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An analysis of the 'legal high' mephedrone

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ABSTRACT

'Legal highs' are compounds, plant or fungal material which can be readily bought from the internet without legal restriction and the single chemicals may be structurally related to illegal drugs of abuse such as the amphetamines. Several recent deaths in the UK have been attributed to these legal highs and unfortunately there is little chemical or biological literature on these materials or certified standards. Here, we detail the analysis of the widely consumed synthetic *N*-methyl-cathinone analogue known as mephedrone ((**1**) 2-aminomethyl-1-tolyl-propan-1-one (4′-methylmethcathinone)) and report its spectral data and molecular properties. Material was purchased from an internet site and examined by extensive one- and two-dimensional NMR studies, high-resolution mass spectrometry, elemental analysis and optical rotation, which demonstrated the sample to be of high purity and racemic in nature.
Additionally, we report the molecular modelling properties of methyl-cathinones and compare them to their corresponding methyl-amphetamine series. This indicated that the methyl-cathinones are considerably more hydrophilic than the methyl-amphetamines which may account for the higher doses that are needed to demonstrate similar effects. The presence of a ketone in the side chain introduces a far more planar quality to the methyl-cathinones which is absent in the methyl-amphetamine series, and this planarity may contribute to toxicity.

In the last few years there has been a dramatic increase in the sale of legal highs.[1] These materials 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, for example the legal high methylone (**2**) and methylenedioxy-methamphetamine (**8**, MDMA, ecstasy) (Fig. 1). Legal highs may also be plant materials that contain hallucinogenic natural products as part of their secondary metabolism, for example, the seeds of convolvulaceous plants of the genera *Argyreia, Convolvulus* and *Ipomoea* producing ergine-type tryptamine analogues.[2]

In some cases, legal high plant materials have been adulterated with either plant extracts or synthetic chemicals, as seen with 'Spice', a plant material contaminated with one or a cocktail of cannabinoid receptor agonists such as JWH-018.[3]

Several deaths amongst young people in the United Kingdom[4] have recently been attributed to the consumption of legal highs, in particular to mephedrone ((**1**) 2-aminomethyl-1-tolyl-propan-1-one (4′-methylmethcathinone)), a synthetic drug related to the plant natural product cathinone (**13**). Mephedrone was first synthesised in 1933 but surprisingly there is a paucity of published data relating to this compound.[5] A very recent publication has dealt with the analysis of **1** and other beta-keto amphetamines in urine by GC–MS.[6] Cathinone (**13**) is the stimulant alkaloid found in *Catha edulis*, the leaves of which are chewed in some Somali, Yemeni and Ethiopian communities.[7] This compound is controlled by the UK 1971 Misuse of Drugs Act and is currently classified as a class C drug and in Schedule 1 of the Act having no medicinal use.

Surprisingly very little is known about the chemistry and biology of the synthetic cathinone derivatives despite an increasing number appearing on the internet for sale. These include mephedrone (**1**), methylone (**2**), methedrone (**3**), butylone (**4**) and methylenedioxypyrovalerone (MDPV, **5**) (Fig. 1). Unfortunately these names are confusing and do not relate to systematic nomenclature (Fig. 1). Methyl-cathinones are very similar in structure to several existing illegal drugs of abuse including methcathinone (**6**) which is a class B drug, and the highly addictive and destructive class A drug methamphetamine colloquially known as 'crystal meth' (**12**).

Strikingly and most worryingly from the perception perspective for young people who are tempted to try these materials, some of these cathinones such as methylone (**2**) show exceptional structural similarity with the class A drug MDMA (**8**, ecstasy) possessing just one carbonyl in place of a methylene moiety (Fig. 1). As ecstasy is still widely consumed as a recreational and illicit drug of abuse, the appearance of methylone on the internet, which is marketed as a high-purity plant food, may well induce young people to experiment with this chemical because of its structural resemblance to ecstasy and the false implication that it might be safe to consume. Ecstasy has been demonstrated to have toxic effects in a variety of systems[8–10] but unfortunately there is a paucity of literature

