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Fluoromethcathinone, a new substance of abuse

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ABSTRACT

We have identified a new compound in capsules marketed as plant feeders available from internet suppliers. It is apparent from internet forums that these so-called plant feeders are being used as recreational drugs. The material is identified as being 3′-fluoromethcathinone. The compound in the capsule was identified by GC–MS, 1H, ^{13}C and ^{19}F NMR as well as FTIR. Other materials identified in the tablet were caffeine and a methylamine salt. The exact position of the fluorine in the fluoromethcathinone was determined by comparison with materials synthesised in our laboratory. Internet-based companies are known to sell 4′-fluoromethcathinone (flephedrone). We present GC–MS data for the three isomers of fluoromethcathinone and their *N*-acetyl derivatives and provide a rapid method for determining the positional isomers of fluoromethcathinone using FTIR or ^{19}F NMR.

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1. Introduction

Recent changes in the attitudes of drug users and widespread access to the internet have seen an increase in the availability of designer drugs. Particularly noteworthy are the drugs which are specifically designed to fall outside of UK law, hence the sale of these materials is legitimate and uncontrolled. These materials are not licensed as drugs but are often marketed as plant feeders, it is clear from surveying open forums on the internet that these plant feeders are being used as recreational drugs.

We have observed a large number of tablets containing benzylpiperazine (BZP) from the various internet suppliers. However BZP is shortly going to become controlled under the Misuse of Drugs Act [1] therefore there is likely to be a decline in the number companies distributing preparations containing this material. In particular it is likely that the number of UK-based companies will decline. In Schedule 2 parts I, II and III to the act a number of substances are named as being Class A, B, and C, respectively in the UK. These classes represent the, sometimes predicted, potential for a substance to cause a social problem. Class A drugs being the most likely and Class C being the least likely [1]. It is possible, however, to purchase various Class C compounds through the internet at present, compounds such as ketamine and diazepam for example, so it is likely that BZP will be available to those that want it for some time to come.

Some companies are moving on to sell a range of compounds based on analogues of cathinone **1** (Fig. 1). Presently only a select number of cathinone analogues are controlled in the UK [1] one example of this is methcathinone **2**, popularised by its ease of synthesis from ephedrine [2]. Therefore compounds such as 4′-methylmethcathinone **3** (also referred to by users as mephedrone, meph, mmcat and miaow) and 3,4-methylenedioxymethcathinone **4** (Fig. 1) (sometimes referred to as methylone) are currently available from these on-line stores to name but two.

The trivial naming of these materials appears to stem from the fact that methcathinone can be synthesised by the oxidation of ephedrine [2]. Methcathinone then aquired the alternative name ephedrone. Those that provide new trivial names for compounds such as these are likely to encounter problems in the future. When and if changes in the law force the illicit manufacturer of 4′-methylmethcathinone (mephedrone) to replace the 4,-methyl group with a 4,-ethyl group, will this adopt the name ephedrone as well? There is also an extreme risk of misidentification by the consumer. 4′-Methoxymethcathinone has been given the trivial name methedrone. This is all too similar to mephedrone and methylone and the uncontrolled sale of these materials will undoubtedly end with the incorrect materials being sold.

There are a few studies on the effects of the cathinones in humans such as investigations into the efficacy of the isomers of methcathinone **2** (Fig. 1) [3] and studying their efficacy as monoamineoxidase inhibitors [4]. However these studies are insignificant when compared to the number of papers written on the effects of the non-keto (amphetamine) analogues of these compounds.

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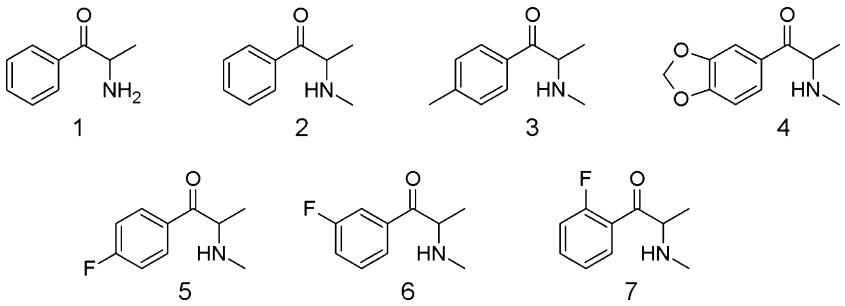


Fig. 1. Cathinone **1** methcathinone **2**, some ring substituted methcathinones **3**, **4** and the isomers of fluoromethcathinone **5**–**7**.

It is known that the β-keto amphetamines show a threefold decrease in their activity in certain parts of the brain [5]. This is probably why the β-keto amphetamines have not gained the popularity of the amphetamines as recreational drugs, users complain of high doses (200 mg of 4′-methylmethcathinone taken orally) and a frequent need to redoes as the effects last around 2–4 h. Some users report taking as much as 2 g in a 4 h period to prolong the effects.

The synthesis of these materials appears to be relatively simple [6]. Even the chiral synthesis of these materials has been reported using amino acids as precursors [7] which would not appear to be a challenge to someone with a low level of chemistry knowledge. This is making the synthesis of these materials attractive to those wishing to exploit the law surrounding the cathinone analogues.

These compounds are often discovered through seizure at street level [8]. Our own studies of these materials have involved purchase of materials from the internet and screening the tablets for their contents. Our latest find was in a capsule named 'Lift' (Fig. 2). The capsules are orange and white and contain about 250 mg of an off white powder. GC–MS analysis of the powder found it to contain caffeine and a compound previously unknown to us.

We have analysed other capsules from the same supplier, those found in cream capsules (Sub Coca Dragon), those in yellow capsules (High Spirit) and those in yellow and cream capsules (NeoDove 2). All contained the new compound among other chemicals. The work presented in this manuscript has been conducted on the orange and white capsule pictured above.

We present herein our analysis of the new and previously unseen compound.

2. Materials and methods

2.1. Nuclear magnetic resonance spectroscopy (NMR)

Deuterium oxide was purchased from Sigma–Aldrich.

NMR data was collected using a JEOL Eclipse^{+} 400 spectrometer. The data was recorded in D_2O using HOD for standardisation in ^{1}H experiments and trifluoroacetic acid (TFA_d) referenced to −78 ppm for internal standardisation in ^{19}F experiments.

2.2. Attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR)

FTIR data was collected on a PerkinElmer spectrum one Fourier transform spectrometer fitted with an ATR-3 top plate. Data was collected between 4000 and 400 cm^{-1}.

2.3. Gas chromatograph–mass spectrometry (GC–MS)

All solvents and reagents used in the GC–MS studies were purchased from Sigma–Aldrich.

GC–MS data was collected using an Agilent 6890N GC with a manual injection, split liner, an HP5MS column (30 m × 0.25 mm, 0.50 μm) linked to an Agilent 5973 Mass Selective Detector. Injection volume 1 μl, Split 50:1, column oven temperature 80 °C, injection temperature 280 °C, carrier gas helium, flow rate 1.0 ml/min, ion source temperature 200 °C, interface temperature 250 °C. Column oven temperature programme: 80 °C 4 min, 20.00 °C/min 280 °C 8 min, 20.00 °C/min 290 °C 11.5 min.

