Vol. 10, No. 1, 2019
ISSN 2233-4203/ e-ISSN 2093-8950
REVIEW www.msletters.org | Mass Spectrometry Letters

Amphetamine-type Stimulants in Drug Testing

Heesun Chung[1,*] and Sanggil Choe[2]

[1]*Graduate School of Analytical Science and Technology, Chungnam National University, Daejeon, Korea*
[2]*Forensic Toxicology Section, Seoul Institute, National Forensic Service, Seoul, Korea*

Received September 2, 2018; Revised December 18, 2018; Accepted December 18, 2018
First published on the web March 31, 2019; DOI: 10.5478/MSL.2019.10.1.1

Abstract : Amphetamine-type stimulants (ATS) are a group of β-phenethylamine derivatives that produce central nervous system stimulants effects. The representative ATS are methamphetamine and 3, 4-methylenedioxymethamphetamine (MDMA), and abuse of ATS has become a global problem. Methamphetamine is abused in North America and Asia, while amphetamine and 3, 4-methyle nedioxym ethamphetamine (Ecstasy) are abused in Europe and Australia. Methamphetamine is also the most abused drug in Korea. In addition to the conventional ATS, new psychoactive substances (NPS) including phenethylamines and synthetic cathinones, which have similar effects and chemical structure to ATS, continue to spread to the global market since 2009, and more than 739 NPS have been identified. For the analysis of ATS, two tests that have different theoretical principles have to be conducted, and screening tests by immunoassay and confirmatory tests using GC/MS or LC/MS are the global standard methods. As most ATS have a chiral center, enantiomer separation is an important point in forensic analysis, and it can be conducted using chiral derivatization reagents or chiral columns. In order to respond to the growing drug crime, it is necessary to develop a fast and efficient analytical method.

Keywords : Amphetamine-type stimulants, ATS, methamphetamine, new psychoactive substances, NPS

Introduction

Amphetamine-type stimulants (ATS)

The term 'ATS' was adopted at the WHO meeting in 1996 in Geneva to describe amphetamines, 3,4-methylenedioxymethamphetamine (MDMA) and other psychostimulants.[1] This term was also used by other international organizations such as United Nations International Drug Control Programme (UNDCP).[2,3] ATS is now the term used for a group of drugs, mostly synthetic in origin, that are chemically derived from β-phenethylamine and produce central nervous system stimulant effects. ATS include amphetamine-like stimulants (α-methylphenethylamines) such as amphetamine and methamphetamine, and MDA-type derivatives (3, 4-methylenedioxyphenethylamines) such as 3,4-methylenedioxyamphetamine (MDA) and MDMA (Figure 1).

*Reprint requests to Heesun Chung
E-mail: hschung@cnu.ac.kr

ATS may produce one or more dose-related symptoms including increased alertness, increased heart rate, increased blood pressure, increased respiration rate, increased body temperature, and euphoria.[4-7] Chronic abuse can result in agitation, tremors, hypertension, memory loss, hallucinations, psychotic episodes, paranoid delusions, and violent behavior.[8,9] Withdrawal from high doses of ATS could result in severe depression.[10]

ATS have become a major factor in international drug control because of certain characteristics such as simple and flexible manufacturing techniques, readily available raw materials, high profit margins for producers, and low prices for consumers.[11] The well-known synthetic methods of methamphetamine and MDMA are shown in Figure 2. Ephedrine/pseudoephedrine and safrole are the most widely used precursors for methamphetamine and MDMA, respectively.

History of ATS

Amphetamine was first synthesized in 1887 in Germany by Romanian chemist Lazăr Edeleanu who named it phenylisopropylamine.[12-14] It was commercially available in 1934 as an inhaler used to relieve nasal congestion marketed under the name Benzedrine.[15] Methamphetamine, also called 'meth', 'crystal', or 'speed', was synthesized from ephedrine by Nagai Nagayoshi in Japan in 1893.[16] In 1919, the first crystallized methamphetamine (methamphetamine hydrochloride), which was purer and stronger, was also synthesized in a Japanese lab via reduction of ephedrine

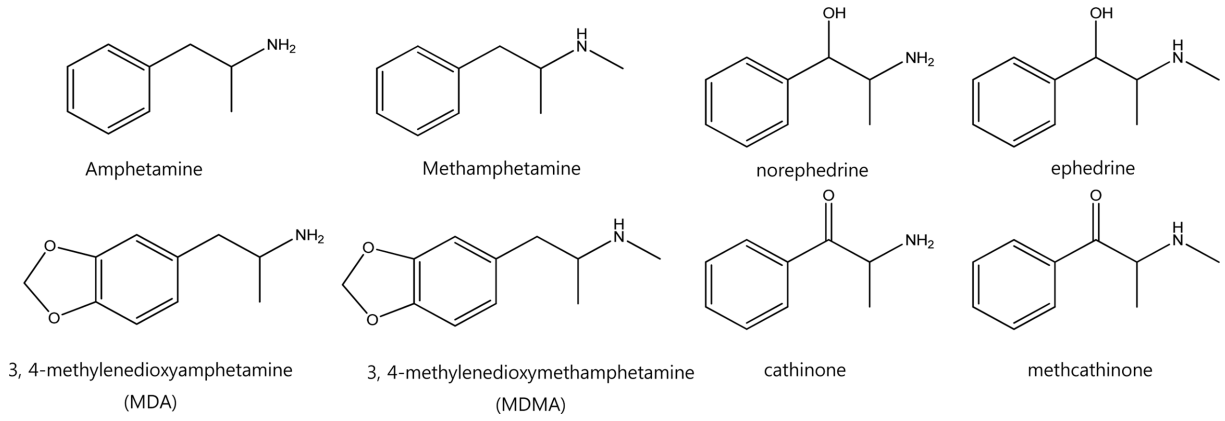

Figure 1. Structures of various phenethylamines. Methamphetamine and 3, 4-methylenedioxymethamphetamine are the representative Amphetamine-type stimulants (ATS), and cathinone and methcathinone are widely abused New Pshcyoactive Substances (NPS) recently.