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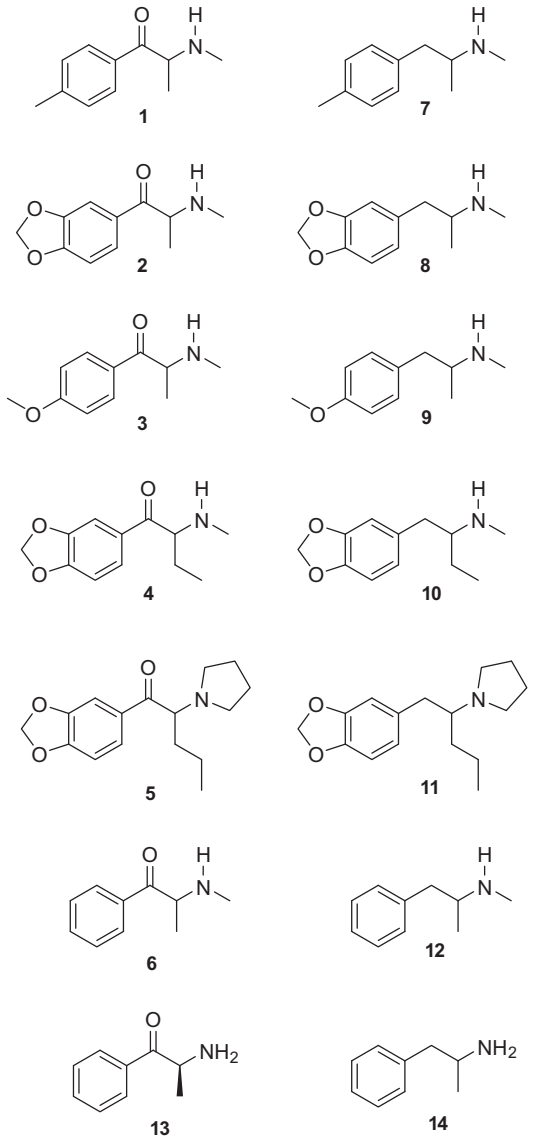


Figure 1. Cathinone and amphetamine derivatives. Mephedrone (4′-methylmethcathinone, 4′-MMC, **1**), methylone (**2**), methedrone (**3**), butylone (**4**), methylenedioxypyrovalerone (MDPV, **5**), methcathinone (**6**), 4′-methylmethamphetamine (**7**), methylenedioxy-methamphetamine (MDMA, 'ecstasy', **8**), 4′-methoxymethampetamine (4′-MMA, **9**), methylenedioxy-ethylamphetamine (MDEA, **10**), methylbenzodioxolylbutanamine (MBDB, 'Eden', **11**), methamphetamine ('crystal meth', **12**), *S*-cathinone (**13**), amphetamine (**14**).

Figure 2. Sample of mephedrone obtained from the internet.

pertaining to the chemistry, biology and toxicity of the synthetic and natural cathinones.

To partly address the lack of data on these compounds, we have acquired a sample of mephedrone and conducted an extensive spectroscopic analysis and the full spectral data are reported here. Additionally, we have subjected a series of methyl-cathinones and their corresponding methyl-amphetamine analogues to molecular modelling studies to predict physical differences such as log *P* and log *BBB* (log of the ratio of the concentration in the brain, to that in the blood), and ascertained how different the series are from each other with respect to molecular conformation.

A sample of mephedrone (**1**, 500 mg, Fig. 2) was acquired from an internet site where the material was marketed at 99.8% purity as a plant food and 'not for human consumption'. 474.0 mg were recoverable from the plastic sample bag and a portion of this was subjected to full structure elucidation.[11]

