublet (CH**CH_3**, 1.46 ppm, J = 7.2 Hz). Unlike the previously reported spectra (which were run in CD_2Cl_2–$CDCl_3$ [9] or CD_3OD [11]) a broad signal at 9.35 ppm was consistently observed and corresponded to the ammonium salt protons. A similar spectrum was obtained for the corresponding hydrobromide (**3b**) (see Supplementary information). It was also observed that in CD_3OD both salts gave spectra consistent with that obtained by Gibbons et al. where the peak for the ammonium salt protons are absent due to rapid exchange with the solvent confirming that the synthesised sample is identical to the "*street*" samples obtained by the other researchers. In all cases the ^{1}H NMR spectrum indicated that both these samples were clean with no apparent starting materials or unreacted reagents such as methylamine which has been seen before in other legal highs such as the fluorinated cathinone analogue, flephedrone [15].

The ^{13}C NMR spectra (obtained at 60 °C in d_6-DMSO, Fig. 2) supports that both materials are predominantly pure with nine distinct carbon signals. Full spectral analysis using both HMQC and HMBC methods allowed unambiguous assignment of all carbon and hydrogen resonances and gave data which was consistent with the literature and indicated that both samples were (±)-mephedrone. For (**3a**) the *N*-methyl resonance (δ = 2.59 ppm) gave a ^{3}J correlation to C2 which is in turn coupled to the methyl doublet (C3). In the HMBC spectrum (see Supplementary information), the protons of the methyl resonance (δ = 1.46 ppm) are coupled to a deshielded carbon (δ = 195.8 ppm, C1) completing the assignment of the 2-aminomethyl-propan-1-one side chain. Further couplings in the HMBC spectrum between H2′/H6′ and C1 (^{3}J) supports placement of the propan-1-one side chain at C1′ on the aromatic nucleus (between C6′ and C2′) and correlations between H2′/H6′ and H3′/H5′ confirmed the AA′BB′ aromatic system. The methyl singlet at 2.41 ppm (C7′) exhibits a ^{3}J HMBC correlation to C3′/C5′ and a ^{2}J correlation to C4′ concluding the assignment of all resonances. Similar observations were obtained for the hydrobromide (**3b**) and the data for both salts is presented in Table 1.

The HRESIMS analysis of the two salts (**3a** and **3b**) gave an $[M+H]^+$ peak at 178.1226 (calculated for $C_{11}H_{16}NO$ = 178.1226) supporting the molecular formula of $C_{10}H_{15}NO$ and the identity of both samples as (±)-mephedrone. The mass spectrum of the hydrochloride salt (**3a**) is shown in Fig. 3 and exhibits a $[M+H]^+$ parent ion (m/z = 178.1226) of low abundance (6%, $C_{11}H_{16}NO$), with the observed fragment ions (through collision induced decomposition) at m/z = 160.1120 (47%, calculated for $C_{11}H_{14}N$ = 160.1121), 145.0885 (100%, calculated for $C_{10}H_{11}N$ = 144.0886), 130.0651 (7%, calculated for C_9H_8N = 130.0651), 119.0855 (16%, calculated for C_9H_{11} = 119.0855) and 91.0542 (5%, calculated for C_7H_7 = 91.0542). An analogous CID fragmentation pattern was observed for the hydrobromide salt (**3b**, see Supplementary information for MS spectra).

The infrared spectra of (±)-mephedrone hydrochloride (**3a**, Fig. 4) and hydrobromide (**3b**, see Supplementary information) was collected on an attenuated total reflection infrared (ATR–FTIR) spectrometer and shows strong C=O absorption bands at 1685.9 (**3a**) and 1682.8 cm^{-1} (**3b**), respectively. Both samples exhibit additional broad C=C absorptions at 1606.3 (**3a**) and 1604.4 (**3b**) cm^{-1}, indicative of an aromatic nucleus, and 2717.5 (**3a**) and 2738.5 (**3b**) cm^{-1} due to the NH_2^+ stretch. The data is consistent with the ATR–FTIR spectrum reported by Camilleri et al. [9].

The theoretical wavelength of maximum absorbance (as calculated from Scott's Rules [16]) was determined to be 256 nm. The ultraviolet spectrum of (±)-mephedrone hydrochloride (**3a**) obtained in absolute ethanol (Fig. 5a) is in agreement with the theoretical value and shows λ_{max} at 259.5 nm (A = 0.735,

resolved. The chemical shifts of all signals were observed to be consistent at both ambient (25 °C) and high (60 °C) temperatures. For consistency the ^{13}C NMR spectra were obtained under analogous conditions.

