Analyst

PAPER

View Article Online
View Journal | View Issue

Cite this: *Analyst*, 2014, **139**, 389

Forensic electrochemistry: the electroanalytical sensing of synthetic cathinone-derivatives and their accompanying adulterants in "*legal high*" products†

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Received 22nd October 2013
Accepted 21st November 2013

DOI: 10.1039/c3an01985c

www.rsc.org/analyst

The production and abuse of new psychoactive substances, known as "*legal highs*" which mimic traditional drugs of abuse is becoming a global epidemic. Traditional analytical methodologies exist which can provide confirmatory analysis but there is a requirement for an on-the-spot analytical screening tool that could be used to determine whether a substance, or sample matrix contains such legal, or formally "*legal highs*". In this paper the electrochemical sensing of (±)-methcathinone and related compounds at a range of commercially available electrode substrates is explored. We demonstrate for the first time that this class of "*legal highs*" are electrochemically active providing a novel sensing protocol based upon their electrochemical oxidation. Screen-printed graphite sensing platforms are favoured due to their proven ability to be mass-produced providing large numbers of reliable and reproducible electrode sensing platforms that preclude the requirement of surface pre-treatment such as mechanical polishing as is the case in the use of solid/re-usable electrode substrates. Additionally they hold potential to be used on-site potentially being the basis of an on-site legal high screening device. Consequently the electroanalytical sensing of (±)-methcathinone (**3a**), (±)-4′-methylmethcathinone [**3b**, 4-MMC, (±)-mephedrone] and (±)-4′-methyl-*N*-ethylcathinone (**3c**, 4-MEC) is explored using screen-printed sensing platforms with the effect of pH explored upon the analytical response with their analytical efficiency evaluated towards the target legal highs. Interesting at pH values below 6 the voltammetric response quantitatively changes from that of an electrochemically irreversible response to that of a quasi-reversible signature which can be used analytically. It is demonstrated for the first time that the electroanalytical sensing of (±)-methcathinone (**3a**), (±)-mephedrone (**3b**) and 4-MEC (**3c**) are possible with accessible linear ranges found to correspond to 16–200 μg mL^{-1} for **3a** (at pH 12) and 16–350 μg mL^{-1} for both **3b** and **3c** in pH 2, with limits of detection (3σ) found to correspond to 44.5, 39.8 and 84.2 μg mL^{-1} respectively. Additionally adulterants that are commonly incorporated into cathinone legal highs are electrochemically explored at both pH 2 and 12.

Introduction

"*Legal highs*" are a class of compounds which are reported to provide similar effects to the traditional well studied illegal drugs – but are not controlled under the Misuse of Drugs Act.[1] The popularity of "*legal highs*" has escalated and its consequences have been reported in the media, usually with fatal consequences.[2] Wide varieties of products are currently available through "*head shops*" (a store that sells drug-related paraphernalia) and on-line websites. Many "*legal high*" products are typically marketed for non-medical usage (*e.g.* plant feeders, bath salts and dog food) and "*not for human consumption*" in order to bypass legislative controls.

The most prominent synthetic cathinone-based "*legal highs*" are (±)-methcathinone (**3a**) and its derivative, (±)-mephedrone (**3b**), which are structurally related to the natural stimulant, (±)-cathinone (**4a**) and possesses a pharmacological similarity to the **phenethylamine** class of psychoactives (*e.g.* methamphetamine (**5**)). Since the legislative change (16th April 2010) there has been a rise in the number of new derivatives entering the UK recreational drug market for example: (±)-4′-methyl-*N*-ethylcathinone (**3c**, 4-MEC); (±)-benzedrone (**4b**, 4-MBC), naphyrone (**6a**) and MDPV (**6b**) (Scheme 1).[3–5] In recent years

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3an01985c

(±)-mephedrone has been pushed to the forefront by the media following a number of deaths, linked to its use, worldwide.[6,7] Internationally there has been a tightening of the legislation regarding synthetic cathinone derivatives, for example cathinones are illegal in the UK as well as Germany, Norway, Sweden, The Netherlands, Finland, Romania, Republic of Ireland, Denmark, Canada and Israel.[3,8] Despite their controlled status cathinone-derivatives are still prevalent in many "*legal high*" products[9,10] hence the development of methods for their detection and quantification is both timely and urgently required.

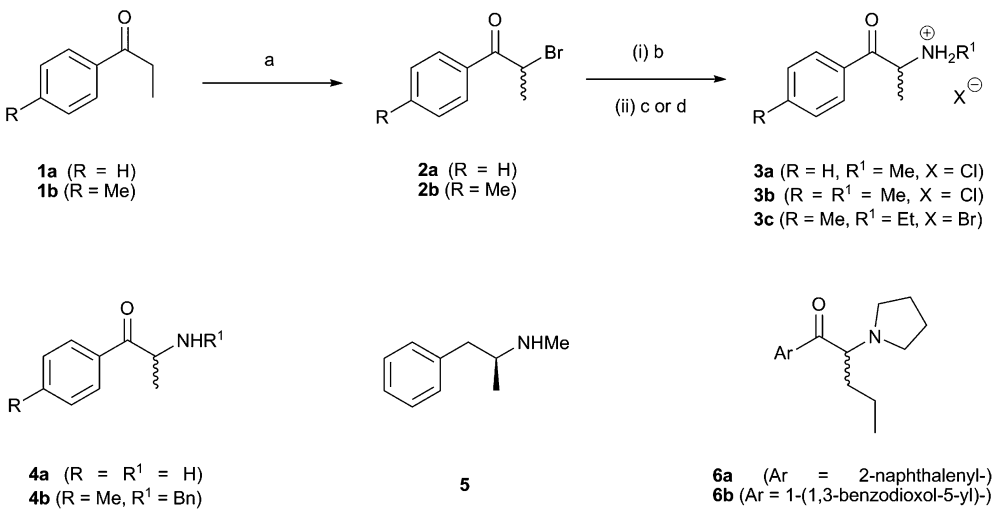
The laboratory-based analysis of synthetic cathinones has been published by a number of groups using a range of chromatographic techniques including HPLC and GC-MS with LC-MS methods seemingly the preferred and established technique of choice.[5,7,10–29] Table 1 provides a thorough overview of all the reported analytical methodologies to date. Of note, Santali *et al.* provided the first fully validated HPLC method for the quantification of (±)-mephedrone[12] where limits of detection and quantification of 0.1 and 0.3 μg mL^{-1} respectively were reported. Khreit *et al.* further refined this method enabling the detection of both (±)-mephedrone and two novel derivatives, 4-MEC (**3c**) and 4-MBC (**4b**), in seized samples of "*NRG-2*". In this case the limits of detection and quantification were reported as 0.03 and 0.08 for (**3c**) and 0.05 and 0.14 μg mL^{-1} for (**4b**) both in their pure form and in the presence of common adulterants such as caffeine and benzocaine.[5,10] There has also been work using chromatographic methods on the detection of cathinone based "*legal highs*" in biological matrices[13,26] in which Beyer *et al.* were able to detect and quantify 25 designer cathinones in a validated LC-MS-MS method.[26]

Recently direct analysis in real time mass spectrometry (DART-MS) has been utilised to quantify and characterise the multitude of new and emerging "*legal highs*"; DART-MS, a method which uses a new ion source that has been developed for rapid, non-contact analysis of materials at ambient pressure and at ground potential, it is based on the reactions of electronic or vibronic excited-state species with reagent molecules and polar or nonpolar analytes.[30] With the rapid changes in structures that appear in "*legal high*" products, to circumvent legislative controls, the myriad of structurally related compounds are challenging to efficiently differentiate; direct analysis in real time mass spectrometry (DART-MS) attempts to detect and characterise cathinone drug mixtures with speed and efficiency.[31] Whilst DART-MS is a faster technique that requires less sample preparation than previously mentioned chromatographic methods, it is only a qualitative technique serving to decrease the back-log that currently exists in crime labs by speeding up the sample testing process and characterising new analogues.[31]

Another recent development in the detection of synthetic cathinone derivatives is the use of surface enhanced Raman-spectroscopy (SERS).[32,33] Mabbott *et al.* have been working towards a new optimization strategy for the SERS detection of (±)-mephedrone using a portable Raman system employing a fractional factorial design approach to significantly reduce the statistical experiments whilst maintaining statistical integrity.[33] Within their work, four optimized SERS protocols for which the reproducibility of the SERS signal and the limit of detection of (±)-mephedrone were established reporting an estimated limit of detection of 1.6 μg mL^{-1}.