The HRESIMS gave an $[M+H]^+$ peak at 178.1233 (calculated for 178.1232) supporting the molecular formula of $C_{11}H_{15}NO$ and the identity of the sample as mephedrone ((**1**) 2-aminomethyl-1-tolyl-propan-1-one (4′-methylmethcathinone)). The ^{1}H NMR spectrum (Fig. 3 and Table 1) showed the characteristic AA′BB′ aromatic system for a 1,4 unsymmetrically substituted aromatic system (δ 7.42 2H, δ 7.62 2H), a deshielded one-hydrogen quartet at 5.09 ppm (*CH*–CH_3), a deshielded three-hydrogen singlet at 2.77 ppm (N–CH_3), a slightly deshielded methyl singlet attributable to a methyl attached to an aromatic ring (δ 2.45) and finally a methyl doublet (δ 1.57, J = 7.2). The ^{1}H NMR spectrum indicated that this compound was clean with no apparent starting material or unreacted reagents such as methylamine which has been seen before in other cathinone legal highs such as the fluorinated analogue flephedrone.[12] The ^{13}C NMR spectrum (Table 1) again supported a predominantly pure material with nine carbons evident. Full spectral analysis using HMQC and HMBC spectra allowed unambiguous assignment of all carbon and hydrogen resonances (Table 1 and Fig. 4) and gave final proof that compound **1** was mephedrone.[13] The *N*-methyl resonance gave a ^3J correlation to C-2 which was in turn coupled to by the methyl doublet (C-3). In the HMBC spectrum, the hydrogens of this methyl resonance also coupled to a deshielded carbon (δ 196.6, C-1) and this completed the 2-aminomethyl-propan-1-one side chain. Further couplings in the HMBC spectrum between H-2′/6′ and C-1 (^3J) supported placement of the side chain at C-1′ on the aromatic ring (between C-6′ and C-2′). This was further supported by a NOESY correlation between H-2 and H-2′/6′. COSY correlations between H-2′/6′ and H-3′/5′ confirmed the presence of an AA′BB′ aromatic system. The methyl singlet at 2.45 ppm (C-7′) exhibited a ^3J HMBC correlation to C-3′/5′ and a ^2J correlation to C-4′ completing the assignment of all resonances (Table 1). This data is consistent with that recently reported by Camilleri et al. for material recovered from capsules obtained from an internet company.[14]

Elemental analysis was carried out to establish whether the sample was present as a free base or as a salt. Analysis revealed 62.04% (C), 7.57% (H) and 6.55% (N) which corresponded very closely for the theoretical percentage for the hydrochloride salt of 61.82% (C), 7.56% (H) and 6.56% (N). The material was also subjected to measurement of optical rotation and an $[\alpha]_D$ of 0 with a concentration (*c*) of 0.5 indicated that the sample was racemic. This is unsurprising given that the current proposed synthesis of mephedrone is by bromination of 1-tolyl-propan-1-one yielding the 2-bromo-1-tolyl-propan-1-one racemic product. This is then conveniently treated with methylamine which displaces bromide resulting in a racemic 2-methylamino-1-tolyl-propan-1-one (mephedrone).[5] It is possible that an excess of methylamine is used to drive the reaction to completion and the purity of this particular sample may be due to removal of the volatile methylamine under vacuum.

