FACT SHEET

4-Fluoro-amphetamine

September 2014

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A. General information

Recent collected/seized sample in Belgium

Substance: 4-FA
Date of seizure: July 2014
Date of analysis: August 2014
Product type: tablet
Color: yellow
Region: Antwerp
Diameter: 10.1 mm
Thickness: 5.1 mm
Tablet contents: 145 mg 4-FA

Yellow ecstasy tablets containing 4-fluoro-amphetamine have been found in Belgium during the summer. It concerned yellow tablets with a “Route66” logo (see picture).

Created
February 2009

Updated
August 2014

Type
Psychotropic substances

Group
Phenethylamines

Name
4-Fluoroamphetamine (4-FA)

Nature of substance
4-FMP is an analog of amphetamine, which is a central nervous system stimulant.

Systematic chemical name
1-(4-Fluorophenyl)propan-2-amine

B. Alerts

Alerts
Belgium (2014): (see above)

Austria (2009): Beside pills containing PMA, on 3rd and 4th July 2009, ChEck iT! tested again a number of samples. In four samples, sold as pulverized MDMA, further amphetamine-derivatives were found. One pill, sold as “ecstasy“, contained the amphetamine derivative 4-fluoroamphetamine. 4-fluoroamphetamine was also found in four samples sold as “speed“.
Reports to EMCDDA

4-FA was already found in the beginning of 2009 in France, and has since been found all across the European Union. Most recent examples:

**Greece:** On 4 March 2014 the Greek FP reported a seizure of 2.9 gr. beige powder (the seized amount was contained in a plastic bag), seized in the second semester of 2012 by the police at Athens. The sample was analysed by the Third Chemical Service of Athens – Department of Narcotics (General Chemical State Laboratory) by using GC/MS, FT-IR.

**Latvia:** On 12 November 2013 the Latvian FP reported a seizure of 49,42 g light yellow powder seized by the customs at Riga.

**Greece:** On 2 May 2013 the Greek NFP reported a seizure of 2.40g greyish powder seized on 26/04/2013 during police control of the luggage of a tourist who had just arrived at the airport of Thessaloniki.

**Belgium:** On 17 January 2013 the Belgian NFP reported a seizure of 1kg white powder seized in August 2012 by customs at Brussels airport, sent from China.

**Czech Republic:** On 2 April 2012 the NFP reported a seizure of 17,88g off-white powder seized on 15/12/2011 by the Police at Cesky Tesin, stock on border with Poland.

**Slovenia:** On 27 February 2012 the NFP reported a seizure of 1,3g white powder seized at Ljubljana by the Customs on 01/02/2012 and analyzed by the National Forensic Laboratory on 15/02/2012.

**Hungary:** On 13 October 2011 the NFP reported a seizure of 2 blue tablets + fragments (0.62 g) seized in September 2011 by the Police at Kaposvár. Containing 2C-D and fluoramphetamine.

**Italy:** On 8 September 2011 the NFP reported numerous seized samples of white; beige; pale yellow powders, agglomerated powders, tablets, seized at Police Department, Treviso during 2011. 4-MEC was found in mixture with MDPV alone or with MDPV and 4-FA. Mixture of cocaine, 4-MEC and MDPV were also identified.

**Bulgaria:** On 15 July 2011 the NFP reported 3 seizures totaling 5,60g of white powder in packages with inscription „TOP DROP and „LOVES” seized at Sofia in April and May 2011.

**Germany:** On 20 April 2011 the NFP reported that the German police in Hessen has seized about 100 tablets with green and blackberry colour, in large parts with heart logo in November 2010. Forensic checks resulted now that the active agents of these tablets are Dimethoxymethamphetamine and Fluormethamphetamine.
C. Pictures

4-FA tablet, seized during the summer of 2014 in Belgium.

4-FA powder, found in Belgium in 2009

D. Clinical information

Usage
Modes and scope of the established or expected use

Routes of administration: orally ingested or snorted

Dosage: 50-150 mg

Subjective effects in man: The subjective effects of 4-FMP are comparable with those of amphetamine but slightly weaker (provoking also euphoria, increased energy, mood elevation, excessive talking, bruxism (jaw clenching), insomnia and suppressed appetite) but more hallucinogenic and with a come down not as difficult. People have described the effects of 4-FMP as being “MDMA light”. Contrary to amphetamine, the drug is used not only for the stimulating effects, but also for its entheogenic properties.
Health risks

Pharmacology: 4-FMP is a long acting central nervous system (CNS) stimulant and a weak monoamine oxidase inhibitor that inhibits the dopamine reuptake. Studies comparing the pharmacological properties of 4-FMP with those of amphetamine using several in vivo and in vitro tests (Marona-Lewicka et al., 1995) suggest that the two substances resemble. However, user reports point that the substance is being used for other properties than it’s stimulating action.

Mechanism of action: The toxicity of 4-FMP determined by oral administration to female white mice was compared to the toxicity of amphetamine (Suter et al., 1941). The fluorinated amphetamine was found to be slightly more toxic than regular amphetamine (LD$_{50}$ = 25 mg/kg).

Social risks
Unknown.

Other uses
None known.

It is worrying that this drug is not only popular on the Net but it seems to replace regular amphetamine. The effect seems to be very similar to that of amphetamine. Slightly weaker, but a bit more hallucinogenic and the come down not as difficult either. Also, 4-FA can be sold as amphetamine.

The treatment of overdose cases/intoxications is mainly the same as the treatment for MDMA or amphetamine intoxication. Calming the patient and preventing seizures (diazepam) is important. Also, severe hyperthermia can be an issue; in these cases, immediate and active (intravenous) cooling may be necessary. Otherwise, treatment remains symptomatic, no specific antidotes are available.

E. Legal status

Belgium: controlled

Also controlled in: Czech Republic, Denmark, Finland, France, Germany, , Hungary, Italy, Latvia, Lithuania, Norway, Poland, Portugal, Slovakia, Slovenia, Sweden, Turkey, United Kingdom.
F. Chemistry

Systematic chemical name
1-(4-Fluorophenyl)propan-2-amine

Other names
4-Fluoroamphetamine, para-fluoroamphetamine, 4-FMP, Flux, 4-FA

Chemical Abstracts Service (CAS) registry number
459-02-9

Molecular information

**Molecular structure:**

![Molecular structure diagram]

**Molecular formula:** C₉H₁₂FN

**Molecular weight:** 153.20 g/mol

Identification and analytical profile were kindly provided by the Latvian focal point and can be found at the end of this document.

- KMR_4_FA_1313510.pdf
- KMR_4_FA_1313510_spectra.pdf

**Synthesis, manufacture and precursors**
Racemic 4-FMP can be synthesized from 4-fluorobenzyl methyl ketone precursor, which is commercially available, by means of Leuckart amination.

**Other chemical names and variants**
(RS)-1-(4-Fluorophenyl)propan-2-amine
G. References


Europol Drugs Newsletter, July 2009, ALERT 2009-001 (SYNERGY) 4-Fluoroamphetamine Europol Drugs Unit_Newsletter 2009-001.pdf


TESTĒŠANAS PĀRSKATS

par nezināmas izcelsmes parauga identitātes noskaidrošanu

Paraugs:
Nezināmas izcelsmes paraugs Nr 1313510

Pasūtītājs:
LRleM Valsts policijas
Kriminālistikas pārvalde
2013. gada 28. oktobra vēstule Nr. 20/5-29115
Kontaktpersona: I.Vovere
tālr.: 67208405

Atskaites sastādišanas datums:
2013. gada 29. oktobris
**KMR spektroskopija**

Balstoties uz $^1$H un $^{13}$C kodolu magnētiskās rezonances spektrometrijas datiem, var apgalvot, ka paraugs Nr. **1313510** ir 4-fluoramfetamins (skat attēlu).

![Chemical structure](image)

1. **Att.** Paraugam Nr. 1313510 atbilstošā ķīmiskā struktūra - 4-fluoramfetamins.

$^1$H un $^{13}$C kodolu magnētiskās rezonances spektri tika uzņemti uz Varian Inova 600 MHz KMR spektrometra. Kā šķidinātājs izmantots DMSO-d$_6$ un tā nepilnīgi deiterēta piemaisījuma piķis (pie 2.50 ppm $^1$H, 39.52 ppm $^{13}$C) izmantots ķīmisko nobīžu kalibrācijai. Eksperimentu parametri redzami pievienotajās spektru izdrukās. Signālu identifikācijai izmantota sekojoša atomu numerācija, kas parādīta 1. attēlā:

$^1$H KMR spektrs:

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Pētāmajai vielai nepiederoši signāli, kas redzami spektrā:

- 3.89, s: - ūdens
- 2.50, p: - nepilnīgi deiterēts DMSO-d$_6$

$^{13}$C KMR spektrs:

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<td>3</td>
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Pētāmajai vielai nepiederoši signāli, kas redzami spektrā:
39.94 - DMSO-d₆ (KMR šķīdinātājs)
39.80 - DMSO-d₆ (KMR šķīdinātājs)
39.66 - DMSO-d₆ (KMR šķīdinātājs)
39.52 - DMSO-d₆ (KMR šķīdinātājs)
39.38 - DMSO-d₆ (KMR šķīdinātājs)
39.24 - DMSO-d₆ (KMR šķīdinātājs)
39.10 - DMSO-d₆ (KMR šķīdinātājs)

OSI direktora vietneks:

[Signature]

Dr. chem. O. Pugovičs
Parameter | Value
---|---
1 Title | FA_1313510
2 Solvent | DMSO
3 Temperature | 25.0
4 Number of Scans | 2
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6 Acquisition Time | 2.0486
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Isomeric Fluoro-methoxy-phenylalkylamines: a new series of controlled-substance analogues (designer drugs)

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Abstract

An impressively large number of clandestinely produced controlled-substance analogues (designer drugs) of amphetamine with high structural variety have been encountered in forensic samples in recent years. The continuous designer drug exploration and their widespread consumption results in an increasing number of reports regarding abuse and intoxication. This study presents the analytical properties of a series of new fluoro-methoxy-substituted controlled-substance analogues of amphetamine. Three ring positional isomeric fluoroamphetamines, two isomeric fluoromethoxyamphetamines, two N-alkyl 4-fluoroamphetamines, and one 4-fluorophenylbutan-2-amine were identified and differentiated by gas chromatography–mass spectrometry (GC–MS), 1H- and 13C-nuclear magnetic resonance (NMR), and gas chromatography–infrared spectroscopy (GC–IR). The regioisomeric 2-, 3-, and 4-fluoroamphetamines and the regioisomeric fluoro-methoxyamphetamines show virtually identical mass spectra so that this method is insufficient to discriminate between these closely related compounds. The mass spectra of the acetylated compounds allowed a differentiation of the 4-fluoroamphetamine from its regioisomeric 2- and 3-fluoroamphetamines. The gas chromatographic properties of the three regioisomeric fluoroamphetamines and their acetylated and trifluoroacetylated derivatives are also so similar that a complete separation of these compounds could not be achieved under GC–MS conditions. The two isomeric compounds 5-fluoro-2-methoxyamphetamine and 3-fluoro-4-methoxyamphetamine on the other hand showed significant different gas chromatographic retention times so that a separation was uncomplicated. The trifluoroacetylation of these compounds proved to be an effective method for their mass spectral differentiation. Gas chromatography–infrared spectroscopy and 1H- and 13C-nuclear magnetic resonance allowed an unequivocal differentiation of all studied regioisomeric fluoroamphetamines and fluoro-methoxyamphetamines.

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Keywords: Fluoroamphetamines; Fluoro-methoxyamphetamines; Designer drugs; Fluorophenylalkylamines; Mass spectra; NMR; Illicit synthesis; Drug abuse

1. Introduction

Amphetamine and its derivatives are widely abused central nervous system stimulants and are well documented in literature [1]. The large number of structurally closely related amphetamine variants seriously affects the ability to detect novel amphetamine controlled-substance analogues [2–4] and makes their identification an arduous task [5–10,32].