Clearly identifiable from a survey of the literature is that there are a number of laboratory-based analytical methods for "*legal highs*" which have been developed and can be used for a confirmatory approach (see Table 1). To date there is, to the best of our knowledge, no established portable hand-held type device which can be used to screen for the presence of the "*legal high*" cathinone and related compounds is available – therefore the work described herein is both novel, timely and pertinent.

Electrochemistry is an advantageous analytical tool which is cost effective, portable and exhibits sensitivity and selectivity towards many target analytes.[34–39] To enable translation from the laboratory into the "*field*", screen-printed electrodes are a favourable approach since they provide a low cost, single-shot



Scheme 1 *Reagents and conditions*: (a) Br_2/HBr (48% aq. solution)/CH_2Cl_2/rt/1 h; (b) $NH_2R^1 \cdot HCl/NEt_3/CH_2Cl_2$/rt/24 h; (c) 4 M HCl-dioxane/$^{i-}$PrOH/rt/1 h; (d) 33% HBr-AcOH/AcOH/rt/1 h.

Table 1 A survey of the current literature reported for the analytical measurement of **3a**, **3b** and **3c**[a]

Analytical method	Target analyte (cathinones)	Analytical linear range	Limit of detection	Matrix	Reference
GC-(EI/CI)-MS, NMR spectroscopy	(±)-4-Fluoromethcathinone, (±)-1-(3,4-methylenedioxyphenyl)-2-(methylamino)pentan-1-one (pentylone), (±)-3,4-methylenedioxy-α-pyrrolidinobutyrophenone (MDPBP), (±)-3,4-methylenedioxypyrovalerone (MDPV), (±)-4-methyl-α-pyrrolidinopropiophenone (MPPP)	N/A – qualitative analysis	N/A – qualitative analysis	Mobile phase	17
Gas chromatography–mass spectrometry with electron ionisation (GC–MS-EI)	(±)-4-Methylmethcathinone ((±)-mephedrone, **3b**)	Δ	0.2 mg L^{-1}	Blood	7
Liquid chromatography triple quadrupole tandem mass spectrometry (LC-QQQ-MS/MS)	32 cathinone derivatives	2–5000 ng mL^{-1}	≈ 10 pg mL^{-1}	Blood serum	14
Liquid chromatography-tandem mass spectrometry (LC-MS/MS)	(±)-4-Methylmethcathinone ((±)-mephedrone, **3b**), (±)-3,4-methylenedioxymethcathinone (bk-MDMA, (±)-methylone), (±)-2-methylamino-1-(3,4-methylenedioxyphenyl)butan-1-one (bk-MBDB, (±)-butylone), (±)-4-methoxymethcathinone (bk-PMMA, (±)-methedrone), (±)-3,4-methylenedioxypyrovalerone (MDPV)	N/A – qualitative analysis	N/A – qualitative analysis	Urine	18
High performance liquid chromatography (HPLC)	(±)-4-Methylmethcathinone ((±)-mephedrone, **3b**)	0.5–10 μg mL^{-1}	0.1 μg mL^{-1}	Mobile phase	12
Liquid chromatography-tandem mass spectrometry (LC-MS/MS)	(±)-4-Methylmethcathinone ((±)-mephedrone, **3b**), (±)-butylone, (±)-3,4-methylenedioxypyrovalerone (MDPV), (±)-4-fluoromethcathinone ((±)-flephedrone), (±)-methylone and (±)-methedrone	Δ	2 ng mL^{-1}	Mobile phase	19
Liquid chromatography-electrospray tandem mass spectrometry (LC-ESIMS/MS)	(±)-Cathinone, (±)-methcathinone (**3a**), (±)-ethcathinone, (±)-amfepramone, (±)-4-methylmethcathinone ((±)-mephedrone, **3b**), (±)–4-fluoromethcathinone ((±)-flephedrone), (±)-methedrone, (±)-methylone, (±)-butylone, (±)-cathine, (±)-norephedrine, (±)-ephedrine, (±)-pseudoephedrine, (±)-methylephedrine and (±)-methylpseudoephedrine	10–250 mg L^{-1}	0.5–3 mg L^{-1}	Blood	20
High performance liquid chromatography (HPLC)	(±)-4-Methylmethcathinone ((±)-mephedrone, **3b**)	20–120 mg mL^{-1}	0.8 mg mL^{-1}	Mobile phase	21
Gas chromatography-mass spectrometry (GC/MS)	(±)-4-Methylmethcathinone ((±)-mephedrone, **3b**)	N/A – qualitative analysis	N/A – qualitative analysis	Aqueous	22
Gas chromatography-mass spectrometry (GC/MS)	16 '*legal high*' cathinone derivatives including (±)-methcathinone (**3a**), (±)-4-methylmethcathinone ((±)-mephedrone, **3b**), 4-(±)-4-methyl-*N*-ethylcathinone (4-MEC, **3c**)	N/A – qualitative analysis	N/A – qualitative analysis	Methanol	29
Gas chromatography-ion trap mass-spectrometry using electron and chemical ionization modes, NMR spectroscopy	(±)-4-Methylmethcathinone ((±)-mephedrone, **3b**), (±)-butylone, (±)-4-methyl-*N*-ethylcathinone, (±)-4-fluoromethcathinone ((±)-flephedrone) and (±)-3,4-methylenedioxypyrovalerone (MDPV)	N/A – qualitative analysis	N/A – qualitative analysis	Aqueous	5
Surface enhanced Raman scattering (SERS)	(±)-4-Methylmethcathinone ((±)-mephedrone, **3b**)	N/A – qualitative analysis	N/A – qualitative analysis	Aqueous	32

Table 1 (*Contd.*)