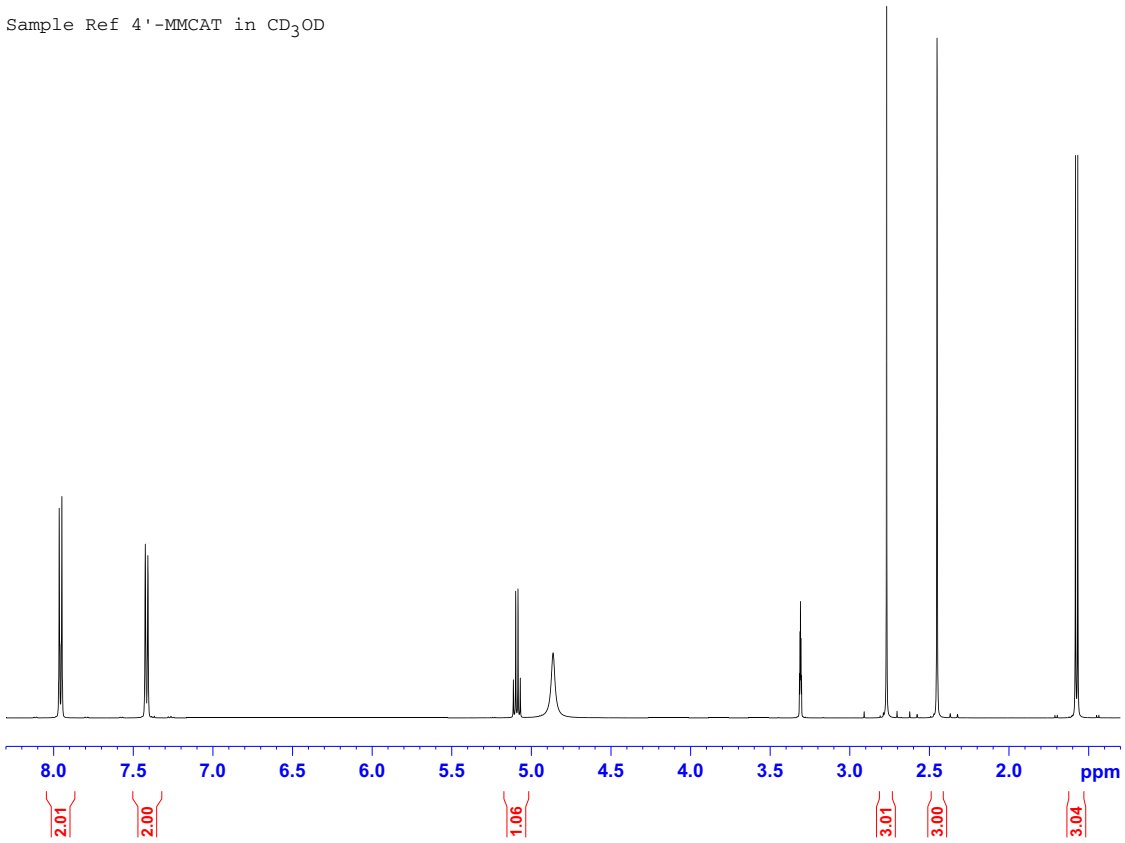


Figure 3. ^{1}H NMR spectrum of mephedrone (**1**) in CD_3OD.

Table 1
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectral data and ^{1}H–^{13}C long-range correlations of **1** recorded in CD_3OD

Position	**1**			
	^{1}H	^{13}C	^{2}J	^{3}J
1	—	196.6	—	
2	5.09 q J = 7.2	60.5	C-1, C-3	N–CH_3
3	1.57 d J = 7.2	16.3	C-2	C-1
1′	—	131.7	—	
2′/6′	7.62 d J = 8.5	130.1	C-3′/5′	C-2′/6′, C-4′, C-1
3′/5′	7.42 d J = 8.5	131.0	C-2′/6′	C-3′/5′, C-1′
4′	—	147.6	—	—
7′	2.45 s	21.8	C-4′	C-3′/5′
N–CH_3	2.77 s	31.7		C-2

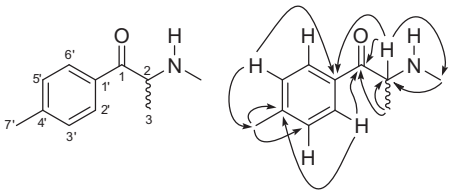


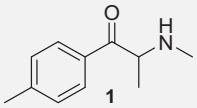
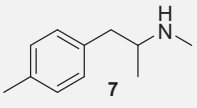
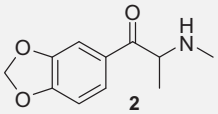
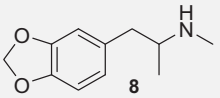
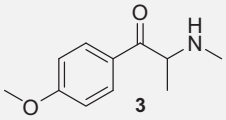
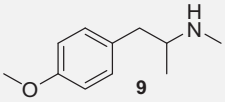
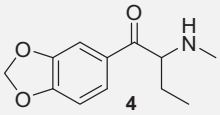
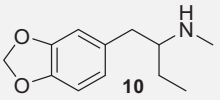
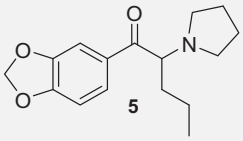
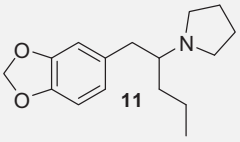
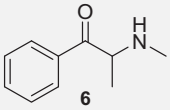
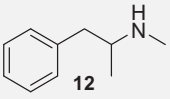
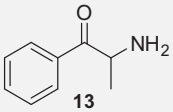
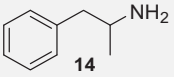
Figure 4. Structure of **1** and key HMBC correlations.

