Electrochemical sensing of amphetamine-type stimulants (pre)-precursors to fight against the illicit production of synthetic drugs

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Abstract

The illicit drug precursor market for the manufacture of amphetamine-type stimulants (ATS), mainly amphetamine, methamphetamine and methylenedioxymethamphetamine (MDMA), has emerged quickly in the last years. The evidence of a more complex and sophisticated drug market underlines the pressing need for new on-site methods to quickly detect precursors of synthetic drugs, with electrochemical analysis as a promising technique. Herein, the electrochemical fingerprints of ten common ATS precursors- 3-oxo-2-phenylbutanenitrile (APAAN), 3-oxo-2-phenylbutanamide (APAA), methyl 3-oxo-2-phenylbutanoate (MAPA), benzyl methyl ketone (BMK), 1-(1,3-benzodioxol-5-yl)propan-2-one (PMK), ephedrine, pseudoephedrine, safrole, sassafras oil and piperonal- are reported for the first time. The electrochemical screening disclosed the redox inactivity of BMK, which is an

essential starting material for the production of ATS. Therefore, the local derivatization of BMK at an electrode surface by reductive amination is presented as a feasible solution to enrich its electrochemical fingerprint. To prove that, the resulting mixture was analyzed using a set of chromatographic techniques to understand the reaction mechanism and to identify possible electrochemical active products. Two reaction products (i.e. methamphetamine and 1-phenylpropan-2-ol) were found and characterized using mass spectrometry and electrochemical methods. Subsequently, the optimization of the reaction parameters was carefully addressed to set the portable electrochemical sensing strategy. Ultimately, the analysis concept was validated for the qualitative identification of ATS precursors in seizures from a forensic institute. Overall, the electrochemical approach demonstrates to be a useful and affordable analytical tool for the early identification of ATS precursors to prevent trafficking and drug manufacture in clandestine laboratories.

Keywords

Electrochemical fingerprint, screen-printed electrodes, forensics, amphetamine-type stimulants, BMK

1. Introduction

The diversity and availability of chemical starting materials, known as drug precursors, needed to manufacture illicit drugs allow their production to occur anywhere.[1] This has a large impact on the local drug market and the production activities used in illicit laboratories.[2] In the period from 2015 to 2019 approximately 24000 clandestine laboratories were dismantled worldwide, with more than 98% primarily manufacturing amphetamine-type stimulants (ATS), meaning 95% manufacturing methamphetamine; 2% amphetamine; and 1% MDMA (**Figure 1**).[3] ATS appear

prominently in drug markets worldwide, with interconnected and complex global patterns, leading to a wide-range impact on both security and public health.[4] The emergence of these chemical precursors to produce ATS promotes the development of the international precursor control system.[5] This is a key component to disrupt the manufacturing chain in the early stages and avoid precursor and ATS distribution. Despite such regulations and controls, there is still a discrepancy between the low quantities of precursors seized (i.e. 31 Mt of ATS-related precursor chemicals were seized in 2008) and the increase in ATS-consuming users (i.e. 47.4 Mt of ATS seizures were confiscated in 2008), providing enough evidence to confirm that most of the trafficking of precursors needed for the manufacture of ATS goes undetected.[6] This means that criminal organizations rapidly seek alternative strategies to circumvent the international regulations and continue with the illicit manufacture.[7] Lately, various approaches have been used to produce synthetic drugs or their precursors with alternative chemicals that are not listed as illicit drugs or drug precusors.[8] One approach involves utilizing derivatives or new forms of chemicals such as N-protected derivatives of drugs that are outside international control and that can be easily converted into illicit drugs.[9,10] Another approach relies on the illicit production of precursors from a non-controlled substance (e.g. benzyl methyl ketone –BMK– from 3-oxo-2-phenylbutanenitrile –APAAN–, 3-oxo-2-phenylbutanamide –APAA– or methyl 3-oxo-2-phenylbutanoate –MAPA–) (**Figure 1**). This situation is constantly evolving and requires new advances that address the challenges of the rapid detection and identification of precursors to gain more insights on the ATS market and map their production, distribution and use.[11]

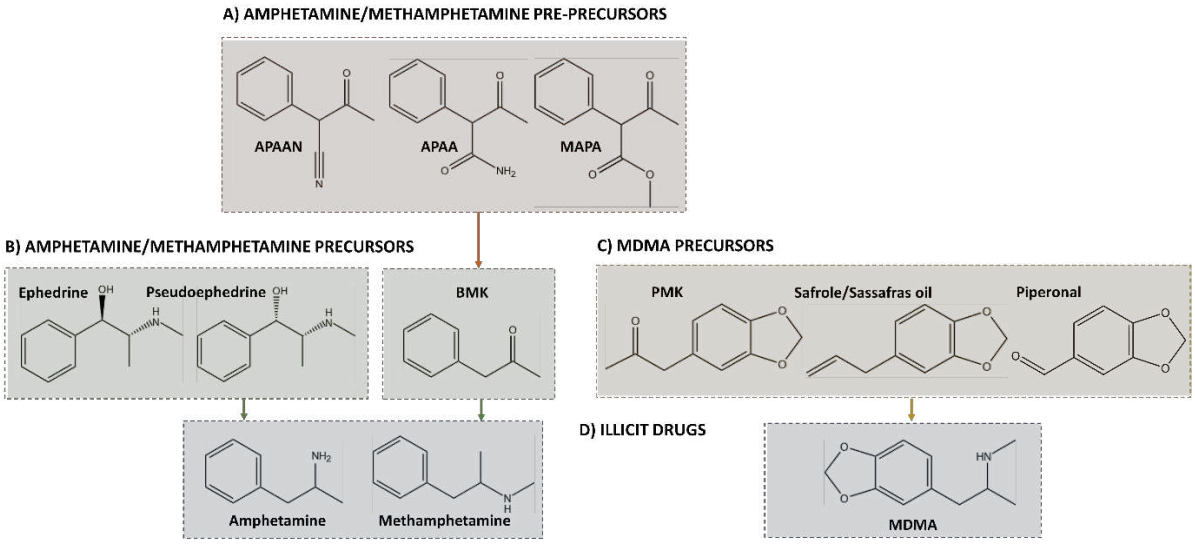

Figure 1. Main precursors in ATS production: A) Chemical structures of amphetamine/methamphetamine pre-precursors (highlighted in orange). B) Chemical structures of amphetamine/methamphetamine precursors (highlighted in green). C) Chemical structures of MDMA precursors (highlighted in yellow). D) Chemical structures of illicit drugs (highlighted in blue).

Nowadays, the methods used to detect ATS precursors are mainly based on a screening test followed by a confirmatory analysis. Concerning on-site detection, chemical color tests are the most common kits employed by law enforcement agents.[12–14] This presumptive test employs chemicals to react with functional groups of drug precursors to form a colored compound that can be visually evaluated. Despite this simple procedure, the effectiveness of the analysis in terms of sensitivity and specificity in decentralized settings can be dramatically reduced by drug concentration, the color of the suspected sample and the increasing number of cutting agents within pills.[15] In fact, the predominant color should be a result of the color change induced by the analytes and other substances present in the sample. Furthermore, the analysis is limited to a subjective interpretation of the results which depends on the experience of the analyst.