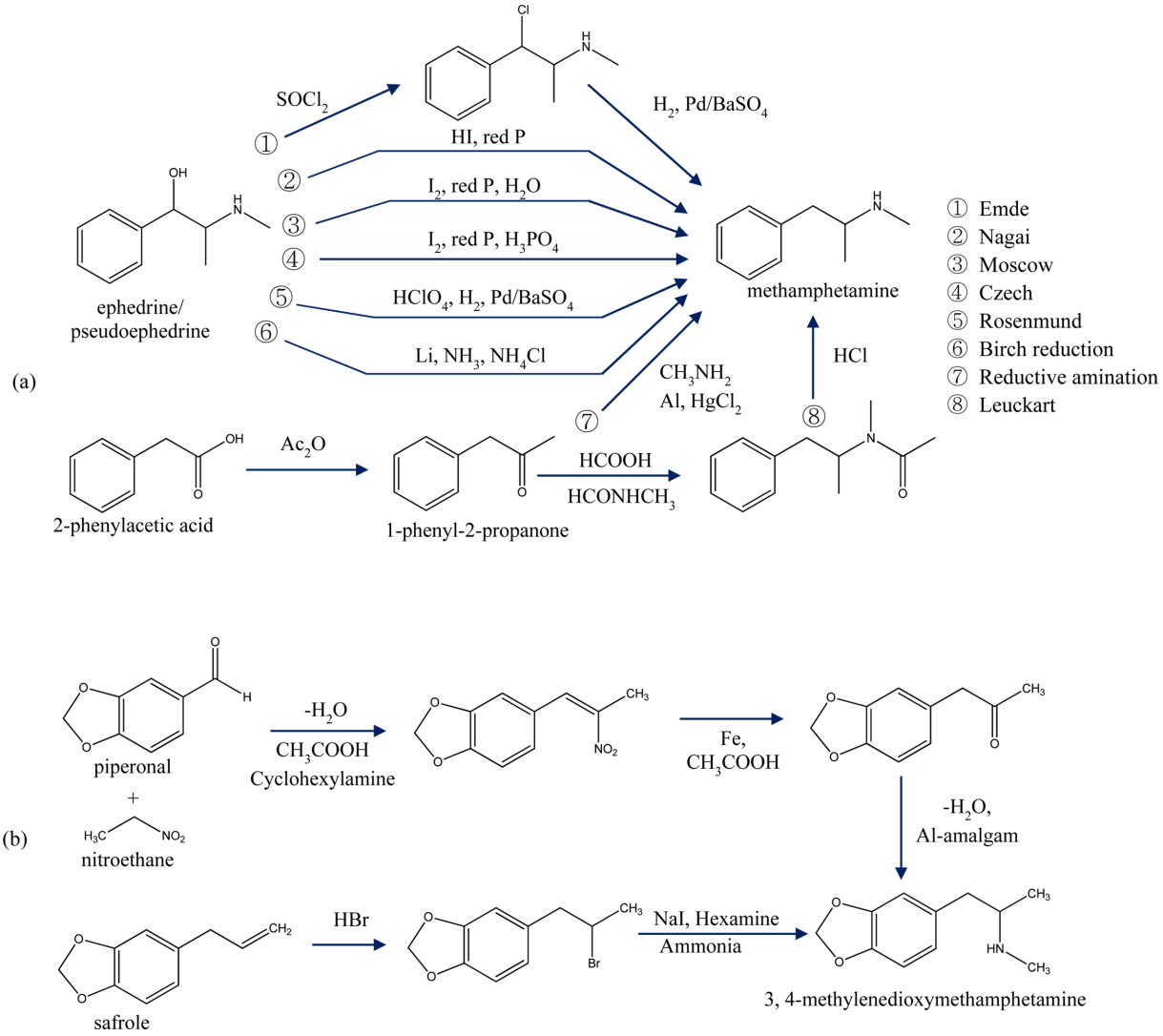

Figure 2. Synthetic routes of methamphetamine (a) and 3, 4-methylenedioxymethamphetamine (b).

using red phosphorus and iodine.[17] There are several commercial medicines containing methamphetamine. Desoxyn has been approved by the FDA for treating Attention Deficit Hyperactivity Disorder,[18,19] and Pervitin was a tablet form given to soldiers during World War II for its performance-enhancing stimulant effects and to induce extended wakefulness.[20,21] Obetro was introduced as a treatment for obesity in the 1950s,[22] and Philopon was commercialized in Japan in 1941.[23]

Both stimulants were illicitly trafficked and sold owing to their potential for recreational use. During the early 1970s in the United States, they became schedule II controlled substances,[24] and in 1971 under the UN Convention on Psychotropic Substances, they were started to be controlled as psychotropic agents.[25]

MDMA was first synthesized by Merck in Germany in 1912 in an attempt to develop an appetite suppressor,[26] but it became popular as a recreational drug in the 1980s and has no approved medical uses.[27,28] MDA was first synthesized in 1910 but its psychoactive effects were not discovered until 1930. Although MDA was patented as a cough suppressant and an anorectic under the trade name 'Amphedoxamine' in 1961,[29] it was being recreationally used in the late 1960s. MDMA and MDA act primarily by increasing the activity of the neurotransmitters serotonin, dopamine, and noradrenaline in parts of the brain.[30,31] Due to their stimulant and hallucinogenic effects, they were scheduled under the UN Convention on Psychotropic Substances.[25]

Trends in ATS abuse

The abuse of ATS has emerged as a global problem. After the introduction of ATS into medical practice in the 1930s, the parent drugs of the ATS group, amphetamine and methamphetamine, began to be used for non-medical purpose.[32] ATS abuse started among occupational groups, then moved on to students, athletes, and then to recreational users. Chronic abuse became a problem in a few countries, notably in northern Europe and Japan.[33]

By the mid-1990s, abuse of ATS had become a global phenomenon. According to World Drug Report 2017,[34] the overall global quantities of ATS seized doubled from 93 tons in 2010 to 191 tons in 2015, with methamphetamine accounting for 61-80% annually. Seizure data suggests that ATS markets continued to increase globally from 2010 to 2015. Methamphetamine dominates the global ATS market, accounting for almost 70% annually. Amphetamine is the main substance, particularly in Europe, and amphetamine seizures annually accounted for 20-32% of global ATS seizures. Ecstasy seizures accounted for less than 5% of global ATS seizures annually.

Amphetamine has long been a prominent feature of synthetic drug markets in the Near and Middle East and Western and Central Europe, but there are now signs of increasing seizures in Southeastern Europe, and the amounts of amphetamine seized in Central America have increased greatly since 2014.

Although MDMA accounts for a relatively small portion of the global ATS market, the Netherlands and Belgium are the most prominent areas where manufacturing facilities are increasing. Manufacturing of MDMA is also occurring in other regions and sub regions, including Asia, North America, Oceania, and South America.

