

# Analysis of NRG 'legal highs' in the UK: Identification and formation of novel cathinones

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A large number of cathinone derivatives have shown a wide range of bioactive properties, attracting great interest from communities associated with pharmaceutical research. Some of these derivatives have gained popularity as so-called recreational 'legal highs' due to their availability on the Internet and high street shops. A previous study described the qualitative analysis of 24 'legal high' Energy-1 (NRG-1) and NRG-2 products obtained from 18 websites following the ban on mephedrone and derivatives in April 2010. The majority of these products contained a mixture of cathinones just carrying a new label. Here, three additional cathinone products have been detected; two from an NRG-1 sample and one from an NRG-3 sample. This report describes their identification. NRG-1 sample 1 consisted of a mixture of 4 cathinones namely 4-fluoromethcathinone (1), 1-(3,4-methylenedioxyphenyl)-2-(methylamino)pentan-1-one (pentylone, 2), 3,4-methylenedioxy- $\alpha$ -pyrrolidinobutyrophenone (MDPBP, 3) and 3,4-methylenedioxypropylvalerone (MDPV, 4). The sample labelled as NRG-3 (mislabelled with the chemical structure of mephedrone) consisted of a mixture of 4-methyl- $\alpha$ -pyrrolidinopropiophenone (MPPP, 5) and (2), whereas the remaining NRG-1 sample 2 (also mislabelled with the chemical structure of mephedrone) consisted of a mixture of (2) and (3). Qualitative analyses were carried out by GC-(EI/CI)-MS, NMR spectroscopy and confirmation by preparation of standards. The preparation of brominated precursors carrying the 3,4-methylenedioxyphenyl nucleus revealed extensive  $\alpha,\alpha$ -dibromination: the mass spectral and NMR data of these intermediates are also presented and discussed. Copyright © 2010 John Wiley & Sons, Ltd.

**Keywords:** legal highs; NRG-1; NRG-3; cathinones; naphyrone; mephedrone

## Introduction

The long-lasting interest in the medicinal exploration of cathinone derivatives is a reflection of their diverse range of biologically active properties. The ability of a number of derivatives to affect the central nervous system has been recognized for a long time.<sup>[1,2]</sup> One of the pharmacological properties reported for a range of cathinones involves the inhibition of monoamine uptake which makes it an interesting target for a range of therapeutic applications including antidepressant therapy, neurodegeneration, drug addiction, and smoking cessation.<sup>[3–9]</sup>

Recreational use of certain cathinones expected to offer psychostimulatory or entactogenic properties is not surprising. One of the reasons for this increasingly widespread phenomenon included the fact that a number of these derivatives were legally available from the Internet ('legal highs') and that these drugs were perceived to be pure and safe.<sup>[10]</sup> Product availability and identity was found to vary when products were purchased online and analytically characterized.<sup>[11,12]</sup> Detailed analytical data have been published in the scientific literature for a number of cathinones, including several 3,4-methylenedioxy cathinones,<sup>[13]</sup> 3,4-methylenedioxypropylvalerone (MDPV),<sup>[14]</sup> 4-methyl- $\alpha$ -pyrrolidinobutyrophenone (MPBP) and 4-methyl- $\alpha$ -pyrrolidinohexanophenone (MPHP),<sup>[15]</sup> 4-methylmethcathinone (mephedrone),<sup>[16–18]</sup> butylone and methylone<sup>[19]</sup>, fluorinated mephedrone derivatives,<sup>[20,21]</sup>  $\alpha$ -phthalimidopropiophenone, and *N*-ethylcathinone.<sup>[18]</sup>

In the UK, mephedrone and closely related cathinones have been scheduled as Class B drugs under the Misuse of Drugs Act (1971) in April 2010 which was expected to impact directly on the product range offered online. However five (out of six) 'legal high' products purchased after introduction of the ban were found to contain mephedrone, 4-fluoromethcathinone, 3-fluoromethcathinone and/or methylone.<sup>[12]</sup> In a separate study carried out over a six-week period following the ban on mephedrone, a total of 24 products have been purchased from 18 websites. A significant proportion of these products were found to contain a variety of cathinones such as mephedrone, butylone, 4-methyl-*N*-ethylcathinone, 4-fluoromethcathinone and MDPV. Benzocaine, caffeine, lidocaine, and procaine have also

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been detected.<sup>[22]</sup> Of particular interest was the characterization of 'Energy-1' (NRG-1), a product advertised as a legal replacement claimed to consist of naphyrone (naphthylpyrovalerone, O-2482). Only one of 13 NRG-1 products appeared to contain a candidate consistent with naphyrone.<sup>[22]</sup> These studies highlighted that both consumers and online sellers were, most likely without knowledge, confronted with the risk of criminalization and potential harm. Since mid-July 2010 naphyrone and related derivatives have also been classified as Class B drugs.<sup>[23]</sup>

Three cathinone products, two NRG-1 samples and one NRG-3 sample, were obtained as part of the previous study on the characterization of 24 products.<sup>[22]</sup> Unambiguous identification of the products was not possible without the availability of reference standards and this study reports on the qualitative determination of five cathinones present in these products. GC-El/CI-IT-MS and 1D/2D NMR analyses were employed and confirmation was obtained from organic synthesis of the target molecules. This report adds full qualitative characterization of three previously unreported cathinones to the scientific literature. In addition, this appears to be the first time that the characterization of an NRG-3 sample is reported.