In January 2003, a series of clandestinely prepared fluoromethoxy-substituted phenylalkylamines were seized in the federal state of Sachsen–Anhalt (Germany), which were so far unknown on the illicit market. The white powders consisted of nearly pure 2-fluoroamphetamine sulfate 1, respectively hydrochloride salts of 3- and 4-fluoroamphetamine 2–3, 5-fluoro-2-methoxyamphetamine 4, 3-fluoro-4-methoxyamphetamine 5, N-methyl-4-fluoroamphetamine 6,
Little is known about the pharmacological properties of fluoroamphetamine derivatives, less for fluoro-methoxy-substituted amphetamines. The 2,5-dimethoxy-4-fluoroamphetamine (DOF) is known to have less psychoactivity than its well-known analogues 4-bromo-2,5-dimethoxyamphetamine (DOB), and 2,5-dimethoxy-4-iodoamphetamine (DOI) [1].

The mono-substituted fluoroamphetamine analogues, however, obviously have a potential for abuse. Drug discrimination studies in rats showed that 3, a fluoro-substituted (−)-amphetamine, showed short-term serotonin-releasing effects [11]. The substitution of a hydrogen atom by a fluorine atom is commonly employed to increase the lipophilicity and to enhance the passing of the blood brain barrier of central nervous system (CNS) agents like amphetamine derivatives [12,13]. It is therefore likely that fluoroamphetamine and fluoro-methoxy amphetamines elicit pharmacological effects.

The detection and identification of unknown drugs is typically performed by gas chromatography–mass spectrometry (GC–MS) due to the high sensitivity and ability to separate organic compounds in complex mixtures. The usually performed electron impact (EI) ionization method is often insufficient to discriminate closely related amphetamine derivatives because of their often virtually identical mass spectra [4,6,7,9]. One of the major drawbacks of mass spectrometry is its inability to locate aromatic ring substituents so that the employment of NMR spectroscopy becomes unavoidable. $^1$H- as well as $^{13}$C-NMR spectroscopy has been a very helpful tool in the structure elucidation of substituted amphetamines and designer drugs [21,22], especially for those with one or more substituents, like a methoxy or an ethoxy group or one or more methyl groups in the aromatic ring [9,23–25]. These spectroscopic techniques allow the unambiguous determination of the position of substituents in the aromatic ring by analysis of the chemical shift and also the splitting of the signals and the corresponding coupling constants. Infrared (IR) spectroscopy and gas chromatography–infrared spectroscopy (GC–IR) have been successful in differentiating closely related amphetamine isomers [14,15]. In order to add a significant level of confidence in identifying the designer drugs 1–8 this technique was also applied. The synthesis [16] and some spectroscopic data of the three fluoro-amphetamines 1–3 have been published [17].

This paper describes the analytical techniques necessary for the differentiation and identification of regioisomeric fluoro-methoxy-phenylalkylamines 1–8 using GC, GC–MS coupling, IR- and NMR-spectroscopy.

2. Instrumentation

2.1. GC

For separation studies of compounds 1–3 a Varian 3400 CX gas chromatograph with a fused silica capillary column DB1 (30 m × 0.32 mm, thickness 0.25 μm) and flame
2.2. GC–MS

The electron impact mass spectra were obtained with a Finnigan TSQ 70 (Finnigan MAT, Bremen) with a DEC-Station 2100, coupled to a Varian 3400 CX gas chromatograph. A fused silica capillary column DB1 (30 m × 0.32 mm, thickness 0.25 μm) was used. The temperature program consisted of an initial temperature of 80 °C held for 1 min, followed by a linear ramp to 280 °C at 15 °C/min. The final temperature was held for 15 min. The split/splitless injector and detector temperatures were 280 °C, the carrier gas was helium. The following optimized detector parameters were used:

- EI-mode: ionization voltage, 70 eV; scan time, 1 s; and scan range, 40–600 Da.
- CI-mode: ionization voltage, 70 eV; source temperature, 150 °C; reactant gas, methane; source pressure, 0.2 Pa; scan time, 1 s; and scan range, 50–600 Da.

2.3. NMR spectroscopy

The spectra were recorded with a Bruker ARX 300 NMR spectrometer, at a resonance frequency of 300.13 MHz for 1H-NMR spectra and 75.47 MHz for 13C-NMR spectra at 300 K. The 1H-NMR spectra were recorded using standard pulse programs. The 13C-NMR spectra are recorded with 1H decoupling using composite pulse decoupling.

Five to ten milligrams of the compounds were dissolved in 100 μl of DMSO-d6 and 500 μl of CDCl3 were added (compounds 2–8), compound 1 was dissolved in 300 μl of D2O, then 300 μl of acetone-d6 were added. Tetramethysilane (TMS) was used as an internal standard for both 1H- and 13C-NMR spectra.

For the determination of the (HH) and (HF) coupling constants two-dimensional J-resolved spectra were recorded using the manufacturer’s pulse program with an optimized sweep width for the aromatic region (corresponding to 0.3–0.7 ppm) using 256 data points in the F2 region and 128 data points in the F1 region, which was set to 60 Hz.

2.4. IR, GC–IR

The infrared spectra were acquired using a Bruker IFS 66 Fourier Transform Infrared (FT-IR) spectrometer with a resolution of 2 cm⁻¹. In cases of vapor-phase spectra, a resolution of 8 cm⁻¹ was used and the sample was introduced by an interfaced Carlo Erba 6000 gas chromatograph equipped with a SE 30 capillary column.

In cases of solid-phase spectra the compounds were prepared as potassium bromide (KBr) pellets.

3. Results and discussion

3.1. GC

The retention times of 3- and 4-fluoroamphetamine 2 and 3 are so similar that a separation of these compounds was not possible under standard GC–MS operating conditions. Only the 2-fluoroamphetamine 1, having an calculated Kovats retention index [18] of 1103, could be separated partially from co-eluting 2 and 3 with an index of 1109. The acetylated and trifluoroacetylated compounds 1–3 showed no better results under these circumstances.

The isothermal measurements on a separately operated GC showed a somewhat better separation (Fig. 2). 2-Fluoroamphetamine 1 could be baseline separated from its isomeric compounds 2 and 3 under these optimized conditions but the co-eluting compounds 2 and 3 showed still overlapping peaks with only partial separation. The calculated Kovats indices were 1106 for 1, 1112 for 2, and 1114 for 3.

The fluoro-methoxyamphetamines 4 and 5, having calculated Kovats retention indices of 1318 and 1363, respectively, could be separated under standard GC–MS operating conditions without difficulties.

3.2. Mass spectrometry

3.2.1. Mass spectrometry of the pure compounds

The electron impact mass spectra of the phenalkylamines 1–8 (Fig. 3) show intense immonium ions [7] and molecular ions with very low intensities [19]. The nominal molecular weights were, therefore, established by chemical ionization (CI) using methane as reagent gas for all compounds [20].
The electron-donating ability of the nitrogen atom in the isomeric fluoroamphetamines 1–3 induces a fast α-cleavage reaction (α) and produces intense immonium ions at m/z 44 and molecular ions of low intensities at m/z 153 (Scheme 1). The significant fragment at m/z 109 corresponds to a fluorobenzyl cation or a fluoro-substituted tropylum cation generated by an α-cleavage of the benzyl bond (Scheme 2). There is no observable ortho effect reaction [19], which could give any information for the aromatic fluoro position so that the isomeric fluoro-amphe-

Fig. 3. EI mass spectra for the fluoro-methoxy-substituted phenylalkylamines 1–8.
Scheme 1. α-Cleavage reaction of fluoro phenethylamine derivatives.

Scheme 2. Benzyl bond cleavage reaction in fluoro phenethylamine derivatives.

tamines 1–3 show virtually identical mass spectra (Fig. 3, 1–3).

The mass spectra of the isomeric fluoro-methoxymphetamines 4 and 5 are dominated also by their intense immonium ions at m/z 44 and the molecular ions at m/z 183 have very low intensities (Fig. 3, 4 and 5). The analogous cleavage of the benzyl bond (Scheme 2) gives fluoromethoxy-substituted benzyl or tropylium cations at m/z 139. There is no significant fragment to allow differentiation between the two isomeric fluoromethoxymphetamines 4 and 5, so that mass spectrometry is not sufficient to identify these underivatized compounds unambiguously. The 4-fluoromethamphetamine 6 shows the expected immonium ion at m/z 58 and a low intensity molecular ion at m/z 167 (Fig. 3, 6).

The mass spectra of the fluorophenethylamines 7 and 8 show the expected intense immonium ions at m/z 72 and 58, respectively and fluorobenzyl cations at m/z 109 (Fig. 3, 7 and 8). The fragment at m/z 44 in the mass spectrum of N-ethyl-4-fluoroamphetamine 7 (Fig. 3, 7) can be explained by an olefin loss reaction of immonium ions with an ethyl or larger alkyl group at the nitrogen producing other immonium ions by loosing the whole side-chain (Scheme 3) [19].

3.2.2. Mass spectrometry of the derivatized compounds

The unfavorable mass spectrometric properties of the pure compounds caused us to study the mass spectra of the acetylated and trifluoroacetylated compounds (Figs. 4–6). It was found that the mass spectrum of the acetylated 4-fluoroamphetamine 3 (Fig. 4, 3) showed a significant fragment at m/z 136 with an abundance of about 20%. The mass spectra of the acetylated 1 and 2 (Fig. 4, 1 and 2) show this fragment with a much lower relative abundance of about 5–6%. These measurements were reproducible so that the higher relative abundance of about 20% of the fragment at m/z 136 seems to be a good indicator for the acetylated 3. This fragment is generated by the inductive route of the McLafferty rearrangement (Scheme 4) [19]. The radical electron at the oxo-group rearranges the H-atom at the γ-position (rH) of the aliphatic chain. A following inductive cleavage (i) by the positive charge at the carbonyl C-atom breaks the β-bond, forming a neutral enolized acetamide and an ionized 3-(4-fluorophenyl)-propene with m/z 136.

The mass spectra of the acetylated 4 and 5 (Fig. 5) show the analogous fluoromethoxy McLafferty products at m/z 166. The spectra of these isomeric compounds show a significant abundance difference for the fragments at m/z 139 and 109 (Fig. 5). The acetylated 4 shows a relative intense ion at m/z 109 (9%), but a very low relative abundance for the fragment at m/z 139 (3%). The acetylated 5 on the other hand presents a relatively low abundance ion at m/z 109 (1.5%), but a relative high abundance ion at m/z 139 (9%). The fragment at m/z 139 corresponds to the mass of a fluoromethoxybenzyl cation, which could yield a fluorobenzyl cation at m/z 109 by loss of formaldehyde. It seems that the high intensity of the fluoromethoxybenzyl cation at m/z 139 in the mass spectrum of acetylated 5 could find an explanation in the negative inductive effect of the fluoro atom ortho to the leaving methoxy group.

The mass spectra of the trifluoroacetylated compounds 4 and 5 show other differences (Fig. 6). The mass spectrum of the trifluoroacetylated 4 shows three significant fragments with m/z 109 (fluorobenzyl cation), 140 and 166 (McLafferty product). The odd electron ion at m/z 140 is generated by a γ-H-atom rearrangement to the aromatic ortho position, which is known to accompany the benzyl bond cleavage reaction common in alkyl aromatics [19] (Scheme 5). The radical of an ionized aromatic π-bond rearranges a γ-H-atom of the

Scheme 3. Olefine loss reaction of immonium ions with an ethyl or larger alkyl group.
alkyl chain or an amino group to the aromatic ortho position. A following α-cleavage reaction at the benzyl bond generates an odd electron ion at \( m/z \) 140. The positional isomeric trifluoroacetylated 5 on the other hand shows only two significant fragments with \( m/z \) 139 (fluoromethoxybenzyl cation) and the McLafferty product at \( m/z \) 166.

Trifluoroacetylation, therefore, proves to be an excellent method for the differentiation of 5-fluoro-2-methoxyamphetamine 4 from its regioisomeric 3-fluoro-4-methoxyamphetamine 5.