There are distinct regional abuse patterns with ATS abuse. Methamphetamine is abused in North America and Asia, while amphetamine and MDMA are abused in Europe and Australia.[35] In Japan, almost 90% of all violations against drug control laws were related to methamphetamine,[36] and methamphetamine is also the most abused drug in Korea.[37]

New psychoactive substances (NPS) and trends in their abuse

In addition to the conventional ATS, the escalating use of stimulants belonging to the group of new psychoactive substances (NPS), phenethylamine and synthetic cathinones, has been observed at a high prevalence with a growing number of intoxicated patients. NPS are narcotics or psychoactive drugs (in a pure form or as a preparation) that are not controlled by the Single Convention on Narcotic Drugs of 1961 or the Convention on Psychotropic Substances of 1971, but may pose a public health threat.

At first, the substances were referred to with various names such as street drugs, designer drugs, etc., and then they were referred to as novel psychoactive substances in the US and new psychoactive substances in Europe.[38] Since 2013, these substances are defined as NPS by the United Nations Office on Drugs and Crime (UNODC).[39]

The number of controlled drugs which are regulated under the 1961 UN convention has not changed over the last 50 years. Moreover, the number of controlled drugs regulated under the 1971 UN convention has not changed much either. However, the number of NPS, new substances having diverse chemical groups, spreading to the global NPS market since 2009 continues to increase. More than 100 countries have reported the presence of NPS and more than 739 NPS have been identified,[40] which is almost 3 times higher than the combined number of drugs controlled under the 1961 (120 narcotics) and 1971 (124 psychotropic substances) conventions.

UNODC classifies NPS into 9 groups by their chemical structures: synthetic cannabinoids, phenethylamines, cathinones, piperazines, tryptamines, ketamine, plant-based substances, aminoindanes, and phencyclidine-type substances.[41] Among all NPS, cathinones and phenethylamines are most similar to ATS in their chemical structure, and they were the second and third most commonly used NPS.

Cathinone is a naturally occurring monoamine alkaloid that has a β-ketone functional group on the amphetamine structure. It is an active ingredient of Khat (*Catha edulis*)

and produces amphetamine-like effects.[42] Synthetic cathinones are designer phenethylamines that have emerged in the last decade as abused drugs and were sold as "bath salts" in order to skirt law enforcement regulation.[43] Structurally, many of the synthetic cathinones are similar to MDMA and more than 620 different compounds have been reported.[44,45] Although many synthetic cathinones have been investigated as anorectics, central nervous system stimulants, and antidepressants, their clinical utility has been hindered by problems with abuse and dependence.[46] Circa 1994, methcathinone was listed as a Schedule I drug under the UN Convention on Psychotropic Substances

Although more evidence continues to emerge about the harmful effects of NPS use, data on toxicity, the long-term effects, and risk of use remain limited for many NPS. In addition, as the synthetic methods of these substances are usually unknown, the purity and composition of NPS cannot be guaranteed.

Analysis of ATS

Test for seized ATS

Seized ATS are commonly found as powder, crystalline, or tablets in the form of salts such as hydrochloride, sulfate, or bromide. While illicit amphetamine is frequently encountered as the sulfate salt in powder form, methamphetamine is encountered as the hydrochloride salt in crystalline form, and MDMA as the hydrochloride salt in tablet form.

To identify ATS in seized materials, presumptive tests can be used for a fast screening procedure, and then highly sensitive instruments are essentially required for a confirmation test.[47,48] Presumptive tests can provide an indication of the presence or absence in the samples and eliminate negative results quickly. Color tests using several different reagents are used to test for ATS. The Marquis test, Simon's test, and Chen's test are the most important methods. Amphetamine and methamphetamine produce an orange color with the Marquis test, whereas MDA and MDMA produce a dark blue color. Simon's test reacts with the secondary amine, so methamphetamine produces a deep blue but amphetamine does not react. The Chen test can be used to distinguish ephedrines, which have a β-hydroxyl group on the phenethylamine structure and produce a purple color, from amphetamine and methamphetamine, which do not react with Chen's test.[49]

For a confirmatory test, gas chromatography with flame ionization detector (FID) or nitrogen-phosphorous detector (NPD) and DB-5 capillary column (5% phenyl 95% dimethylpolysiloxane) shows satisfying resolution for ATS. Identification is accomplished by comparing the retention time of the target compound with that of a standard.[50] Gas chromatography with mass spectrometry (GC/MS) is the gold standard to analyze ATS,[51,52] and currently liquid chromatography with mass spectrometry (LC/MS), including tandem MS (LC/MS/MS) and ion trap MS, are commonly used in ATS testing.[53] If a reference standard is unavailable, quadrupole-time-of-flight (QTOF) mass[54,55] and nuclear magnetic resonance (NMR)[56,57] can be useful tools for the identification of ATS.

ATS analysis in biological specimens

Several biological specimens such as urine, hair, oral fluid, and sweat can be used for ATS testing. Urine is the most widely used matrix, although hair, oral fluid, and sweat are good alternate samples for drugs of abuse testing. The advantages of a urine specimen include that it is a well-known specimen, drugs concentrate in the urine, and it is an easy sample to work with.[58-60] The advantage of using oral fluid is that concentrations of drugs in the oral fluid correlate with concentrations of drugs in the blood.[61,62] However, sample collection is not easy. Sweat can be used as an alternative matrix because the parent drug is present in higher concentrations than its metabolites in the sweat.[63,64] However, again it is not easy to collect sweat. Hair has become very popular in drug testing because it makes a good specimen for analyzing long-term exposure to drugs of abuse.[65,66]

Urine is still the best specimen for drug testing. Screening tests can be performed easily with urine using immunoassays. When the presence of drugs is positively identified by immunoassay, a confirmation test using GC/MS or LC/MS should be conducted. For the confirmation test, specimens need to be extracted, derivatized if necessary, and analyzed.