## Experimental

### Cathinone samples

Three cathinone products (2 × NRG-1 and 1 × NRG-3) were obtained from two websites. 4-Fluoromethcathinone (**1**) and 3,4-methylenedioxypropylvalerone (MDPV, **4**) were available as standards from previous research.<sup>[22,24]</sup> 1-(3,4-Methylenedioxyphenyl)-2-(methylamino)pentan-1-one (pentylone, **2**) was prepared as a reference standard from piperonylonitrile and butylmagnesium chloride.<sup>[6]</sup> 3,4-Methylenedioxy- $\alpha$ -pyrrolidinobutyrophenone (MDPBP, **3**) and 4-methyl- $\alpha$ -pyrrolidinopropiophenone (MPPP, **5**) were synthesized from 3,4-methylenedioxybutyrophenone and 4-methylpropiofenone, respectively.<sup>[5]</sup> In each case the chemistry involved bromination at the  $\alpha$ -carbon of the ketone, with subsequent reaction with the appropriate amine. Mass spectral and NMR data of brominated intermediates and amine products are also reported.

### Instrumentation

Samples were subjected to MS using both electron ionization (EI) and chemical ionization (CI) modes. Both EI and CI mass spectra (scan range  $m/z$  40 –  $m/z$  500) were obtained on a Varian 220-MS ion trap MS equipped with a Varian 450-GC gas chromatograph and a Varian 8400 autosampler. Data handling was carried out with the workstation, Version 6.91 software. The carrier gas was helium at a flow rate of 1 mL/min using the EFC constant flow mode. A CP-1177 injector (275 °C) was used in split mode (1 : 20). Transfer line, manifold and ion trap temperatures were set at 280, 80, and 220 °C, respectively. HPLC grade methanol was used as the liquid CI reagent. CI ionization parameters (0.5 s/scan): CI storage level 19.0  $m/z$ ; ejection amplitude 15.0  $m/z$ ; background mass 55  $m/z$ ; maximum ionization time 2000  $\mu$ s; maximum reaction time 40 ms; target TIC 5000 counts. The number of ions in the trap was controlled by an automatic gain control function. Separations were carried out using 30 m × 0.25 mm (0.25  $\mu$ m film thickness) Factor Four capillary column (VF-5 ms, Varian). The column temperature was programmed as follows: 100 °C held for 1 min, then heated at

20 °C/min to 280 °C and held constant for 10 min; total run time was 20 min.

NMR spectra were recorded using a Bruker Avance 300 spectrometer at 300.1 MHz (<sup>1</sup>H NMR) or 75.5 MHz (<sup>13</sup>C NMR). NMR spectra were recorded in CDCl<sub>3</sub> and obtained by <sup>1</sup>H, proton decoupled <sup>13</sup>C, DEPT-135, HSQC and HMBC experiments. Chemical shifts are reported relative to TMS at  $\delta$  = 0 ppm. When d<sub>6</sub>-DMSO was used, chemical shifts were determined relative to the residual solvent peak at  $\delta$  = 2.51 (<sup>1</sup>H NMR) and  $\delta$  = 39.6 ppm (<sup>13</sup>C NMR).

#### NMR data for pentylone free base (**2**)

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.50 (1H, dd,  $J_{ortho}$  = 8.1 Hz,  $J_{meta}$  = 1.8 Hz, H-6), 7.37 (1H, d,  $J_{meta}$  = 1.5 Hz, H-2), 6.80 (1H, d,  $J_{ortho}$  = 8.4 Hz, H-5), 5.97 (2H, s, O-CH<sub>2</sub>-O), 3.94 (1H, dd,  $J$  = 7.3 Hz,  $J$  = 4.9 Hz, 2'-CH), 2.32 (3H, s, NMe), 1.65-1.20 (4H, m, 3'-CH<sub>2</sub>, 4'-CH<sub>2</sub>), 0.81 (3H, t,  $J$  = 7.0 Hz, 5'-Me). <sup>13</sup>C NMR (CDCl<sub>3</sub>): 201.5 (C=O), 151.9 (Ar-q), 148.2 (Ar-q), 131.1 (Ar-q), 124.3 (C-6), 107.9 (C-2 & C-5), 101.8 (O-CH<sub>2</sub>-O), 63.8 (N-CH<sub>3</sub>), 51.2 (C-2'), 36.1 (C-3'), 19.0 (C-4'), 14.0 (C-5'). Tentative assignment due to impurities in the sample.