We then conducted molecular modelling studies to predict the molecular properties log *P* and log *BBB* of a series of methyl-cathinones and to compare them with the commonly abused methyl-amphetamine analogous series (Table 2).[15] This showed that the cathinones were generally more hydrophilic, with their log *P* values lower by one unit when compared with the equivalent methyl-amphetamine analogue. Similarly, the log *BBB* of the methyl-cathinones were also lower than the corresponding analogues.

We also modelled both series in an attempt to understand their shape in the protonated form. The predicted pK_a value (9.9) of *d*-amphetamine was in good agreement with its experimental value of 9.5,[16] indicating that the predicted values of pK_a (8.4–9.5) for the methyl-cathinones should be accurate and that they were most likely to be protonated at physiological pH. Conformational studies were very revealing as the methyl-cathinones were much more planar with respect to the methyl-amphetamines (Fig. 5) and the presence of the carbonyl group at C-1 introduces this planarity with the aryl ring, and a hydrogen bond is formed with the protonated amino group. This is very different for the methyl-amphetamines which are far less planar and in which the amino group is perpendicular to the pi-cloud of the aryl ring (as opposed to parallel in the cathinone series). This planarity in the cathinones could result in intercalation with DNA and may indicate why these compounds could be toxic. The molecular lipophilicity potential surfaces indicated that the methyl-cathinones were less lipophilic in nature and therefore less likely to penetrate the blood–brain barrier.

Whilst there is a paucity of biological data relating to mephedrone, both enantiomers of methcathinone (**6**) which differ purely in the lack of the methyl group on the aryl ring compared to mephedrone, have been shown to be toxic to rat dopamine neurons and the *S*-enantiomer was also toxic against serotonin neurons.[17] Given the close structural similarity between mephedrone and methyl-cathinone it is highly likely that mephedrone will display neurotoxicity. As 'street-mephedrone' is clearly a racemic mixture, it is also possible that this will display toxicity towards both dopamine and serotonin neurons and this may in part explain some of the very unfortunate deaths seen recently with this material. Very recently a case report on multiple-drug fatal-toxicity caused by co-adminis-

Table 2
Predicted molecular properties, virtual log *P* and log *BBB* of cathinones and amphetamines. All *R* and *S* stereoisomers were modelled and the values for the *R*-enantiomers are given below

Cathinones			Ampetamines		
	*v*Log *P*	Log *BBB*	Log *BBB*	*v*Log *P*	
 1	−1.36	0.25	0.39	−0.25	 7
 2	−2.63	0.23	0.33	−1.47	 8
 3	−1.65	0.14	0.47	−0.54	 9
 4	−2.07	0.33	0.46	−0.98	 10
 5	−0.06	0.59	0.72	0.63	 11
 6	−1.75	0.19	0.37	−0.74	 12
 13	−2.58	0.13	0.25	−1.21	 14