For the extraction, there are several ways to extract the target compounds from the matrix. Liquid- liquid extraction is still very useful and easy method to use, but using solvent is not good for health and extracts may not be clean.[67] Solid phase extraction shows higher selectivity and cleaner extracts but is very costly.[68] There are other extraction methods such as solid supported liquid extraction, which is simple because there is no need for conditioning and washing steps and therefore it can save time.[69] Solid-phase microextraction also can be used, and protein precipitation is typically used for LC/MS analysis.[70,71]

In order to enhance the thermal stability and volatility of analytes, a derivatization procedure is needed for the analysis of ATS by GC/MS. Derivatization of ATS by a fluoroacyl reagent is used to improve the chromatographic characteristics of analytes, and to increase the sensitivity of the assay.[72,73]

In order to provide good results, a quality procedure should be conducted. Accuracy should be within ±20%, less than two standard deviations (2SD) of target concentration, and precision should be within 10% of the coefficient value. The limit of detection and the limit of quantitation need to be measured, sensitivity and linearity should be provided, and selectivity and specificity need to

be shown. The recovery, efficiency, and interferences of the test also need to be provided, and the matrix effect is a critical parameter in LC-MS analysis of biological samples.[74]

Chiral analysis of ATS

Either α- or β- carbon, or both of the two carbons of phenethylamine can be chiral. Most ATS in illicit markets have been encountered as either a single isomer or racemate. The stereoisomers may have different pharmacological actions or levels of pharmacological activities, and their stereochemical properties sometimes create difficulties for forensic analysis.

Methamphetamine has one chiral center resulting in a pair of enantiomers, *d*-(S)-methamphetamine and *l*-(R)-methamphetamine. While the *d*-isomer is the most frequently abused drug, the *l*-isomer is used as a nasal decongestant, and the *d*-isomers of methamphetamine and amphetamine have five times more psychostimulant activity than the *l*-isomers. Although under the 1971 UN Convention on Psychotropic Substances each isomer and racemate are scheduled, in the United States, only the *d*-isomer is a schedule II controlled substance.[75] In South Korea, although both isomers are controlled under the narcotics control law, it is important to distinguish the two isomers in urinalysis because some prescribed medicines can be converted to the *l*-isomer.

For chiral separation of ATS, GC/MS[76,77] and LC-MS/MS[78,79] have been performed. In addition to these methods, capillary electrophoresis[80,81] using cyclodextrins as a chiral selector agent, and supercritical fluid chromatography using a cellulose-based packed column were introduced.[82]

There are two widely used techniques to conduct chiral separation. First, pre-column derivatization with a chiral derivatization reagent (CDR) to make diastereomers is one way. This method is inexpensive and provides high sensitivity, but it is time consuming and the reagents are very sensitive to moisture. The second method is a direct analytical method using a relatively expensive, but easy and time-saving chiral stationary phase column. Figure 3

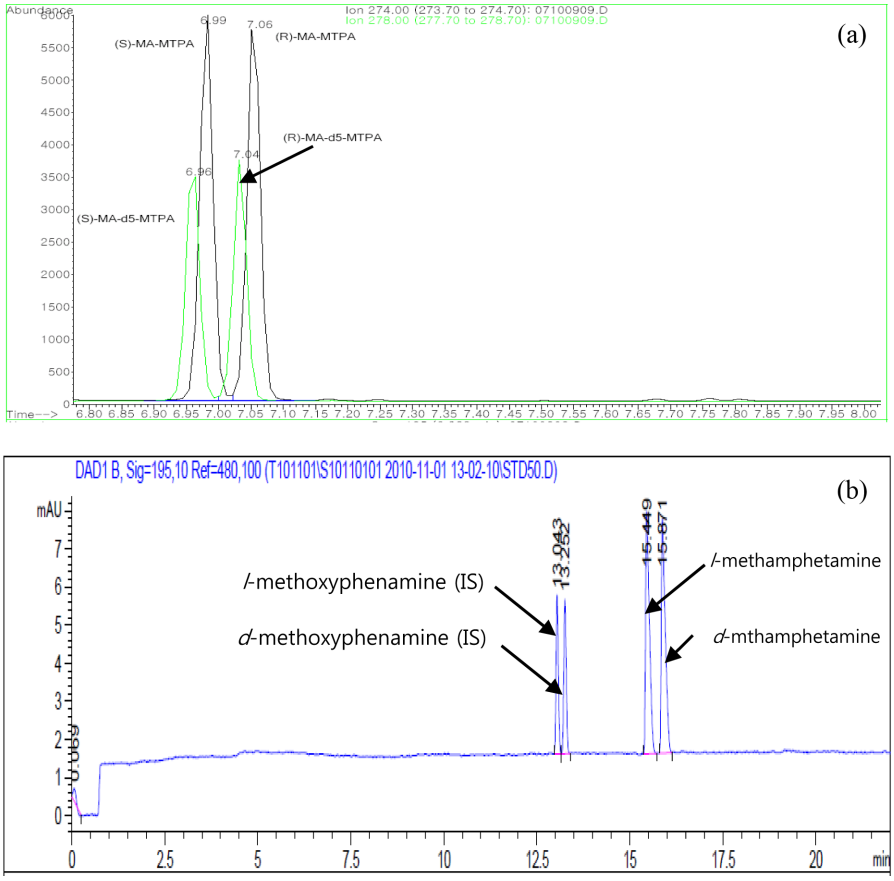

Figure 3. Chiral analysis of *d*- and *l*-methamphetamine. (a) is a chromatogram of GC/MS after (S)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl) derivatization using HP-5MS capillary column and splitless mode. The fragment ion at m/z = 274 is the base ion for MA-MTPA, and m/z = 278 is the base ion for MA-d5-MTPA. (b) is an electropherogram of capillary electrophoresis using 40 mM of 2-hydroxypropyl-β-cyclodextrin in 50 mM phosphate buffer as run buffer.

(a) shows chiral separation after (S)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl) derivatization with GC/MS. A HP-5MS (30 m × 0.25 mm × 0.25 μm) capillary column and splitless mode were used, and 1 μL of prepared sample was injected. Figure 3 (b) shows capillary electrophoresis separation using β-cyclodextrin. 2-Hydroxypropyl-β-cyclodextrin (40 mM) in 50 mM phosphate buffer (pH 2.5) was used as the run buffer, and 50 mg/L of methamphetamine racemate was injected for 2 seconds with 10 mbar pressure.