The trifluoroacetylation of the compounds 1–3 showed no improvement regarding their mass spectral differentiation.

![Fig. 4. El mass spectra for the acetylated fluoroamphetamines 1–3.](image)

![Fig. 5. El mass spectra for the acetylated fluoromethoxyamphetamines 4 and 5.](image)
3.3. NMR spectroscopy

Conventional $^1$H- and broadband decoupled $^{13}$C-NMR spectra of compounds 1–8 were recorded. When first looking at the aliphatic region of the $^1$H-NMR spectra at 300 MHz of compounds 1–8 the typical ABM$^X_3$ pattern is exhibited (Fig. 7) in the region from 2.7 to 3.6 ppm and at 1.3 ppm. The M part, i.e. the methine proton $H_M$, shows further coupling with the protons of the ammonium group leading to a broad and not fully resolved multiplet at 3.45 ppm. The denomination of the different spin systems of the fluorine-substituted amphetamines and the numbering used in Tables 1 and 2 are given in Fig. 8. The NH protons showed a broad signal between 8 and 10 ppm and do not deliver any structural information. A detailed analysis of the coupling constants in the aliphatic region of substituted amphetamines has been reported already in 1971 [26]. In order to explore the substitution pattern of the aromatic ring, coupling of the protons with the fluorine substituent has to be considered as well. Coupling constants over three, four, and five bonds in aromatic systems are observable using routine techniques.

![Fig. 6. El mass spectra for the trifluoroacetylated fluoromethoxyamphetamines 4 and 5.](image)

![Scheme 4. The McLafferty rearrangement in the acetylated fluoroumpheamines 1–3.](image)

![Scheme 5. γ-H-atom rearrangement (rH) of the alkyl chain to the aromatic ortho position.](image)
which are in the order of 9, 5, and 1–2 Hz, respectively [27]. For the methylene group of propanamine 1, a $^4J_{HF}$ coupling with the fluorine atom in ortho position of the aromatic ring is observed (see Table 1, $^4J_{HF} = 1.2$ Hz). The data obtained by first order analysis of the multiplets are summarized in Table 1.

The 4-substituted amphetamines 3, 6–8 show an AA’XX’ system for the aromatic protons (6.9–7.3 ppm), with additional $^3J_{HF}$ and $^4J_{HF}$ splitting. The HX’ and HAA’ signals appear as a pseudo-triplet at 7.0 ppm and as a doublet of doublets at 7.2 ppm, see Fig. 7. In these cases, the 4-position of the fluorine atom is easily determined.

For structures 2, 4, and 5, with the fluorine in meta position to the alkyl chain, overlapping multiplets are observed. To analyze these spin systems a two-dimensional $^1$H-$^1$J-resolved technique was used [28,29]. This allowed the separation of HH and HF couplings and the determination of chemical shift and coupling constants of the aromatic protons in amphetamines 2 and 4 (see Table 1). Only for 5 this technique was not successful. In amphetamine derivative 5, the two protons ortho to the alkyl chain and one proton ortho to the methoxy group were identified by a HH-long range correlation spectrum [28,29].

$^1$H decoupled $^{13}$C-NMR spectra of the amphetamines 1–8 were also recorded, and the chemical shifts and the corresponding carbon fluorine couplings are given in Table 2. The coupling constants are in the order of 250 Hz ($^1J_{CF}$), 10–25 Hz ($^2J_{CF}$), and 2–10 Hz ($^3J_{CF}$) and ($^4J_{CF}$) for the aromatic ring. In all 4-substituted amphetamine derivatives 3, 6–8 the $^{13}$C-NMR spectra show only four signals for the aromatic carbon atoms due to the symmetry of the structure.
Table 1

1H-NMR chemical shifts and coupling constants (in Hz) of compounds 1–8* in a 9/1 mixture (v/v) of CDCl₃ and DMSO-d₆.

<table>
<thead>
<tr>
<th>Compound</th>
<th>H-1$_{\alpha}$</th>
<th>H-1$_{\beta}$</th>
<th>H-2</th>
<th>H-3</th>
<th>NH</th>
<th>H$_{\alpha}$-2</th>
<th>H$_{\alpha}$-3</th>
<th>H$_{\alpha}$-4</th>
<th>H$_{\alpha}$-5</th>
<th>H$_{\alpha}$-6</th>
<th>other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.89, dd.</td>
<td>3.14, br dd.</td>
<td>3.50, sext.</td>
<td>1.14, d.</td>
<td>–</td>
<td>–</td>
<td>7.19 t'</td>
<td>7.38 t'</td>
<td>7.24 t'</td>
<td>7.40 d'</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>3J$_{HH}$ = 13.7</td>
<td>3J$_{HH}$ = 13.7</td>
<td>3J$_{HH}$ = 6.5</td>
<td>3J$_{HH}$ = 6.6</td>
<td>3J$_{HH}$ = 10.8</td>
<td>3J$_{HH}$ = 8.5</td>
<td>3J$_{HH}$ = 7.2</td>
<td>3J$_{HH}$ = 1.2</td>
<td>3J$_{HH}$ = 1.2</td>
<td>3J$_{HH}$ ≈ 2.0</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>2.83, dd.</td>
<td>3.34, dd.</td>
<td>3.52, br m</td>
<td>1.34, d.</td>
<td>8.49, br s</td>
<td>6.98, dt'</td>
<td>–</td>
<td>6.94, td'</td>
<td>7.23, td.</td>
<td>7.03, br d</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>3J$_{HH}$ = 13.3</td>
<td>3J$_{HH}$ = 13.3</td>
<td>3J$_{HH}$ = 4.7</td>
<td>3J$_{HH}$ = 6.5</td>
<td>3J$_{HH}$ = 9.6</td>
<td>3J$_{HH}$ ≈ 7.9</td>
<td>3J$_{HH}$ = 8.2</td>
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<td>3J$_{HH}$ ≈ 1.4</td>
<td>–</td>
</tr>
<tr>
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<td>2.78, dd.</td>
<td>3.27, dd.</td>
<td>3.43, br m</td>
<td>1.29, d.</td>
<td>8.48, br s</td>
<td>7.23, dd.</td>
<td>6.99, t.</td>
<td>–</td>
<td>6.99, t.</td>
<td>7.23, dd.</td>
<td>–</td>
</tr>
<tr>
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<td>3J$_{HH}$ = 13.4</td>
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<td>3J$_{HH}$ = 5.5</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>3.88, dd.</td>
<td>3.16, dd.</td>
<td>3.62, br m</td>
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<td>8.42, br s</td>
<td>–</td>
<td>6.97, dd.</td>
<td>6.91, td.</td>
<td>–</td>
<td>6.96, dd.</td>
<td>OCH$_3$: 3.80, s</td>
</tr>
<tr>
<td></td>
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<td>3J$_{HH}$ = 8.9</td>
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<td>3J$_{HH}$ = 5.5</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>2.73, dd.</td>
<td>3.21, dd.</td>
<td>3.40, br m</td>
<td>1.30, d.</td>
<td>8.38, br s</td>
<td>6.90–7.02, complex m</td>
<td>–</td>
<td>–</td>
<td>6.90–7.02, complex m</td>
<td>OCH$_3$: 3.86, s</td>
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</tr>
<tr>
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<td>3J$_{HH}$ = 13.4</td>
<td>3J$_{HH}$ = 4.8</td>
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<td>3J$_{HH}$ = 5.5</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>2.82, dd.</td>
<td>3.40, dd.</td>
<td>3.32, br m</td>
<td>1.30, d.</td>
<td>9.51, very br s</td>
<td>7.23, dd.</td>
<td>7.01, t.</td>
<td>–</td>
<td>7.01, t.</td>
<td>7.23, dd.</td>
<td>N-CH$_3$: 2.70, t</td>
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<td>complex m, 3J$<em>{HH}$ = 13.1, 3J$</em>{HH}$ = 3.4</td>
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<td>3J$_{HH}$ = 8.6</td>
<td>3J$_{HH}$ = 8.2</td>
<td>3J$_{HH}$ = 8.7</td>
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<td>3J$_{HH}$ = 5.4</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>2.82, dd.</td>
<td>3.45, dd.</td>
<td>3.33, br m</td>
<td>1.29, d.</td>
<td>9.49, very br s</td>
<td>7.23, dd.</td>
<td>7.00, t.</td>
<td>–</td>
<td>7.00, t.</td>
<td>7.23, dd.</td>
<td>N-CH$_3$:CH$_2$: 3.05, very br m</td>
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<td></td>
<td>3J$_{HH}$ = 13.0</td>
<td>3J$_{HH}$ = 13.0</td>
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<td>3J$_{HH}$ = 8.7</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>2.91, dd.</td>
<td>3.22, dd.</td>
<td>3.31, br m</td>
<td>1.72, qunt., 8.46, br s</td>
<td>7.23, dd.</td>
<td>6.99, t.</td>
<td>–</td>
<td>6.99, t.</td>
<td>7.23, dd.</td>
<td>4-CH$_2$: 1.05, t.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3J$_{HH}$ = 13.7</td>
<td>3J$_{HH}$ = 13.7</td>
<td>3J$_{HH}$ = 5.4</td>
<td>3J$_{HH}$ = 7.2</td>
<td>3J$_{HH}$ = 8.6</td>
<td>3J$_{HH}$ = 8.6</td>
<td>3J$_{HH}$ = 8.7</td>
<td>3J$_{HH}$ = 8.7</td>
<td>3J$_{HH}$ = 8.7</td>
<td>3J$_{HH}$ = 8.7</td>
<td>–</td>
</tr>
</tbody>
</table>

* Analysis of the multiplets (AB-part-systems and AA’XX’-systems) according to first order, absolute values of the coupling constants are given.

* In 50% D$_2$O/50% acetone-d$_6$, partially.

* Overlapping signals, further splitting due to $^4$J$_{HH}$ and $^3$J$_{HH}$ couplings.
### Table 2

<table>
<thead>
<tr>
<th>Compound</th>
<th>C-1</th>
<th>C-2</th>
<th>C-3</th>
<th>C-4</th>
<th>C-5</th>
<th>C-6</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33.0</td>
<td>47.6</td>
<td>16.9</td>
<td>122.2</td>
<td>160.6</td>
<td>115.1</td>
<td>129.9</td>
</tr>
<tr>
<td>2</td>
<td>40.4</td>
<td>49.2</td>
<td>17.8</td>
<td>139.1</td>
<td>112.6</td>
<td>162.8</td>
<td>113.9</td>
</tr>
<tr>
<td>3</td>
<td>39.8</td>
<td>49.1</td>
<td>17.6</td>
<td>132.5</td>
<td>113.9</td>
<td>115.4</td>
<td>161.7</td>
</tr>
<tr>
<td>4</td>
<td>35.8</td>
<td>47.7</td>
<td>18.3</td>
<td>126.4</td>
<td>153.8</td>
<td>111.3</td>
<td>114.2</td>
</tr>
<tr>
<td>5</td>
<td>40.4</td>
<td>49.2</td>
<td>17.8</td>
<td>139.1</td>
<td>112.6</td>
<td>162.8</td>
<td>113.9</td>
</tr>
<tr>
<td>6</td>
<td>38.5</td>
<td>56.7</td>
<td>15.2</td>
<td>131.9</td>
<td>113.9</td>
<td>115.4</td>
<td>161.7</td>
</tr>
<tr>
<td>7</td>
<td>40.0</td>
<td>55.1</td>
<td>15.2</td>
<td>132.3</td>
<td>113.9</td>
<td>115.4</td>
<td>161.7</td>
</tr>
<tr>
<td>8</td>
<td>37.6</td>
<td>54.7</td>
<td>24.6</td>
<td>132.2</td>
<td>131.0</td>
<td>115.5</td>
<td>161.8</td>
</tr>
</tbody>
</table>

* Measured in D$_2$O.