#### NMR data for MDPBP free base (**3**)

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.77 (dd,  $J_{ortho}$  = 8.2 Hz,  $J_{meta}$  = 1.7 Hz, 1H, H-6), 7.62 (1H, d,  $J_{meta}$  = 1.7 Hz, H-2), 6.83 (1H, d,  $J$  = 8.3 Hz, H-5), 6.02 (2H, s, OCH<sub>2</sub>O), 3.75 (1H, dd,  $J$  = 8.7 Hz,  $J$  = 4.8 Hz, C-2'), 2.75-2.66 (2H, m, 2 × A-H), 2.62-2.53 (2H, m, 2 × A-H), 1.97-1.81 (m, 2H, CH<sub>2</sub>-3'), 1.79-1.73 (m, 4H, 2 × CH<sub>2</sub>-B), 0.83 (t,  $J$  = 7.5 Hz, 3H, 4'-CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75.5 MHz):  $\delta$  198.8 (C=O), 151.7 (Ar-q), 148.0 (Ar-q), 131.8 (Ar-q), 124.9 (C-6), 108.6 (C-2), 107.8 (C-5), 101.8 (O-CH<sub>2</sub>-O), 70.6 (C-2'), 51.2 (2 × CA), 24.1 (C-3'), 23.4 (2 × CB), 10.4 (4'-CH<sub>3</sub>).

#### NMR data for MPPP hydrochloride salt (**5**)

<sup>1</sup>H NMR (d<sub>6</sub>-DMSO) 10.84 (1H, br s, NH), 7.95 (2H, d,  $J_{ortho}$  = 8.1 Hz), 7.43 (2H, d,  $J_{ortho}$  = 7.9 Hz), 5.47 (1H, apparent pentet,  $J$  = 7.2 Hz, CH-2'), 3.69-3.47 (2H, m, 2 × AH), 3.27-3.00 (2H, m, 2 × AH), 2.42 (3H, s, 4-CH<sub>3</sub>), 2.10-1.85 (4H, m, 4 × BH), 1.50 (3H, d,  $J$  7.2 Hz, 3'-Me). <sup>13</sup>C NMR (d<sub>6</sub>-DMSO):  $\delta$  195.7 (C=O), 145.6 (Ar-q), 130.5 (Ar-q), 129.7 (Ar-CH), 129.0 (Ar-CH), 63.8 (C-2'), 52.9 (CA), 51.6 (CA), 23.1 (CB), 23.0 (CB), 21.3 (4-CH<sub>3</sub>), 15.8 (3'-Me).

#### NMR data for 1-(3,4-methylenedioxyphenyl)-2,2-dibromobutan-1-one (**8**)

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.07 (1H, dd,  $J_{ortho}$  = 8.4 Hz,  $J_{meta}$  = 1.8 Hz, H-6), 7.86 (1H, d,  $J_{meta}$  = 1.8 Hz, H-2), 6.88 (1H, d,  $J_{ortho}$  = 8.4 Hz, H-5), 6.08 (2H, s, O-CH<sub>2</sub>-O), 2.70 (2H, q,  $J$  = 7.1 Hz, 3'-CH<sub>2</sub>), 1.30 (3H, t,  $J$  = 7.1 Hz, 4'-Me). <sup>13</sup>C NMR (CDCl<sub>3</sub>): 186.7 (C=O), 151.9 (Ar-q), 147.3 (Ar-q), 128.0 (C-6), 126.5 (Ar-q), 111.2 (C-2), 107.5 (C-5), 101.9 (O-CH<sub>2</sub>-O), 68.3 (quat. 2'-CBr<sub>2</sub>), 40.4 (3'-CH<sub>2</sub>), 11.9 (4'-Me).

#### NMR data for 1-(3,4-methylenedioxyphenyl)-2,2-dibromopentan-1-one (**10**)

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.04 (1H, dd,  $J_{ortho}$  = 8.4 Hz,  $J_{meta}$  = 1.8 Hz, H-6), 7.83 (1H, d,  $J_{meta}$  = 1.8 Hz, H-2), 6.85 (1H, d,  $J_{ortho}$  = 8.4 Hz, H-5), 6.06 (2H, s, O-CH<sub>2</sub>-O), 2.66-2.59 (2H, m, 3'-CH<sub>2</sub>), 1.83-1.69 (2H, m, 4'-CH<sub>2</sub>), 1.05 (3H, t,  $J_{HH}$  = 7.5 Hz, 5'-Me). <sup>13</sup>C NMR (CDCl<sub>3</sub>): 186.6 (C=O), 151.8 (Ar-q), 147.2 (Ar-q), 127.9 (C-6), 126.5 (Ar-q), 111.1 (C-2), 107.5 (C-5), 101.9 (O-CH<sub>2</sub>-O), 66.6 (quat. 2'-CBr<sub>2</sub>), 49.0 (CH<sub>2</sub>-3'), 20.9 (CH<sub>2</sub>-4'), 13.5 (5'-Me).