Analytical method	Target analyte (cathinones)	Analytical linear range	Limit of detection	Matrix	Reference
Liquid chromatography-tandem mass spectrometry (LC-MS/MS)	(±)-3,4-Methylenedioxypyrovalerone (MDPV), (±)-4-fluoromethcathinone ((±)-flephedrone), (±)-4-methylmethcathinone ((±)-mephedrone, **3b**), (±)-3-fluoromethcathinone, (±)-α-methylaminobutyrophenone and (±)-4-methoxymethcathinone.	0.1–10 μg mL^{-1}	Δ	Urine	23
Surface enhanced Raman scattering (SERS)	(±)-4-methylmethcathinone ((±)-mephedrone, **3b**)	0.1–100 μg mL^{-1}	1.6 μg mL^{-1}	Aqueous	33
Ultra-high-performance liquid chromatography (UHPLC) with TOF-MS	(±)-3,4-Methylenedioxypyrovalerone (MDPV), (±)-4-methylmethcathinone ((±)-mephedrone, **3b**)	N/A – qualitative analysis	N/A – qualitative analysis	Blood	24
Liquid chromatography-tandem mass spectrometry (LC-MS/MS)	(±)-3,4-Methylenedioxypyrovalerone (MDPV), (±)-4-methylmethcathinone ((±)-mephedrone, **3b**)	N/A – qualitative analysis	N/A – qualitative analysis	Urine	13
Solid phase extraction. gas chromatography-mass spectrometry (GC/MS)	(±)-Methcathinone, (±)-4-methylmethcathinone ((±)-mephedrone, **3b**), (±)-2-methylamino-1-(3,4-methylenedioxyphenyl)butan-1-one ((±)-butylone)	N/A – qualitative analysis	N/A – qualitative analysis	Aqueous	25
Atmospheric pressure ion mobility time-of-flight mass spectrometer (APIM(tof) MS)	(±)-4-Methylmethcathinone ((±)-mephedrone, **3b**), (±)-butylone, (±)-4-Me-PPP, and (±)-4-methyl-*N*-ethylcathinone (4-MEC, **3c**)	3 to 11 μM	Δ	Aqueous	52
Low-temperature plasma probes for ambient ionization mass spectrometry	(±)-4-Methylmethcathinone ((±)-mephedrone, **3b**), (±)-methylone and (±)-3,4-methylenedioxypyrovalerone (MDPV)	0–2000 pg	0.5–5.0 pg	Solid	53
Liquid chromatography-tandem mass spectrometry (LC-MS/MS)	25 designer cathinones and their related ephedrines	10–1000 ng mL^{-1}	Δ	Blood	26
Gas chromatography-mass spectrometry (GC/MS)	(±)-4-Methylmethcathinone ((±)-mephedrone, **3b**)	N/A – qualitative analysis	N/A – qualitative analysis	Hair	15
Microcrystalline identification	(±)-4-Methylmethcathinone ((±)-mephedrone, **3b**)	0.1–10 g L^{-1}	3 g L^{-1}	Aqueous	54
Liquid chromatography-tandem mass spectrometry (LC-MS/MS)	(±)-4-Methylmethcathinone ((±)-mephedrone, **3b**)	5–100 pg/mg	2.5 pg/mg	Hair	55
Flow injection analysis tandem mass spectrometry (FIAMS-MS)	(±)-4-Methylmethcathinone ((±)-mephedrone, **3b**)	Δ	<4 μg L^{-1}	Urine	56
Ultra HPLC-electrospray ionization-tandem mass spectrometry (UHPLC-ESI-MS/MS)	(±)-4-Methyl-*N*-ethylcathinone (4-MEC, **3c**), (±)-4-methylmethcathinone ((±)-mephedrone, **3b**), (±)-methylenedioxypyrovalerone (MDPV),	Δ	1–20 ng mL^{-1}	Oral fluid	27
Direct analysis in real time mass spectrometry (DART-MS)	Various synthetic cathinone designer drugs	N/A – qualitative analysis	N/A – qualitative analysis	Solid	31
High-performance liquid chromatography-diode array detection (HPLC-DAD)	(±)-4-Methylmethcathinone ((±)-mephedrone, **3b**), 4-(±)-4-methyl-*N*-ethylcathinone (4-MEC, **3c**) and (±)-4-fluoromethcathinone ((±)-flephedrone)	25–2400 ng mL^{-1}	40 ng mL^{-1}	Urine	28
Liquid chromatography-tandem mass spectrometry (LC-MS/MS)	(±)-Cathinone, (±)-methcathinone (**3a**)	10–1000 ng mL^{-1}	Δ	Blood plasma	11
Gas chromatography-mass spectrometry (GC/MS)	(±)-Cathinone, (±)-methcathinone (**3a**)	12.5–5000 ng mL^{-1}	Δ	Urine	16

Table 1 (*Contd.*)

Analytical method	Target analyte (cathinones)	Analytical linear range	Limit of detection	Matrix	Reference
Differential pulse voltammetry – (electrochemical reduction of target analyte using mercury)	(±)-4-Methylmethcathinone ((±)-mephedrone, **3b**)	2.65×10^{-4} –1.77 μg mL^{-1}	2.21×10^{-3} μg mL^{-1}	Aqueous buffer	40
Molecularly imprinted film at a NH_2-graphene modified screen-printed electrode. Cyclic voltammetry (CV) and an electrochemistry impedance method	(±)-Methcathinone (**3a**), (±)-cathinone	Δ	3.3–8.9 pg mL^{-1}	Aqueous buffer	57
This work	(±)-Methcathinone (**3a**) (±)-4-methylmethcathinone ((±)-mephedrone, **3b**) (±)-4′-methyl-*N*-ethylcathinone (4-MEC, **3c**)	**3a:** 31.2–200 μg mL^{-1} (pH 12) **3b:** 39.2–666.7 μg mL^{-1} (pH 12), 16.1–300 μg mL^{-1} (pH 2) **3c:** 95.2–1000 μg mL^{-1} (pH 12) 16.1–300 μg mL^{-1} (pH 2)	**3a:** 24.2 μg mL^{-1} (pH 12) **3b:** 13.2 μg mL^{-1} (pH 12), 15.8 μg mL^{-1} (pH 2) **3c:** 36.3 μg mL^{-1} (pH 12) 16.1 μg mL^{-1} (pH 2)	Aqueous buffer	N/A

[a] Δ = not disclosed.

disposable yet highly reproducible and reliable platform for electrochemical measurement of the target analyte.[34–38] The use of electrochemistry with screen-printed electrodes as a tool for the detection and analysis of cathinone-derived designer drugs has not been reported before. However we find that there is only one study reporting the electrochemical behaviour of (±)-mephedrone using a mercury dropping electrode by Krishnaiah *et al.*[40] reporting an analytical range of 2.7×10^{-4} to 1.8 μg mL^{-1} with a detection limit of 2.2×10^{-3} μg mL^{-1}, however there is a difference in their approach to the research presented in this paper as it involves electrochemically reducing (±)-mephedrone in basic conditions. Whilst yielding favourable analytical responses, a problem arises with the use of the Dropping Mercury Electrode; mercury is widely reported as a harmful chemical and thusly not sanctioned in labs globally;[41–45] additionally the issue of translating the research from the laboratory into the field still needs to be addressed.

Consequently in this paper, for the first time, the electroanalytical sensing of (±)-mephedrone (**3b**) and 4-methylethcathinone (**3c**) another synthetic cathinone derivative that frequently occurs in "*legal highs*" are reported using both commercially available solid macroelectrodes (boron-doped diamond, glassy carbon) and disposable screen-printed graphite macroelectrodes. Screen-printed electrodes are favourable since they offer a low cost, single-shot disposable yet highly reproducible and reliable sensing platform for electrochemical measurement of the target analytes. Additionally adulterants that are typically found in street samples are electrochemically characterised for their potential interference in the simultaneous sensing of **3b** and **3c**.

Experimental

All chemicals used were of analytical grade and were used as received without any further purification from Sigma-Aldrich (Gillingham, UK). All solutions were prepared with deionised water of resistively no-less than 18.2 Ω cm. All solutions (unless stated otherwise) were vigorously degassed with nitrogen to remove oxygen prior to analysis.