Interpretation of ATS

Toxicokinetics of ATS

There are several factors that influence the elimination of ATS: individual factors (age, genetics, liver/kidney function, and metabolism), route of administration (intravenous, smoking, intranasal, and oral), frequency, and dose. Among the ATS, amphetamine is most frequently taken orally or intra-nasally in does ranging from 5-15 mg daily in occasional users and 100-2,000 mg daily in habitual users.[83] Methamphetamine is supplied as the hydrochloride salt in 2.5-5 mg tablets, but illicit methamphetamine is usually taken intravenously in doses of 30-45 mg per injection.[84]

Amphetamine peak plasma levels of the oral doses of 2.5-15 mg reached 30-170 mg/L in 2 h, and the plasma elimination half-life ranged from 8 to 12 h.[85] While a single oral dose of 0.125 mg/kg of methamphetamine administered to 6 adults resulted in an average peak plasma concentration of 0.02 mg/L at 3.6 h,[86] an oral dose of 30 mg administered to 10 young men led to an average concentration ranging from 0.062 to 0.291 mg/L at 3-5 h.[87]

Amphetamine and methamphetamine begin to appear in urine within 20 min, and can be detected for a period of 1 to 5 days in urine. The screening cut-off levels of methamphetamine in Korea are fixed at 250 mg/L.[88] Hair testing can be used to test for long-term exposure, and segmental analysis to prove exposure for one year has been reported.[89]

After oral ingestion of methamphetamine, 44% of methamphetamine remains chemically unchanged upon urinary excretion, and between 6% and 20% will be excreted in the form of the major metabolite amphetamine.[90] The concentrations of methamphetamine and amphetamine in the urine of chronic abusers were 1-90 mg/L and 25-300 mg/L, respectively.[91]

Oral fluid is an alternative matrix to plasma and urine biological samples that can be easily collected and used to detect recent use of illicit ATS.[92,93] In some cases, oral fluid drug concentrations reflect concurrent plasma concentrations, and the disposition of methamphetamine showed that the concentration of methamphetamine and metabolite concentrations in oral fluid follow a similar time course as in plasma.[94] Urine drug concentrations were substantially higher than those in oral fluids.

Medicines metabolized to methamphetamine

One of the important points to be considered with the analysis of ATS in biological samples is that several non-proprietary drug preparations used as decongestants and anorectics contain ephedrine and its analogues, which can produce positive results on screening tests using immunoassays because of cross-reactivity. While the false positive case with ephedrine analogs from screening tests can be excluded by a confirmation test, forensic chemists additionally have to check for the presence of parent drug and conduct chiral analysis if a subject took any metabolic precursors of amphetamine or methamphetamine.

Fourteen prescription drugs are known to be metabolized to methamphetamine and amphetamine: benzphetamine, clobenzorex, ethylamphetamine, famprofazone, fencamine, fenethylline, fenproporex, mefenorex, mesocarb, prenylamine, selegiline, amphetaminil, dimethylamphetamine, and furfenorex (Figure 4).[95,96]

In Korea, a 37-year-old man had a considerable concentration of methamphetamine in his urine, but he denied taking any illegal drug. Instead he claimed that he took an OTC pain killer, named “Geworin” that contains famprofazone, whose metabolites include *d*- and *l*-methamphetamine and amphetamine.[97] Chiral analysis was conducted by GC/MS, and *d*- and *l*-isomers of both amphetamine and methamphetamine were detected in his urine.[98] A similar case was reported during a sport competition event in Taiwan. From urine samples, 2688 ng/mL of methamphetamine and 462 ng/mL of amphetamine were detected and the athlete claimed to take “Gewolen” for treating abdominal pain, which also contains famprofazone.[99]

There was another case related to methamphetamine metabolites produced from medicine. Drug testing showed a low level of methamphetamine in a man’s urine by GC/MS in Korea. He had recently taken *l*-deprenyl (selegiline) for the treatment of Parkinson’s disease, and he denied taking any illegal drugs. Deprenyl has been used for the treatment of Parkinson’s disease, and only *l*-isomers of methamphetamine and amphetamine are known metabolites.[100] Enantiomeric separation was performed in his urine, and only *l*-methamphetamine and *l*-amphetamine were detected without any *d*-isomers.

In the US, a patient was accused of abusing an illicit drug, but GC/MS found only *l*-methamphetamine in his urine, confirming he had used Vicks VapoInhaler®, which contains only the *l*-enantiomer. In order to confirm the results, further studies were conducted in the US. Vicks VapoInhaler® was administered to 28 people in accordance with the manufacturer’s directions, and the results showed that no *d*-methamphetamine or *d*-amphetamine was detected in urine at an LOQ of 10 mg/L. Instead, *l*-methamphetamine concentrations were detected in