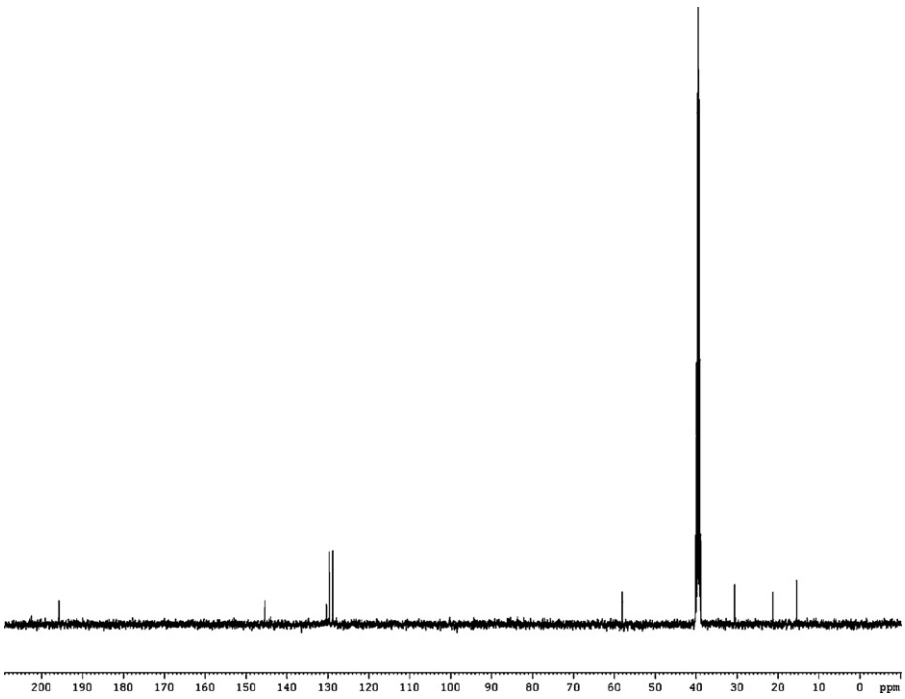
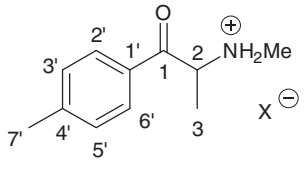


Fig. 2. ^{13}C NMR spectrum (100 MHz, d_6-DMSO, 60 °C) of (±)-mephedrone.HCl (**3a**).

Table 1
^{1}H (400 MHz), ^{13}C (100 MHz) NMR spectral data and ^{1}H–^{13}C long-range correlations of (±)-mephedrone hydrochloride (**3a**) and hydrobromide (**3b**) in d_6-DMSO. Chemical shifts (δ) in ppm; coupling constants (J) in Hz.



3a (X = Cl)
3b (X = Br)

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Position	(±)-Mephedrone hydrochloride (**3a**)				(±)-Mephedrone hydrobromide (**3b**)			
	^{1}H	^{13}C	^{2}J	^{3}J	^{1}H	^{13}C	^{2}J	^{3}J
1	–	195.8	–	–	–	195.5	–	–
2	5.08 q, J = 7.2	58.1	C1, C3	NCH_3	5.14 q, J = 7.2	58.1	C1, C3	NCH_3
3	1.46 d, J = 7.2	15.5	C2	C1	1.46 d, J = 7.2	15.1	C2	C1
1′	–	130.4	–	–	–	130.2	–	–
2′/6′	7.96 d, J = 8.3	128.9	C3′/C5′	C2′/C6′, C4′, C1	7.94 d, J = 8.2	128.6	C3′/C5′	C2′/C6′, C4′, C1
3′/5′	7.41 d, J = 8.3	129.7	C2′/C6′	C3′/C5′, C1′	7.43 d, J = 8.2	129.4	C2′/C6′	C3′/C5′, C1′
4′	–	145.5	–	–	–	145.2	–	–
7′	2.41 s	21.2	C4′	C3′/C5′	2.43 s	20.9	C4′	C3′/C5′
NCH_3	2.59 s	30.6	–	C2	2.64 s	30.5	–	C2
NH_2^+	9.35 br s	–	–	–	8.95 br s	–	–	–