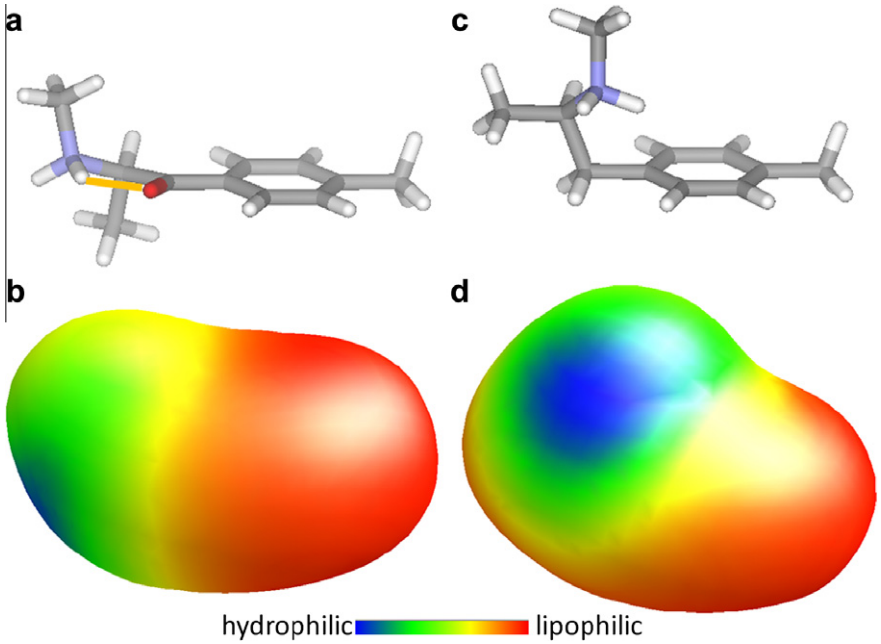


Figure 5. The lowest energy structures and their molecular lipophilicity potential surfaces of mephedrone (**1**) (a and b) and its amphetamine analogue (**7**) 4′-methylmethamphetamine (c and d). The intramolecular hydrogen bond is depicted by an orange line.

tration of heroin and mephedrone has been published.[18] This suggested that the overall contribution of mephedrone to the death could not be neglected.

In April the UK government introduced generic classification to cover many cathinone derivatives including mephedrone and these materials have been placed in the class B category of the 1971 Misuse of Drugs Act.

Acknowledgments

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11. The specific rotation was measured on a Perkin–Elmer polarimeter model 343. High-resolution accurate mass measurement was obtained in the W positive mode on a Micromass Q-TOF Ultima Global Tandem Mass Spectrometer from Micromass. The sample was dissolved in methanol and spiked with [Glu]-Fibrinopeptide B peptide as an internal standard ($[M+2H]^{2+}$ = 785.8426). Experimental conditions were: Detector Voltage MCP 2000 V, Tof Voltage 10.15 kV, Capillary Voltage 1.8, Cone Voltage 110 V, RF lens1 50, and Collision Energy 10 V for MS. Resolution was set between 19,000 FWHM. NMR spectra were recorded on a Bruker AVANCE 500 MHz spectrometer. Chemical shifts values (δ) were reported in parts per million (ppm) relative to the appropriate internal solvent standard and coupling constants (J values) were given in hertz. IR spectra were recorded on a Nicolet 360 FT-IR spectrophotometer. A Carlo-Erba Elemental Analyser model 1108 (Carlo-Erba, Milan, Italy) equipped with an automatic sampler for 50 samples and operated under an Eager 200 for Windows software system was utilised in this study. A Sartorious Ultra Micro Balance model 4504MP8 (London, UK) was used for all weighings and tin capsules were supplied by Elemental Microanalysis Ltd (Okehampton, UK) were used to accommodate the standards and samples.
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13. *2-Aminomethyl-1-tolyl-propan-1-one hydrochloride (**1**) mephedrone:* Off-white crystalline solid; $[\alpha]_D^{22}$ 0 (*c* 0.5, CH_3OH); UV (CH_3OH) λ_{max} (log ε): 206 (2.750), 260 (2.781) nm; IR ν_{max} (thin film) cm^{-1}: 3415, 2939, 2728, 1687, 1607, 1510, 1464, 1420, 1249, 1127, 1035, 972, 913, 830; ^1H NMR and ^{13}C NMR (CD_3OD): see Table 1; HRESIMS (*m*/*z*): 178.1233 $[M+H]^+$ (calcd for $C_{11}H_{16}NO$, 178.1232).
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