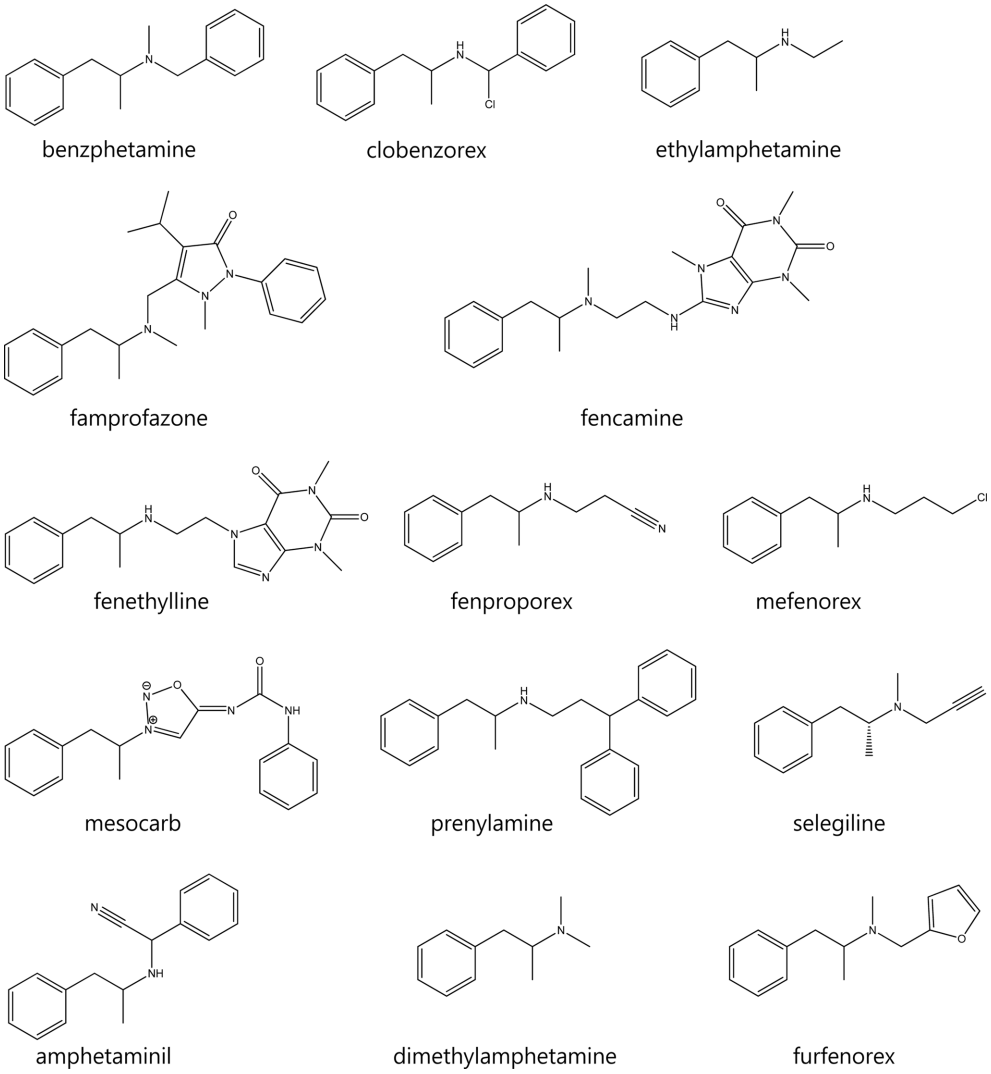

Figure 4. Metabolic precursor medicines of methamphetamine and amphetamine.

concentrations ranging from 11.0 to 1,440 μg/L (the median peak concentration was 62.8 μg/L).[101]

As enantiomers do not change into each other during any metabolic processes in the body (absorption, metabolism, distribution, and excretion), the presence of *l*-isomers of methamphetamine and amphetamine can be utilized to prove the use of legal medicines containing the *l*-isomer or its metabolic precursors.

Conclusion

The abuse of ATS has emerged as a global problem. The abuse of these potent stimulants began to appear in a few countries of North America, Europe and the Far East, gradually spreading to neighboring countries in the respective regions as well as to other regions. In addition to the conventional ATS, the escalating use of NPS including the stimulants phenethylamine and synthetic cathinones was observed with a growing number of intoxicated patients and a high prevalence.

For the detection of ATS in seized materials, presumptive tests using several reagents and confirmation tests using highly sensitive instruments were introduced. Various biological samples including urine, blood, saliva, and hair can be used to prove the abuse of ATS, and useful sample preparation steps are required. Chiral analysis is important in forensics, for which derivatization methods using chiral reagents or chiral separating columns are used.

Developing a fast and efficient analytical method for seized drugs and biological samples would be a great tool to prevent drug smuggling and trafficking, and it would also be able to contribute to making a drug-free society.

Acknowledgement

This work was supported by the National Research Foundation of Korea Grant funded by the Ministry of Science, ICT and Future Planning (NRF-2016M3A9E1918321) and a grant (16182 MFDS 382) from Ministry of Food and Drug Safety, Korea in 2018.

References

1. World Health Organization. *A report from the WHO meeting on amphetamines, MDA and other psychostimulants, Programme on substance abuse division of health and prevention of substance abuse*, World Health Organization: Geneva, **1997**.
2. United Nations Drug Control Program. *Amphetamine-type stimulants : a global review*, United Nations International Drug Control Programme:Vienna, **1996**.
3. United Nations Office for Drug Control and Crime Prevention. *Global illicit drug trends*, United Nations Publication: New York, **1999**.
4. Harro, J. *Int. Rev. Neurobiol*. **2015**, 120, 179.
5. Fasihpour, B.; Molavi, S.; Shariat, S. V. *J. Ment. Health* **2013**, 22, 341.
6. McKetin, R.; McLaren, J.; Lubman, D. I.; Hides, L. *Addiction* **2006**, 101, 1473.
7. Moallem, N. R.; Courteny, K. E.; Ray, L. A. *Drug Alcohol Depend*. **2018**, 187, 1.
8. Niemi-Pynttari, J. A.; Sund, R.; Putkonen, H.; Vorma, H.; Wahlbeck, K.; Pirkola, S. P. *J. Clin. Pshchiatry* **2013**, 74, e94.
9. Kittirattanapaiboon, P.; Mahatnirunkul, S.; Booncharoen, H.; Thummawomg, P.; Dumrongchai, U.; Chutha, W. *Drug Alchol Rev.* **2010**, 29, 456.
10. Ren, W.; Luan, X.; Zhang, J.; Gutteea, P.; Cai, Y.; Zhao, J.; Gu, Y.; Wu, C.; Su, H.; Tao. J.; Xie, Y.; Lv, D.; Feng, L., He, J. *J. Affect. Disord.* **2017**, 221, 164.
11. United Nations Office of Drugs and Crime. United Nations General Assembly, Special session on the world drug problem: New York, **1998**.
12. Edeleano, L. Über einige Derivate der Phenylmethacrylsäure und der Phenylisobuttersäure, In: Berichte der Deutschen chemischen Gesellschaft zu Berlin; 20. Jg. **1887**, Band 3, S. 616.
13. Rassool, G. H. *Alcohol and Drug Misuse: A Handbook for Students and Health Professionals*. Routledge: London. **2009**, 113.
14. Levy, W. O.; Kalidas, K.; Miller, N. S. *Principles of Addictions and the Law: Application in Forensic, Mental Health, and Medical Practice.* Academic Press, **2010**, 307.
15. Rasmussen, N. *J. Hist. Med. Allied Sci.* **2006**, 61, 288.
16. Grobler, S. R.; Chikte, U.; Westraat, J. *ISRN Dentistry* **2011**, 2011, 1.
17. Park, D.; Nordahl, T. *J. Addict Res. Ther.* **2014**, 5, 1.
18. Desoxyn Prescribing Information. United States Food and Drug Administration, **2013**.
19. Hart, C. L.; Marvin, C. B.; Silver, R.; Smith, E. E. *Neuropsychopharmacology* **2012**, 37, 586.
20. Rasmussen, N. *J. Interdiscip. Hist.* **2011**, 42, 205.
21. Defalque, R. J.; Wright, A. J. *Bull. Anesth. Hist.* **2011**, 29, 21.
22. Rasmussen, N. *On Speed: The many lives of amphetamine.* New York University Press, **2008**, 148.
23. Reding, N. *Methland: The death and life of an American small town*. Boomsbury: New York, **2009,** 45.
24. Controlled Substances Act, United States Food and Drug Administration. **2009**, Retrieved 4 November 2013.
25. Convention on Psychotropic Substances, United Nations, **1971**; see https://www.unodc. Org/pdf/convention_1971_en.pdf.
26. Freudenmann, R. W.; Oxler, F., Bernschneider-Reif, S. *Addiction* **2006**, 101, 1241.
27. Sessa, B.; Nutt, D. l. *Br. J. Psychiatery* **2015**, 206, 4.
28. Siegel, R. K. *J. Psychoactive Drugs* **1986**, 18, 349.
29. Karch, S. B.; Drummer, O. H. *Karch's pathology of drug abuse, 5th ed.*. CRC Press, **2016**, 396.
30. Breen, A. R.; Mechan, A. O.; Elliott, J. M.; O'shea, E.; Colado, M. I. *Pharmacol. Rev.* **2003**, 55, 463.
31. Schenk, S.; Foote, J.; Aronsen, D.; Bukholt, N.; Highgate, Q.; Wetering, R.; Webster, *Pharmacol. Biochem. Behav.* **2016**, 148, 38.
32. United Nations Office of Drugs and Crime, *Global illicit drug trends 2001*, United Nations, **2002**.
33. United Nations Office of Drugs and Crime, *The challenge of synthetic drugs in East and South-East Asia, Trends and patterns of amphetamine-type stimulants and new psychoactive substances*, A report from the global SMART Programme, Vienna, **2017**.
34. United Nations Office of Drugs and Crime. *Market analysis of synthetic drugs: Amphetamine-type stimulants, new psychoactive substances, World Drug Report 2017*, United Nations Office of Drugs and Crime. **2018**.
35. Kwon, N. K.; Han, E. *Forensic Sci. Int.* **2018**, 286, 81.
36. United Nations International Drug Control Programme. *Amphetamine-type stimulants: A problem requiring priority attention, United Nations General Assembly, Special session on the world drug problem*, New York, **1998**.
37. Korean Association Against Drug Abuse (KAADA), Statistical results for drugs in Korea, 2014-2016.
38. United Nations Office of Drugs and Crime. What are NPS? See https://www.unodc.org/LSS/Page/NPS.
39. United Nations Office of Drugs and Crime. New psychoactive substances: overview of trends, challenges and legal approaches, **2016.**
40. Law of Republic of Korea: Narcotics Control Act, In: eds., **2016**, Ministry of Food and Drug Safety. See https://elaw.klri.re.kr/eng_service/lawView.do?hseq=37716&lang=ENG
41. United Nations Office of Drugs and Crime. Categories of new psychoactive substances sold in the market. United