To overcome these drawbacks, current gold standards in forensic analysis such as expensive gas/liquid-chromatography coupled with mass spectrometry, sophisticated spectroscopic methodologies (i.e. Fourier-transform infrared spectroscopy –FTIR– and Raman spectroscopy) or time-consuming nuclear magnetic resonance analyses serve as highly accurate and sensitive confirmatory tests.[16–21] In these cases, the samples are analyzed and the results are then compared with a reference library of known substances.[22] Unfortunately, these techniques are constrained by the existing compounds on the library, laboratory settings and qualified personnel which makes them unsuitable for on-site scenarios where rapid decision making is paramount of importance.

Today, the electrochemical detection of illicit drugs is being exploited due to their relevant advantages for fast on-site analysis of suspicious samples i.e. affordability, portability, sensitivity and selectivity.[23,24] Particularly, the electrochemical fingerprint approach, in which the analyte is identified based on the electrochemical pattern in a given analytical context, has proved to be an effective alternative for the detection of illicit drugs.[25] So far, this analytical strategy has been reported for the selective detection of heroin, ketamine, cocaine and ATS.[26–30] Nevertheless, the electrochemical sensing of ATS is still a challenging area. The structural similarity of ATS compounds (i.e. amine moiety present in their structure) and the high potential values required for amine oxidation, restricts the selectivity of these sensors. For these reasons, different approaches have been recently introduced which proved to improve the selectivity of the sensors for ATS substances such as derivatizations.[29] Interestingly, Dennany *et al.* also demonstrates that electrochemiluminescence is a viable technique to develop on-scene sensors for the selective identification of amphetamine and methamphetamine.[31,32] Concerning the electrochemical detection

of ATS precursors, there is limited literature regarding the electrochemical detection of ATS precursors. To illustrate, **Table S1** compiles some electrochemical methods for the detection of ATS precursors that have been reported to date. Mostly, the state of the art on ATS precursors is focused on ephedrine analysis. Moreover, the proposed electrochemical strategies use complex modifications of the electrodes and are mainly, analytically validated in pharmaceutical dosages, biological fluids and wastewater. For example, the use of molecularly imprinted polymer for selective ephedrine detection [33] or by using nanomaterials.[34] Importantly, there is still no work that exploits the electrochemical fingerprint of ATS precursors for their identification and confiscation in the illegal market. Therefore, the development of electrochemical methods to detect ATS precursors opens new possibilities to prevent drug trafficking and contribute to the security of nations.

The present work shows for the first time the electrochemical fingerprint of ATS precursors intended for their early detection in seized samples. A collection of ten precursors: three pre-precursors of amphetamine/methamphetamine –APAAN, APAA and MAPA–, three precursors of amphetamine/methamphetamine –ephedrine, pseudoephedrine and BMK–, and four precursors of MDMA –1-(1,3-benzodioxol-5-yl)propan-2-one (PMK), safrole, sassafras oil and piperonal– are selected in this study according to their relevance in the synthetic production of ATS.[35] First, the electrochemical behavior is investigated by square wave voltammetry (SWV) on graphite screen-printed electrodes (SPEs) in a wide range of pHs. The electrochemical screening revealed the redox inactivity of BMK in contrast to the unique electrochemical profile for the other precursors under study. Therefore, inspired by the strategy to convert redox inactive molecules into oxidizable products at carbon SPEs in our group,[29,36] a derivatization process for this molecule is explored to provide a

suitable identification by low-cost electrochemical techniques. It is well known that the reductive amination of carbonyl compounds is an attractive method in organic synthesis for the transformation of ketones to the corresponding amine analogs.[37] Therefore, the direct reductive amination proves to be a feasible approach for the conversion of BMK to an electrochemically active compound containing an amine group, i.e. methamphetamine. Typically, the in-situ formation of C-N bond is achieved by mixing the precursor containing a ketone group with a primary amine such as methylamine (CH_3NH_2 or $MeNH_2$) in the presence of a reducing agent (i.e. $NaBH_4$) in an organic solvent.[38] Subsequently, liquid chromatography coupled to quadrupole time-of-flight mass spectrometry (LC-QTOFMS) was used to confirm the nature and structure of the resulting products and consequently, to elucidate the reaction mechanism of the process. Besides, the results were correlated with the electrochemical signals obtained during the derivatization process. Thereafter, the optimization of the reaction parameters was carefully addressed to set the electrochemical sensing strategy. Ultimately, the principle was applied for the qualitative identification of confiscated samples that were validated by gas chromatography coupled to mass spectrometry (GC-MS) provided by a forensic institute. Besides, the results of the electrochemical approach are compared with the ones obtained with another portable technique i.e. FTIR, showing a more accurate qualitative detection for the electrochemical analysis. Overall, the electrochemical fingerprint demonstrates to be a useful analytical tool that can be efficiently integrated with the analysis by law enforcement agents in the field, helping to extend the knowledge on the ATS market and supply.

2. Material and methods

2.1. Materials

Standards of 3-oxo-2-phenylbutanamide (APAA), 3-oxo-2-phenylbutanenitrile (APAAN), methyl 3-oxo-2-phenylbutanoate (MAPA), benzyl methyl ketone (BMK), 1-(1,3-benzodioxol-5-yl)propan-2-one (PMK), ephedrine, pseudoephedrine, piperonal, safrole, sassafras oil and methamphetamine hydrochloride were provided by National Institute for Criminalistics and Criminology (NICC, Belgium). Confiscated samples were also provided by NICC. Qualitative analysis of the confiscated samples was performed by using gas chromatography/mass spectrometry (GC-MS).

Analytical grade salts of potassium chloride (KCl), potassium dihydrogen phosphate monobasic (KH_2PO_4) and potassium hydroxide (KOH) were purchased from Sigma-Aldrich (Overijse, Belgium). 40% solution methylamine ($MeNH_2$) in water, 1-phenylpropan-2-ol, sodium borohydride ($NaBH_4$) and ethanol were obtained from Sigma-Aldrich (Overijse, Belgium), and used without further purification for the derivatization process.

Electrochemical measurements were performed in phosphate buffer saline (PBS) containing 20 mM KH_2PO_4 and 100 mM KCl. pH screening was performed in 60 mM Britton-Robinson buffer with 100 mM KCl. All solutions were prepared in 18.2 MΩ cm^{-1} doubly deionized water (Milli-Q water systems, Merck Millipore). The pH was measured using a pH-meter (914 pH/Conductometer, 2.914.0020, Metrohm, Switzerland). Adjustment of the pH was performed using concentrated KOH and HCl solutions.

2.2. Electrochemical method

Square wave voltammograms were recorded using a MultiEmStat3 potentiostat (PalmSens, The Netherlands) with MultiTrace. Disposable Italsens graphite screen-printed electrodes (SPEs) (PalmSens, Netherlands), containing a graphite working electrode (Ø = 3 mm), a carbon counter electrode, and a pseudo silver reference electrode (Ag/AgCl) were used for all measurements except for those related to BMK derivatization. In-house SPEs were employed for BMK derivatization measurements: A semi-automatic screen-printing machine is used to fabricate the SPEs based on carbon working (Ø = 3 mm) and counter electrodes, and a Ag/AgCl reference electrode on PET film. First, Ag/AgCl patterns are printed and cured at 120 °C for 10 min in a box oven. Thereafter, carbon patterns are printed and subsequently cured at 120 °C for 5 min in a box oven. Finally, the dielectric pattern is printed on top and cured with a UV oven. The SWV parameters that were used: potential range of -0.1 to 1.5 V, frequency 10 Hz, 25 mV amplitude and 5 mV step potential. Most of the voltammograms are background corrected using the “moving average correction” (peak width=1) tool in the PSTrace software to get the values of peak potential (Ep) and peak intensity (Ip).