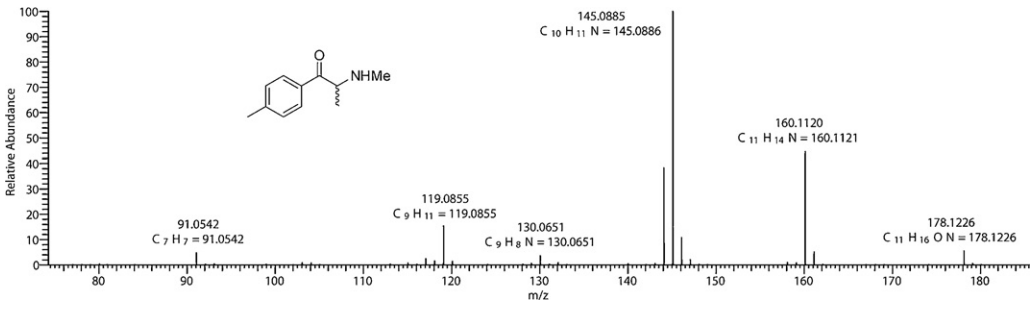

Fig. 3. HRESIMS spectrum of (±)-mephedrone.HCl (**3a**).

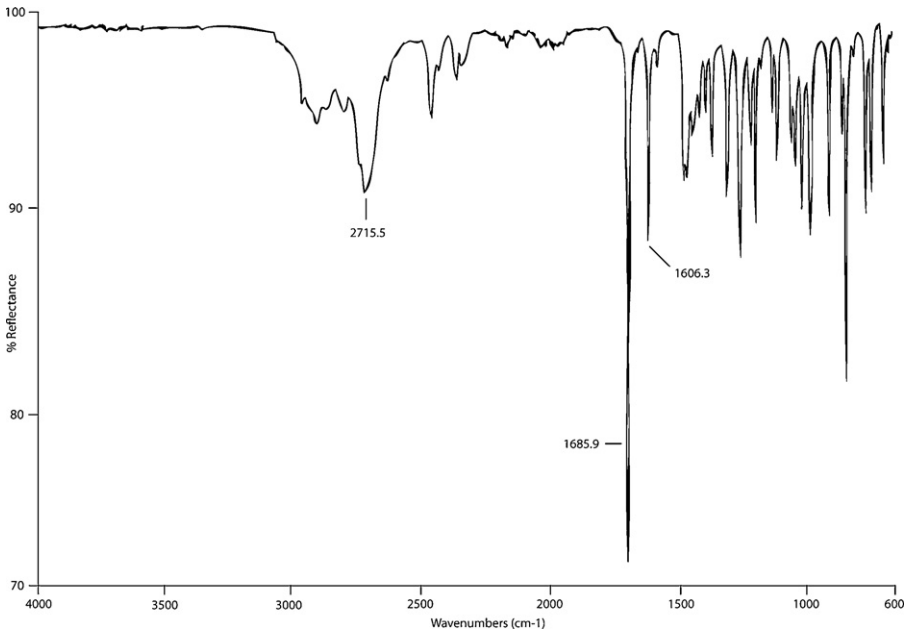

Fig. 4. ATR–FTIR spectrum of (±)-mephedrone.HCl (**3a**).