Voltammetric measurements were carried out using a μ-AutolabIII (Eco Chemie, The Netherlands) potentiostat/galvanostat and controlled by Autolab GPES software version 4.9 for Windows XP. Experiments were performed using boron doped diamond, glassy carbon and screen-printed graphite macroelectrodes; both the boron doped diamond and glassy carbon electrodes have a 3 mm diameter working area. Screen-printed graphite macroelectrodes (denoted as SPEs herein) which have a 3 mm diameter working electrode were fabricated in-house with appropriate stencil designs using a DEK 248 screen printing machine (DEK, Weymouth, UK). For the fabrication of the screen printed sensors, firstly, a carbon–graphite ink formulation (product code: C2000802P2; Gwent Electronic Materials Ltd, UK) used previously was screen printed onto a polyester (Autostat, 250 micron thickness) flexible film (denoted throughout as standard-SPE). This layer was cured in a fan oven at 60 degrees for 30 minutes. Next a silver/silver chloride reference electrode was included by screen printing Ag/AgCl paste (product code: C2040308D2; Gwent

Electronic Materials Ltd, UK) onto the polyester substrates. Note that is all studies, measurements were performed using an external reference electrode rather than the on-board reference electrode since this is the first report of the electrochemical sensing of legal highs allowing accurate peak potentials/voltammetry to be reported for future work. Finally, a dielectric paste (product code: D2070423D5; Gwent Electronic Materials Ltd, UK) was then printed onto the polyester substrate to cover the connections. After curing at 60 degrees for 30 minutes the screen printed electrodes are ready to be used. The reproducibility of the batch of screen printed sensors were found to correspond to 0.76% RSD using the $Ru(NH_3)^{2+/3+}$ redox probe in 1 M KCl. Note that a *new* SPE was utilised for each experiment performed, including during concentration studies.

The synthetic cathinone hydrochloride (or hydrobromide) salts, were prepared at the University of Strathclyde prior to the legislative change on 16th April 2010 using the methods outlined below. ^{1}H and ^{13}C NMR spectra were acquired on both JEOL AS-400 (JEOL, Tokyo, Japan) and Bruker Avance 400 (Bruker, Karlsruhe, Germany) NMR spectrometers operating at a proton resonance frequency of 400 MHz. Infrared spectra were obtained in the range 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 were visualised using ultra-violet light (254 nm). Microanalysis was carried out using a PerkinElmer 2400 Series II elemental analyser (PerkinElmer, San Jose, USA). Melting points were determined using differential scanning calorimetry (DSC; Netzsch STA449 C, Netzsch-Gerätebau, Wolverhampton, UK). 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).

Synthesis of (±)-2-bromopropiophenone (2a) and (±)-2-bromo-4′-methylpropiophenone (2b)

The pre-requisite α-bromoketones (**2a**/**2b**) were prepared using the method reported by Kalendra *et al.*:[46] to a solution of the desired ketone (**1a**/**1b**, 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 seconds) and additional bromine (100 mmol total including the original drop) was introduced drop wise with stirring. The mixture was stirred for 1 h and then concentrated *in vacuo* to give a dark orange oils (yield: 95–99%). The α-bromoketones were used in the subsequent step without further purification.

(±)-2-Bromopropiophenone (2a)

Yield = 95.7% (from **1a**); R_f [SiO_2, EtOAc–*n*-hexane (1 : 3)] = 0.81; ^{1}H-NMR (400 MHz, 25 °C, $CDCl_3$) δ ^{1}H (ppm) = 8.02 (2H, dd, J = 7.4 and 1.5 Hz, Ar-H), 7.59 (1H, tt, J = 7.4 and 1.5 Hz, Ar-H), 7.49 (2H, t, J = 7.4 Hz, Ar-H), 5.30 (1H, q, J = 7.0 Hz, *CH*(Br)CH_3) and 1.91 (3H, d, J = 7.0 Hz, CH(Br)*CH_3*); ^{13}C-NMR (400 MHz, 25 °C, $CDCl_3$) δ ^{13}C (ppm) = 193.2 (C=O), 134.0 (ArCH), 133.6 (ArC), 128.9 (2 × ArCH), 128.7 (2 × ArCH), 41.4 (*CH*(Br)CH_3) and 20.1 (CH(Br)*CH_3*); *m*/*z* (EI, 70 eV) 215 (2, $[M^{81}Br]^+$), 213 (2, $[M^{79}Br]^+$), 105 (100) and 77 (36%).

(±)-4′-Methyl-2-bromopropiophenone (2b)

Yield = 99.4% (from **1b**); R_f [SiO_2, EtOAc–*n*-hexane (1 : 3)] = 0.79; ^{1}H-NMR (400 MHz, 25 °C, $CDCl_3$) δ ^{1}H (ppm) = 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 (3H, d, J = 7.0 Hz, CH(Br)*CH_3*); ^{13}C-NMR (400 MHz, 25 °C, $CDCl_3$) δ ^{13}C (ppm) = 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 (Ar*CH_3*) and 20.3 (CH(Br)*CH_3*); *m*/*z* (EI, 70 eV) 228 (5, $[M^{81}Br]^+$), 226 (5, $[M^{79}Br]^+$), 118 (100), 108 (12), 91 (85) and 65 (70%).

Synthesis of the hydrochloride or hydrobromide salts of (±)-methcathinone (3a), 4′-methylmethcathinone (4-MMC, 3b) and 4′-methyl-*N*-ethylcathinone (4-MEC, 3c)

The target compounds were prepared *via* the methods reported by Santali *et al.*[12] and Khreit *et al.*[10]: to a suspension of required α-bromoketone (**2a**/**2b**, 20 mmol) and amine hydrochloride (20 mmol) in dichloromethane (40 mL) was added triethylamine (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 the crude freebases a viscous yellowish-orange oils. The cathinone hydrochloride or hydrobromide salts were isolated by treatment with 3 M HCl in dioxane or 33% HBr in acetic acid respectively. Subsequent recrystallization of the salts using acetone afforded analytically pure (>99.5% by elemental analysis) samples that were fully characterized and gave analytical and spectroscopic data which was consistent with the reported literature.

(±)-2-(Methylamino)-1-phenyl-propan-1-one hydrochloride [(±)-methcathinone hydrochloride] (3a)

Yield = 67.2% (from **2a**); mpt. (acetone) 191.95 °C; R_f [SiO_2, EtOAc–*n*-hexane (1 : 3)] = 0.10; $[\alpha]_D^{22}$ = 0 (c = 0.5 g per 100 mL in MeOH); found: C, 60.17; H, 7.09; N, 7.02. $C_{10}H_{14}ClNO$ requires C, 60.15; H, 7.07 and N, 7.01%; UV (EtOH): λ_{max} = 248.0 nm (A = 0.427, c = 9.95 × 10^{-4} g per 100 mL); IR (ATR-FTIR): 2708.2 (NH_2^+), 1689.9 (C=O), 1597.2 cm^{-1} (C=C); ^{1}H NMR (400 MHz, 60 °C, d_6-DMSO) δ ^{1}H (ppm) = 9.63 (2H, br s, CH(*NH_2^+*CH_3)CH_3); 8.04 (2H, dd, J = 7.2 and 1.5 Hz, C2′/C6′), 7.73 (1H, tt, J = 7.2 Hz, C4′), 7.60 (2H, t, J = 7.2 Hz, C3′/C5′), 5.14 (1H, q, J = 7.2 Hz, *CH*($NH_2^+CH_3$)CH_3), 2.61 (3H, s, CH(NH_2^+*CH_3*)CH_3) and 1.49 (3H, d, J = 7.2 Hz, CH($NH_2^+CH_3$)*CH_3*); ^{13}C NMR (400 MHz, 60 °C, d_6-DMSO) δ ^{13}C (ppm) = 195.9 (C=O, C1), 134.2 (ArC, C4′), 132.9 (ArC, C1′), 128.8 (2 × ArCH, C3′/C5′), 128.4 (2 × ArCH, C2′/C6′), 57.9 (*CH*CH_3, C2), 30.4 (NH_2^+*CH_3*) and 15.1 (CH*CH_3*,

C3); LRMS (ESI+, 70 eV): m/z = 164 (100, $[M + H]^+$), 146 (42), 131 (4) and 105 (1%); HRMS (ESI+, 70 eV) calculated for [M + H] $C_{10}H_{14}NO$: 164.1070, found: 164.1069.