Electrochemical measurements were performed with the corresponding buffers containing 100 mM KCl by applying 80 µL of the solution onto the SPE.

2.3. BMK derivatization by reductive amination

The derivatization process of BMK was investigated following a synthesis protocol found in the literature [38]. It is well known that after mixing the reagents, the ketone group of BMK reacts with the primary amine of $MeNH_2$ in presence of a hydride source ($NaBH_4$) that reduces the in-situ formed imine leading to a product which contains a

secondary amine, known to be electroactive in the potential window of a graphite SPE.[39]

Reaction samples for preliminary HPLC investigations and LC-QTOFMS were prepared by mixing BMK and $MeNH_2$ in ethanol for 48 h at room temperature to form an imine product. Subsequent reduction of this imine product by adding dropwise $NaBH_4$ at 0 ºC produces the alkylated secondary amine (**Figure S1A**). However, the temperature and the reaction time were adjusted to room temperature and four minutes (two minutes for each imine and secondary amine formation) to take into account on-site applicability. This adjusted protocol was used for further HPLC and electrochemical analysis.

2.4. HPLC analysis

HPLC chromatograms were collected on a Shimadzu HPLC-diode array detector (DAD) system (Kyoto, Japan) consisting of an autosampler SIL-20AC HT, an integrator CBM-20A, a gradient pump LC-20AT, a degassing unit DGU-20A5R and a DAD SPD-M20A. Data acquisition and processing were completed with LabSolutions software (Shimadzu). The separation column used in this work was a 100 x 4.6 mm, 2.6 µm diameter particles, 100 Å, Kinetex C-18 LC column from Phenomenex (California, United States). The injection volume was 25 µL. Mixtures of acetonitrile (≥99.9% purity from Sigma Aldrich), water and orthophosphoric acid (85% purity from Sigma Aldrich), whose composition was adjusted according to a gradient profile, served as eluents. Mobile phase A consisted of 0.07% orthophosphoric acid in ultrapure water, and mobile phase B consisted of 0.07% orthophosphoric acid in acetonitrile:ultrapure water at a ratio of 80:20). The gradient started at 0 min at 2% B,

from 0 to 13 min: 2% B to 100% B, from 13 to 15 min: 100% B, from 15 to 15.1 min: 2% B and finally, from 15.1 until 22 min 2% B. The flow rate was set at 1 mL min^{-1}.

2.5. LC-QTOFMS analysis

The chromatography-mass spectrometry experiments were performed on a liquid chromatograph coupled to a quadrupole time-of-flight mass spectrometer (LC-QTOFMS) using electrospray ionization (ESI) in positive mode. The apparatus consisted of a 1290 Infinity LC (Agilent Technologies, Wilmington, DE, United States) connected to a 6530 Accurate-Mass QTOF-MS (Agilent Technologies) with a heated-ESI source (JetStream ESI). Further information on the LC-QTOFMS conditions can be found in the Supporting Material.

2.6. ATS precursors qualitative detection in confiscated samples

A solution of 20 mg mL^{-1} or 20 µL mL^{-1} of the suspicious substance was prepared in ethanol, which was later diluted in buffer (10-fold) to achieve a (pre)-precursor concentration of ca. 10 mM. First, PBS pH 7 was used to identify MDMA precursors. Later, if no peak was observed a consecutive analysis at PBS pH 12 was performed to detect amphetamine and methamphetamine (pre)-precursors. Finally, if still no peak was shown in the electrochemical data, 20 µL of the unknown substance were used for the derivatization reaction under the optimal conditions, followed by the electrochemical analysis in PBS pH 12 to identify BMK (**Figure 2**).

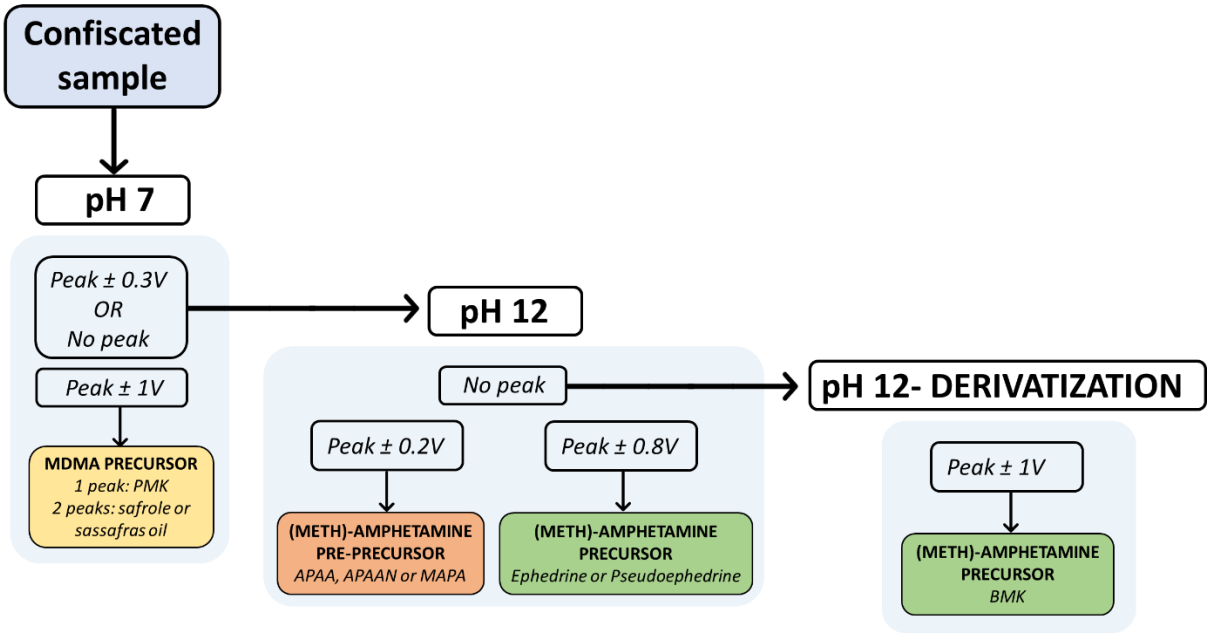

Figure 2. Flowchart towards the electrochemical detection of ATS precursors.

For validation purposes, a portable Attenuated Total Reflectance (ATR) FTIR spectrometer (Bruker Alpha 2, UK with a diamond crystal) was used to analyze the confiscated samples from precursors. For each spectrum, 128 scans were accumulated at 4 cm^{-1} spectral resolution, the wavenumber range was between 4000 and 475 cm^{-1}. The analysis of the spectrum by a main component (in some cases a mixture of 2 compounds analysis was needed) has been done using the OPUS 8.2 software loaded with the TICTAC Drug Library (TICTAC Communications Ltd., London, United Kingdom).