Samples were prepared for GC–MS analysis by suspending 5–10 mg of the hydrochloride salt in 1 ml of ether. The solution is made basic by the addition of one drop of concentrated ammonia. The ether layer is decanted from any aqueous phase and ammoniumchloride deposits and injected directly.

N-Acetylation was achieved by added five drops of pyridine and five drops of acetic anhydride to a flask containing the hydrochloride salt of the cathinone (5–10 mg). The suspension was agitated for 5 min to allow complete consumption of the amine. The reaction was quenched with the addition of methanol (1 ml) and the mixture was injected directly into the GC–MS.

2.4. Synthesis of authentic samples

Fluoropropiophenones were purchased from Alfa Aesar and used without further purification. All other materials were acquired from Sigma–Aldrich and used without purification.

The following synthetic procedure was used to prepare the isomeric fluoromethcathinones (Scheme 1).

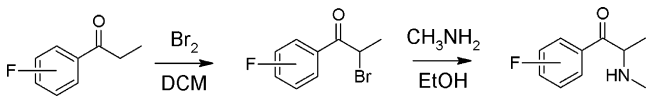
2.4.1. α-Bromination

To a flask containing the appropriate fluoropropiophenone in DCM (5%) was added and one drop of bromine in DCM. This solution was stirred for 5 min for the reaction to initiate. An equimolar amount of bromine solution was added over a period of a further 10 min. After this time the solvent was removed under vacuum to yield the corresponding α-bromophenone, yields range from 95% to 100%.

2.4.2. Methamination

The corresponding fluoro α-bromopropiophenone was reacted with methylamine in ethanol. The solution was stirred for 20 min at room temperature. After this time the solvent and excess amine were removed under vacuum. The resultant residue was dissolved in aqueous HCl and extracted with ether. The aqueous phase

Fig. 2. 'Lift' capsule purchased from internet supplier.



Scheme 1. Synthesis of fluoromethcathinones.

was made basic by the addition of solid potassium carbonate. The amine was extracted with ether. The ether was dried and to this was added acidic methanol. The solvent was removed under vacuum and the resultant slurry was suspended in acetone. This solvent was removed under vacuum and the solids were once again suspended in acetone, filtered and washed with acetone to yield the amine hydrochloride. Yields of the methcathinones were 4′-fluoro 27%, 2′-fluoro 20% and 3′-fluoro 8%.

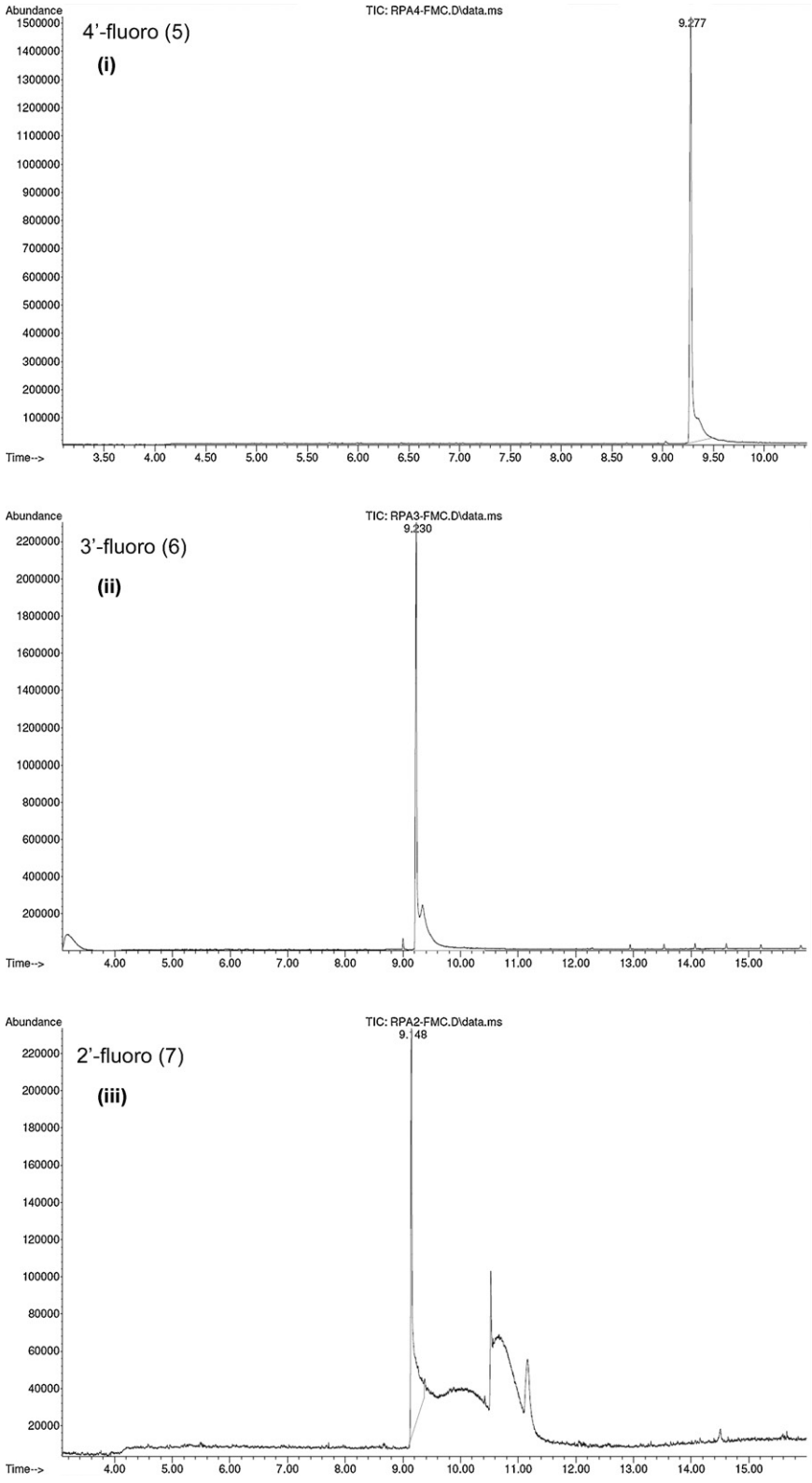


Fig. 3. GC traces for **5**, **6** and **7**, respectively.