(±)-4′-Methylmethcathinone hydrochloride [(±)-mephedrone hydrochloride] (4-MMC, 3b):

yield = 51.2% (from **2b**); Mpt. (acetone) 251.18 °C; R_f [SiO_2, EtOAc–*n*-hexane (1 : 3)] = 0.11; $[\alpha]_D^{22} = 0$ (c = 0.5 g per 100 mL in MeOH); found: C, 61.81; H, 7.52; N, 6.57. $C_{11}H_{16}ClNO$ requires C, 61.82; H, 7.55 and N, 6.55%; UV (EtOH): λ_{max} = 259.5 nm (A = 0.735, $c = 9.95 \times 10^{-4}$ g per 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 ^{1}H (ppm) = 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, ArCH_3) and 1.46 (3H, d, J = 7.2 Hz, CH($NH_2^+CH_3$)CH_3); ^{13}C NMR (400 MHz, 60 °C, d_6-DMSO) δ ^{13}C (ppm) = 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$, C2), 30.6 ($NH_2^+CH_3$), 21.2 ($ArCH_3$, C7′) and 15.5 (CH$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.

(±)-4′-Methyl-*N*-ethylcathinone hydrobromide (4-MEC, 3c):

yield = 41.5% (from **2b**); Mpt. (acetone) 206.08 °C; R_f [SiO_2, EtOAc–*n*-hexane (1 : 3)] = 0.10; $[\alpha]_D^{22} = 0$ (c = 0.5 g per 100 mL, MeOH); found: C, 52.90; H, 6.65; N, 4.95. $C_{12}H_{18}BrNO$ requires C, 52.95; H, 6.67 and N, 5.15%; UV (EtOH): λ_{max} = 260.0 nm (A = 0.693, $c = 1.02 \times 10^{-3}$ g per 100 mL); IR (ATR-FTIR): 2735.4 (NH_2^+), 1687.3 (C=O), 1605.4 cm^{-1} (C=C); ^{1}H NMR (400 MHz, 60 °C, d_6-DMSO) δ ^{1}H (ppm) = 8.92 (2H, br s, CH($NH_2^+CH_2CH_3$)CH_3); 7.98 (2H, d, J = 8.4 Hz, AA′BB′), 7.41 (2H, d, J = 8.4 Hz, AA′BB′), 5.21 (1H, q, J = 6.8 Hz, CH($NH_2^+CH_2CH_3$)CH_3), 3.04 (2H, dq, J = 12.4, 7.2 Hz, CH($NH_2^+CH_2CH_3$)CH_3), 2.42 (3H, s, ArCH_3), 1.53 (3H, d, J = 7.2 Hz, CH(NH_2^+ CH_2CH_3)CH_3) and 1.28 ppm (3H, t, J = 7.2 Hz, CH(NH_2^+ CH_2CH_3)CH_3); ^{13}C NMR (100 MHz, 60 °C, d_6-DMSO) δ ^{13}C (ppm) = 195.5 (C=O, C1), 145.2 (ArC, C4′), 130.2 (ArC, C1′), 129.4 (2 × ArC, C3′/C5′), 128.6 (2 × ArCH, C2′/C6′), 56.5 ($CH$$CH_3$, C2), 40.2 ($NH_2^+CH_2CH_3$, C4); 20.9 ($ArCH_3$, C7′), 15.7 (CH$CH_3$, C3) and 10.8 ppm ($NH_2^+CH_2CH_3$, C5); LRMS (ESI+, 70 eV): m/z = 192 (34, $[M + H]^+$), 174 (100), 159 (30), 145 (57), 131 (16), 119 (25) and 91 (6%); HRMS (ESI^+, 70 eV) calculated for [M + H] $C_{12}H_{18}NO$: 192.1383, found: 192.1381.

Results and discussion

Samples of (±)-methcathinone (**3a**), (±)-4′-methylmethcathinone (**3b**, 4-MMC, (±)-mephedrone) and (±)-4′-methyl-*N*-ethylcathinone (**3c**, 4-MEC) were prepared as their corresponding hydrochloride or hydrobromide salts as detailed in the experimental section. The synthesis of the three racemic target compounds was achieved using a modification of the previously reported methods[9,10] from (±)-2-bromopropiophenone (**2a**) and (±)-4′-methyl-2-bromopropiophenone (**2b**) in 67.2%, 51.2% and 41.5% overall yield, respectively as stable, colourless to off-white powders after recrystallisation from acetone (Scheme 1). To ensure the authenticity of the material utilised in this study the synthesised samples were fully structurally characterised (see Experimental Section) and the purity of both samples was confirmed by elemental analysis (>99.5% in all cases).

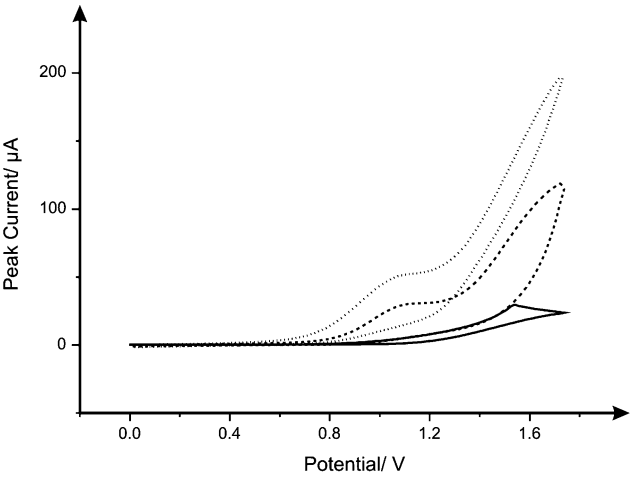


Fig. 1 Voltammetric profiles observed at a boron-doped (solid line), glassy carbon (dashed line) and SPE (dotted line) electrode in a solution of 500 µg mL^{-1} **3a** in a pH 12 PBS buffer. Scan rate: 100 mV s^{-1} *vs.* SCE.

The electrochemical detection of (±)-methcathinone (**3a**) in aqueous based buffer solutions at a range of commercially available electrodes was first considered. Fig. 1 depicts the voltammetric profiles observed at a boron-doped, glassy carbon and screen-printed graphite (SPEs) electrodes in a solution of 500 µg mL^{-1} (**3a**) in aqueous pH 12 PBS buffer. It is evident that the electrochemical oxidation of **3a** is possible which is observed to occur at the lowest overpotentials for SPEs, followed by glassy carbon, and boron-doped diamond with the SPE also giving the largest voltammetric peak. This difference is reflected by the greater % global coverage of edge plane – like/sites defects residing on the screen-printed graphite electrode over the other electrode surfaces which has been reported before for other target analytes.[47] Of interest is the response of the disposable screen-printed graphite electrodes since these allow a portable mass-produced economical sensor to be potentially realised and due to their scales of economy, a single sensor can be used for each voltammetric scan without recourse to electrode polishing as is the case for boron-doped and glassy carbon electrodes; consequently, it is only this electrode platform we consider further.