3. Results and discussion

3.1. Electrochemical behavior of the ATS (pre)-precursors at carbon SPEs

In this section, the electrochemical fingerprints of ATS (pre)-precursors (**Figure 1**) were evaluated in a wide range of pHs (i.e. from 5 to 12) by using universal Britton-Robinson buffer (**Figure 3**). Note that a phosphate buffer with higher buffering capacity was chosen for further experiments in the selected pH. Hence, an aliquot of 100 mM

stock solution of the corresponding (pre)-precursors was diluted into the buffer to obtain a concentration of 10 mM and interrogated by SWV. In general, as the pH increases from pH 5.0 to pH 12.0, the electrochemical signals based on the oxidation of each target at the surface of the SPE shift to more negative potentials, showing a pH dependence on the electrooxidation of each compound (**Figure S2**). Understanding the electrooxidation at certain conditions (i.e. pH) allows the development of specific electrochemical strategies for the selective detection of (pre)-precursors.

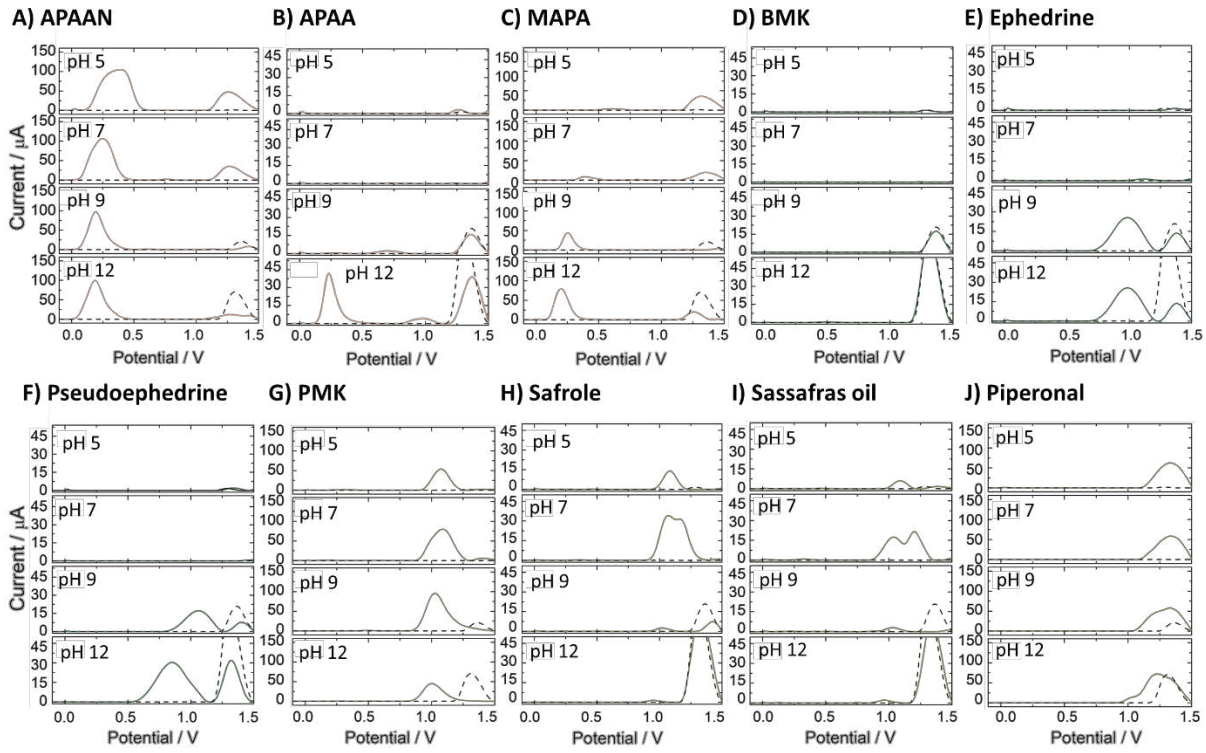

Figure 3. pH screening (from pH 5 to 12 in Britton-Robinson buffer) of 10 mM amphetamine/methamphetamine pre-precursors (A-C, orange), amphetamine/methamphetamine precursors (D-F, green) and MDMA precursors (G-J, yellow) at SPEs by SWV. The black dotted line indicates the blank of Britton-Robinson buffer at the selected pHs. Potentials refer to a Ag/AgCl reference electrode.

3.1.1. Amphetamine/methamphetamine (pre)-precursors electrochemical behavior at SPEs

Figure 3 indicates that in the case of amphetamine and methamphetamine (pre)-precursors, pH 12 seems the best condition since it shows enriched fingerprints (i.e. a compromise between the number of signals and the intensity of all compounds).

APAAN shows an electrochemical oxidation at Ep 0.23 V (vs. Ag/AgCl), as well as APAA and MAPA pre-precursors since they are structurally related analogs. It is important to mention that APAA shows other oxidation processes occurring with very low intensities, that is why these signals will not be used for the electrochemical detection of this compound. As expected, ephedrine and pseudoephedrine exhibit an oxidation peak at Ep 0.90 and 0.85 V (vs. Ag/AgCl) respectively, that might be attributed to the oxidation of the secondary amine present in their core structure (**Figure 1**), into a primary amine product. Indeed, a similar oxidation process has been previously reported for the electrochemical detection of illicit drugs containing secondary amines such as methamphetamine or ketamine with a Ep at 0.80 V 0.95 V (vs. Ag/AgCl), respectively.[27,30,40]

Special attention was put on the electrochemical fingerprint of BMK since it does not exhibit any electrochemical process. Hence, a flat line was observed in its electrochemical profile over all range of pHs. Potential solutions to enrich the fingerprint are assessed to unravel the presence of BMK precursor in section 3.2.

3.1.2. MDMA precursors electrochemical behavior at SPEs

Under the same conditions, MDMA precursors, i.e. PMK, safrole, sassafras oil and piperonal (**Figure 1**), were interrogated varying the pH with pH 7 displaying the richest electrochemical fingerprint. At pH 7, a first peak was observed for PMK, safrole and

sassafras oil around Ep 1.07 V (vs. Ag/AgCl). These results showed an agreement with the work published by Cumba *et al.* where the oxidation of the methylenedioxy group present in MDMA was reported.[41] This group is also commonly found in the precursors as it is the characteristic group of MDMA. However, a second peak at Ep 1.17 V (vs. Ag/AgCl) was also observed for safrole and sassafras oil precursors.[42] It is suggested that this peak is the result of further oxidation of the polymeric species from the radical cation generated during the first oxidation process.[43] Interestingly, piperonal displayed an oxidation peak at Ep 1.33 V (vs. Ag/AgCl) showing a shift of the expected oxidation peak from the methylenedioxy group. This difference in terms of peak potential may be attributed to the nature and electrophilic properties of the substituted aromatic ring.[44] This hypothesis was proved also by Garrido *et. al* where the effect of a methyl group in the aromatic nucleus was shown. In their work, the electrochemical behavior of 1,2-(methylenedioxy)benzene and 3,4-(methylenedioxy)toluene was studied at pH 7. The work demonstrate that a methyl group in the aromatic nucleus affects significantly the stabilization of the radical cation formed and therefore, it produced a potential shift towards negative values due to the electron donating effect of this methyl group.[45]