The signal of the fluorine-substituted carbon atom is found at approximately 160 ppm and is easily identified as a doublet. In all derivatives 1–8, the fluorine and also the methoxy group lead to high frequency shifted signals in the range of 150–160 ppm (see Table 2). Furthermore, the aromatic carbon atom bearing the alkyl chain is revealed by its low intensity under the experimental conditions of the recording of the spectra. The evaluation of the coupling constant of the doublets of this carbon atom (C$_{ar}$) allows the determination of the position of the fluorine atom in the monosubstituted fluoroamphetamine 1 and 2 as well. The fluorine in ortho position leads to a splitting of about 16 Hz corresponding to a $^2$J$_{CF}$ coupling for compound 1. For the amphetamine 2, a coupling constant of ca. 8 Hz is observed for C$_{ar}$, which is characteristic for a $^3$J$_{CF}$ coupling constant, thus showing the fluorine atom positioned meta to the aliphatic chain.

The methoxy-substituted fluoroaminephetamines 4 and 5 require more detailed discussion because the $J_{CF}$ coupling constants are also influenced by the methoxy group: in 5, the methoxy group vicinal to the fluorine atom is proven by the splitting of the methoxy carbon signal (C$_{ar}$) due to a $^2$J$_{CF}$ coupling of 10.5 Hz, which is not observable in compound 4. The meta position of the fluorine atom in 5 on the other hand is shown by a $^3$J$_{CF}$ coupling, leading to a doublet for C$_{ar}$1 (Fig. 8). The same reasoning holds for compound 4, but the small coupling of only 2.0 Hz shows the methoxy group to be in para position to the fluorine atom.

A further diagnostic tool is the small splitting of the benzylic and homobenzylic carbon atoms of the alkyl chain in the range of 1–2 Hz in those cases where the fluorine atom is positioned either ortho or meta to the propanamine residue.

For both the $^1$H- and $^{13}$C-NMR spectra the chemical shifts of the aromatic group were found to be in the same range and order when compared with calculated shifts using tabulated increments for the aromatic ring [27].

In summary, conventional $^{13}$C-NMR spectra recorded under routine conditions of the fluorinated amphetamine derivatives 1–8 in a suitable solvent, together with a detailed analysis of the carbon fluorine coupling constants, allows the unambiguous assignment of the substitution pattern of the aromatic ring.

### 3.4. IR spectroscopy

For most organic compounds, the absorbances in the region from 1600 to 900 cm$^{-1}$ are due to skeletal vibrations of the whole molecule and usually not characteristic for functional groups. This fingerprint region, therefore, has importance in differentiating aromatic positional isomers. The solid- and vapor-phase IR-spectra of all studied compounds 1–8 (Figs. 9 and 10) show significant differences in this region and allowed their identification unambiguously. The solid phase IR-spectra show N–H stretching vibration at about 3450 cm$^{-1}$ and broad –NH$_3^+$ absorption bands from about 2700 to 2250 cm$^{-1}$ due to intermolecular hydrogen bonding (Fig. 9) [30].

The IR-spectra of isolated molecules in the vapor phase differ significantly from the corresponding condensed-phase spectra. The absorption bands of vapor-phase spectra shift to higher wave numbers and exhibit less fine splitting due to rotational bands (Fig. 10).

The N–H absorption bands near 3450 cm$^{-1}$ become quite weak in the vapor phase and may be lost in noise [31].
Consequently, all studied compounds 1–8 showed no visible N–H stretching bands in the vapor-phase IR-spectra. The NH\textsubscript{2}-deformation band for primary amines is found at about 1600–1610 cm\textsuperscript{-1} in the solid-phase spectra and at about 1608–1623 cm\textsuperscript{-1} in the vapor-phase spectra. For symmetry reasons, the IR-spectra of the 4-fluoro-substituted phenalkylamines 3, 6–8 are less complex and their vapor-phase spectra show two intense bands at 1234 and
Fig. 10. Aromatic (top) and aliphatic (bottom) region of the $^1$H-NMR spectrum of 4-fluorophenethylamine (3), signals originating from the nmr solvent (2.6 ppm), water (3.2 ppm), and sample impurities (1.2 ppm) are not assigned.
1512 cm⁻¹ due to aromatic ring vibrations. These compounds therefore can be easily identified from the other regioisomeric compounds.

4. Conclusion

In conclusion, this work represents the detection and identification of clandestinely produced regioisomeric fluoro-methoxy-substituted amphetamines 1–5 with gas chromatography–mass spectrometry, which is seriously affected by their virtually identical mass spectra. This situation is further complicated by the almost identical retention times of the regioisomeric fluoroamphetamines 2 and 3, which made a separation impossible by GC–MS. Even on a separately operated gas chromatograph and optimized GC conditions, only partial separation of 2 and 3 was achieved.

The acetylation of the regioisomeric fluoroamphetamines 1–3 provided no better gas chromatographic results, but allowed a mass spectroscopic differentiation of the 4-fluoroamphetamine 3 from its isomers 1 and 2 by its more intense McLafferty product at m/z 136.

Trifluoroacetylation on the other hand proved to be an excellent method for the mass spectroscopic differentiation of 5-fluoro-2-methoxyamphetamine 4 from its regioisomeric 3-fluoro-4-methoxyamphetamine 5.

The ¹H- and ¹³C-NMR spectra allowed an unequivocal determination of the aromatic substitution pattern and of the aliphatic structure of all compounds.

IR-spectroscopy using solid- or vapor-phase IR-spectra allowed the identification and differentiation of all studied fluoromethoxy amphetamines 1–8 without difficulties. The insufficient gas chromatographic separation of the regioisomeric 2 and 3 still remains a problem also for these techniques. In the real life of forensic laboratories, this situation is further complicated by complex matrices like blood or urine due to separation problems and the low sensitivity of NMR spectroscopy.

References

Differentiation of regioisomeric ring-substituted fluorophenethylamines with product ion spectrometry

F. Westphal, P. Rösner, Th. Junge

Abstract

The electron ionization (EI) of aromatic ring-substituted isomers gives virtual identical mass spectra which seriously affects their analysis. Especially regioisomeric meta- and para-ring-substituted compounds cannot show any ortho-effect reactions making their differentiation by mass spectrometry impossible. Furthermore, o-, m- and p-substituted compounds can only be separated insufficiently by chromatography due to their very similar retention that do not allow univocal identification. Product ion mass spectrometry has proved to be a useful tool to differentiate structurally closely related fluorophenethylamines even in the case of the meta- and para-isomers. A series of N-alkylated o-, m- and p-fluoroamphetamines and 1-(4-fluorophenyl)butan-2-amines have been synthesized in microscale and studied by product ion spectrometry. The combination of chemical ionization (CI) and product ion spectrometry of hydrogen fluoride loss ions \([M+H]^+ / C_0\) and \([M+H]^+ / C_223\) allows a univocal differentiation of all studied fluoro-substituted phenethylamines without prior derivatization. This method with submicrogram detection limits provides great advantages for the differentiation between aromatic regioisomeric fluorophenethylamine designer drugs where other methods such as nuclear magnetic resonance (NMR) spectrometry lack sufficient sensitivity or might fail because complex mixtures have to be analyzed.

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Product ion mass spectrometry

1. Introduction

The easy synthesis of phenethylamine-derivatives has led to a proliferation of structurally closely related compounds on the illegal drug market. In many cases the traditionally employed capillary gas chromatography/mass spectrometry (GC/MS) cannot discriminate these isomeric drugs variants. In particular, the differentiation of aromatic regioisomeric compounds becomes difficult or even impossible in the case of meta- and para-isomers. The mass spectroscopic differentiation of ortho-substituted compounds from the meta- and para-regioisomers is only possible, if an ortho-effect reaction opens an additional reaction channel generating additional fragments specific for the ortho-isomers. The meta- and para-isomers fragment in such a similar way that their mass spectroscopic discrimination is impossible.

The meta- and para-isomeric drug variants also show very similar retention indices so that this method of differentiation often fails too. Designer drugs of the amphetamine and phenethylamine type are particularly problematic. Usually their EI mass spectra show only a base peak ion (the immonium ion) at low masses caused by the fast α-cleavage reaction accompanied by a few fragments of higher masses with low abundance.

One possibility to obtain additional structural information offers the product ion spectrometry. This method contributes valuable information for structure elucidation, especially in cases where other efficient methods as NMR-spectroscopy are not available or cannot be used because complex compound mixtures or trace amounts have to be analyzed. Product ion mass spectrometry of immonium ions formed by electron ionization has been successfully applied to a number of new phenethylamine type designer drugs to determine and differentiate structure isomerism of the alkyl-amino moiety as well as the ring substitution pattern of methylenedioxyamphetamine [1–8].

In Germany, regioisomeric and in the aromatic moiety fluoro-substituted amphetamines appeared on the illegal market in 2003 for the first time. Fluorinated compounds can have an elevated lipophilicity enhancing absorption into biological membranes, a changed preferred conformation or altered electrostatic interactions opposite to their unsubstituted analogs. Fluorination generally leads to more stable compounds by slowing down metabolism due to the resistance to enzymatic cleavage of the C–F bond [9–14]. This causes changes in activity, duration of action and toxicity of the drug. The structures of the fluoroamphetamines...
seized in 2003 were identified by mass spectrometry, infrared spectroscopy and NMR-spectroscopy [15]. A mass spectroscopic differentiation of ortho-, meta- and para-fluoroamphetamines has not been successful (Fig. 1, [16]). Also chemical ionization (CI) mass spectrometry (using methane as reactant gas) delivered only little additional information (Fig. 2). The protonated ortho-, meta- and para-isomers lose ammonia and hydrogen fluoride to a different extent. However, these differences are not sufficient for the univocal identification of the isomers. This is due to the impossibility of regulating the reactant gas pressure precisely. So product ion spectrometry was applied to examine selected fragments under defined conditions.

This article reports our findings that the product ion spectrometry of the fragments generated by loss of hydrogen fluoride from the quasi-molecular ions ([M+H]+) during CI proves to be a successful choice to differentiate the ortho-, meta- and para-fluoroisomers. This technique was successfully applied on the non-substituted fluoroamphetamines, a series of N-alkylated fluoroamphetamines, one p-fluorophenylbutan-2-amine and some of its N-alkylated derivatives.

2. Methods

2.1. Chemicals

o-, m-, p-Fluoroamphetamine, and 1-(4-fluorophenyl)butan-2-amine were provided by the Landeskriminalamt Sachsen-Anhalt, Magdeburg (Germany), for research purposes and were parts of the originally seized compounds. N-alkylated derivatives were prepared by adding the corresponding bromoalkane (methyl bromide, n-propyl bromide and iso-propyl bromide) to a dilute solution of the appropriate amine in diethyl ether. All solvents and reagents used were of analytical grade.

2.2. Mass spectrometry (GC–MS and GC–MS–MS)

The electron ionization mass spectra were obtained on a Finnigan TSQ 70 with a DEC-Station 2100 coupled to a Varian 3400 CX gas chromatograph.

GC–MS parameters: fused silica capillary column DB1 30 m × 0.32 mm, film thickness 0.25 μm, temperature program: initial 80 °C held 1 min, 15 °C/min to 280 °C, final temperature held 15 min, splitless injection, injector temperature 280 °C, detector temperature 280 °C, ion source temperature 150 °C, carrier gas helium.

Electron ionization (EI): ionization energy 70 eV, emission current 200 μA, scan time 1 s, scan range 30–600 Da.

Chemical ionization (CI): ionization energy 70 eV, emission current 200 μA, source temperature 150 °C, reactant gas methane, source pressure 1.5 mTorr (0.2 Pa), scan time 1 s, scan range 30–600 Da.