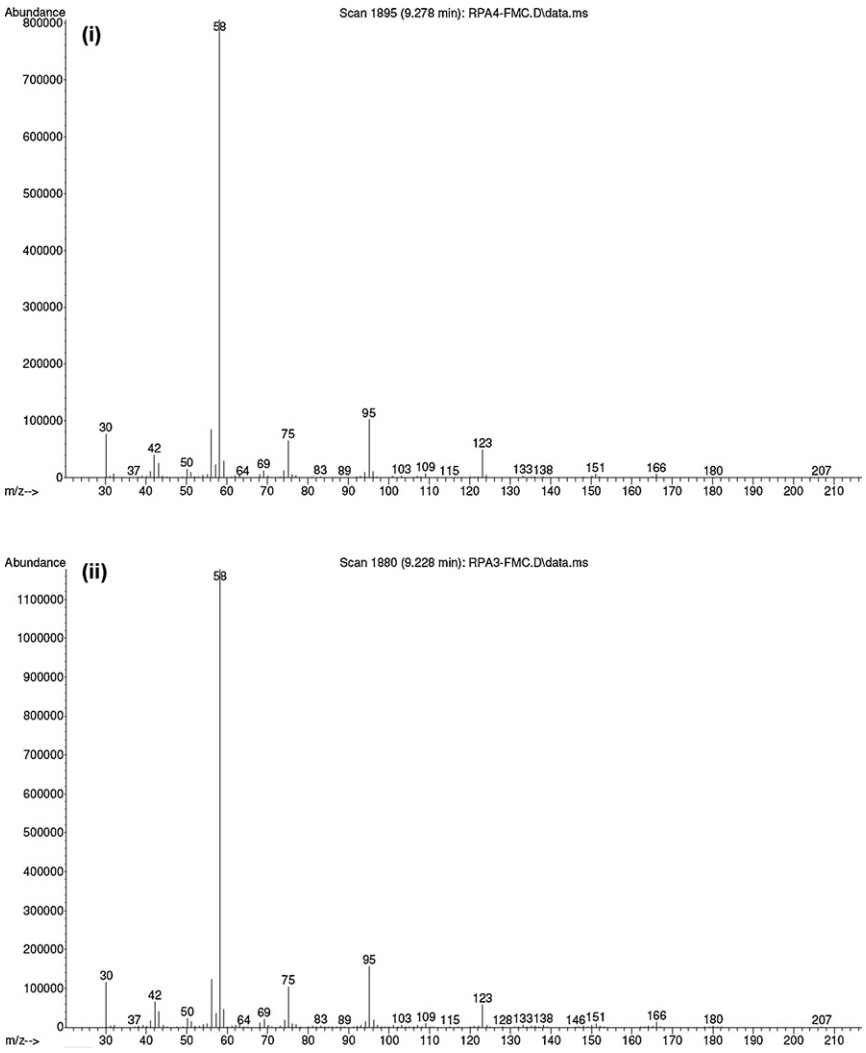


Fig. 4. MS traces for **5** and **6**, respectively.

3. Results and discussion

3.1. Gas chromatography

GC–MS analysis of the capsule showed the presence of caffeine and a fluoromethcathinone.

During our studies of the GC–MS analysis of cathinone analogues we have encountered some issues with stability upon injection [9]. Apparently pure compounds by NMR can appear to have a significant shoulder when analysed by GC–MS. 4′-Methylmethcathinone **3** is a prime example of this [9].

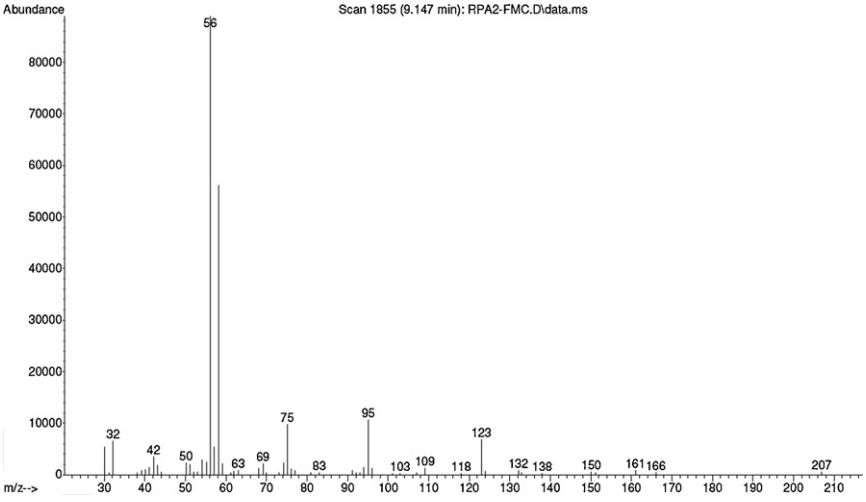


Fig. 5. MS trace for **7**.

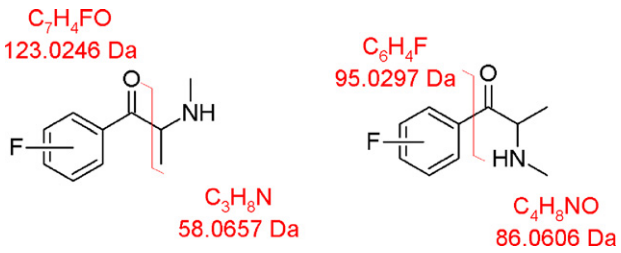


Fig. 6. Major EIMS fragmentations for fluoromethcathinone.

The fluoromethcathinones each have different apparent stabilities, 4′-fluoromethcathinone **5** has a very slight shoulder and slight tailing of the peak is observed. 3′-Fluoromethcathinone **7** has a pronounced shoulder and 2′-fluoromethcathinone **6** degrades significantly (Fig. 3).

The retention times of the three compounds are as follows:

4′-fluoromethcathinone **5**	9.28 min
3′-fluoromethcathinone **6**	9.23 min
2′-fluoromethcathinone **7**	9.15 min

Derivatisation of the fluoromethcathinones to their respective acetamides improves the stability issue but does not avoid the issues associated with similar retention times. All three gave a single sharp peak at the following retention times;

N-acetyl-4′-fluoromethcathinone	11.44 min
N-acetyl-3′-fluoromethcathinone	11.46 min
N-acetyl-2′-fluoromethcathinone	11.66 min

3.2. Mass spectrometry

A GC–MS study into the positional isomerism of fluoroamphetamine was not able to differentiate between these isomers [10]. However, another study into the positional isomers of ethoxyamphetamine was more diagnostic and could offer some discrimination between the 2′-, 3′- and 4′- isomers of this compound [11], the same was observed for methoxyamphetamine [12].