### NMR data for $\alpha$ -bromo-4-methylpropiofenone (**11**)

$^1\text{H}$  NMR ( $d_6$ -DMSO): 7.94 (2H, d,  $J_{\text{ortho}} = 8.4$  Hz), 7.35 (2H, d,  $J_{\text{ortho}} = 8.1$  Hz), 5.78 (1H, q,  $J_{\text{HH}} = 6.6$  Hz, CH-2'), 2.39 (3H, s, 4-CH<sub>3</sub>), 1.77 (3H, d,  $J_{\text{HH}} = 6.6$  Hz, 3'-CH<sub>3</sub>).  $^{13}\text{C}$  NMR ( $d_6$ -DMSO): 193.1 (C=O), 144.3 (Ar-q), 131.2 (Ar-q), 129.3 (Ar-CH), 128.9 (Ar-CH), 43.1 (2'-CH), 21.2 (4-CH<sub>3</sub>), 20.0 (3'-CH<sub>3</sub>).

## Results and Discussion

A representative GC-IT-MS trace obtained from NRG-1 sample 1 obtained from a website is shown in Figure 1B. This white-powdered product was delivered in a silver foil bag and labelled as 'Energy-1 (NRG-1)'. It can be seen that a total number of four products were detected following GC-IT-MS analysis. A mass spectral and chromatographic comparison with synthesized standards (Figure 1E) confirmed that this mixture consisted of four cathinones **1–4** (Figure 1A). Both 4-fluoromethcathinone (**1**) and MDPV (**4**) have been detected in a number of NRG-1 products<sup>[22,24]</sup> and analytical data were in agreement with standards and data reported in previous studies.<sup>[15,20]</sup>

The additional presence of 1-(3,4-methylenedioxyphenyl)-2-(methylamino)pentan-1-one (pentylone, **2**) and 3,4-methylenedioxy- $\alpha$ -pyrrolidinobutyrophenone (MDPBP, **3**) was interesting. The corresponding electron and chemical ionization mass spectra for cathinones **1–4** are summarized in Figures 2A1–D2 where compound identification was instigated by the appearance of side-chain specific iminium ions  $\text{CHR}=\text{N}^+(\text{R}^1\text{R}^2)$  ( $\text{C}_n\text{H}_{2n+2}\text{N}^+$ ).<sup>[22,25,26]</sup> For example, pentylone (**2**) gave a base peak at  $m/z$  86 (Figure 2B1) under EI-IT-MS conditions due to the formation of the  $\text{CH}(\text{C}_3\text{H}_7)=\text{N}^+(\text{H})\text{CH}_3$  iminium ion. The fact that  $m/z$  44 was also present indicated secondary fragmentation of  $m/z$  86 by a neutral loss of propene. Correspondingly, the piperonyl ion appeared at  $m/z$  149 followed by a neutral loss of CO to give the 3,4-methylenedioxyphenyl species at  $m/z$  121.<sup>[13,22]</sup>

Extensive fragmentation is a desirable feature when directing compound identification but this can also hamper the differentiation between isomers due to mass spectral similarity. Under EI-IT-MS conditions the presence of both  $m/z$  86 and  $m/z$  44 (**2**, Figure 2B1) might also occur in the presence of an  $\alpha$ -methyl-*N*-propyl derivative as this could potentially give rise to similar fragmentation and base peak formation (unpublished observations). A chromatographic match (Figure 1E), however, provided support that compound (**2**) was consistent with pentylone. The associated CI mass spectrum showed a fragment at  $m/z$  205 (Figure 2B2) indicating the potential loss of *N*-methylamine  $[\text{M} + \text{H} - 31]^+$ .

Compound **3** detected in the NRG-1 sample 1 (Figure 1B) showed a base peak at  $m/z$  112 (Figure 2C1). This indicated that an aliphatic substituent was not present since the aliphatically based iminium ion series follows a  $[16 + 14n]$  pattern yielding an even-electron ion series at  $m/z$  44,  $m/z$  58,  $m/z$  72,  $m/z$  86 etc. A corresponding species  $[\text{M} + \text{H} - 71]^+$  was detected at  $m/z$  191 under CI conditions (Figure 2C2) which was consistent with a loss of pyrrolidine. Final confirmation of the presence of MDPBP was obtained by organic synthesis and showed identical mass spectral and chromatographic behaviour.