Nations Office of Drugs and Crime, **2014**. See https://www.unodc.org/doc/wdr2013/Chp1_F.pdf.
42. Patel, N. B. *East Afr. Med. J.* **2009**, 77, 329.
43. Grecco, G. G.; Kisor, D. F.; Magura, J. S.; Sprague, J. E. *Toxicol. Appl. Pharmacol.* **2017**, 328, 18.
44. Guirguis, A.; Corkery, J. M.; Stair, J. L.; Kirton, S. B.; Zloh, M.; Schifano, F. *Hum. Psychopharmacol.* **2017**, 32.
45. Hayashi K.; Wakabayashi C.; Ikushima Y.; Tarui M. *Subst. Abuse Treat Prev. Police* **2017**, 12, 91.
46. Capriola, M. *Clin. Pharmacol*. **2013**, 5, 109.
47. Velapoldi, R. A.; Wicks, S. A. *J. Forensic Sci*., **1994**, 19, 636.
48. O'Neal C. L.; Crouch D. J.; Fatah A. A. *Forensic Sci. Int*. **2000**, 109, 189.
49. United Nations Office of Drugs and Crime. *Recommended methods for the identification and analysis of amphetamine, methamphetamine, and their ring-substituted analogues in seized materials*, United Nations Office of Drugs and Crime: New York, **2006**.
50. Miyaguchi, H.; Tokeshi, M.; Kikutani, Y.; Hibara, A.; Inoue, H.; Kitamori, T. *J. Chromatogr. A* **2006**, 1129, 105.
51. Bodnar Willard M. A.; McGuffin, V. L.; Smith, R. W. *Forensic Sci. Int.* **2017**, 270, 111.
52. Souza, D. Z.; boehl, P. O.; Comiran, E.; Mariotti, K. C.; Pechansky, F.; Duarte, P.; Boni, R. D.; Froehlich, P. E.; Limberger, R. P. *Anal. Chim. Acta* **2011**, 696, 67.
53. Lehmann, S.; Kieliba, T.; Beike, J.; Thevis, M.; Mercer-Chalmers-Bender, K. *J. Chromatogr. B* **2017**, 1064, 124.
54. Baz-Lomba, J. A.; Reid, M. J.; Thomas, K. V.; *Anal. Chim. Acta* **2016**, 914, 81.
55. Madireddy, S. B., Bodeddula, V. R.; Mansani, S. K.; Wells, M. J.; Boles, J. O. *J. Hazard. Mater.* **2013**, 254, 46.
56. Machado, Y.; Neto, J. C.; Barbosa, P. E. N.; Lardeiro, R. A.; Alves, R. B. *Forensic Sci. Int.* **2017**, 275, 302.
57. Taschwer, M.; Weiβ J. A.; Kunert, O.; Schmid, M. G. *Forensic Sci. Int.* **2014**, 244, e56.
58. Alsenedi, K. A.; Morrison, C. *J. Chromatogr. B* **2018**, 1076, 91.
59. Chen, P.; Chen, S.; Chen, J.; Hanung, W.; Liu, H.; Kong, P.; Yang, O. H.; *Anal. Chim. Acta* **2016**, 946, 1.
60. Mercieca, G.; Odoardi, S.; Cassar, M.; Rossi, S. S. *J. Pharm. Biomed. Anal.* **2018**, 149, 494.
61. Gjerde H.; Langel K.; Favretto D.; Verstraete A. G. *Forensic Sci. Int.* **2015**, 256, 42.
62. Quintela O.; Cruz A.; Castro A.; Concheiro M.; López-Rivadulla M. *J. Chromatogr. B* **2005**, 825, 63.
63. Koster R. A.; Alffenaar J. W.; Greijdanus B.; VanDerNagel J. E.; Uges D. R. *Ther. Drug Monit.* **2014**, 36, 35.
64. Fucci N.; De Giovanni N.; Scarlata S. *Forensic Sci. Int.* **2008**, 174, 107.
65. Martins, L. F.; Yegles, M.; Thieme, D.; Wenning, R. *Forensic Sci. Int.* **2008**, 176, 38.
66. Lee, S.; Park, Y.; Yang, W.; Han, E.; Choe, S.; In, S.; Lim, M.; Chung, H. *J. Chromatogr. B* **2008**, 865, 33.
67. Beckett, A. H.; Rowland, M. *J. Pharm. Pharmacol.* **1965**, 109s.
68. Chen, X.; Wijsbeek, J.; Veen, J. V.; Franke, J. P.; De Zeeuw, R. A. *J. Chromatogr. B* **1990**, 529, 161.
69. Maquille A.; Guillarme D.; Rudaz S.; Veuthey J. *Chromatographia* **2009**, 70, 1373.
70. Theodoridis, G.; Koster, E. H. M.; De Jong, G. J. *J. Chromatogr. B* **2000**, 745, 49.
71. Myung, S.; Min, H.; Kim, S.; Kim, M.; Cho, J.; Kim, T. *J Chromatogr. B* **1998**, 716, 359.
72. Hornbeck, C. L.; Czarny, R. J. *J. Anal. Toxicol* **1989**, 13, 251.
73. Lee, S.; Han, E.; Park, Y.; Choi, H.; Chung, H. *Forensic Sci. Int.* **2009**, 190, 1.
74. Peters, F. T.; Drummer, O. H.; Musshoff, F. *Forensic Sci. Int*, **2007**, 165, 216.
75. Shu, I.; Alexander, A.; Jones, M.; Jones, J.; Negrusz, A. *J. Chromatogr. B* **2016**, 128, 145.
76. Souza, D. J.; Boehl, P. O.; Comiran, E.; Mariotti, K. C.; Pechansky, F.; Duarte, P. C.; De Boni, R.; Froehlich, P. E.; Limberger, R. P. *Anal. Chim. Acta* **2011**, 696, 67.
77. Raihana, W. W.; Gana, S. H.; Tan, S. C. *J. Chromatogr. B* **2011**, 879, 8.
78. Wang, T.; Shen, B.; Shi, Y.; Xiang, P.; Yu, Z. *Forensic Sci. Int.* **2015**, 246, 72.
79. Al-Dirbashi, O.; Wada, M.; Kuroda, N.; Inuduka, S.; Nakashima K. *Biomed. Chromatogr.* **1999**, 13, 543.
80. Scarcella, D.; Tagliaro, F.; Turrina, S.; Manetto, G.; Nakahara, Y.; Smith, F. P.; Marigo M. *Forensic Sci. Int*. **1997**, 89, 33.
81. Tagliaro, F.; Manetto, G.; Bellini, S.; Scarcella, D.; Smith, F. P.; Marigo, M. *Electrophoresis* **1998**, 19, 42.
82. Segawa, H.; Iwata, Y. T.; Yamamuro, T.; Kuwayama, K.; Tsujikawa, K.; Kanamori, T.; Inoue, H. *Forensic Sci. Int*. **2017**, 273, 39.
83. De Cresce, R.; Mazura, A.; Lifshitz, M.; Tilson, J. *Drug testing in the workplace*, American Society of Clinical Pathology Press: Chicago, **1989**, 108.
84. Han, E.; Lee, S.; In, S.; Park, M.; Park, Y.; Cho, S.; Shin, J.; Lee, H. *Forensic Sci. Int.* **2015**, 254, 59.
85. Kwong T. C.; Chamberlain R. T.; Frederick D. L.; Kapur B.; Suhchine I. *Clin. Chem.* **1988**, 34, 605.
86. Cook, C. E.; Jeffcoat, A. R.; Sadler, B. M.; Hill, J. M.; Voyksner, R. D.; Pugh, D. E.; White, W. R.; Perez-Reyes, M. *Drug Metab. Dispos.* **1992**, 20, 856.
87. Shappel, S. A.; Kearns, G. L.; Valentine, J. L.; Neri, D. F.; DeJohn, C. A. *J. Clin. Pharmacol*. **1996**, 36, 1051.
88. Choi, H.; Choi, S.; Park, M.; Son, H.; Kim, E.; Han, E.; Chung, H. *Kor. J. Forensic Sci.* **2002**, 3, 139.
89. Lee, S.; Han, E.; Park, Y.; Choi, H.; Chung, C. *Forensic Sci. Int*. **2009**, 190, 16.
90. Caldwell, J.; Dring, L. G.; Williams, R. T. *Biochem. J.* **1972**, 129, 11.
91. Beckett, A. H.; Rowland, M. *J. Pharm. Pharmacol*. **1965**, 109s.
92. Bosker, W. M.; Heustis, M. A. *Clin. Chem.* **2009**, 55, 1910.
93. Drummer, O. H. *Clin. Biochem. Rev.* **2006**, 27, 147.