3.2. BMK derivatization by reductive amination

As shown in **Figure 3**, BMK, an important precursor of amphetamine and methamphetamine, does not exhibit any oxidation process at graphite SPE in the pH range from 5 to 12. Therefore, a derivatization method is performed to locally generate an oxidizable product at the electrode surface that can be unraveled by electrochemistry (**Figure S1**). To confirm the efficiency of the selected derivatization process, preliminary HPLC analyses were performed by studying the reaction mixture with an excess of reducing agent according to the reaction found in the literature

(**Figure S1A**).[38] In short, BMK and $MeNH_2$ were mixed in ethanol for 48 h at room temperature to form an imine product. Then, $NaBH_4$ was added at 0 °C to reduce the imine product formed and in-situ generate the secondary amine. **Table S2** provides an overview of all the products identified in the derivatization process of BMK with their corresponding structure and additional information. The chromatographic separation resulting under the specified conditions is depicted in **Figure S1B**. Under these conditions, BMK was converted in two main products with t_{R1} 6.42 min (methamphetamine) and t_{R2} 9.78 min (1-phenylpropan-2-ol) during the chemical derivatization.

This reaction was then adapted to on-site requirements, i.e. room temperature and four min of reaction time for a fast analysis (**Figure 4**). It was found that there were still fewer amounts of unreacted BMK present (t_R at 10.35 min) suggesting that more reaction time or higher temperatures are needed to complete the reaction. However, the findings suggest that small variations in the protocol successfully lead to the same products and that within the timeframe of on-site analyses enough derivatization takes place to allow characterization. The first product that elutes at t_{R1} 6.42 min was confirmed to be methamphetamine by HPLC and by LC-QTOFMS analysis by comparing the retention time and the fragmentation pattern spectrum with a standard of methamphetamine (**Figure S3-S5**).

On the other hand, the second product at t_{R2} 9.78 min. may correspond to 1-phenylpropan-2-ol, formed during the side-reaction of BMK with $NaBH_4$ (**Figure 4A**), as the retention time is identical to its standard (**Figure S3**). In this case, no additional LC-QTOFMS analyses could be performed due to the low ionization efficiency of the 1-phenylpropan-2-ol product in positive ion mode ESI mode.[46]

Overall, the derivatization reaction of BMK at room temperature and four minutes reaction time was elucidated by HPLC and LC-QTOFMS showing the formation of methamphetamine and most probably, 1-phenylpropan-2-ol. Importantly, methamphetamine can be detected electrochemically using a graphite SPE, thus it can be used as an indirect target for the identification of BMK.

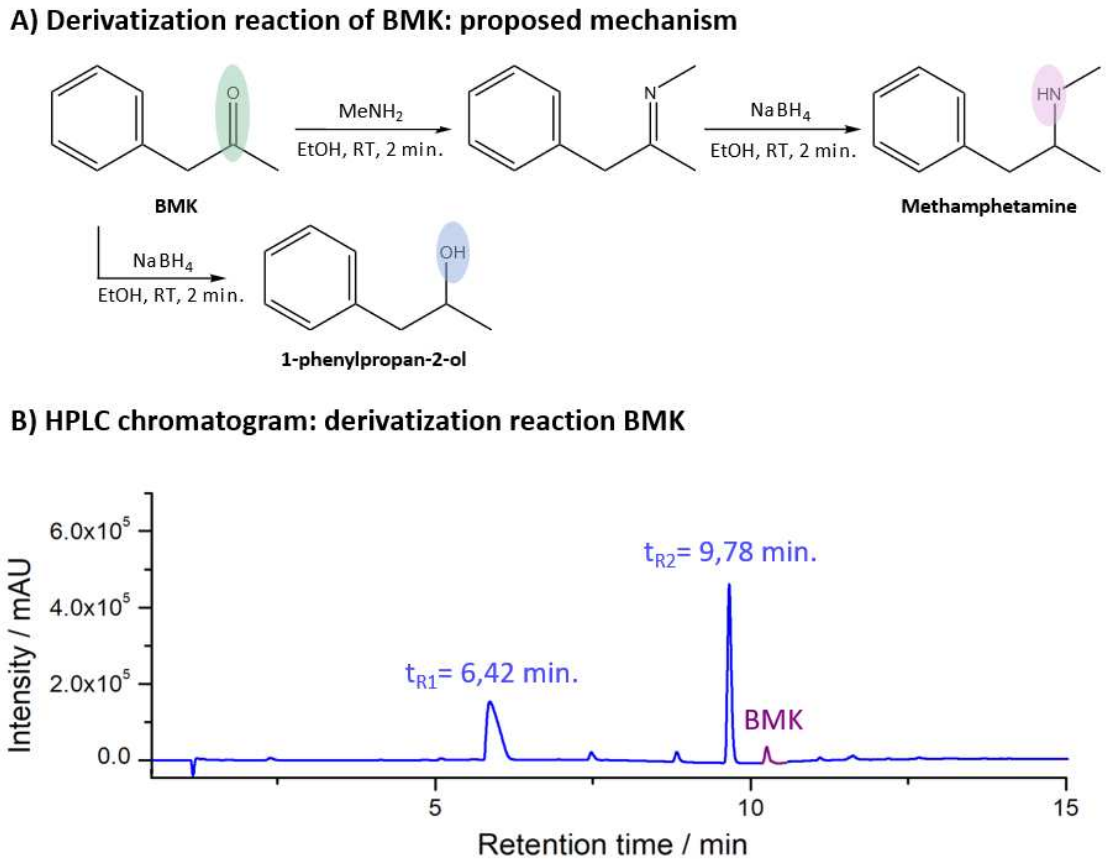

Figure 4. A) Reductive amination reaction of the carbonyl group from BMK (marked in green) to form the amine group (marked in purple) associated with methamphetamine and possible side reaction of BMK with the reducing agent $NaBH_4$ to form the alcohol 1-phenylpropan-2-ol (marked in blue). B) Liquid chromatogram of reductive amination reaction samples (initial concentrations of 1 M BMK, $MeNH_2$ and $NaBH_4$ with a dilution factor of 1000-fold, $\lambda = 210$ nm). Blue line: mixture sample, purple

line: BMK standard. Reaction conditions: four minutes reaction time at room temperature.

3.3. Electrochemical detection of derivatized BMK

The electrochemical detection of the BMK derivatization products was assessed by SWV measurements on diluted samples (500-fold) in PBS pH 12 (initial concentrations of the reagents 1 M). The dilution step is needed to bring the reaction products, i.e. methamphetamine and 1-phenylpropan-2-ol, into an aqueous solution with the suitable electrolyte and pH to control the conditions of the electrochemical analysis. Following the literature, pH 12 is typically used for the detection of methamphetamine,[39] so this condition was selected for the preliminary indirect analysis of BMK. Later, this parameter will be optimized and adjusted, if necessary. **Figure 5A and 5B** displays the electrochemical profile of the diluted solution, with and without 'moving average baseline', as well as, the signals obtained when analyzing 1 mM pure standards solutions of methamphetamine and 1-phenylpropan-2-ol.