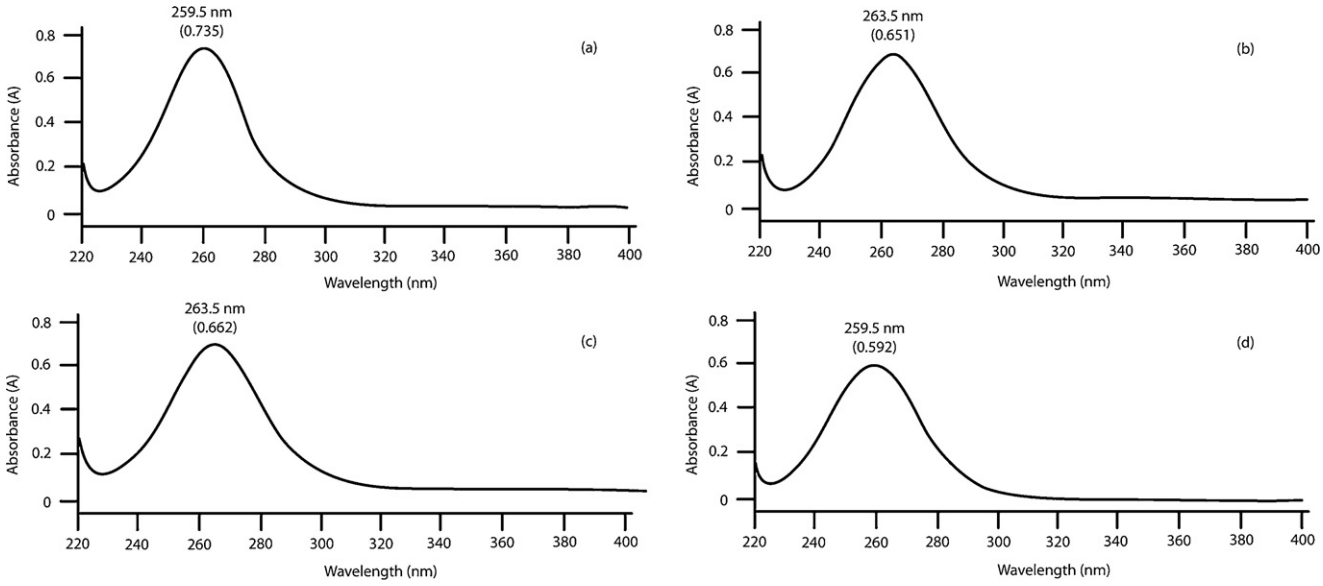

Fig. 5. UV spectra of (±)-mephedrone.HCl (**3a**). (a) (**3a**, $c = 9.9 \times 10^{-4}$ g/100 mL in EtOH); (b) (**3a**, $c = 9.1 \times 10^{-4}$ g/100 mL in H_2O); (c) (**3a**, $c = 9.1 \times 10^{-4}$ g/100 mL in 0.1 M aqueous HCl); (d) (**3a**, $c = 9.1 \times 10^{-4}$ g/100 mL in 0.1 M aqueous NaOH).

$c = 9.9 \times 10^{-4}$ g/100 mL). Similar spectra were obtained in deionised water ($\lambda_{max} = 263.5$ nm, $A = 0.651$, $c = 9.1 \times 10^{-4}$ g/100 mL) or 0.1 M aqueous hydrochloric acid ($\lambda_{max} = 263.5$ nm, $A = 0.662$, $c = 9.1 \times 10^{-4}$ g/100 mL) with a slight bathochromic shift (*circa.* 4 nm) observed due to the solvent effect. In 0.1 M aqueous sodium hydroxide a hypsochromic shift (with a slight hyperchromic shift reduction in absorbance intensity) to 259.5 nm ($A = 0.592$, $c = 9.1 \times 10^{-4}$ g/100 mL) was observed in the spectrum of (**3a**) and may be due to a change in the ionisation of the sample (Fig. 5d). Similar ultraviolet spectra were obtained for the corresponding hydrobromide salt (**3b**) and the UV data for (**3a**) and (**3b**) is summarised in Table 2.

Previous researchers have reported utilising HPLC and LC–MS techniques to determine (±)-mephedrone for quality/impurity

Table 2
Ultraviolet spectral data of (±)-mephedrone hydrochloride (**3a**) and hydrobromide (**3b**).

Solvent	(±)-Mephedrone hydrochloride (**3a**)				(±)-Mephedrone hydrobromide (**3b**)			
	EtOH	H_2O	0.1 M HCl	0.1 M NaOH	EtOH	H_2O	0.1 M HCl	0.1 M NaOH
Concn. (g/100 mL)	9.9×10^{-4}	9.1×10^{-4}	9.1×10^{-4}	9.1×10^{-4}	1.11×10^{-3}	1.02×10^{-3}	1.02×10^{-3}	1.02×10^{-3}
λ_{max} (nm)	259.5	263.5	263.5	259.5	257.5	263.5	264.0	259.5
Absorbance (A)	0.735	0.651	0.662	0.592	0.665	0.617	0.614	0.548