CI–MS–MS product ion mode: ionization energy 70 eV, emission current 200 μA, collision gas argon, collision energy approximately 20 eV, collision gas pressure approximately 1.5 mTorr (0.2 Pa). The exact target-thickness [17] was set using n-butyl benzene and adjusting intensity ratios m/z 92/91 to 0.2 and m/z 65/91 to 0.02 by variation of collision energy and collision gas pressure. This ensures the reproducibility of the product ion mass spectra and the use of a product ion mass spectra library for the identification of the structure of the product ions [18].
For mass spectrometric measurements of o-, m-, p-fluoroamphetamines, and 1-(4-fluorophenyl)butan-2-amine 1 mL diluted NaOH (5% in water) and 4 mL diethyl ether were added to approximately 2 mg of the compounds in a screw-capped glass vial. The vial was closed and shaken for a few seconds. After separation an aliquot of the ether layer was transferred into an autosampler vial. 1 μL was injected into the GC–MS system. For mass spectrometric measurement of the N-alkylated derivatives 1 μL of the reaction mixture after the alkylation procedure described above was injected into the GC–MS system.

3. Results and discussion

The product ion mass spectra of the quasi-molecular ions ([M+H]\(^+\)) examined first also have not been sufficient for discrimination of the three regioisomers. But collision-induced dissociation (CID) spectra of the ions with \(m/z\) 134 generated by the loss of hydrogen fluoride from the quasi-molecular ions ([M+H]\(^+\)) have made possible a univocal differentiation of all three regioisomeric fluoroamphetamines (Fig. 3).

The ion with \(m/z = 134\) built from the ortho-fluoroisomer shows a product ion spectrum very similar to a 2-methylindolinium ion. This was proved by product ion mass spectrometry of the protonated molecular ion of 2-methylindoline (Fig. 4). Obviously a methylindolinium cation is built after loss of hydrogen fluoride by intramolecular ring closure to the ortho-position in case of the ortho-fluoroamphetamine. The slight differences in fragment ion intensities in the product ion spectra might be explained by the different inner energies the two species have because of their different origin of building.

The base peak ion at \(m/z\) 106 of 2-methylindoline is best represented by an anchimeric stabilized amine tropylium cation generated by an inductively (i) driven hydrogen (rH) and carbon chain (r) rearrangement with loss of ethylene in analogy with the formation of tropylium ions from alkyl benzenes (Fig. 5).

On the other hand, the meta- and para-fluoroamphetamines behave quite differently (Fig. 3). The meta-isomer shows an immonium base peak ion with \(m/z = 44\). The para-isomer shows a less intensive immonium ion and an ion with \(m/z = 119\) generated by loss of methyl with significant intensity.

The original regioisomeric structural information of the fluorine atoms position is obviously preserved during the hydrogen fluoride loss reaction which leads to a variation of the product ion mass spectra depending on the type of the fluorine position (Figs. 3 and 6). This preservation of the meta- and para-substitution pattern information in the hydrogen fluoride loss ion with \(m/z = 134\) might be explained by an anchimeric assistance of the amino group building chelate-like intermediates with meta- and para-cyclophane structures as depicted in Fig. 3.

A ring closure formation with building of cyclophane like structures is obviously energetically more demanding for the meta- and para-isomers than in the case of the ortho-fluoroisomer. This might explain the favoured alternative generation of
immonium ions with $m/z$ 44 in the case of meta- and para-isomers. The energetically most demanding process would be the building of a para-cyclophane like structure. This might explain that a significant methyl loss reaction only takes place in the para-isomeric fluoroamphetamine (Fig. 6).

Starting from the three regioisomeric fluoroamphetamines and the p-fluorophenylbutanamine a series of N-alkylated amines were synthesized (Fig. 7).

Interestingly, the N-alkylated amphetamines show the same phenomena as the non-substituted amines:

- The ortho-fluoroamphetamines show fragment-rich spectra without an immonium ion and with methyl loss fragments.
- Meta-fluoroamphetamines show immonium ions with a total ion current (TI) > 50% while methyl loss fragments actually cannot be seen.
- The para-fluoroamphetamines show all (except one) intensive immonium ions (with TI < 50%) und intensive fragments of a methyl loss. The one exception is the N,N-dipropyl-p-fluoroamphetamine which generates no immonium ion after CI-CID.

Following these observations the product ion spectrometry obviously represents an interesting opportunity to differentiate also N-alkylated ortho-, meta-, and para-substituted fluoroamphetamines. This is an important result because alkylated amphetamines normally are the first designer drugs entering the illegal drug market, after the free amino compounds have been scheduled.

During the low energy product ion spectrometry with collision energies of about 20 eV an additional energy of about 5 eV is transferred to an already excited ion. This excess energy allows the observation of decomposition processes which cannot be seen during common electron ionization mass spectrometry because the obtainable excitation energies are too low. Obviously, the product ion spectrometry opens additional analytically valuable reaction channels suitable for a differentiation of aromatic regioisomeric fluoroamphetamines.

The amphetamine homologous 1-(4-fluorophenyl)butan-2-amine and its N-alkyl derivatives show the analogous behaviour: as para-substituted derivatives all of them (except for one of them) show an intensive immonium ion (with an intensity of <50% TI).
and generally an intensive fragment of an ethyl loss (butanamine derivative, \([\text{M+H-HF-29}]^+\)) (Fig. 8 and Table 1). In this case, the N,N-diethyl-substituted derivative shows no immonium ion in the spectrum after CI-CID. The analogous behaviour of the para-fluorophenylbutanamine derivatives suggests that the ortho- and meta-isomers of this butanamines would react in the same manner as their amphetamine-homologs. This could not be examined since the ortho- and meta-flourinated butanamines have not been synthesized yet.

An overview of the fragmentation behaviour of all examined fluorophenethylamines is presented in Table 1.

These results show that a differentiation between the regioisomeric fluoro-substituted amphetamine and phenylbutan-2-amine derivatives can be carried out by product ion spectrometry of hydrogen fluoride loss ions \([\text{M+H-HF}]^+\) after chemical ionization when defined collision gas pressure and collision energy conditions are maintained.

As a summary the following observations for differentiation of the fluorophenethylamines can be derived:

- All examined ortho-fluoroamphetamines show fragment-rich hydrogen fluoride loss product ion spectra with fragments after methyl loss but without immonium ions. The intensity ratios of methyl loss fragments relative to the intensity of the \([\text{M+H-HF}]^+\) ions are \(<1\) in all examined cases. An analogous behaviour of the ortho-fluorophenylbutan-2-amines with an ethyl loss instead of a methyl loss may be predicted.

- The examined meta-fluoroisomers show product ion spectra with immonium base peak ions with more than 50% of the total ion current (TI) while methyl loss ions virtually cannot be seen. An analogous behaviour of the meta-fluorophenylbutan-2-amines with an ethyl loss instead of a methyl loss may be predicted.

- The examined para-fluoroisomers (except for two of them) show intensive immonium ions with less than 50% of the TI and intense methyl loss ions (in case of the amphetamines) or ethyl loss ions (in case of the phenylbutanamines), respectively. The intensity ratios of the methyl or ethyl loss ions relative to the \([\text{M+H-HF}]^+\) ions are \(>1\) in all examined cases. So even the para-substituted compounds that do not form any immonium ion can clearly be differentiated from the other regioisomers.

By dilution of a fluoroamphetamine standard has been shown that even at concentrations of 1 \(\mu\)g/ml fluoroamphetamine (1 ng
Table 1
Characteristic ion intensities and intensity ratios of ortho-, meta-, para-fluoroamphetamines (FA) and -butanamines (FBA). $I_{+}$: intensities of the immonium ions (% basepeak and % TI); $I_{-15}$: intensity of methyl loss ions (% basepeak and % TI); $I_{M+H-N}$: intensity of ethyl loss ions (% basepeak and % TI).

<table>
<thead>
<tr>
<th>Derivative</th>
<th>$I_{+}$ (% basepeak)</th>
<th>$I_{-15}$ (% basepeak)</th>
<th>$I_{M+H-N}$ (% basepeak)</th>
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<tbody>
<tr>
<td>o-FA</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>o-FA ME</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>o-FA PR</td>
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</tr>
<tr>
<td>o-FA iPR</td>
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<td>0</td>
</tr>
<tr>
<td>o-FA 2ET</td>
<td>0</td>
<td>0</td>
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<td>m-FA</td>
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<tr>
<td>m-FA ET</td>
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</tbody>
</table>

Fig. 9. CI-CID-spectra of the $[M+H-N]^+$ ion originating from the fluoroamphetamine seized in Saxony (above) and p-fluoroamphetamine (below) (each: CI (methane), 20 eV, collision gas: argon).

absolute after injection of 1 μl) a structure elucidation in full scan mode has been possible with this method. In MRM mode much lower concentrations should be detectable. So this method should be applicable for the analysis of biological fluids as blood or urine after standard workup for GC–MS measurement. However, experiments with spiked samples of blood and urine were not conducted.

In 2007 the second seizure of a fluoroamphetamine occurred in Saxony, Germany. The substitution pattern was assigned after measurement of the CID-spectrum with the described product ion technique. Concerning the identical mass spectra after product ion spectrometry the isomer of the seized compound was univocally identified as p-fluoroamphetamine (Fig. 9). Recently seizures of fluoroamphetamines in Germany took place in Bavaria and Hesse.

4. Conclusion

The regioisomeric fluoroamphetamines show very similar mass spectra and similar retention indices so that a differentiation by normal EI mass spectrometry becomes not possible. Even derivatization does not solve this problem. Product ion spectrometry on the other hand gives unambiguous information for the determination of the aromatic substitution pattern of fluoroamphetamines.

Product ion mass spectrometric investigation of HF-loss-ions $[M+H-N]^+$ generated by collision-induced dissociation of the protonated molecular ion during chemical ionization under defined conditions shows analytically valuable fragmentation processes and provides access to the unequivocal differentiation of aromatic regioisomeric fluoroamphetamine derivatives. This method with submicrogram detection limits provides great advantages for the discrimination of aromatic regioisomeric fluorophenethylamine designer drugs where other methods such as nuclear magnetic resonance (NMR) spectrometry lack sufficient sensitivity or might fail because complex mixtures have to be analyzed as in seized tablets containing multiple compounds or possibly in fluids of biological origin. The presented method to identify the aromatic substitution pattern was successfully applied to a seized fluoroamphetamine derivative in 2007 on the German illegal drug market and to further fluoroamphetamine seizures upcoming in Germany in the last months.

The examined para-substituted fluorophenylbutan-2-amines behaved analogously to the corresponding p-fluoroamphetamines. An analogous behaviour of the o- and m-fluorophenylbutan-2-amines to the corresponding o- and m-fluoroamphetamines is probable but remains to be confirmed. Whether the differentiation of regioisomeric fluorophenethylamines by product ion spectrometry represents a generally applicable method also for the differentiation of bromo-, chloro- and iodo-substituted regioisomeric phenethylamines is subject of further investigations.

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Detection of the synthetic drug 4-fluoroamphetamine (4-FA) in serum and urine

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ABSTRACT

4-Fluoroamphetamine (4-FA) was detected in the blood and urine of two individuals suspected for driving under the influence (DUI). The test for amphetamines in urine subjected to immunoassay screening using the CEDIA DAU assay proved positive. Further investigations revealed a 4-FA cross-reactivity of about 6% in the CEDIA amphetamine assay. 4-FA was qualitatively detected in a general unknown screening for drugs using GC/MS in full scan mode. No other drugs or fluorinated phenethylamines were detected. A validated GC/MS method was established in SIM mode for serum analysis of 4-FA with a limit of detection (LOD) of 1 ng/mL and a lower limit of quantification (LLOQ) of 5 ng/mL. Intra-assay precision was approx. 4% and inter-assay precision approx. 8%. Applying this method, the 4-FA serum concentrations of the two subjects were determined to be 350 ng/mL and 475 ng/mL respectively. Given the pharmacological data of amphetamine, 4-FA psychoactive effects are to be expected at these serum levels. Both subjects exhibited sympathomimetic effects and psychostimulant-like impairment accordingly.