Next, attention was turned to exploring the effect of pH upon the electrochemical signal. A plot of peak potential (E) *vs.* pH, as shown in Fig. 2, was constructed where a linear range with a gradient of 0.031 V is observed (E/V = −0.031 V + 1.41E/pH R^2 = 0.99). Such a value is close to that expected for 1 proton and 2 electron process (30 mV per pH unit at 25 °C) as deduced from the following equation:

$$E^0_{f,eff} = E^0_f(A/B) - 2.303\,\frac{mRT}{nF}\ \text{pH} \qquad (1)$$

Below pH 8 the voltammetric peak shifts out of the accessible voltammetric window; we note that the molecule has a reported

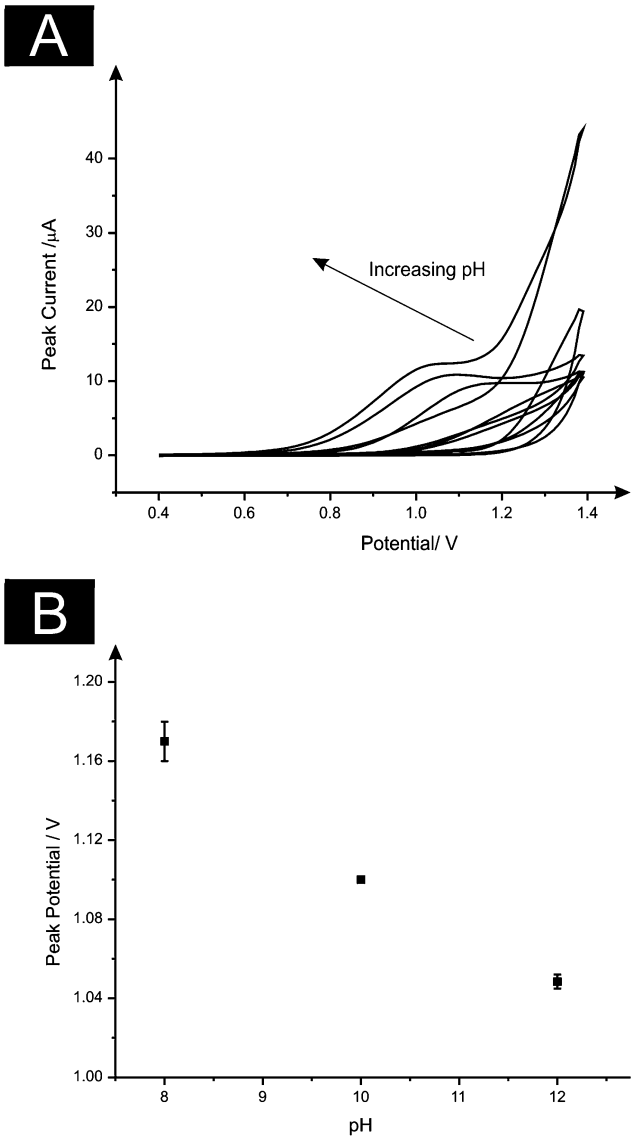


Fig. 2 Cyclic voltammetric responses (A) of **3a** obtained in phosphate buffer solution at different pHs. Part B depicts a plot of peak potential, E_P, as a function of pH for the electrochemical oxidation of 500 μg mL^{-1-1} **3a**. In all cases SPEs were utilised. Scan rate: 100 mV s^{-1} *vs.* SCE. The responses shown in (B) represent are an average response (squares) with corresponding error bars ($N = 3$).

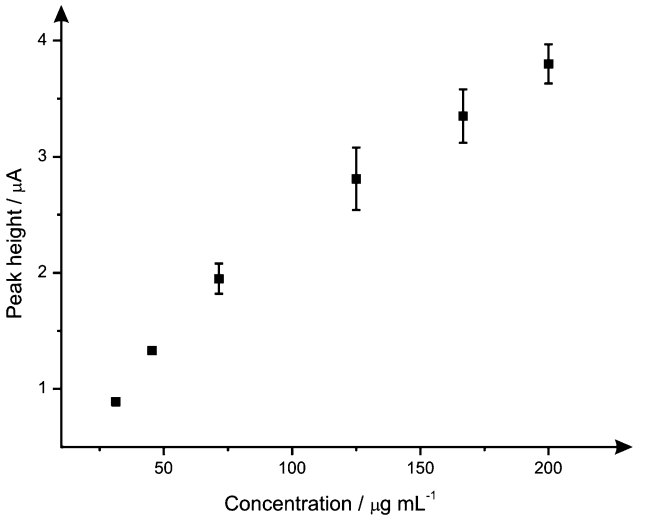


Fig. 3 A typical calibration plot corresponding to the addition of **3a** into a pH 12 phosphate buffer solution over the range 31.3–200.0 μg mL^{-1} using a *new* SPE for each addition. The responses shown are an average response (squares) with corresponding error bars ($N = 3$).

pK_a value of *ca.* 8.[48] Given the chemical similarity between (**3a**) and that of amphetamines, as is evident from inspection of Scheme 1, prior work by Oliveira-Brett *et al.* exhibited similar electrochemical behaviour which is thought to be the result of the electrochemical oxidation of the secondary amine.[49]

Next, the effect of scan rate upon the electrochemical oxidation of (**3a**) was explored in 500 μg mL^{-1} pH 12 solution where a plot of peak height against the square-root of scan rate was found to be linear indicating a diffusional process (I_p/A = 16.9 A$(V\ s^{-1})^{-0.5}$ + 3.61 A $R^2 = 0.91$); this plot is shown in ESI Fig. 1.† The peak potential is observed to shift to more positive values with increasing scan rate with a linear relation between E_p and ln υ (E_p (V) = 0.029 ln υ (V s^{-1}) + 0.89; $R^2 = 0.90$). For an irreversible electrochemical process, the relationship between E_p and υ is given by eqn (2):

$$E_p = E_f^0 - \frac{RT}{\alpha nF}\ln\frac{RTk^o}{\alpha nF} + \frac{RT}{\alpha nF}\ln\upsilon \quad (2)$$

where E_f^0 is the formal potential, α is the transfer coefficient, n is the number of electrons transferred in the rate determining step, R, T and F have their usual meanings and k^o is the heterogeneous rate constant. From the plot of E_p and ln υ the gradient is found to correspond to 0.0296 where αn is deduced to be 0.87. Assuming α is 0.5, a value of $n = 1.7$, which is close to the value of 2 deduced above with the pH study discussed above.

Next attention was turned towards exploring the analytical performance of the SPEs towards (**3a**). Fig. 3 shows a typical calibration plot of peak height against (**3a**) concentration which exhibits a linear range from 31.2 to 200.0 μg mL^{-1} with a limit of detection (3σ) found to correspond to 24.2 μg mL^{-1} (I_p/A = 0.017 A μg^{-1} mL^{-1-1} + 0.57 A $R^2 = 0.98$); note that this is the first instance of **3a** being electroanalytically quantified.