It is known that electron ionisation mass spectrometry (EIMS) is unhelpful in the analysis of amphetamines [11]. It would appear that the analysis of the β-keto amphetamines suffer similar difficulties. The EIMS for all three isomers of fluoromethcathinone show similar fragmentation (Figs. 4 and 5). The MS shows very

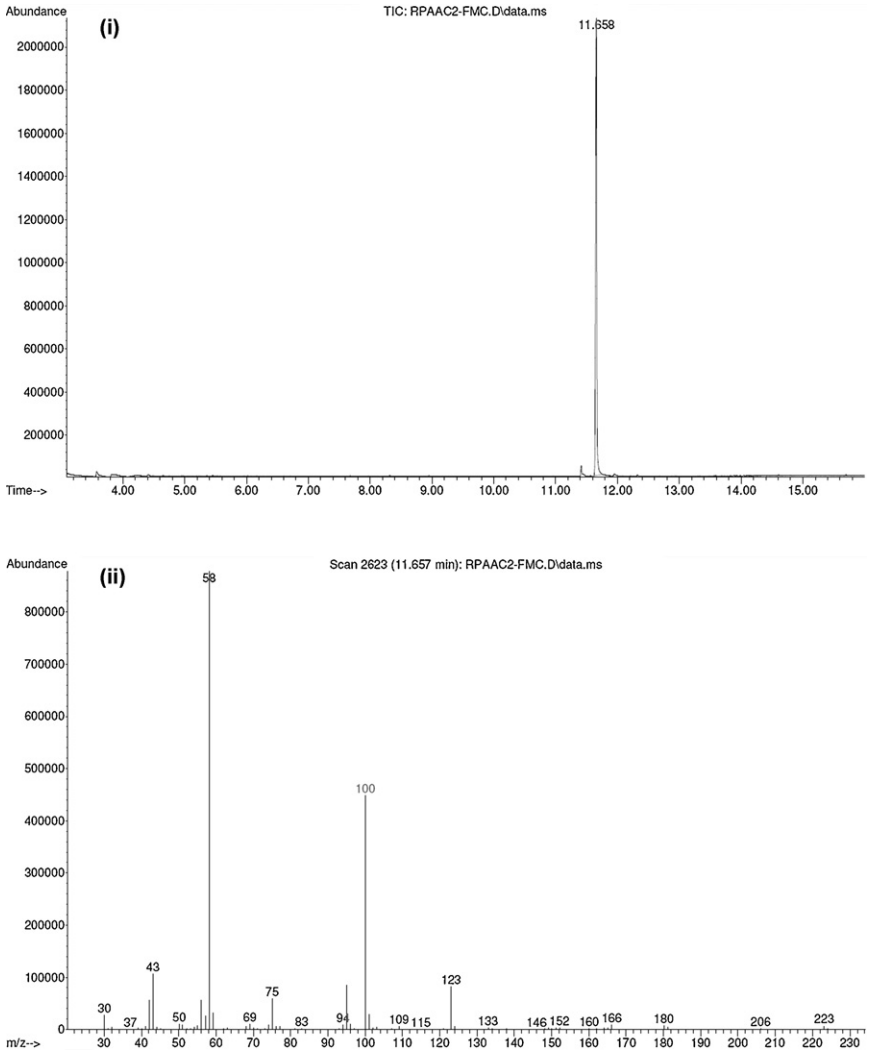


Fig. 7. GC–MS data for *N*-acetyl-2′-fluoromethcathinone.

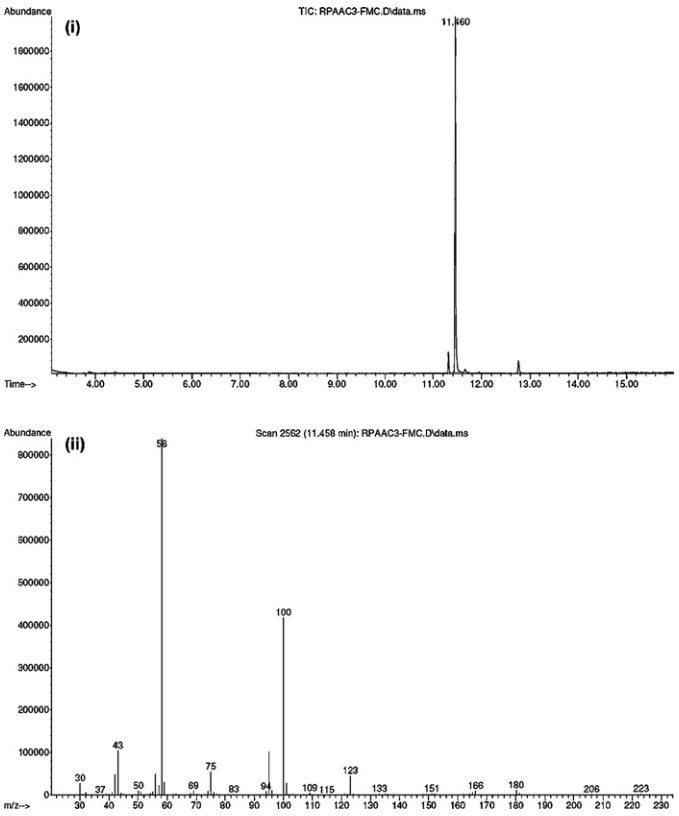


Fig. 8. GC–MS data for *N*-acetyl-3′-fluoromethcathinone.

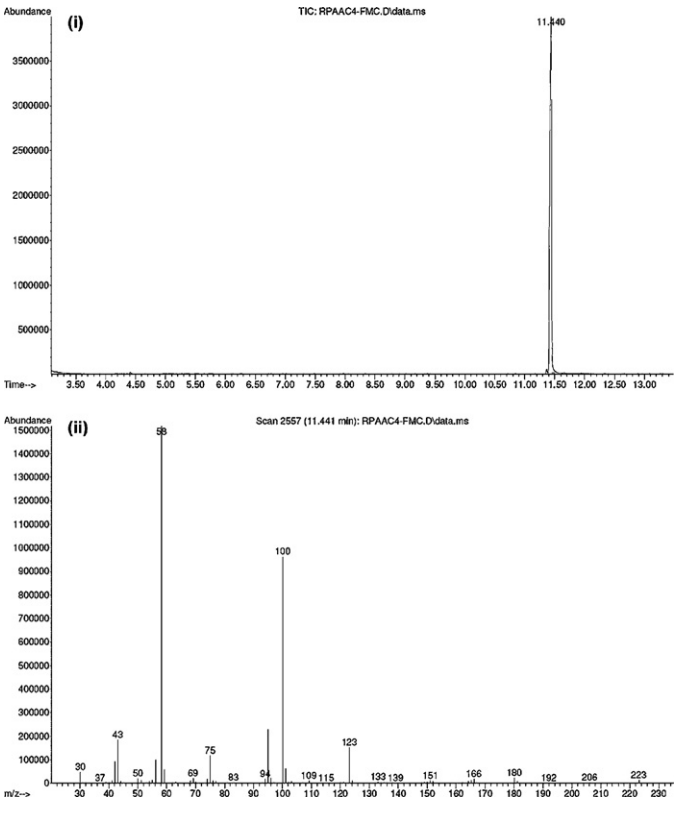


Fig. 9. GC–MS data for *N*-acetyl-4′-fluoromethcathinone.