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1. Introduction

4-Fluoroamphetamine (4-FA) belongs to the class of para-substituted phenethylamine-type synthetic drugs that also includes 4-fluoromethamphetamine (4-FMA), 4-fluoromethcathinone (4-FMC), 4-methylmethamphetamine (4-MMA) and 4-methoxymethamphetamine (PMMA). 4-FA is a dopamine reuptake inhibitor and serotonin releasing agent. Therefore, 4-FA, as with most amphetamine derivatives, should produce mainly sympathomimetic effects and also exhibit entactogenic properties [1–8]. The subjectively perceived effects should be euphoria, mood elevation, excessive talking, bruxism, insomnia and suppressed appetite.

The quantity of 4-FA tablets that have been seized over recent years has increased considerably. As far back as 2005, Rösner et al. had already reported on fluoro-substituted amphetamines [9]. Since 2008, larger quantities of drug preparations containing 4-FA have been seized in several German federal states and in Switzerland. In January and June 2009, Eve & Rave Berlin and Streetwork Zürich published pill warnings concerning Ectasy tablets containing 4-FA [10,11]. This indicates that the designer drug 4-FA is in fact currently appearing on the drug scene. New drugs are frequently recognized by streetwork organizations at an earlier stage than by the forensic laboratories. 4-FA should, consequently, be present in blood or urine samples collected from drug users, and laboratories that concentrate on drug testing ought to take this new compound into consideration.

However, the question arises as to whether 4-FA is at all detectable in the toxicological screening procedures commonly used for testing urine, blood and serum, respectively. The usual drug screening procedures in most laboratories consist of immunochromatographic pre-testing and chromatographic confirmation analysis of positive results. The CEDIA DAU assay is widely used in German laboratories for immunoassay testing of urine. Liquid or gas chromatography coupled with mass spectrometry is usually applied for confirmation analysis. As a rule, target analyses are performed; general unknown analyses are performed less frequently. 4-FA was actually detected in a general unknown screening of blood and urine from two individuals suspected of driving under the influence. Previously performed target analyses for common amphetamine-type stimulants, such as amphetamine or methamphetamine, had proven negative. Without further investigation, both individuals had been falsely diagnosed as not having used drugs. The objective of this paper is, therefore, to emphasize the importance of taking new emerging designer drugs into consideration in the forensic-toxicological analysis of biological samples.

2. Materials and methods

2.1. Instrumentation and reagents

Instrumentation: gas chromatograph: HP 6890 with auto-sampler (Agilent Technologies, Waldbronn, Germany), mass-spectrometer: HP 5973 (Agilent...
Table 1

<table>
<thead>
<tr>
<th>LOD (ng/mL)</th>
<th>LLOQ (ng/mL)</th>
<th>Accuracy (low) (%)</th>
<th>Accuracy (high) (%)</th>
<th>Intra-assay (low) (%)</th>
<th>Intra-assay (high) (%)</th>
<th>Inter-assay (low) (%)</th>
<th>Inter-assay (high) (%)</th>
<th>Recovery (low) (%)</th>
<th>Recovery (high) (%)</th>
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<td>1.0</td>
<td>5.0</td>
<td>17.4</td>
<td>10.4</td>
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<td>3.7</td>
<td>8.9</td>
<td>8.5</td>
<td>95.0</td>
<td>101.6</td>
</tr>
</tbody>
</table>

2.2. Immunoassay screening of urine

The CEDIA DAU amphetamine/ecstasy assay was used for the immunoassay testing of urine. The assay was performed on a Hitachi 912 analyzer using 200 μL of urine. Amphetamine was used as the calibrator. The calibration range was 0–5000 ng/mL. The cut-off concentration for d-amphetamine of 50 ng/mL proposed by the manufacturer was lowered to 250 ng/mL because of the higher sensitivity and considerably lower number of false-negative cases.

2.3. Sample preparation procedure for GC/MS analysis

Serum or urine was purified for GC/MS general unknown analysis of basic compounds such as amphetamine-type stimulants, cocaine, opiates and other alkaloids containing nitrogen as well as for target analysis of 4-FA by solid phase extraction using the Caliper Rapid Trace SPE workstation. 1 mL of serum or urine was diluted with 6 mL of phosphate buffer (0.1 M, pH 6) and 50 μL of the internal standard was added (methanolic solution of 1 ng/μL of amphetamine-D$_3$). The mixture was then applied to a solid phase extraction column (Bakerbond C18, 500 mg), which had been conditioned by flushing with 2–3 mL of methanol and 2 mL of water. The column was rinsed with 2–3 mL of water, 2–3 mL of water/methanol (80:20; v/v) and 1 mL M1-acetic acid. The column was dried for 10 min. Elution was carried out in two steps. First neutral or slightly acidic compounds such as cannabinoids were eluted with 3 mL dichloromethane/acetic acid (50:50; v/v), followed by elution of basic compounds such as amphetamine derivatives with 3 mL dichloromethane/2-propanol/ammonia (40:10:2; v/v/v). The first eluate was discarded. Amphetamine-type stimulants were derivatized with pentafluoropropionic anhydride (PFPA) to the respective pentafluoropropionic acid (PFP) derivatives. 100 μL PFPA was added to the extract and the mixture was incubated at 70 °C for 30 min. The derivatization reagent was subsequently evaporated at room temperature under a nitrogen stream. For GC/MS analysis, the dried residues were dissolved in 50 μL water-free ethyl acetate.

2.4. GC/MS analysis

The carrier gas used was He (constant flow: 1 mL/min), the injection volume was 1 μL (splitless injection), the injector temperature was 250 °C and the transfer line temperature was 280 °C. The oven temperature program was 2 min isothermally at 60 °C, 0.4 °C/min to 170 °C, 8 °C/min to 270 °C, 7.75 min isothermally at 270 °C, 30 °C/min to 300 °C and 5 min isothermally at 300 °C. EI ionization (70 eV) was used, ion source temperature 230 °C, quadrupole temperature 106°C. For a general unknown drug screening, the full scan mode in a scanning range of m/z = 30–600 was used. For target analysis of 4-fluoroamphetamine, the following ions were measured in selected ion monitoring (SIM) mode (dwell time per ion: 15 ms): amphetamine-D$_3$–PFPA derivative (IS, m/z = 98-target, 128, 194, Ret: 5.5 min), 4-fluoroamphetamine–PFPA derivative (m/z = 109-target, 136, 190, 299, Ret: 5.6 min). For quantification, the peak areas of the ions specified as “target” were used. Quantification was based on peak area ratios relative to the respective internal standard (IS).

2.5. Validation of the GC/MS method for quantitative determination of 4-FA in serum

The GC/MS method for quantitative determination of 4-FA in serum was validated according to current standards [12,13]. Method validation was performed using the Microsoft Excel-based validation program Valisat [14]. Drug-free serum was used as a blank matrix for the validation measurements. Calibration curves in two different calibration ranges were used. The calibration levels were obtained by spiking 1 mL serum with 50 μL of methanolic solutions containing appropriate quantities of 4-FA. The lower calibration range consists of levels 5, 10, 20, 40, 60, 80, 100 ng/mL 4-FA. The upper calibration levels were 100, 200, 300, 400 and 500 ng/mL. Each calibration level was measured in six repetitions. The calibration was linear in the range tested. Accuracy and precision were calculated from the results of two analysts. 4-FA was performed on eight different days at two concentration levels (low, high). The recovery rates were determined in six repetitions at the two concentration levels low and high. At low level, the concentration was 20 ng/mL and at high level 100 ng/mL. Validation data are presented in Table 1. The limit of detection (LOD) and the lower limit of quantification (LLOQ) were calculated statistically from the calibration data and by means of signal-to-noise-ratios (S/N). For the LLOQ, a signal-to-noise-ratio of 10:1 is required while the S/N required for the LOD is 3:1. Positive results lower than the LLOQ were given as approximate values.

3. Results and discussion

3.1. Case history

A blood and urine sample of a driver suspected of DUI was tested for drugs of abuse in the toxicological laboratory of the Institute of Legal Medicine. The driver’s behavior during the police traffic check and subsequent medical examination was indicative of the use of sympathomimetic drugs. His pupils were dilated to approx. 6 mm and did not contract rapidly in response to light. His fingertips were trembling. In the Romberg test he showed tremor and swaying. His behavior was restless. Overall he seemed to have been impaired by psychostimulant drugs.

Approximately three months later, a second case of possible ingestion of an unknown psychostimulant drug occurred. Once again it appeared to be a case of DUI. The driver mentioned during the examination that he had used “Speed”. He showed symptoms that can be associated with the influence of psychostimulants, such as slow pupil light reflex, tremor and restlessness.

3.2. Toxicological investigation

The urine sample from the first individual was subjected to immunoassay screening for drugs of abuse using the CEDIA DAU assay. The CEDIA DAU amphetamine/ecstasy test produced a clearly positive result (measured CEDIA value >5000 ng/mL amphetamine equivalents). This appeared to be in agreement with the psychophysical findings of psychostimulant impairment. Surprisingly, the confirmation analysis of the positive amphetamine test result in urine proved negative. Only trace amounts of amphetamine, close to the limit of detection of the method used, were detected. These trace amounts did not explain the clearly positive test result in the CEDIA DAU assay. The chromatographic confirmation was carried out by GC/MS in SIM mode as a target analysis for amphetamine, methamphetamine, methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA) and methylenedioxymethamphetamine (MDE). The sample was purified prior to analysis by solid phase extraction following the addition of deuterated internal standards. Pentafluoropropionic acid anhydride (PFPA) was used for derivatization. This method is analogous to procedures by Becker et al. and Röhrich et al. [15–18]. It is validated and used routinely at the Institute of Legal Medicine for confirmation analysis of drugs of abuse in serum or urine. Even in a target analysis of the individual’s serum, neither relevant concentrations of amphetamine nor methamphetamine nor methylenedioxymphetamines were detectable. Similar to the urine analysis, only negligible traces of amphetamine were found in the serum.
However, it is a well-known fact that various phenethylamine derivatives may cross-react in commercial amphetamine assays. Tyramine, for example, was identified as a compound which produces false-positive amphetamine test results in the Triage assay [19]. To ascertain whether the positive amphetamine result in the CEDIA DAU assay could be caused by other cross-reacting phenethylamine-derivatives than the amphetamine derivatives tested, the urine sample was subjected to a general unknown screening for drugs using GC/MS in full-scan mode. The sample preparation and derivatization was the same as for the SIM procedure, although full-scan mode was used in a scan range of m/z = 40–600. Following a retention time of about 0.05 min subsequent to the retention of pentafluoropropionylated amphetamine, a prominent chromatographic peak of a substance was detected that could not be directly identified (see Fig. 1). The mass spectrum of this compound had three major signals of m/z = 109, 136 and 190 (base peak). The initially unknown compound was identified relatively quickly as the pentafluoropropionic acid (PFP) derivative of 4-FA (Fig. 2). Further fluorinated phenethylamines or other drugs were not detected in the urine sample except for a small concentration of 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (THC-COOH), which was of minor importance in this case.

In the second case, ingestion of 4-FA was also proven. As in the first case, immunoassay testing proved positive for amphetamines, but no amphetamine, methamphetamine or MDMA could be found in the initial target analysis. Here again, 4-FA was detected in the GC/MS general unknown screening.

3.3. GC/MS procedure for 4-FA serum analysis

A GC/MS method for sensitive detection and quantification of 4-FA in serum was developed. Unfortunately, a deuterated standard
of 4-FA was not commercially available. Because of the fact that the PFP derivatives of amphetamine and 4-FA have very similar retention times and show nearly identical fragmentation patterns, it appears to be acceptable to use the obtainable deuterated amphetamine as the internal standard. Amphetamine-D$_{11}$ at least was applied as internal standard. As shown in Fig. 3, there is no significant interference among pentafluoropropionylated amphetamine, amphetamine-D$_{11}$ and 4-FA. The only difficulty could arise from the identical mass $m/z = 190$, which occurs in the mass spectra of amphetamine as well as 4-FA. Therefore, the fragments containing $m/z = 98$ (amphetamine-D$_{11}$-PFP) and $m/z = 109$ (4-fluoroamphetamine-PFP) were used as the target for quantification. The method validation revealed a high sensitivity for 4-FA with a limit of detection (LOD) of 1 ng/mL. The lower limit of quantification (LLOQ) was 5 ng/mL. The intra-assay precision was approx. 4 and the inter-assay precision was approx. 9% (see Table 1). Applying this method, the 4-FA serum concentrations of the two suspects were determined to be 350 ng/mL and 475 ng/mL, respectively.