Focus was then turned to the synthetic cathinone derivatives that are commonplace in "*legal high*" samples: (±)-4′-methyl-methcathinone (**3b**, 4-MMC) and (±)-4′-methyl-*N*-ethyl-cathinone (**3c**, 4-MEC). Voltammetric profiles for (**3b**/**3c**), as shown in Fig. 4, reveal similar electrochemistry as observed for (**3a**) in a pH 12, 500 μg mL^{-1} aqueous buffer solution. A study into the effect of scan rate on the oxidation of both (**3b**/**3c**) in 500 μg mL^{-1} pH 12 buffer solution where a plot of peak height against the square-root of scan rate revealed a linear response indicating a diffusional process (**3b** I_p/A = 9.00 A$(V\ s^{-1})^{-0.5}$ + 2.00 A $R^2 = 0.94$; **3c**: I_p/A = 18.54 A$(V\ s^{-1})^{-0.5}$ + 6.11 A $R^2 = 0.86$); the corresponding plots are shown in ESI Fig. 2.† The effect of pH was also explored on the voltammetric profiles of both **3b**/**3c** where it was found that as the pH was decreased from basic conditions, the oxidation peak, similar to that observed in the case of **3a**, ceased to exist in neutral pH's, however the key

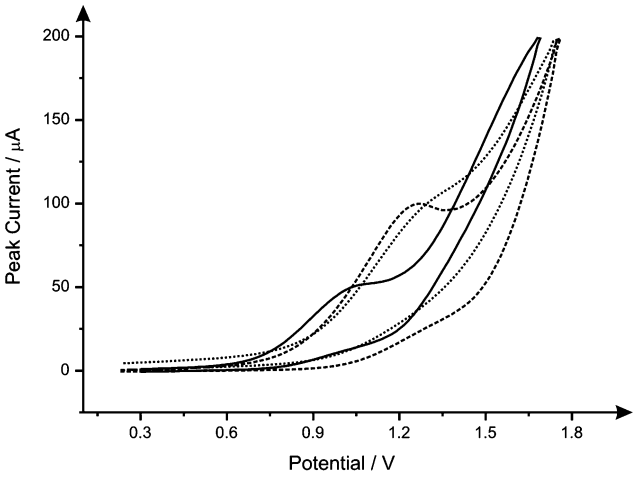


Fig. 4 Voltammetric profiles for both **3b** (dotted line) and **3c** (dashed line) compared to **3a** (solid line) in a pH 12, 500 μg mL^{-1} aqueous buffer solution using SPEs. Scan rate: 100 mV s^{-1} *vs.* SCE.

difference is that as both solutions become more acidic a new, quasi-reversible wave becomes visible, as shown in Fig. 5. We note that the exact origin of this new voltammetric profile is currently unknown but can also provide a useful sensing strategy.

Next the analytical performance of the SPEs in basic conditions (pH 12) were, for the first time, investigated towards the sensing of **3b**/**3c** where calibration plots of peak height against concentration revealing a linear range from 39.2 to 666.7 μg mL^{-1} for **3b** and 95.2 to 1000.0 μg mL^{-1} for **3c** with limits of detection (3σ) found to correspond to 13.2 μg mL^{-1} and 36.3 μg mL^{-1} for **3b** and **3c** respectively.

Given that the pH study of **3b**/**3c** revealed a redox couple in acidic conditions (one that was not present for **3a**) the effect of scan rate upon the electrochemical oxidation of both (**3b**) and (**3c**) at pH 2 was investigated at 500 μg mL^{-1}. A plot of the oxidation wave peak height against the square-root of scan rate was found to be linear indicating a diffusional process for both molecules (**3b:** I_p/A = 39.99 A M^{-1} + 2.99 A R^2 = 0.95, **3c:** I_p/A = 42.1 A M^{-1} + 1.381 A; R^2 = 0.96); the corresponding plots are shown in ESI Fig. 3.† The peak potential is observed to shift to more positive values with increasing scan rate with a linear relation between E_p and ln υ (**3b:** E_p(V) = 0.045 ln υ (V s^{-1}) + 1.19; R^2 = 0.91, **3c:** E_p(V) = 0.04 ln υ (V s^{-1}) + 1.17; R^2 = 0.85). The sensing of **3b** and **3c** was explored at this pH with a series of additions made into a pH 2 aqueous buffer for both molecules as shown in Fig. 6, each molecule displayed linearity through the range of 16.1 to 300.0 μg mL^{-1} with limits of detection (3σ) found to correspond to 15.7 μg mL^{-1} (I_p/A = 0.043 A μg^{-1} mL^{-1-1} + 0.69 A R^2 = 0.99) and 16.2 μg mL^{-1} for (**3b**) and (**3c**) (I_p/A = 0.044 A μg^{-1} mL^{-1-1} + 0.81 A R^2 = 0.99) respectively.

In the majority of legal high samples there are purposely added adulterants contained (to perhaps give each '*legal high*' specimen it's unique 'high'), popular choices are compounds such as caffeine and benzocaine.[10] Consequently an investigation into the electrochemical behaviour into caffeine and benzocaine was undertaken to see if an electrochemical

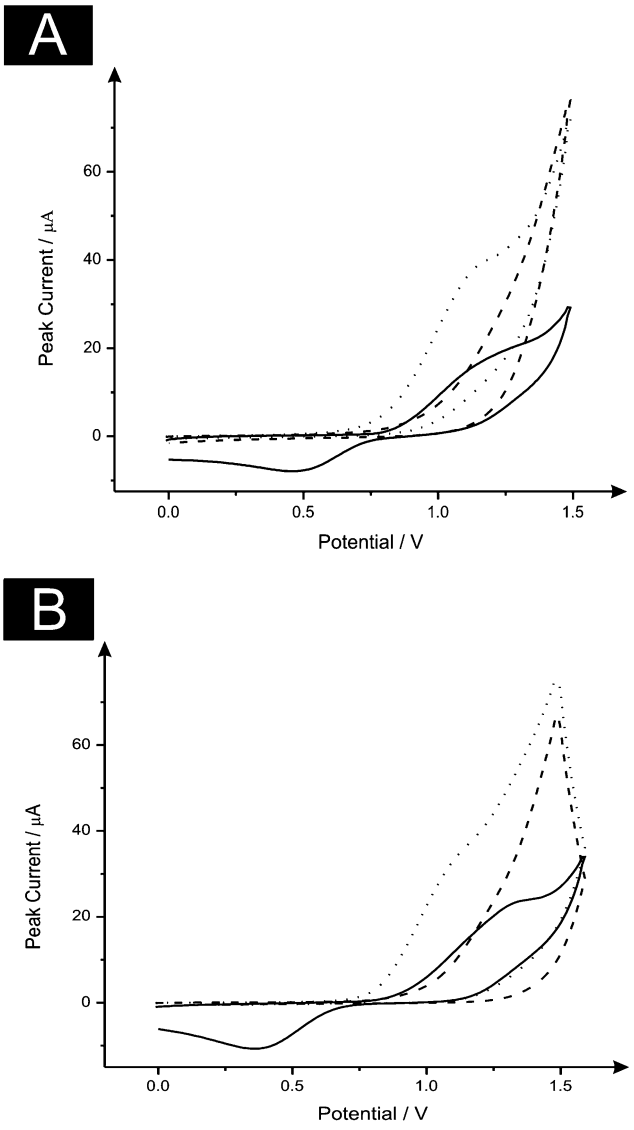


Fig. 5 Cyclic voltammetric responses (A) of **3b** obtained in phosphate buffer solution at pH 2 (solid line), pH 6 (dashed line) and pH 12 (dotted line). Part B shows the cyclic voltammetric responses of **3c** obtained in phosphate buffer solution pH 2 (solid line), pH 6 (dashed line) and pH 12 (dotted line). Scan rate (in all cases): 100 mV s^{-1} *vs.* SCE and using SPE.

technique would be a viable option in real street samples containing cathinones and adulterants. As shown in Fig. 7 the voltammetric profiles of both 500 μg mL^{-1} caffeine and benzocaine in pH 12 can be readily observed which indicate, from inspection of the observed peak potentials with those of the legal highs, that as a concept, using electrochemistry for the detection of illicit substances in 'legal highs' is not viable as the adulterants added to such samples will most likely (voltammetrically) interfere with the signal response from one of the cathinones due to the overlapping voltammetric profiles.