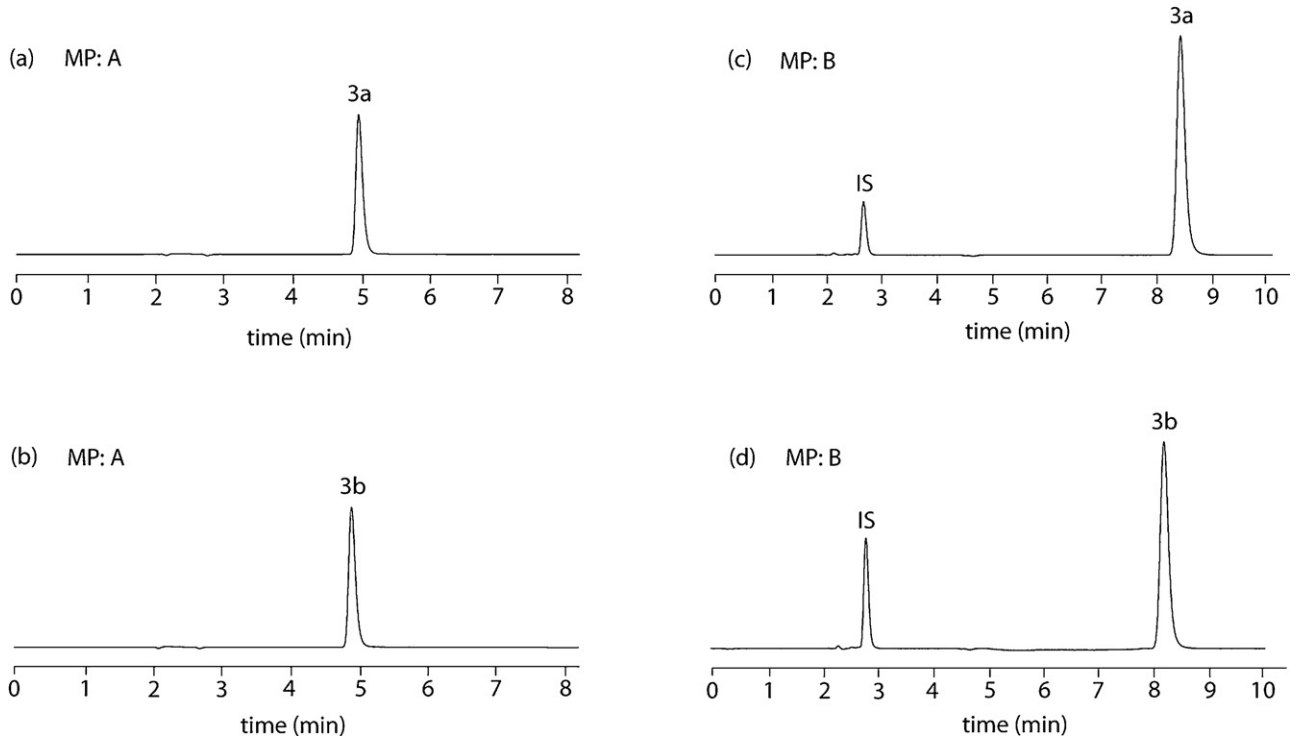

Fig. 6. Representative chromatograms of solutions containing: (a) (±)-mephedrone.HCl (**3a**, 5 μg mL^{-1}); (b) (±)-mephedrone.HBr (**3b**, 5 μg mL^{-1}); (c) (±)-mephedrone.HCl (**3a**, 5 μg mL^{-1}) and nicotinamide (IS, 2.5 μg mL^{-1}) and (d) (±)-mephedrone.HBr (**3b**, 5 μg mL^{-1}) and nicotinamide (IS, 2.5 μg mL^{-1}) obtained using ACE C_{18} column (150 × 4.6 mm i.d., particle size: 3 mm); mobile phases: A: methanol:10 mM ammonium formate (pH 3.5) (40:60); B: methanol:10 mM ammonium formate (pH 3.5) (30:70); detector wavelength: 258 nm.

Table 3
Summary of validation data for the quantification of (±)-mephedrone hydrochloride (**3a**) and hydrobromide (**3b**) by either an internal and external standard HPLC method using ACE C_{18} column (150 mm × 4.6 mm i.d., particle size: 3 μm); internal standard = nicotinamide; detector wavelength = 258 nm.

Parameter	Analyte	External standard method		Internal standard method	
		(**3a**)	(**3b**)	(**3a**)	(**3b**)
Mobile phase	–	*A*[d]	*A*[d]	*B*[e]	*B*[e]
t_o (min)	Uracil	2.2	2.2	2.2	2.2
t_R (min)	Nicotinamide	–	–	2.7	2.7
	Mephedrone	4.7	4.9	8.4	8.5
RRT[a]	Nicotinamide	–	–	0.32	0.32
	Mephedrone	1.00	1.00	1.00	1.00
Capacity factor (k')	Nicotinamide	–	–	0.23	0.23
	Mephedrone	1.14	1.23	2.82	2.86
Response factor (RRF)	Nicotinamide	–	–	0.28	0.34
	Mephedrone	1.00	1.00	1.00	1.00
N (plates)	Mephedrone	12,000 (80,000)[f]	12,000 (80,000)[f]	16,000 (107,000)[f]	16,700 (111,000)[f]
H (m)	Mephedrone	1.25×10^{-5}	1.25×10^{-5}	0.94×10^{-5}	0.90×10^{-5}
Resolution (R_s)	R_s (nicotinamide, mephedrone)	–	–	26.6	26.6
Symmetry factor (A_s)	Nicotinamide	–	–	1.27	1.28
	Mephedrone	1.29	1.33	1.27	1.34
LOD[b] (μg mL^{-1})	Mephedrone	0.09	0.08	0.08	0.13
LOQ[c] (μg mL^{-1})	Mephedrone	0.28	0.25	0.25	0.39
Co-efficient of regression (r^2)	Mephedrone	0.999[g]	0.999[h]	0.999[i]	0.998[j]
Precision (% RSD) (n = 6)	Mephedrone				
	10 μg mL^{-1}	0.36	0.22	0.21	1.85
	5 μg mL^{-1}	0.90	0.58	0.45	0.39
	2.5 μg mL^{-1}	0.87	0.40	0.51	1.59
	1 μg mL^{-1}	0.36	0.10	0.59	2.07
	0.5 μg mL^{-1}	0.72	0.37	0.66	1.61