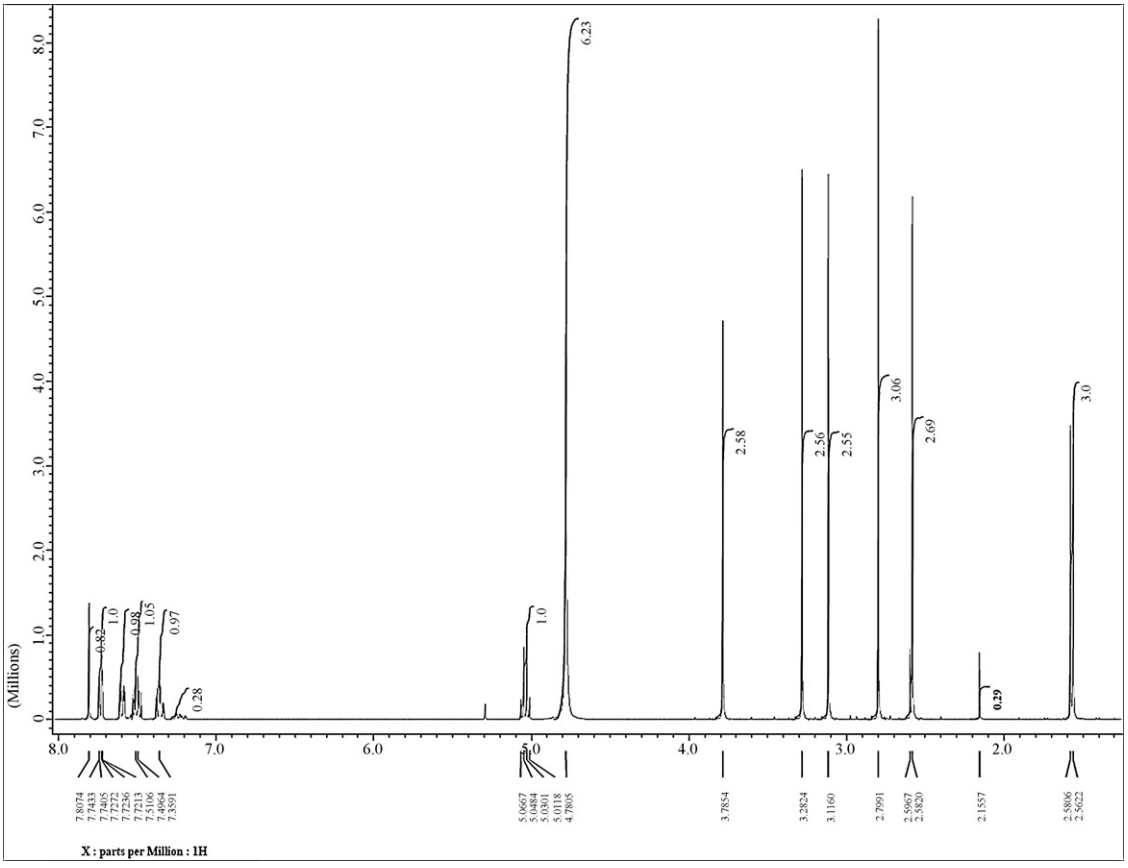


Fig. 10. Direct ^{1}H NMR analysis of the lift capsule in D_2O.

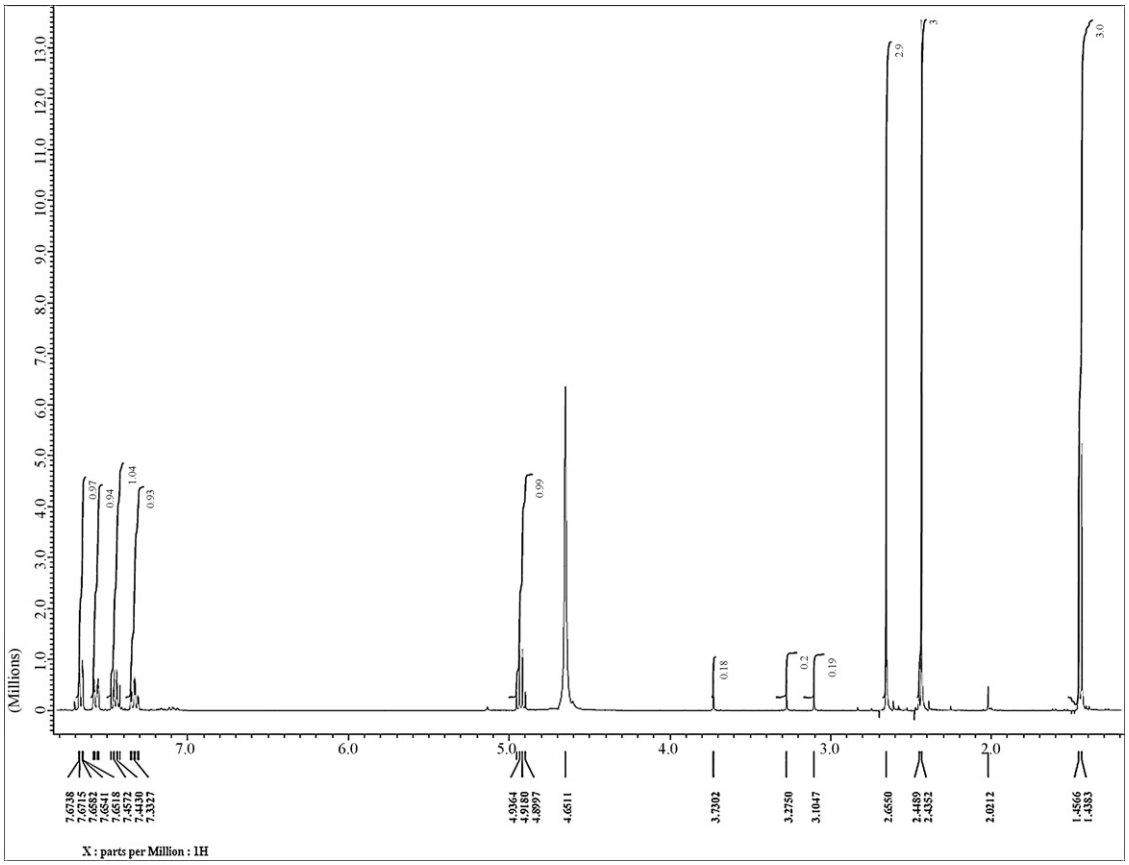


Fig. 11. ^{1}H NMR spectra of the lift capsule after an acetone wash. Sample dissolved in D_2O.

small or absent intensities for the molecular ions (M^+) for the three isomers of the cathinones studied.