With respect to the analytical response for **3b**/**3c** being possible at pH 2 as well as pH 12, attention was turned to the adulterants caffeine and benzocaine to determine whether analyses of mixtures at pH 2 would be a viable option.

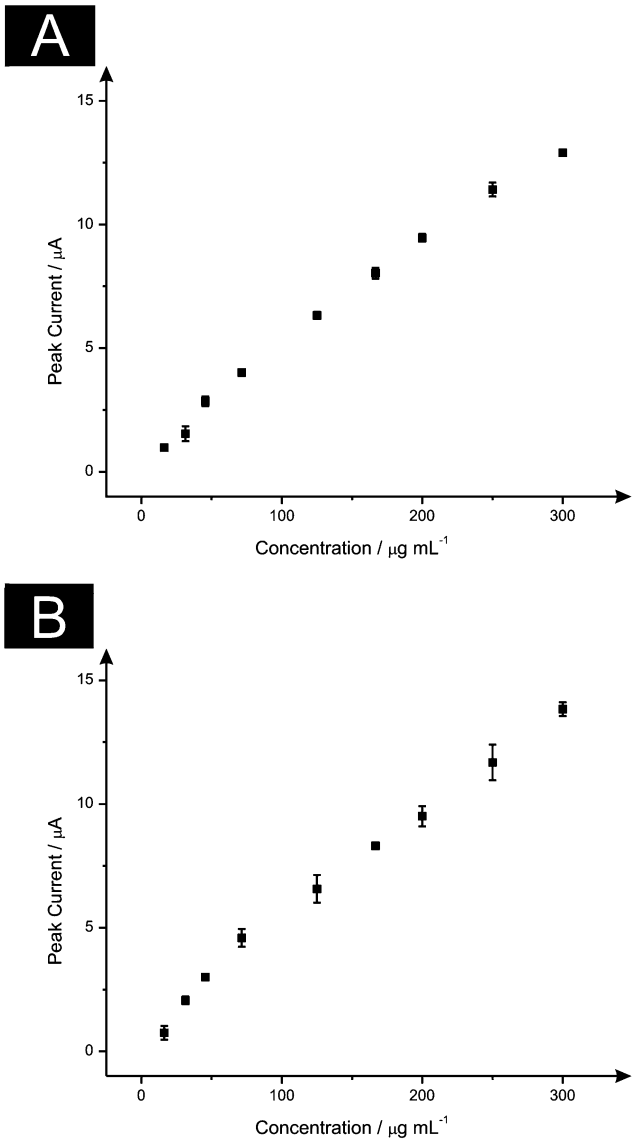


Fig. 6 Typical calibration plot corresponding to the addition of **3b** (part A) and **3c** (part B) into a pH 2 phosphate buffer solution over the range 16.1–300 μg mL^{-1} using a *new* SPE for each addition. The responses shown are an average response (squares) with corresponding error bars ($N = 3$).

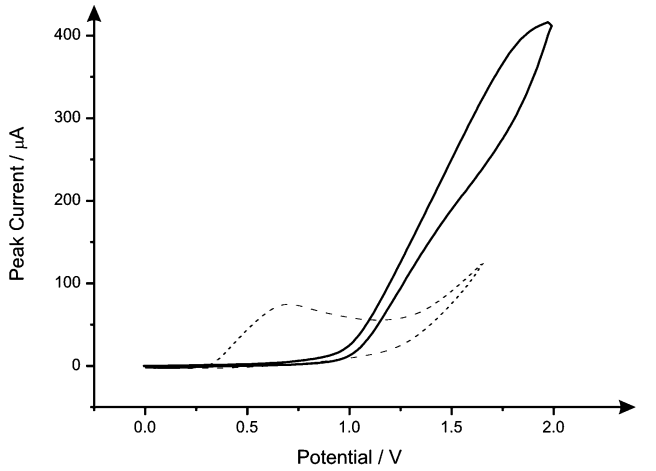


Fig. 7 Voltammetric profiles of both caffeine (solid line) and benzocaine (dashed line) at pH 12 in 500 μg mL^{-1} obtained using SPE. Scan rate: 75 mV s^{-1} *vs.* SCE.

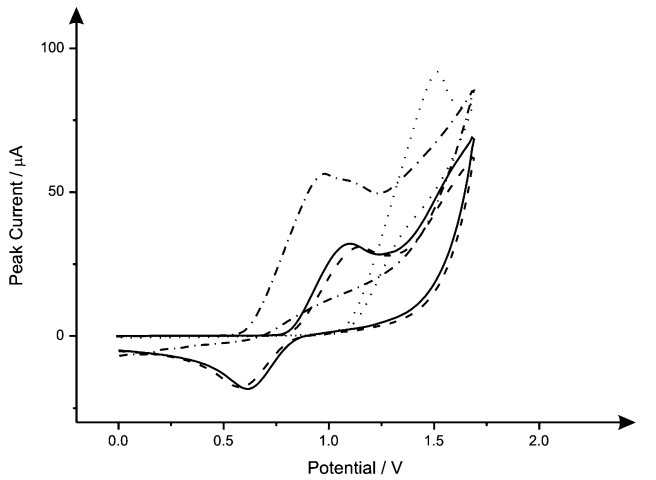


Fig. 8 Comparison of the voltammetric profiles of **3b** (solid line), **3c** (dashed line), caffeine (dotted line) and benzocaine (dashed-dotted line) in 500 μg mL^{-1} pH 2 buffer solution. Scan rate: 100 mV s^{-1} *vs.* SCE. SPEs electrodes.

Voltammetric scans were performed in 500 μg mL^{-1} buffer solution on both molecules revealing voltammetric profiles that would undoubtedly interfere with the responses from **3b** and **3c**; the cyclic voltammetric responses overlaying the responses of all 4 molecules (**3b**, **3c**, caffeine and benzocaine) at 100 mV s^{-1} in 500 μg mL^{-1} pH 2 buffer solutions can be observed from inspection of Fig. 8. We note that the electrochemical oxidation of caffeine at pH 12 and 2, as shown in Fig. 7 and 8 respectively are in good agreement with literature studies using edge plane pyrolytic graphite electrodes which independently reported that an electrochemically irreversible wave is observed.[50] Additionally the voltammetric response of benzocaine is in agreement with literature reports using graphite electrodes in the pH range studied here.[51] It is noted however, that if analytes were present in the solution together, in both pH 2 and 12, as would be expected when analysing a real sample of legal highs, an overlap of voltammetric waves would occur precluding the use of electrochemisty to be used as the basis of a legal high sensor.

Conclusions

For the first time the electrochemical detection of the cathinone class of "*legal highs*" is shown to be viable with a range of electrode materials explored along with solution pH and analytical characteristics being determined. The analytical parameters, in terms of limits of detection and accessible linear range in model solutions are analytically useful. The adulterants, likely to be found in such a "*legal high*" products, caffeine and benzocaine have also been explored at the optimum electrode material and solution pH. At pH 12 and 2 it is found that

there is no electrochemical selectivity over the electrochemical detection of (**3a**), (**3b**) and (**3c**) such that a mixture of these cannot be differentiated from. The interesting case of a redox couple being formed in acidic conditions for **3b** and **3c** offers an additional electrochemical quantification approach however there is still no selectivity between **3b**/**3c** and the adulterants. Consequently, at the pHs studied here and through the use of SPEs, a portable on the spot sensor for these cathinone classes of "*legal highs*" is unlikely to be realised using such electrochemical approaches/technology; current work is directed to overcoming this limiting issue of overlapping voltammetric waves using HPLC with an electrochemical detector.

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