[a] Relative retention time.
[b] Limit of detection (based on the standard deviation of the response and the slope).
[c] Limit of quantification (based on the standard deviation of the response and the slope).
[d] Methanol:10 mM ammonium formate (pH 3.5) (40:60).
[e] Methanol:10 mM ammonium formate (pH 3.5) (30:70).
[f] N expressed in plates per metre.
[g] $y = 41802.8852x - 7406.8403$.
[h] $y = 80556.6788x - 2075.9796$.
[i] $y = 0.37004x - 0.05721$.
[j] $y = 0.3989x - 0.0111$.

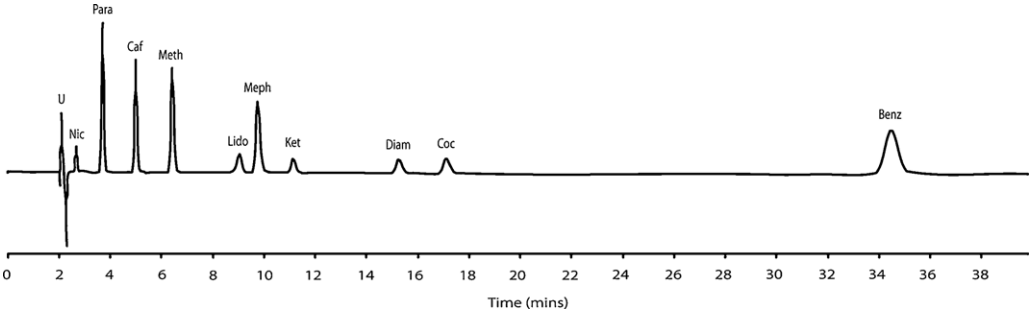

Fig. 7. Representative chromatogram of a solution containing nicotinamide (Nic, 2.5 μg mL^{-1}), paracetamol (Para, 10 μg mL^{-1}); caffeine (Caf, 10 μg mL^{-1}); methylone (Meth, 10 μg mL^{-1}); lidocaine (Lido, 10 μg mL^{-1}); mephedrone (Meph, 10 μg mL^{-1}), ketamine (Ket, 10 μg mL^{-1}); diamorphine (Diam, 10 μg mL^{-1}); cocaine (Coc, 10 μg mL^{-1}) and benzocaine (Benz, 10 μg mL^{-1}) obtained using ACE C18 column (150 × 4.6 mm i.d., particle size: 3 mm); mobile phase: methanol:10 mM ammonium formate (pH 3.5) (28:62); detector: PDA; t_o (2.2 min) was determined from the t_R of uracil (U).

Table 4
Summary of validation data for the quantification of (±)-mephedrone in the presence of eight common adulterants using an internal standard HPLC method using ACE C18 column (150 mm × 4.6 mm i.d., particle size: 3 μm); mobile phase: methanol:10 mM ammonium formate (pH 3.5) (28:62); internal standard = nicotinamide (t_R = 2.67 min, RRT = 0.96; % RSD (t_R) = 1.09, n = 30); detector: PDA.