As expected, the electrochemical fingerprint of the mixture was correlated to the methamphetamine signal with an oxidation signal at Ep 1.09 V (vs. Ag/AgCl). According to the literature, this peak is attributed to the oxidation of the secondary amine group present in the aliphatic part of the methamphetamine structure.[40]

Based on these findings, it can also be assumed that the other side-product, confirmed in the chromatographic technique, is too low in concentration to be detected electrochemically. This means that the electrochemical fingerprint of the derivatized sample shows no electrochemical signal in the expected potential window of 1-phenylpropan-2-ol i.e. Ep 0.445 V (vs. Ag/AgCl) (**Figure 5B**). In contrast, the methamphetamine profile from the standard matches with the electrochemical

fingerprint from the derivatized sample by means of the same peak potential. Therefore, the obtained electrochemical signals can only be attributed to the formation of methamphetamine.

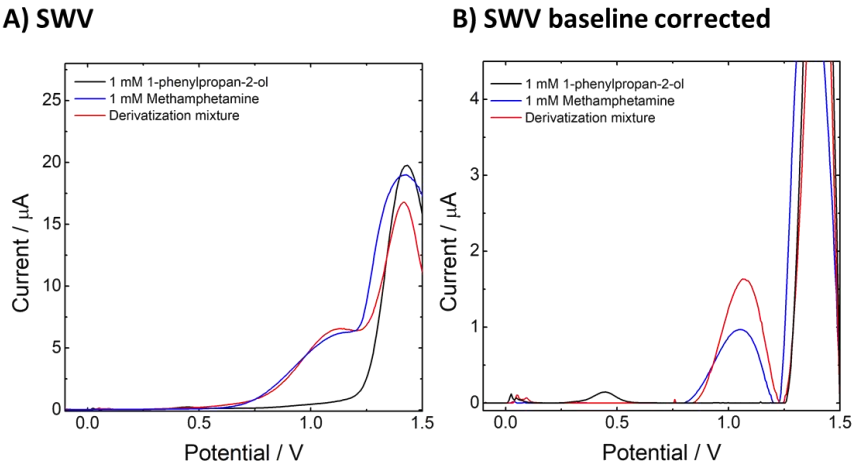

Figure 5. A) Electrochemical fingerprint of 1 mM solution of methamphetamine (blue solid line) and 1 mM 1-phenylpropan-2-ol (black solid line) as well as, unknown concentration of the diluted derivatization mixture (red solid line) in PBS pH 12 on SPE by SWV. B) Corrected baseline SWV of the conditions in A).

Besides, **Figure S6** shows adequate reproducibility (using relative standard deviation, RSD) when analyzing the same derivatization mixture (RSD_{Ep}=0.54% and RSD_{Ip}=8.4%, n=3) at different SPEs and remarkably, acceptable reproducibility for different BMK derivatization reactions (RSD_{Ep}=0.78% and RSD_{Ip}=11.5%, n=9). Importantly, the peak potential was constant in all the measurements which is the key parameter used for the robust identification of the target compounds.

3.4. Optimization of the electrochemical detection of derivatized BMK

Optimization of all the parameters that influence the BMK sensing approach was carefully addressed. It is important to point out that all the measurements were performed after four minutes (two minutes each step, **Figure 4**) of the chemical

reaction as an optimal value for on-site testing. First, preliminary studies were performed on pure methamphetamine to understand what conditions were optimal for its detection, and subsequently, apply those to the proposed electrochemical strategy. **Figure 6A** shows the electrochemical fingerprint upon increasing concentrations of methamphetamine. Accordingly, higher concentrations of methamphetamine lead to higher current intensities. Nevertheless, concentrations higher than 2 mM the oxidation of methamphetamine at graphite electrodes can be masked by the large blank signals. This makes it more challenging to detect methamphetamine, so that, lower concentrations of methamphetamine i.e. from 0.5-2 mM will be the ideal concentration range to be achieved through the derivatization of BMK. Subsequently, 1 mM of methamphetamine was investigated in a pH range from 5 to 12 (**Figure 6B**). At acidic and neutral pHs, the electrooxidation of methamphetamine did not occur. It is suggested that protonated methamphetamine is not easily oxidized, therefore high potential is needed for its oxidation which is located outside of the graphite SPE potential window. On the other hand, basic pHs easily oxidize methamphetamine shifting its peak potential to negative values suggesting the involvement of protons in the oxidation process of its secondary amine. This is in agreement with the pKa=10.1 of methamphetamine.[45] Furthermore, an enhancement in the currents was observed from pH 10 to pH 12, therefore, the last one was selected as the optimal pH value of supporting electrolyte to electrochemically detect methamphetamine.

The influence of the concentration of $MeNH_2$ and $NaBH_4$ participating in the derivatization reaction was evaluated. As expected, **Figure 6C** displays that a higher $MeNH_2$ concentration generates more oxidation signal while maintaining the concentrations of the other reagents. This means that more imine product is formed during the first step of BMK derivatization (**Figure 4A**), which later on can be easily

reduced by $NaBH_4$. A similar phenomenon happens by increasing the concentration of $NaBH_4$ (**Figure 6D**). The higher the $NaBH_4$ concentration, the more efficient the reduction of the imine intermediate and conversion into methamphetamine, generating higher intensity currents (**Figure 4A**). Note that higher concentrations of $MeNH_2$ and $NaBH_4$ were discarded to avoid an increase in the cost per analysis. As a compromise situation between sensitivity and sampling simplicity, 1 M was chosen for $MeNH_2$ and $NaBH_4$.

To further prove the formation of methamphetamine, a pH screening from 5 to 12 was performed after the derivatization reaction shown in **Figure 4A**. **Figure 6E** displays the electrochemical fingerprint of the product formed during the reaction at different pHs, confirming the formation of methamphetamine at pH 12. The electrochemical fingerprint from the product exhibited similar behavior in terms of peak potential and intensity currents that the one obtained for 1 mM pure methamphetamine.

Finally, to obtain the best analytical performance, i.e. 1 mM methamphetamine and lower background signal, a dilution study from the reaction batch to the buffer pH 12 was also performed. The optimized conditions were used and different dilution factors were tested. **Figure 6F** shows an increase in the oxidation signal of methamphetamine when low dilution factors were used. However, this peak is masked with the signal of the background that also increases at low dilutions. Therefore, a dilution factor of 500-fold was selected as the optimal value as it gives a methamphetamine peak intensity sufficient to be detected while keeping the background signal to a minimum.