The base peak observed in the cathinones is a result of the formation of immonium ions m/z 58. However the 2′-fluoromethcathinone **7** shows an additional ion at m/z 56. It is unclear if the formation of the ion at m/z 56 is due to the structural differences or an artefact of the observed degradation. EIMS analysis of the isomers of fluoroamphetamine do not show the same change in the imminium ion [10], thus we can speculate that this ion is a result of pyrolysis upon injection. This is confirmed by the fact that the ratio

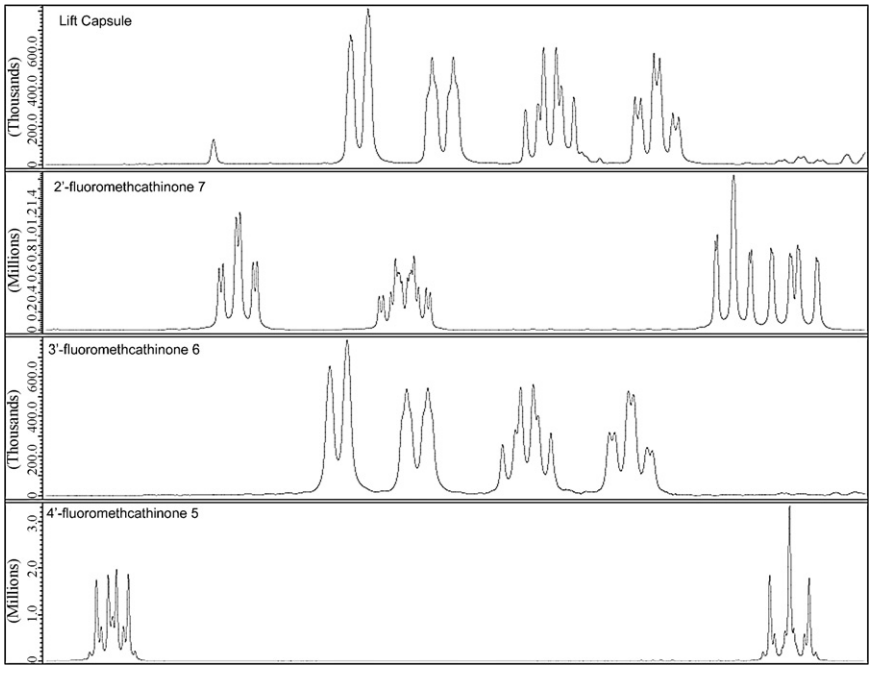


Fig. 12. Expansion of the aromatic region (δ 7–8 ppm) of the ^{1}H NMR for the capsule, 7, 6 and 5 from top to bottom.

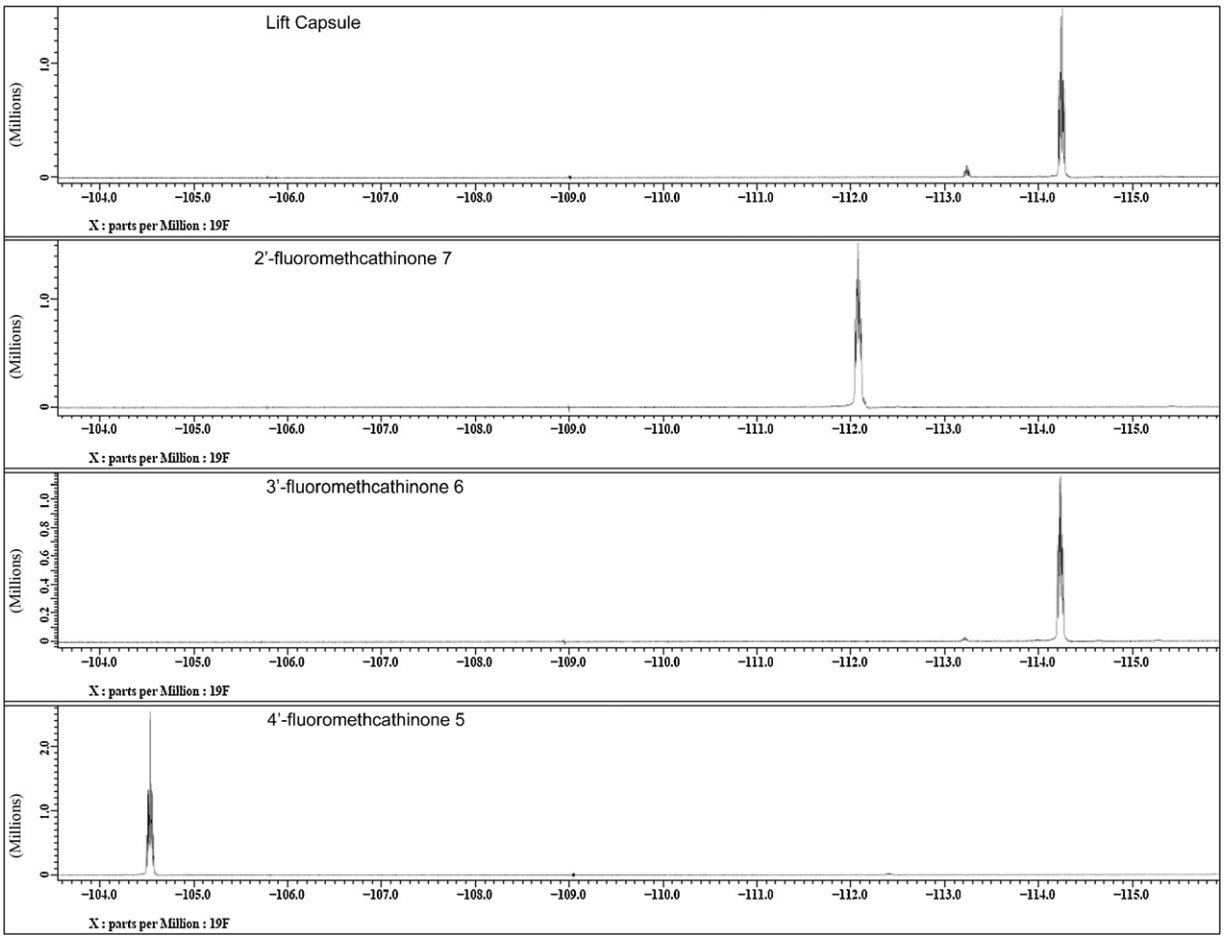


Fig. 13. ^{19}F NMR spectra for the lift capsule and 7, 6 and 5, respectively from top to bottom.

of m/z 56 to m/z 58 appears to change as the major peak is scanned from left to right.

All three isomers of fluoromethcathinone show significant fragments at m/z 95 and m/z 123 these correspond to fluorophenyl cation and a fluorobenzyloxy cation, respectively (Fig. 6).

The data below corresponds to the EIMS data for the corresponding acetamides of the fluoromethcathinones, rmm = 223.

The MS data (Figs. 7–9) shows no significant differences between the three isomers. Isomers of fluoroamphetamine show

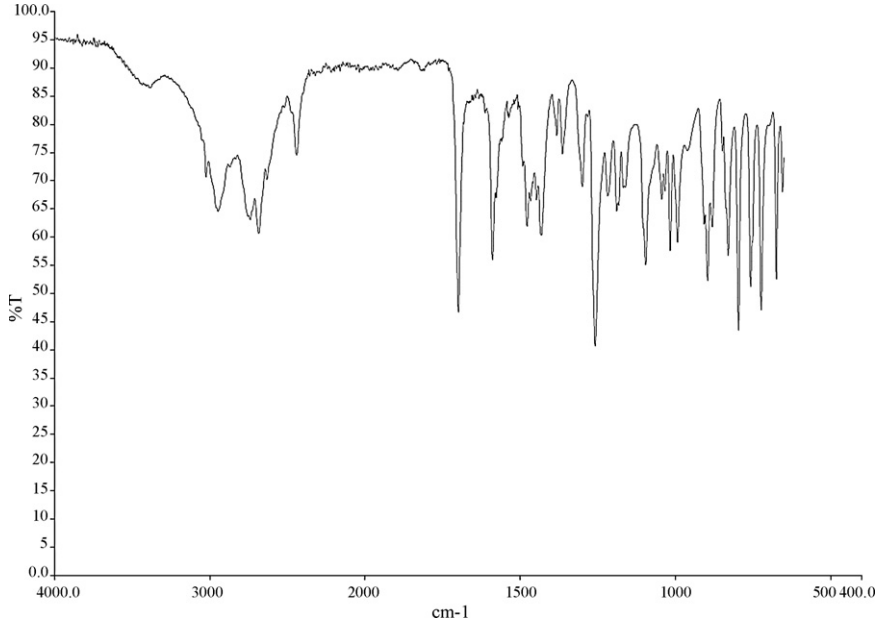


Fig. 14. ATR-FTIR spectra of the contents of the lift capsule, acetone washed.