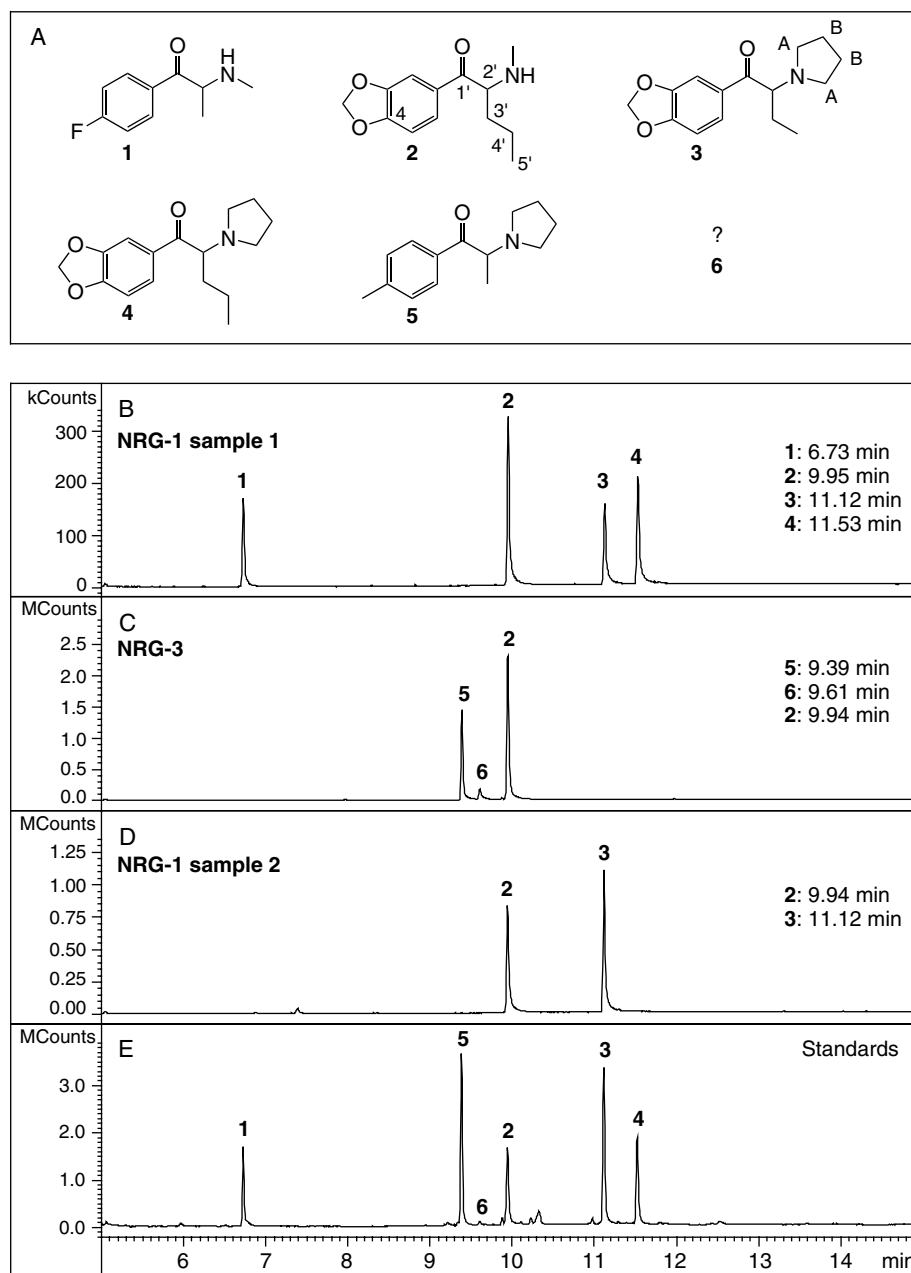
Two additional products originating from a second website were delivered in plastic bags containing white powder. One product was labelled as 'NRG-3' whereas the other sample was labelled as NRG-1 (sample 2). In both cases, a second label was attached on the opposite side of the bags carrying the structure