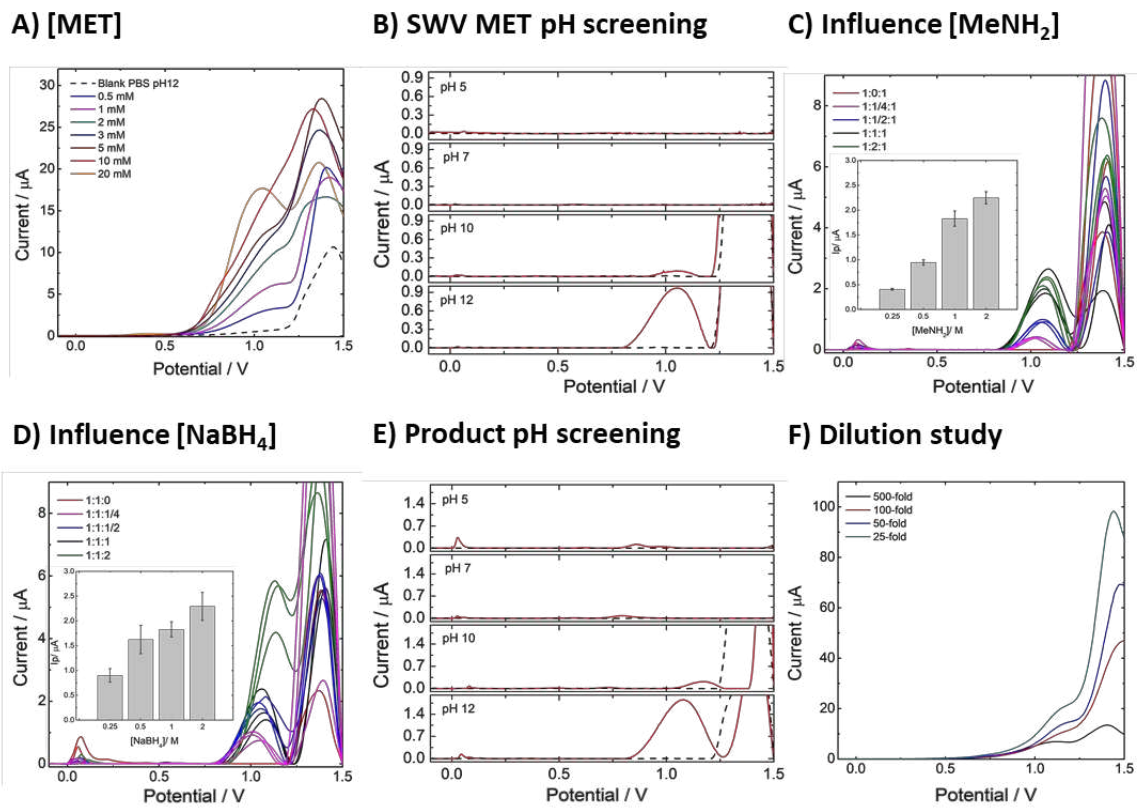

Figure 6. Optimization of the electrochemical detection of derivatized BMK at SPE: A) Calibration curve of methamphetamine in PBS pH 12. B) pH screening of 1 mM methamphetamine (red solid line) and buffer blank (black dashed line) from pH 5 to 12. C) Influence of the concentration of $MeNH_2$ on 1 M of BMK and $NaBH_4$. Reaction time of 4 min, room temperature and dilution step of 500-fold. D) Influence of the concentration of $NaBH_4$ on 1 M of BMK and $MeNH_2$. Reaction time of 4 min, room temperature and dilution step of 500-fold. E) pH screening of derivatized BMK (red solid line) after a total time reaction of 4 min and initial concentrations 1 M of reagents and dilution step of 500-fold and buffer blank (black dashed line). F) Dilution study upon a reaction of initial concentrations 1 M of BMK, $MeNH_2$ and $NaBH_4$. The final volume of 0.5 mL. All the experiments were performed following the scheme presented in **Figure 4A**.

3.5. Identification of confiscated precursors

Nowadays, the rapid identification of ATS precursors by law enforcement agencies in the field is becoming more important to quickly disrupt the distribution chain. Moreover, further insights can be gathered from an evolving ATS market, which in turn, it can be used for mapping their use and manufacturing sites. Hence, 18 confiscated samples previously analyzed by a standard method (i.e. GC-MS) were provided by a forensic laboratory (i.e. NICC, Belgium) and subsequently tested to validate the on-site sensing approach.

The on-site detection of ATS precursors is based on a flowchart procedure (**Figure 2**). To start, a first test at PBS pH 7 is performed to identify the electrochemical fingerprint of MDMA precursors. Based on this, a follow-up measurement at PBS pH 12 may be required if no electrochemical signals are observed at c.a. Ep 1 V (vs. Ag/AgCl) in PBS pH 7. This second measurement will allow the identification of most of the methamphetamine and amphetamine (pre)-precursors with great selectivity by following the profile identification in **Figure 4** and the specific peak potential window for each compound (**Table S3**). The potential window was set to cover changes in pH and concentration due to the sampling procedure (**Table S4**). Hence, a potential window of ± 120 mV of the E_p was used. Next, if the electrochemical profile at pH 12 does not still exhibit oxidation peaks, a preliminary derivatization reaction with the subsequent analysis with PBS pH 12 will be needed to identify BMK.

The electrochemical fingerprint of these 18 confiscated samples was firstly collected at PBS pH 7 (**Figure 7A and 7B)**. The results allow the identification of all 11 MDMA precursors reporting comparable results to the standard method used by the forensic laboratory (i.e. GC/MS) (**Table S5**). Remarkably, the electrochemical sensor was also able to selectively detect the type of MDMA precursor based on the electrochemical

fingerprint in seven samples. Specifically, two samples of safrole and sassafras oil presented a double peak at Ep 1.0 V and 1.18 V (vs. Ag/AgCl) and five PMK samples with a peak at Ep 1.0 V (vs. Ag/AgCl) (**Figure S7A and S7B**). However, four PMK samples (P4, P8, P12 and P15) report a modified electrochemical fingerprint where a second peak was observed at Ep 1.2 V (vs. Ag/AgCl). This may cause an incorrect identification of the type of MDMA precursor although this does not represent a problem for the MDMA precursor's identification. This discrepancy may be attributed to the oxidation of other electrochemical species in the sample or additional electrochemical reactions due to other forms of PMK. Then, seven of the samples that gave no electrochemical signal or exhibited a signal around Ep 0.3 V (vs. Ag/AgCl) were subjected to a second analysis at PBS pH 12 (**Figure 7C**). Based on these results, 5 samples were detected as methamphetamine and amphetamine (pre)-precursors. Besides, the individual identification was successful in all the samples i.e. three samples as APAAN, APAA or MAPA pre-precursors with a peak potential at Ep 0.2 V (vs. Ag/AgCl) and two samples of ephedrine and pseudoephedrine with a peak potential at Ep 0.74 V (vs. Ag/AgCl) (**Figure S7C**). Finally, two samples needed the derivatization reaction (P13 and P18). As expected, a peak at ca Ep 1 V (vs. Ag/AgCl) due to the formation of methamphetamine confirmed the presence of BMK (**Figure S7D**). It is important to mention that the peak potential shifted to positive values in comparison to the electrochemical fingerprint of pure methamphetamine (**Figure 7D,** solid green line) due to a potential pH change associated with the reagents used and by-products formed during the derivatization reaction. Noteworthy, P18 corresponding to fluoro-BMK could also be detected by the derivatization reaction which implies that modifications in the aromatic ring of BMK do not interfere with the identification of the precursor. This is an improvement with respect to spectroscopic techniques and would

indicate the capability of the sensor to detect modified forms of BMK which would help in the future to detect any BMK-derived substance that could be used for the synthetic production of illicit drugs. To summarize, the results showed an accuracy of 100% for a general classification (i.e. MDMA or amphetamine/methamphetamine (pre)-precursors) and 78% for an individual identification according to the standard methods (**Table S5**).