3.4. Possible pharmacological effects of 4-FA

Both individuals showed symptoms such as dilated pupils, slow pupil light reflex, trembling and restlessness which can be associated with the influence of psychostimulants. There are no reference data in the literature concerning serum concentrations of 4-FA and corresponding neuropsychological effects or impairment levels. However, because of its pharmacological properties, it can be assumed that 4-FA may have similar effects to those of amphetamine [1–4]. Accordingly, serum concentrations and pharmacological effects of 4-FA and amphetamine could be comparable. Therefore, psychoactive effects must be assumed at the 4-FA concentrations of 350 ng/mL and 475 ng/mL detected in the respective serums of the two subjects. This would provide a satisfactory explanation as to why both subjects exhibited stimulant effects and amphetamine-like impairment during the medical examination. The trace amounts of amphetamine found in urine and serum of the first subject could either be remainders of amphetamine used a longer time ago or be impurities of the consumed 4-FA. It would be highly speculative to relate the traces of amphetamine detected in the first individual to the observed psychophysical syndromes. These trace amounts of amphetamine could never explain the severe impairment of this individual. His symptoms must have been acute drug effects which most probably were caused by 4-FA. Consequently, 4-FA may have been the reason for his behavioral syndromes associated with neuropsychological disturbances.

3.5. Cross-reactivity of 4-FA in the CEDIA DAU amphetamine/ecstasy assay

With regard to the positive amphetamine test results with CEDIA DAU, it is obvious that 4-FA must have a considerable cross-reactivity with the respective antibodies used in this assay. In fact positive amphetamine test results in the CEDIA DAU assay possibly caused by 4-FA have been observed [20]. Since this seems to be of interest, the cross-reactivity of 4-FA in the CEDIA DAU assay was determined. The investigation was carried out using amphetamine-free urine samples spiked with 4-FA in seven different

<table>
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<th>Response CEDIA DAU (ng/mL)</th>
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<td>2000</td>
<td>129</td>
</tr>
<tr>
<td>3000</td>
<td>186</td>
</tr>
<tr>
<td>5000</td>
<td>307</td>
</tr>
<tr>
<td>10,000</td>
<td>616</td>
</tr>
</tbody>
</table>
concentrations ranging from 300 to 10,000 ng/mL. Each concentration level was measured using the CEDIA DAU amphetamine test in five repetitions. The results are summarized in Table 2 and Fig. 4. The CEDIA DAU assay produced a positive test result exceeding the cut-off concentration of 250 ng/mL, first at a 4-FA concentration of 5,000 ng/mL (average CEDIA DAU value: 307 ng/mL). The cross-reactivity was calculated to be approx. 6% and did not change significantly across the whole concentration range. Cody and Schwarzhoff found similar cross-reactivities for amphetamine analogs in the Abbott TDX assay [21]. However, since the cross-reactivity of 4-FA in the CEDIA DAU assay of about 6% is rather low, the reason for the clearly positive CEDIA result in the first urine sample must have been caused by an extraordinarily high concentration. In fact, a 4-FA concentration of approx. 90 μg/mL, which far exceeds the upper limit of quantification of the applied method, could have been estimated by GC/MS analysis.

4. Conclusions

In recent years numerous new amphetamine analogs have appeared on the drug scene. Many of these new compounds are phenethylamine-type drugs such as 4-FA, and also cathinone derivatives are becoming increasingly significant. This paper clearly demonstrates that 4-FA can, in principle, be detected by means of toxicological screening procedures. 4-FA was obviously cross-reacting in the CEDIA DAU assay for amphetamines in urine. However, the positive CEDIA result could not be confirmed initially by target analysis for widespread derivatives, just as for amphetamine itself. A general unknown screening using GC/MS first revealed the presence of 4-FA. It was found in the serum of users in concentrations of 350 ng/mL and 475 ng/mL, whereby the subjects exhibited psychostimulant-like impairment. Therefore, laboratories focusing on drug testing should bear in mind that positive immunoassay results which cannot be initially confirmed may not necessarily be false-positive. They could also be the result of the cross-reaction of other amphetamine analogs than the derivatives usually tested.

Acknowledgements

The support provided by Dr. K. Waldhauser (Microgenics, Passau, Germany) is gratefully acknowledged. In particular the authors would like to thank A. Eigenwillig, A. Schlaege, A. Toepfer, A. Wegierich, E. Westenberger and C. Wittkowsky for technical assistance. Special thanks to K. Hessas for revision of the English usage.

References

TECHNICAL PROFILE OF 4-FLUOROAMPHETAMINE

SUMMARY

4-Fluoramphetamine fluorinated amphetamine belonging to the phenethylene group of drugs. A number of in vitro and in vivo animal studies have shown that 4-Fluoroamphetamine both inhibits the re-uptake and stimulates the release of dopamine, serotonin (5-HT) and norepinephrine for nerve terminal. It therefore has similar stimulant effects to amphetamines.

There is evidence from seizure data, of its availability in Europe since 9th October 2008, with the first seizure from Denmark. 2006. However, there are user reports available to suggest its use from 2003 onwards. 4-Fluoroamphetamine seizures have been reported from 13 European and neighbouring countries to date.

Users report use of powders, capsules and liquid (dissolved powder by the user); seizures, however, are of powders, paste, tablets, capsules and liquids. The predominant route of use is oral ingestion or nasal insufflation, although users report severe nasal pain and irritation after insufflation. Current reported doses are 80-120mg for oral use and 50-75 mg for nasal insufflation.

Although there is no evidence to suggest that 4-Fluoroamphetamine is available to users through Internet “legal high” suppliers, it does not appear to be readily available. It would appear that there is the potential that users may be mis-sold 4-Fluroamphetamine as either “amphetamine” or an alternative recreational drug.

There is no information on the purity of 4-Fluoroamphetamine, although analysis of
some seizures has shown that other pharmaceutical and recreational drugs were detected together with the 4-Fluoroamphetamine.

User reports suggest that 4-Fluoroamphetamine has stimulant properties, and that the overall desired effects last 12-24 hours. These effects are reported to be “better than amphetamine”, but “not as good as MDMA”. There are no reports of acute toxicity relating to 4-Fluoroamphetamine, either to poisons centres or in the medical literature. This may be because physicians do not realise that there is a difference between 4-Fluoroamphetamine and amphetamine, and simply record amphetamine in medical records. Commonly reported unwanted effects by users include headache, sweating, difficulty sleeping, grinding of teeth, anxiety, anorexia, nausea, “flu-like” symptoms, “mental spaciness” and “moderate hyperthermia”.

There have been two deaths reported in the UK where 4-Fluoroamphetamine has been detected at post-mortem samples, although it is unlikely that the 4-Fluoroamphetamine was of clinical significance in either of these deaths.

In conclusion, there is no evidence to date of acute health effects relating to 4-Fluoroamphetamine use in Europe, and no confirmed deaths directly relating to its use. Whilst seizure data suggests that it is available in Europe, there is no evidence of widespread use. This may be because users are unaware that they are using 4-Fluoroamphetamine rather than amphetamine or another recreational drug; acute health effects may not be reported because clinicians are similarly unaware. Therefore, based on the currently available evidence, we are unable to conclusively state the degree of acute and chronic harm related to 4-Fluoroamphetamine.
SECTION A. PHYSICAL, CHEMICAL, PHARMACEUTICAL AND PHARMACOLOGICAL INFORMATION

A1. Physical and Pharmaceutical Information

A1.1. Physical and Chemical Description

The systematic (IUPAC) name for 4-Fluoroamphetamine is 1-(4-Fluorophenyl)propan-2-amine. It is also known as 4-fluoro alpha-methylphenethylamine, p-fluoroamphetamine; p-fluoro-alpha-methylphenethylamine, 4-FMP, 4-FA, PFA, PAL-303, Flux, Flouroamphetamine and 4flo. There are no official synonyms, non-proprietary names or trademark names for 4-Fluoroamphetamine.

4-Fluoroamphetamine, is one of a number of fluorinated amphetamines belonging to the phenethylamine group of drugs, which are synthetic psychotropics. The molecular formula for 4-Fluoroamphetamine is C$_9$H$_{12}$FN, equating to a molecular weight of 153.20 g/mol.

The chemical structure of 4-Fluoroamphetamine is shown below:

![Chemical Structure of 4-Fluoroamphetamine]

Racemic 4-Fluoroamphetamine can be easily synthesized from the 4-fluorobenzyl methylketone (4-fluoroBMK) precursor by means of Leuckart amination. There are reports from Holland, on the EMCDDA European Information System and Database
on New Drugs, that illicit drug production laboratories previously producing amphetamine have switched to the production of 4-Fluoroamphetamine. It is suggested that this switch may have occurred due to the lack of availability of the benzylmethylketone (BMK) precursor for amphetamine, compared to a relative abundance of the 4-Fluoroamphetamine precursor.

A1.2. Physical/pharmaceutical form
4-Fluoroamphetamine is usually available to users in either white powder or in crystalline form, although there has been one user report of 4-Fluoroamphetamine being available from an Internet “legal high” seller in capsule form [Erowid 1]. It is readily soluble in water, and there is a user report of dissolving 4-Fluoroamphetamine in water / soda prior to use [Erowid 2]. As discussed in Section C., the seizure data reported to the EMCDDA European Information System and Database on New Drugs relates to powder/paste, tablets and liquid; it is not clear as to whether the liquid seizures had been sold with the 4-Fluoroamphetamine already dissolved or if this had been done by the user.

A1.3. Route of administration and dosage
There are only a total of 14 user reports relating 4-Fluoroamphetamine experiences on Erowid, with the first reports dating back to 2003 [Erowid 3]. At least three of these user reports relate to ‘poly-drug’ use, with more than one additional controlled recreational drug being used at the same time as 4-fluoroamphetamine. There have been 2-3 user reports of 4-Fluoroamphetamine experience per year between 2007 and 2009 on Erowid [Erowid 3].
The majority of users report that the predominant route of use is by oral ingestion, either of powder directly or dissolved in liquid(s) or in capsules [Erowid 3]. There are reports of nasal insufflation of 4-Fluoroamphetamine powder, although as discussed in Section D below, the majority of users trying nasal insufflation report severe nasal pain; it is unclear whether this leads to a change in route of future use of 4-Fluoroamphetamine. Whilst there are no user reports of intravenous or intramuscular injection of 4-Fluoroamphetamine, there is a report to the EMCDDA European Information System and Database on New Drugs from Sweden that one individual unknowingly injected 4-Fluoroamphetamine believing that it was amphetamine instead.

The doses reported in the user reports suggest an oral dose of 80-120mg and a nasal insufflation dose of 50-75mg [Erowid 3]; although there are reports of use up to 200mg in a single dose, most users recommend lower doses to prevent unwanted effects occurring.

A2. Pharmacology, including pharmacodynamics and pharmacokinetics
There are no formal human pharmacokinetic studies looking specifically at 4-Fluoroamphetamine.

The onset of desired effects with 4-Fluoroamphetamine is reported by users to be slower than that seen with MDMA and amphetamine, and typically maximal desired effects occur around an hour following ingestion [Erowid 3]. Nasal insufflation is reported to have much faster onset of desired effects, occurring within a “few minutes” of use. User reports seem to suggest that the desired effects last up to 12-
24 hours in duration, but there is no suggestion of a prolonged ‘after effect’ or ‘come down’ phase by users [Erowid 3].