	Para	Caf	Meth	Lido	Meph[f,g]	Ket	Diam	Coc	Benz
t_R (min) (t_0 = 2.2 min)[a]	3.7	4.9	6.4	9.0	9.8	11.1	15.6	17.1	34.4
RRT[b]	0.33	0.51	0.66	0.93	1	1.14	1.60	1.76	3.53
RRF[c]	0.93	0.92	0.93	0.91	1	0.95	0.92	0.91	0.90
Capacity factor (k')	0.78	1.39	2.08	3.33	3.67	4.33	6.45	7.19	15.46
Resolution (R_s)	7.2	7.2	6.9	9.2	2.3	4.2	9.9	3.2	20.9
Symmetry factor (A_s)	1.19	1.26	1.21	0.97	1.36	1.36	1.23	1.30	1.07
LOD[d] (μg mL^{-1})	0.24	0.26	0.23	1.05	0.26	1.08	0.99	1.0	0.28
LOQ[e] (μg mL^{-1})	0.72	0.79	0.70	3.19	0.97	3.27	3.01	3.03	0.86
Co-efficient of regression (r^2)	0.995[h]	0.993[i]	0.995[j]	0.988[k]	0.993[l]	0.987[m]	0.987[n]	0.989[o]	0.993[p]
Precision (% RSD) (n = 6)									
0.5 (g mL^{-1}	2.58	1.77	1.95	n.d.	2.75	n.d.	n.d.	n.d.	2.75
1.0 (g mL^{-1}	2.55	1.89	2.12	n.d.	1.67	n.d.	n.d.	n.d.	1.67
2.5 (g mL^{-1}	1.71	2.49	2.41	2.24	2.68	2.16	2.10	1.77	2.68
5.0 (g mL^{-1}	0.80	1.47	1.10	2.48	0.77	1.65	2.17	1.89	0.77
10.0 (g mL^{-1}	0.34	0.77	0.39	2.72	0.72	1.83	1.70	2.49	0.72
20.0 (g mL^{-1}	n.d.	n.d.	n.d.	1.94	n.d.	2.92	1.69	1.47	n.d.
25.0 (g mL^{-1}	n.d.	n.d.	n.d.	0.86	n.d.	0.72	1.02	0.77	n.d.

Key: Para, paracetamol; Caf, caffeine; Meth, methylone; Lido, lidocaine; Meph, mephedrone; Ket, ketamine; Diam, diamorphine; Coc, cocaine; Benz, benzocaine and n.d., not determined.

[a] Determined from the retention time of uracil eluting from the column.
[b] Relative retention time.
[c] Relative response factor.
[d] Limit of detection (based on the standard deviation of the response and the slope).
[e] Limit of quantification (based on the standard deviation of the response and the slope).
[f] N = 113,000 plates per metre.
[g] $H = 0.8 \times 10^{-5}$ m.
[h] $y = 0.5404x + 0.1208$.
[i] $y = 0.3733x + 0.0719$.
[j] $y = 0.4483x + 0.124$.
[k] $y = 0.203x - 0.2545$.
[l] $y = 0.3785x + 0.0478$.
[m] $y = 0.1512x - 0.2476$.
[n] $y = 0.1693x - 0.1948$.
[o] $y = 0.2139x - 0.2934$.
[p] $y = 0.445x + 0.0606$.

control or toxicological screening purposes, however, no fully validated methods (or limits of detection and quantification) for the substance have been published [17,18]. Singh et al. utilised an ACE C_{18} 250 mm × 4.6 mm (particle size: 5 μm) column and a mobile phase consisting of methanol–ammonium formate (28:72 v/v) containing formic acid (flow-rate: 1 mL min^{-1}; detection: UV at 260 nm) [17]. Under these conditions (±)-mephedrone elutes at *circa*. 11 min with good linearity (r^2 = 0.999) and precision (RSD = 0.41%, n = 10) though no limits of detection or quantification were determined, An initial HPLC chromatographic method using mephedrone hydrobromide salt (**3b**) was developed and the detection wavelength was also suitable for the corresponding hydrochloride salt (**3a**). The analytes eluted at 4.7 (**3a**) and 4.9 (**3b**) min, respectively (Fig. 6a and b) with a slight peak tailing ($A_s \sim 1.3$) observed in each case. Calibration standards were prepared and demonstrated a linear response (r^2 = 0.999) over a 0.5–10 μg mL^{-1} range with excellent repeatability in each case (RSD = 0.36–0.90%, n = 6). The limits of detection and quantification were 0.1 and 0.3 μg mL^{-1} in both cases. The validation parameters for the external standard method are summarised in Table 3.

Nicotinamide (λ_{max} = 262.5 nm, A = 0.852, $c = 2.0 \times 10^{-3}$ g/100 mL, relative response factor (at 258 nm) = 0.3) – which is not normally used as a diluent in illicit-drug manufacture – was selected as an internal standard in line with previous reported studies [19–22]. The mobile phase composition was modified by reducing the percentage of organic modifier to 30% v/v to prevent the internal standard being eluted in the void volume and to maintain a rapid analysis time. The internal standard and