The electrochemical strategy was also compared with current portable technologies to evaluate the performance of commercial techniques for the detection of synthetic drug precursors. Hence, the same confiscated samples of ATS precursors were interrogated with a portable ATR-FTIR device (**Figure S8**). An analysis of main component was conducted where the spectroscopic method showed an accuracy of only 11% in comparison to the standard method. It is clear that the FTIR spectrum library should be improved by including more precursors to get more accurate results. Even with an updated library, this technique is still time-consuming due to sample preparation, exhibits some drawbacks when dealing with liquid samples, and last but not least, it lacks user-friendliness. **Table S5** depicts the comparison between current on-site techniques and the proposed method, exhibiting an improved performance for the electrochemical method.

Overall, the electrochemical analysis demonstrates to be a promising tool for the classification and identification of ATS precursors that can be easily integrated into the screening analysis by law enforcement agencies in the field.

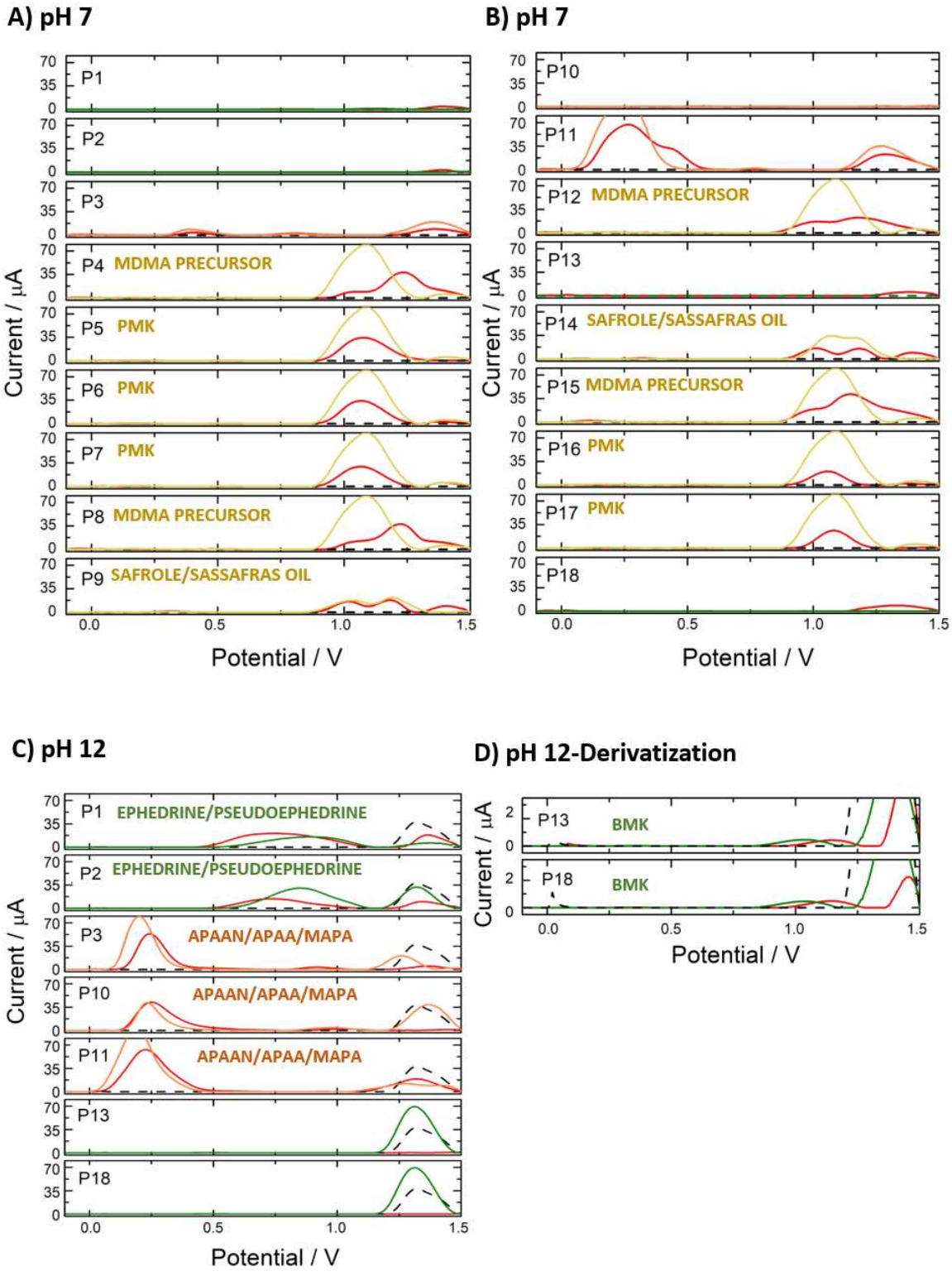

Figure 7. Electrochemical fingerprints of confiscated precursors samples at SPE obtained following the flowchart process: A) and B) pH 7, C) pH 12 and D) pH 12 after the derivatization reaction. The black dashed line corresponds to the blank signal, the

orange solid line to the pure amphetamine/methamphetamine pre-precursor in the corresponding pH, the green solid line to the pure amphetamine/methamphetamine precursor in the corresponding pH, the yellow solid line to the pure MDMA precursor in the corresponding pH and the red solid line to the sample.

4. Conclusions

In this article, an electrochemical method based on the electrochemical fingerprint of ATS precursors on SPEs was exploited for their detection in confiscated samples aiming a quick decision tool for law enforcement agents. First, an electrochemical pH screening revealed optimal pH conditions for the electrooxidation processes of each precursor, unfortunately, exhibiting the redox inactivity of BMK. To circumvent this issue, a derivatization approach was proposed to indirectly unravel the BMK electrochemical fingerprint. Characterization of the reaction products was presented and carried out by means of a multianalytical approach employing chromatographic and electrochemical techniques. It was found that the derivatization step converts BMK into methamphetamine which is electroactive at graphite SPE, proving a viable analytical procedure to unravel the presence of BMK by indirectly detecting a well-known illicit drug such as methamphetamine. The optimization of BMK derivatization was fully addressed exhibiting an oxidation peak at Ep 1.09 V (vs. Ag/AgCl) at SPEs after four minutes reaction at room temperature and a dilution step in PBS pH 12. To prove the capability of the strategy to classify and identify ATS precursors, a flowchart method was introduced and successfully applied to 18 confiscated samples. Interestingly, the analytical sensor offers promising results for the on-site classification and identification of ATS precursors, especially when compared with portable spectroscopic methods. However, future work will follow for the full on-site applicability of the sensor in order to minimize the time of analysis and to integrate a rapid and

simultaneous electrochemical analysis system. Overall, the electrochemical approach demonstrates to be a useful and affordable analytical tool for the early identification of ATS precursors in the field, and thus, to prevent drug manufacture and trafficking.

CRediT authorship contribution statement

Noelia Felipe Montiel: Conceptualization, Methodology, Electrochemical analysis, HPLC analysis, Writing-original draft. **Marc Parrilla:** Supervision, Writing-review & editing. **Nick Sleegers:** LC-QTOFMS analysis, Writing-review & editing. **Alexander L.N. van Nuijs:** Resources, Writing-review & editing. **Filip Van Durme:** Resources, Validation. **Karolien De Wael:** Supervision, Project administration, Funding acquisition, Writing-review & editing.

All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors declare no competing financial interest.

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Appendix A. Supplementary material

Supplementary material related to this article can be found, in the online version.

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