Rat _ex vivo_ models have demonstrated that 4-Fluoroamphetamines, similar to other phenethylene derivatives, inhibited the reuptake of dopamine, serotonin (5-HT) and norepinephrine into pre-synaptic nerve terminals [Nagai F 2007]. In this model, 4-Fluoroamphetamine was also shown to strongly increase the release of these three monoamines from the nerve terminals. There have been several _in vitro_ and _in vivo_ rat and mouse model studies, which have shown that the effects of 4-Fluoroamphetamine are comparable to those seen with amphetamines [Dubin RE 1985, Marona-Lewicka D 1995, Danielson TJ 1986].

**A3. Psychological and behavioural effects**

There are no published formal studies assessing the psychological and/or behavioural effects of 4-Fluoroamphetamine in humans; therefore, the psychological and behavioural effects related to human use of it are based solely on users’ reports [Erowid 3].

The desired psychological and behavioural effects reported by users appear to be broadly similar to that seen with MDMA and amphetamine, including euphoria, increased energy and mood elevation [Erowid 3]. In terms of onset of desired effects, the majority of user reports seem to suggest that it is slower than that seen with amphetamines and MDMA. Unlike amphetamine, however, users report that it is “less edgy” and “more mellow”, and “generally better than amphetamine”.
A4. Legitimate uses of the product

There are no known uses of 4-Fluoroamphetamine as a research, industrial or cosmetic compound. It is not a recognised medicinal product in its own right and is not used for the synthesis of any other medicinal products or active pharmaceutical ingredients (API) and is not recognised as a metabolite of any of these.
 SECTION B. DEPENDENCE AND ABUSE POTENTIAL

B1. Animal in vivo and in vitro data

There are no published animal or in vitro studies investigating the dependence / abuse potential of 4-Fluoroamphetamine.

B2. Human data

There are no published reports of dependence to 4-Fluoroamphetamine. To date, user reports appear to suggest single rather than recurrent use of 4-Fluoroamphetamine, with the majority of these reports suggesting that users would not retry 4-Fluoroamphetamine in the future [Erowid 3].
SECTION C. PREVALENCE OF USE

There are reports to the EMCDDA European Information System and Database on New Drugs, of seizures of 4-Fluoroamphetamine from 13 European and neighbouring countries. The first seizure was in Denmark on 9th October 2008, reported to the EMCDDA European Information System and Database on New Drugs on 5th December 2008; therefore, the majority of reports of seizures are from 2009.

<table>
<thead>
<tr>
<th>Country</th>
<th>Amount and Details of the Seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>2008: One seizure of brown powder</td>
</tr>
<tr>
<td></td>
<td>2009: 6 seizures of powder totalling 33.9g, one seizure of 49.79g of “paste/sticky powder” and one seizure of tablets.</td>
</tr>
<tr>
<td>Croatia</td>
<td>2009: Four seizures of white powder, also containing amphetamine, creatine, mannitol and caffeine.</td>
</tr>
<tr>
<td>Denmark</td>
<td>2008: Two seizures, one of 4g of white powder containing both 4-Fluoroamphetamine and amphetamine</td>
</tr>
<tr>
<td></td>
<td>2009: five confirmed seizures (with one possible additional unconfirmed seizure).</td>
</tr>
<tr>
<td>Estonia</td>
<td>2009: One seizure of 320mg, also containing amphetamine.</td>
</tr>
<tr>
<td>Finland</td>
<td>2009: One seizure of 12 tablets and 2 seizures of powder/capsule totalling 5g/3units.</td>
</tr>
<tr>
<td></td>
<td>2008: One seizure of white powder.</td>
</tr>
<tr>
<td>France</td>
<td>2009: Eight seizures of powder totalling 3115g, one white tablet.</td>
</tr>
<tr>
<td>Germany</td>
<td>2009: Three seizures – two of a few grams of powder and one a package containing 1kg. Additionally detected in seizures of amphetamine.</td>
</tr>
<tr>
<td>Country</td>
<td>Year</td>
</tr>
<tr>
<td>----------</td>
<td>------</td>
</tr>
<tr>
<td>Guernsey</td>
<td>2009</td>
</tr>
<tr>
<td>Hungary</td>
<td>2009</td>
</tr>
</tbody>
</table>
| Netherlands | 2008 | 7 seizures of powder (totalling greater than 212g), one seizure of capsule and two seizures of liquids (one also containing 2C-B and BZP).  
2009: From DIMS: 60 collected samples of powder, six collected samples of tablets and 1 collected sample of liquid.  
From NFI: One seizure of powder >340kg, 98 seizures of powder >>100kg, 98 seizures of powder >>100kg in combination with amphetamine. |
| Slovakia | 2009 | One seizure of powder totalling 16mg |
| Sweden   | 2009 | 162 seizures of powder totalling 7634.4g, seven seizures of liquid totalling 21ml. |
| UK       | 2009 | One seizure of “wet white powder” also containing caffeine and glucose, two seizures of liquid totalling 0.9ml, 107 seizures of powder totalling 99.97kg, seven seizures of paste totalling 13.982kg, one also containing amphetamine. |

There are currently no co-ordinated national or European population surveys on 4-Fluoroamphetamine use. In addition, the recent MixMag survey did not report on either life-time use or recent use within the last month of 4-Fluoroamphetamine [Dick 2010].
SECTION D. HEALTH RISKS

D1. Acute health effects

D1.1. Animal Data

There is no published animal data on the acute health effects of 4-Fluoroamphetamine.

D1.2. Human Data

D1.2.1 User Reports

To date, there have been no large scale published user surveys on the acute health effects experienced by 4-Fluoroamphetamine users.

There are numerous user reports on Erowid of acute health effects following 4-Fluoroamphetamine use [Erowid 3]. Commonly reported acute health effects by users following both oral use and nasal insufflation include:

- Headache
- Difficulty sleeping following use
- Mild grinding of teeth
- Anxiety
- Anorexia
- Nausea
- “Flu like symptoms”
- Generalised aches and chills
- Moderate hyperthermia
- Mental “spaciness”
Following oral use of powder directly, some users report that it has a very unpleasant taste / sourness, which is not “easy to wash out of their mouths” [Erowid 3]. All users of 4-Fluoroamphetamine by nasal insufflation report severe nasal pain and irritation, similar to a severe burning sensation, that can be followed by prolonged symptoms such as “running nasal discharge” [Erowid 3]. Typically the severe nasal pain is reported to be short-lived, lasting less than a few minutes in duration, before the individual may be left with an unpleasant smell in their nose (reported by one to be similar to burnt plastic) [Erowid 4].

It is not possible to determine the incidence of these symptoms based on the user reports available and it is important to note that these are unconfirmed anecdotal reports from users.

D1.2.2. Poisons Information Service Data
The have been no enquiries to the UK National Poisons Information Service relating to 4-Fluoroamphetamine. We have been unable to obtain any published data on calls to other European or neighbouring countries of enquiries relating to 4-Fluoroamphetamine.

D1.2.3. Published case reports of acute 4-Fluoroamphetamine toxicity
There have been no published case reports / case series of acute 4-Fluoroamphetamine toxicity. However, this lack of publication may reflect that clinicians be recording that an individual has used 4-Fluoroamphetamine rather than amphetamine.
D1.2.4. 4-Fluoroamphetamine related deaths

The EMCDDA European Information System and Database on New Drugs includes a single report from the UK where 4-Fluoroamphetamine was detected at post-mortem analysis of a ‘middle aged lady with a history of drug abuse found dead at home’. Toxicological analysis also detected the presence of codeine, paracetamol, Temazepam and amphetamine; no inquest findings were reported. We are aware of one other death in 2009 of an incidental finding of 4-Fluoroamphetamine in post mortem urine toxicological screening of a 46 year old male, where the conclusion of the coroner was that the cause of death “Methadone and alcohol overdose” [Personal communication Dr John Corkery].

D2. Chronic Health Effects

D2.1. Animal Data

There is no animal data on the chronic health effects of 4-Fluoroamphetamine.

D2.2. Human Data

There are no other reported studies suggesting chronic long-term physical health effects relating to 4-Fluoroamphetamine use. In addition there are no reports of individuals developing chronic health problems that do not relate to acute complications following 4-Fluoroamphetamine use.

D3. Factors Affecting Public Health Risks

D3.1. Availability and Quality of the New Psychoactive Substance on the Market (Purity, Adulterants etc)
Although 4-Fluoroamphetamine has been reported to have been purchased from online Internet suppliers of “legal highs” [Erowid 3], it does not appear that readily available to users from this source. It is possible, although not easy, to order it directly from chemical companies synthesizing “research chemicals”. Whilst it does not appear to be readily available from established street level drug dealers, there is the possibility that users may be ‘mis-sold’ 4-Fluoroamphetamine instead of other recreational drugs. This can occur where the dealer is aware that they are selling 4-Fluoroamphetamine instead of the desired product or where they are unaware that the products they are selling contain 4-Fluoroamphetamine. This is supported by reports on the EMCDDA European Information System and Database on New Drugs, where MDMA being sold which actually contained 4-Fluoroamphetamine.

There is no available information on the purity of 4-Fluoroamphetamine in seizures to date. As noted in Section C. analysis of some seizure samples has demonstrated that a large proportion of them also contain amphetamine. Other substances detected (both pharmaceutical adulterants and illicit drugs) include caffeine, glucose, creatine, mannitol, 1-benzylpiperazine (BZP) and 2,5-dimethoxy-4-bromophenethylamine (2C-B).

**D3.2. Availability of the Information, Degree of Knowledge and Perceptions Amongst Users Concerning the Psychoactive Substance and its Effects**

The reports on user websites suggest that users are aware that it is effective in producing the desired effects, and that overall these are thought to be better than amphetamine (less unwanted stimulant effects) and almost comparable to MDMA.
D3.3. Characteristics and Behaviour of Users

There is no available user data to be able to determine the characteristics of those using 4-Fluoroamphetamine, given the sparsity of user reports to date. It is likely that the majority of users will be similar to those using controlled recreational drugs, such as MDMA and amphetamines. Additionally, it is possible that some individuals using amphetamine will be ‘mis-sold’ 4-Fluoroamphetamine instead.


The acute health effects of 4-Fluoroamphetamines have been discussed in Section D1.2. There is no data available to date from law enforcement agencies to suggest that 4-Fluoroamphetamine use has been implicated in road traffic accidents or other trauma.

D3.5. Long-term Consequences of Use

As yet, there have been no long-term follow up studies to determine if 4-Fluoroamphetamine users are at greater risk of health deterioration later in life, or of developing chronic or life-threatening medical conditions.

D3.6. Conditions Under Which the New Psychoactive Substance is Obtained and Used, Including Context-Related Effects and Risks

As noted in Section D3.1. 4-Fluoroamphetamine is not readily available either from on-line Internet suppliers of “legal highs” or established street level drug dealers.
User reports suggest that 4-Fluoroamphetamine is mostly used within the home environment, although there have been some reports of use within discotheques/nightclubs and pubs/bars [Erowid 3].
SECTION E. SOCIAL RISKS

E1. Individual Social Risks

There is currently no information available to comment on this.

E2. Possible Effects on Social Environment

There is currently no information available to comment on this.

E3. Possible Effects on Society as a Whole

There is limited information on acquisitive crime related directly to the sale and/or use of 4-Fluoroamphetamine. The reports to date from Sweden to the EMCDDA European Information System and Database on New Drugs of crime and/or criminal activity related to 4-Fluoroamphetamine, have all related to incidents where the suspect and/or the law enforcement agencies have believed that they have related to amphetamine rather than 4-Fluoroamphetamine.

E4. Economic Costs

As noted in Section D1.2. there are no reports of individuals presenting to healthcare services with acute health effects, therefore it is not possible to be certain of the overall costs associated with 4-Fluoroamphetamine toxicity at this time.

E5. Possible Effects Related to the Cultural Context

There is no data available to suggest that 4-Fluoroamphetamine use is associated with particular demographic / socio-economic groups in society.
E6. Possible Appeal of the new Psychoactive Substance to Specific Population Groups within the General Population

There is no data available to suggest that 4-Fluoroamphetamine use is associated with specific sub-population groups.

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King’s Health Partners
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March 2010
REFERENCES