of mephedrone (4-methylmethcathinone) and the hazard symbol labelled as 'harmful'. Two major peaks were detected following GC-IT-MS analysis of the NRG-3 product (Figure 1C). Compound (**5**) eluted at 9.39 min and was subsequently characterized as 4-methyl- $\alpha$ -pyrrolidinopropiofenone (MPPP) based on mass spectral considerations mentioned above. The side chain of MPPP (**5**) represented the  $\alpha$ -methyl derivative of MDPBP (**3**), hence leading to a shortened base peak at  $m/z$  98 instead of  $m/z$  112 (Figure 2E1). Similarly, the CI-IT-MS spectrum displayed an  $[\text{M} + \text{H} - 71]^+$  ion of minor abundance at  $m/z$  147 (Figure 2E2), again pointing towards pyrrolidine. The EI-IT-MS reported here was consistent with previous analysis on the detection of MPPP and its metabolites in rat urine.<sup>[27,28]</sup> Methane CI-MS spectra were also reported but differed from the CI spectrum presented in the present study due to the use of methanol as a liquid CI reagent and internal ionization which did not give any adduct ions (Figure 2E2). The second major product detected in the NRG-3 sample was consistent with pentylone (**2**) as shown in the GC-MS trace in Figure 1C. However, a significantly less intense peak was observed at 9.61 min and the corresponding mass spectra are shown in Figures 2F1 and 2F2. The CI-IT-MS of this unknown derivative (**6**) appeared to show an  $[\text{M} + \text{H}]^+$  at  $m/z$  236 and two additional species at  $m/z$  218 and  $m/z$  205 (base peak), respectively, which indicated the potential presence of an isomer of (**2**). Its identity is currently unknown. Interestingly, compound (**6**) was also detected in the reference trace (Figure 1E) which consisted of a mixture of synthesised standards. Identical retention time and EI/CI-IT-MS data indicated that the presence of (**6**) observed in the NRG-3 product (Figure 1C) may have originated during synthesis of pentylone (**2**). Figure 1D represents the GC-IT-MS trace corresponding to NRG-1 sample 2 and shows that the two products detected in this mixture were consistent with pentylone (**2**) and MDPBP (**3**).

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of the previously unreported cathinone analogues (**2**), (**3**), and (**5**) have been assigned in the experimental section, the data being entirely consistent with their structures. For each analogue the anticipated coupling pattern was observed for the 2'-CH group with the 3'-substituent (and NH for the protonated ammonium salt of (**5**)). The aromatic protons were very similar for compounds (**2**) and (**3**), consistent with the 1,3,4-trisubstituted aromatic pattern of the 3,4-methylenedioxyphenyl ring. The  $^1\text{H}$  NMR spectra of the pyrrolidine ring in analogues (**3**) and (**5**) were complex, showing non-equivalence of the prochiral CH<sub>2</sub>A protons observed due to the presence of the chiral center at CH-2'.

### Comments on the formation of brominated precursors

The bromination of alkylphenone precursors at the  $\alpha$ -position provided the intermediates required for the preparation of the cathinone standards. A 20% (v/v) solution of bromine in dichloromethane (DCM) was added dropwise in order to initiate the reaction. Once colour formation disappeared, further additions were introduced until the colour of bromine persisted. The DCM layer was washed three times with water and three times with saturated NaHCO<sub>3</sub> solution. The DCM layer was then dried with anhydrous MgSO<sub>4</sub> and removed under reduced pressure to give the crude product. Commonly, the crude brominated product is used without further purification but GC-IT-MS analyses of the brominated products revealed extensive formation of  $\alpha,\alpha$ -dibrominated intermediates (**8**) and (**10**). Interestingly, this was particularly the case with the precursors to cathinones (**2**) and (**3**) possessing



**Figure 1.** A: Structural representations of cathinone derivatives 1–5. The identity of impurity 6 is unknown. B–E: GC-IT-MS traces of NRG-1 and NRG-3 products and confirmation using synthesized derivatives.

the 3,4-methylenedioxy nucleus (**9**) and (**7**) where isolation of the mono-brominated intermediates proved unsuccessful. In contrast, isolation of  $\alpha$ -bromo-4-methylpropiophenone (**11**) was straightforward. A number of alternative bromination agents, such as *N*-bromosuccinimide and copper bromide, might also be of interest for further studies in order to evaluate the extent of by-product formation. Figures 3A1–3E2 summarize GC-IT-MS retention times and EI/CI-IT-MS data for mono- and dibrominated species.

As expected, under EI-conditions base peak formation was observed to be represented by the benzoyl ion at  $m/z$  149 (Figures 3A1–3D1) and  $m/z$  119 (Figure 3E1). CI-IT-MS analyses proved particularly helpful since it allowed for the detection of the brominated  $[M + H]^+$ . The protonated molecules were observed as base peaks which facilitated convenient detection

of the corresponding A + 2 species, reflecting the presence of bromine (Figures 3A2–3E2). The implementation of methanol as a liquid CI reagent, used under low-pressure and internal ionization conditions,<sup>[29]</sup> did not require the use of reagent gases traditionally used and avoided the formation of adduct ions. The main differentiating features in the NMR spectra of the dibrominated precursors, when compared with the mono-brominated analogue, was the absence of a 2'-CH in the  $^1\text{H}$  NMR and the presence of an extra quaternary carbon in the  $^{13}\text{C}$  DEPT-135 for 2'-CBr<sub>2</sub>. Interestingly, when dibrominated precursors were used for the reaction with the corresponding amine, cathinone products (**2**) and (**3**) were formed. The mechanism for this unusual reduction step, however, is currently unknown and requires further work in the future.