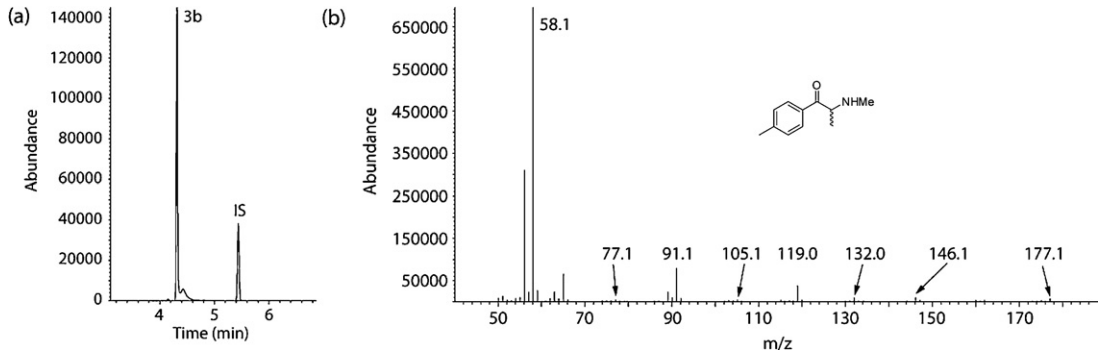

Fig. 8. (a) Representative chromatogram of a solution containing (±)-mephedrone.HBr (**3b**, 1 mg mL^{-1}) and eciosane (IS, 0.5 mg mL^{-1}) obtained using a HP5 MS, 30 m × 0.25 mm i.d., 0.25 μm column; carrier gas: He (1.0 mL min^{-1}); temperature programme (see Section 2 for details); (b) EI mass spectrum (SIM mode) of peak (t_R = 4.3 min) corresponding to (±)-mephedrone.HBr (**3b**, [M$^+$] = 177.1).

(±)-mephedrone hydrochloride (**3a**) eluted at 2.7 and 8.4 min, respectively with good resolution (>25) and are presented in Fig. 6c. Calibration standards (containing 2.5 μg mL^{-1} nicotinamide) were prepared (r^2 = 0.999) over a 0.5–10 μg mL^{-1} range; RSD = 0.21–0.66%, n = 6. An analogous method was developed for the corresponding mephedrone hydrobromide salt (**3b**, Fig. 6d) and a summary of the key validation parameters for the internal standard method is summarised in Table 3. The results obtained for both the hydrobromide and hydrochloride salts indicate that both methods are comparable and superior to the method reported by Singh et al. [17].

The internal standard method was further developed to screen for (±)-mephedrone in the presence of a number of common diluents (caffeine, paracetamol, lidocaine and benzocaine, sucrose, mannitol and lactose) and adulterants (methylone, ketamine, cocaine and diamorphine) [23]. The mobile phase composition was modified and the amount of organic component reduced to 28% v/v to prevent the internal standard being eluted in the void volume and to ensure resolution between the twelve components (Fig. 7). The method was modified to maximise detection of the components and the parameters for the method validation and summarised in Table 4. The strongly UV-absorbing components (paracetamol, caffeine, methylone, mephedrone and benzocaine) demonstrated a linear response (r^2 = 0.993–0.995) over a 0.5–10 μg mL^{-1} range with excellent repeatability (RSD = 0.34–2.75%, n = 6). The limits of detection for these components were determined as being between 0.23 and 0.28 μg mL^{-1}. The method was also suitable for the detection and quantification of analytes that exhibited a weaker UV response (lidocaine, ketamine, cocaine and diamorphine). The analytes demonstrated a linear response (r^2 = 0.987–0.989) over a 2.5–25 μg mL^{-1} range with excellent repeatability (RSD = 0.77–2.92%, n = 6) and limits of detection between 0.99 and 1.08 μg mL^{-1}. The UV-inactive analytes (sucrose, mannitol and lactose) were shown not to interfere with all eleven target analytes.

The GC–MS chromatographic method was developed using the hydrobromide salt (**3b**) in methanol with 0.5 mg mL^{-1} eicosane as internal standard. The method demonstrated good reproducibility of the target analyte peak with a slight shoulder which was minimised when viewed in Selective Ion Monitoring (SIM) mode. Calibration standards (containing 1 mg mL^{-1} eciosane) were prepared and demonstrated a linear response (r^2 = 0.998) over a 0.001–1 mg mL^{-1} range (RSD = 4.3–13.8%, n = 6). The limit of detection was determined as 3.2 μg mL^{-1}. A typical chromatogram (with its corresponding EI mass spectrum) is presented in Fig. 8.

4. Conclusions

A comprehensive HPLC and GC–MS analytical technique for the detection and quantitative analysis of (±)-mephedrone as a pure compound and in the presence of common excipients is reported. It is envisaged that the data presented will be valuable as a reference point for future analysis of these and related compounds.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jpba.2011.05.022.

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