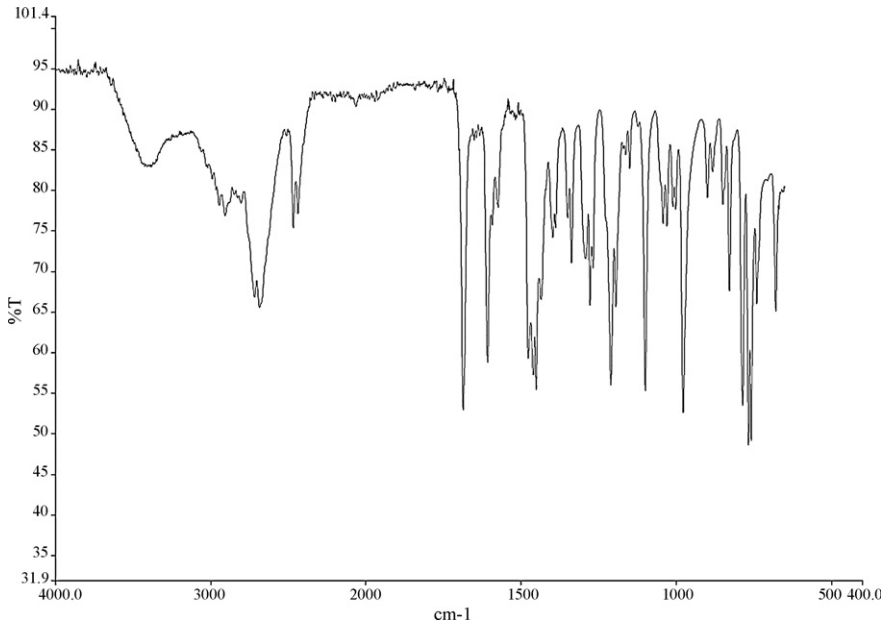


Fig. 15. ATR-FTIR spectra of 2′-fluoromethcathinone **7**.

significant differences in the acetylated derivatives [10]. When the fluorine is in the 4′-position there is an increase in the ion resulting from the inductive route of the Maclaferty rearrangement [10]. The presence of the ketone moiety in the analogous cathinones inhibits the Maclaferty rearrangement in all three isomers. The observed clevage α-to the ketone moiety gives the acetylimminium ion *m*/*z* 100 being the only significant difference between the EIMS of amine and the acetamide.

Searches of internet-based 'legal high' forums suggest that 4′-fluoromethcathinone **5** is freely available under the names '4-FMC' and 'flephedrone'. Using only GC–MS we would have incorrectly assigned the structure of 4′-fluoromethcathinone **5** to the unknown compound.

3.3. ^{1}H NMR spectroscopy

Direct ^{1}H NMR analysis of the powder (Fig. 10) obtained from the capsule confirmed the presence of caffeine.

Simplification of the NMR spectra was achieved by washing the powdered sample with acetone to remove any caffeine (Fig. 11).

This process significantly suppressed the resonances arising from the presence of caffeine. The remaining resonances correspond to the fluoromethcathinone. The resonance at δ 2.43 ppm integrating for three protons corresponds to an equimolar amount of methylamine hydrochloride. The presence of methylamine in the capsule is unlikely to be an intentional additive and is not easily detected by GC–MS owing to the

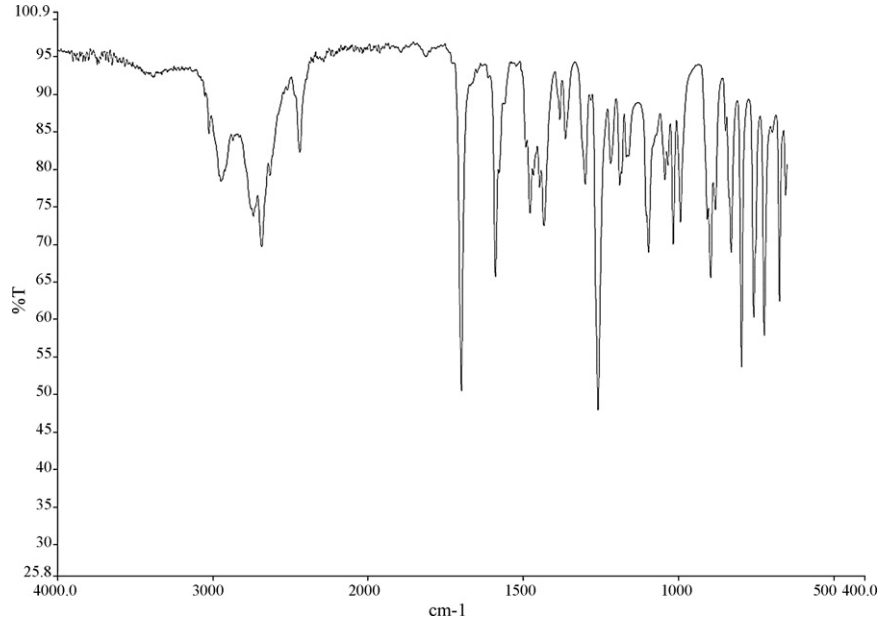


Fig. 16. ATR-FTIR spectra of 3′-fluoromethcathinone **6**.