94. Scheidweiler, K. B.; Huestis, M. A. *J. Chromatogr. B* **2006**, 835, 90.
95. Cody, J. T. *Forensic Sci. Rev.* **1993**, 5, 109.
96. United Nations Office of Drugs and Crime. *Recommended methods for the detection and assay of heroin, cannabinoids, cocaine, amphetamine, methamphetamine and ring-substituted amphetamine derivatives in biological specimens*, United Nations Office of Drugs and Crime: New York, **1995**.
97. Oh, E. S.; Hong, S. K.; Kang, G. I. *Xenobiotica* **1992**, 22, 377.
98. Yoo, Y. C.; Chung, H. S.; Choi, H. K. *J. Anal. Toxicol*. **1994**, 18, 265.
99. Tseng, Y. L.; Lin, C. T.; Wang, S. M.; Liu, R. H. *J. Forensic Sci.* **2007**, 52, 479.
100. La Croix, R.; Pianezzola, E.; Strolin Benedetti, M. *J. Chromatogr. B* **1994**, 656, 251.
101. Smith, M. L.; Nichols, D. C.; Underwood, P.; Fuller, Z.; Moser, M. A.; Flegel, R.; Gorelick, D. A.; Mewmeyer, M. N.; Concheiro, M.; Huestis, M. A. *J. Anal. Toxicol.* **2014**, 38, 524.