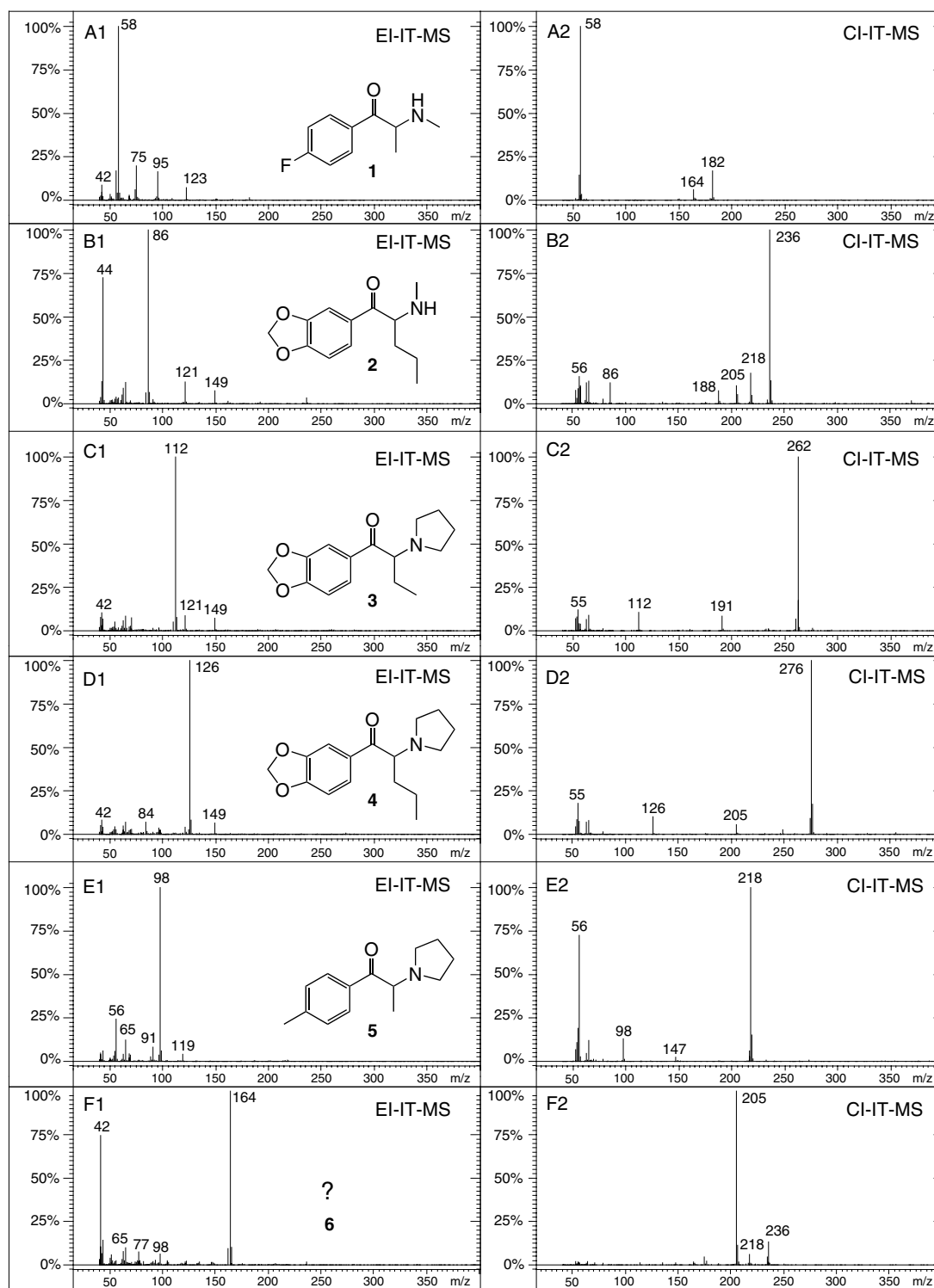


Figure 2. A–F: EI-IT-MS and CI-IT-MS spectra of derivatives 1–6.

One of the key problems in the purchase of controlled drugs online is the actual contents of the packages received. In economic terms these products are experience goods, in that the purchaser has no real way of knowing what they have bought until they take the product and 'experience' it. Whilst much is known about the individual use of particular controlled drugs, such as cocaine and 3,4-methylenedioxy-*N*-methamphetamine (MDMA),

very little is known about the impact of drug-drug interactions. It would appear that these products are increasing the risk of polypharmacy as the user is unaware of the mixtures in their product and in several cases the sample contained different drug(s) altogether. One could speculate that dire consequences would come from taking these products but there is simply not enough evidence to know either way. It is a classic case of 'buyer