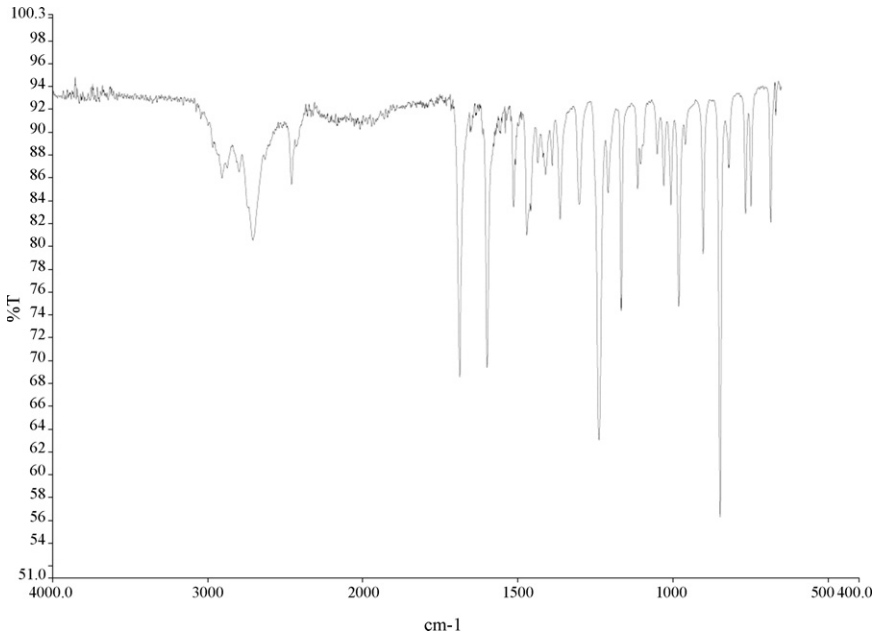


Fig. 17. ATR-FTIR spectra of 4′-fluoromethcathinone **5**.

volatility of methylamine freebase. The presence of methylamine in the tablet is perhaps an artefact of the synthesis being conducted in a low quality clandestine laboratory without adequate analytical equipment.

The presence of fluorine makes determination of the positional isomer very challenging, owing to the fact that both ^{1}H and ^{13}C can spin–spin couple with ^{19}F causing unusual splitting of the peaks in the aromatic region.

Table 1
NMR data for the isomers of fluoromethcathinone.

	δ ppm		
	^{1}H	^{13}C	^{19}F
2'-FMC **7**			
1	–	121.14, d, *J* = 11.53 Hz	
2	–	161.78, d, *J* = 256.0 Hz	−112.09, m
3	7.25, dd, 11.9, 8.4 Hz	117.27, d, *J* = 23.1 Hz	
4	7.88, td, *J* = 7.7, 1.65 Hz	137.63, d, *J* = 10.0 Hz	
5	7.32, t, *J* = 7.9 Hz	131.08, d, *J* = 1.5 Hz	
6	7.69, m	125.44, d, *J* = 3.1 Hz	
7	–	195.31, d, *J* = 3.1 Hz	
8	4.87, q, *J* = 7.1 Hz	62.71, d, *J* = 9.2 Hz	
9	1.52, d, *J* = 7.1 Hz	14.17	
10	2.75	31.08	
3'-FMC **6**			
1	–	134.46, d, *J* = 6.15 Hz	
2	7.66, d, *J* = 7.87 Hz	115.52, d, *J* = 23.06 Hz	
3	–	162.83, d, *J* = 246.75 Hz	−114.23, dt, *J* = 9.25, 5.20 Hz
4	7.33, dt, 8.42, 2.20 Hz	122.41, d, *J* = 21.52 Hz	
5	7.45, dt, *J* = 8.24, 5.68 Hz	131.43, d, *J* = 8.46 Hz	
6	7.57, d, *J* = 9.34 Hz	125.17, d, *J* = 2.31 Hz	
7	–	196.61	
8	4.92, q, *J* = 7.3 Hz	59.97	
9	14.40, d, *J* = 7.3 Hz	15.26	
10	2.64	31.09	
4'-FMC **5**			
1	–	129.02, d, *J* = 2.31 Hz	
2	7.97, m	116.16, d, *J* = 22 Hz	
3	7.22, m	132.19, d, *J* = 10 Hz	
4	–	166.89, d *J* = 256 Hz	−104.53, tt, *J* = 8.67, 5.20 Hz
5	7.22, m	132.19, d, *J* = 10 Hz	
6	7.97, m	116.16, d, *J* = 22 Hz	
7	–	196.22	
8	4.99, q, *J* = 7.1	59.75	
9	1.51, d, *J* = 7.1 Hz	15.44	
10	2.71	31.11	

Table 2
IR Data for the isomers of fluoromethcathinone.

2'-FMC (cm^{-1})	3'-FMC (cm^{-1})	4'-FMC (cm^{-1})	Lift (cm^{-1})
3382	2947	2459	2947
2686	2685	1686	2685
2467	2439	1594	2240
1686	1698	1513	1698
1607	1589	1471	1589
1476	1478	1410	1477
1459	1433	1363	1431
1450	1382	1301	1382
1397	1364	1238	1363
1337	1230	1208	1299
1292	1259	1166	1258
1277	1218	1113	1217
1194	1189	1029	1189
1210	1167	1006	1167
1099	1096	980	1095
1029	1043	902	1043
1042	1016	847	1016
1001	993	819	992
977	896	765	895
899	830	748	880
828	796	684	829
785	757		796
767	723		757
758	674		723
740			674

Therefore in order to unequivocally determine which isomer was found in the capsule it was necessary to synthesise the isomers of fluoromethcathinone to determine the correct isomer by GC–MS and NMR.

The only major differences, other than trivial changes in δH values, between the three compounds is found in the aromatic region of the ^{1}H NMR spectra (Fig. 12).

This data clearly shows that the material in the 'lift' capsule is indeed 3′-fluoromethcathinone **6**.

The use of ^{1}H NMR is not entirely appropriate in the analysis of these compounds as suppliers often mix different analogues and even different compounds, such as caffeine, presumably to alter the effects.

3.4. ^{19}F NMR spectroscopy

The ^{19}F NMR spectra of these compounds are both simple and very different for each isomer. This presents a useful technique for the rapid determination of the identity of fluoromethcathinone in D_2O using trifluoroacetic acid as the internal standard.

The convenience of this method is that it can be conducted in the presence of many other potentially interfering factors. In the case of the 'lift' tablets it can be conducted in the presence of caffeine without any interference from this compound. Also the δF values for each isomer vary a great deal thus this analysis would most likely be possible in the presence of other fluorine containing compounds.

We present below the ^{19}F spectra for 2′-fluoromethcathinone **7**, 3′-fluoromethcathinone **6** and 4′-fluoromethcathinone **5**, respectively (Fig. 13).

The NMR data is presented in Table 1.

3.5. Infrared spectroscopy

We can see from the IR data (Figs. 14–17) some distinct differences in the fingerprint region which would allow for discrimination between the structural isomers of relatively pure samples of fluoromethcathinone. Our sample from the lift capsule, after an acetone wash, still contained 1 M equivalent of methylamine and 6 mol% of caffeine and yet ATR-FTIR is able to discriminate between the isomers.

The wavenumbers obtained are presented in Table 2.

4. Conclusions

This work represents the structural elucidation of a new compound present in a product which we speculate may be intended for use as a legal high. We also identified the presence of caffeine and methylamine hydrochloride in the sample. We have presented GC–MS data for the 3 isomers of fluoromethcathinone and their N- acetyl derivatives. We have also demonstrated a rapid method for the discrimination of the structural isomers of fuoromethcathinone using ^{1}H NMR spectroscopy ATR-FTIR on acetone washed samples of the material or using ^{19}F NMR for crude samples.

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