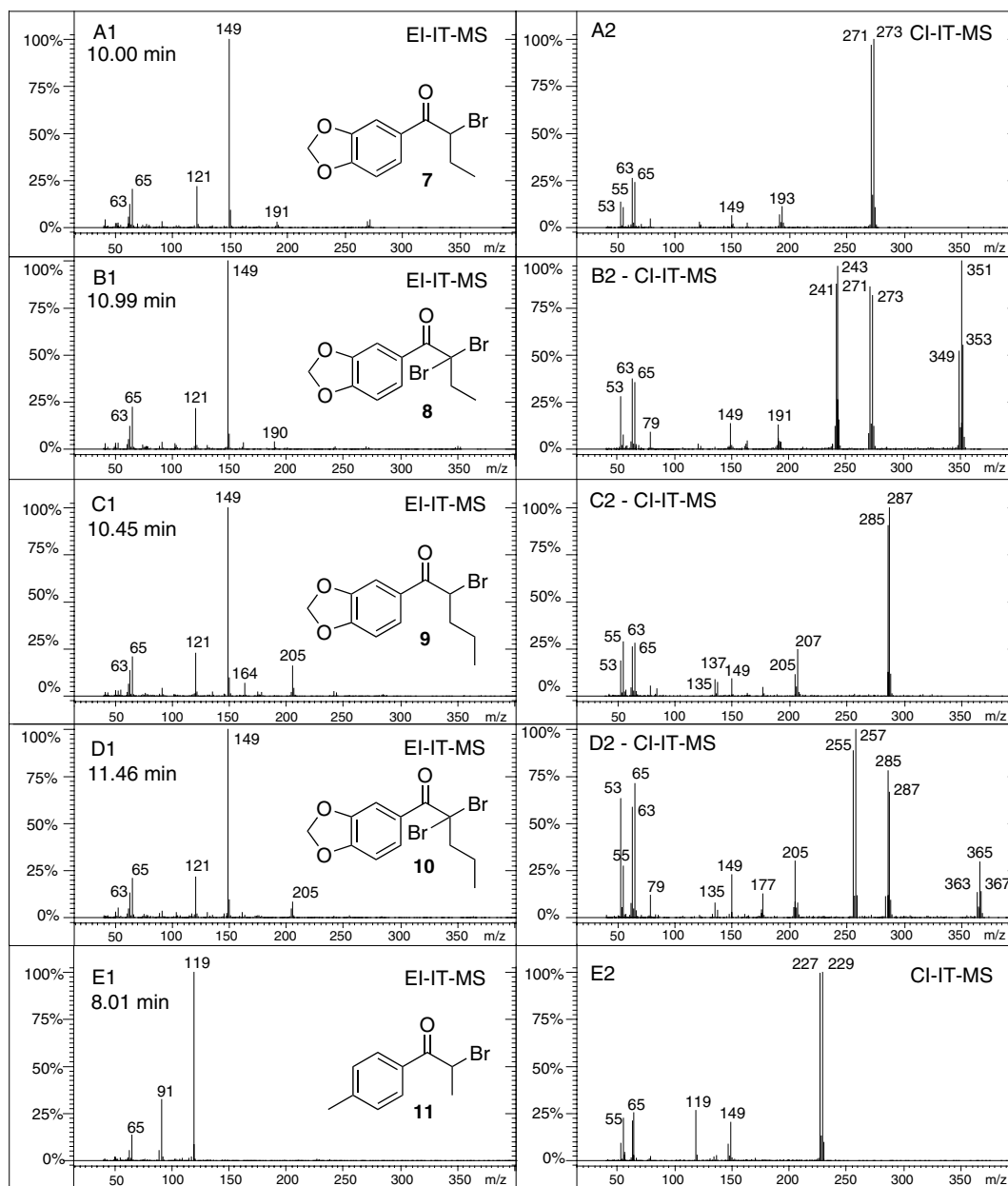


Figure 3. A–E: EI-IT-MS and CI-IT-MS spectra of mono- and dibrominated cathinone precursors detected during synthesis.

beware' which, however, might also equally apply to the seller. The recent classification of mephedrone and naphyrone derivatives as Class B drugs provided an indication about a policy response that may as well extend to structural analogues that are not yet explicitly covered. A variety of policy considerations are potentially available<sup>[10]</sup> and one must ensure the installation of appropriate and context-specific forms of harm reduction strategies.

## Conclusion

The analytical characterization of two NRG-1 samples and one NRG-3 product revealed the presence of a total number of five identified cathinones. The fact that three lesser-known derivatives were identified confirmed that the extent and variety of compound composition of these NRG-type products is less than fully explored.

Taken with results reported earlier it would appear that NRG-1 products advertised online as naphyrone might not be represented by 1-naphthalen-2-yl-2-pyrrolidin-1-yl-pentan-1-one, at least not in the abundance as originally anticipated. In the UK, many of the recently discussed cathinones have been classified as Class B drugs which raises the question about purity levels in the future. The use of MS chemical ionization proved particularly helpful for the characterization of precursors and products and this should facilitate the identification of route-specific impurities.

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