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Comparison of two GC-MS-based Screening Methods in Systematic Toxicological Analysis: Acid hydrolysis and Liquid-liquid Extraction versus Acid Hydrolysis and Solid-phase Extraction with a Particular Focus on Manual versus Semi-automated Data Evaluation

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1 ZUSAMMENFASSUNG

Das Ziel der vorliegenden Studie war zunächst die Entwicklung einer Methode für die systematische toxikologische Analyse (STA) von Urinproben basierend auf salzsaurer Hydrolyse, Festphasenextraktion mittels einer Mischphase (reversed-phase C8 und Kationentauscher) und Acetylierung (U+UhySPEAc). Die Methode war dann mit einer etablierten STA-Methode für Urinproben basierend auf salzsaurer Hydrolyse, flüssig-flüssig Extraktion und Acetylierung (U+UhyAc) zu vergleichen. Zu diesem Zweck wurden Rückstellproben von 100 Urinproben von Patienten aus psychiatrischen Kliniken verwendet, die zuvor bereits einer Routineanalyse (U+UhyAc) unterzogen worden waren. Die Proben wurden nach beiden Methoden aufgearbeitet, und mittels Gaschromatographie-Massenspektrometrie (GC-MS) analysiert. Die GC-MS Daten wurden halbautomatisch mit der Dekonvolutionssoftware AMDIS 32 ausgewertet. Anschließend wurden die Ergebnisse beider Methoden untereinander und mit den Ergebnissen verglichen, die im Rahmen der Routineanalytik durch manuelle Auswertung erhalten wurden. Sowohl die U+UhySPEAc als auch die U+UhyAc Methode deckten ein breites Spektrum an Analyten ab. Die U+UhySPEAc lieferte deutlich sauberere Extrakte, was die Auswertung erheblich erleichterte. Die U+UhyAc Methode war der U+UhySPEAc im Bezug auf die Analysenzeit deutlich überlegen und wies auch in der Nachweisempfindlichkeit und im Analytenspektrum leichte Vorteile auf. Die höhere Nachweisempfindlichkeit ließ sich durch das größere Probenvolumen bei der U+UhyAc Methode erklären. Die halbautomatische Auswertung mittels der AMDIS 32 Software sicherte nicht nur eine objektive Auswertung, sondern verkürzte auch die für die Auswertung benötigte Zeit auf ca. 5-10 min im Vergleich zu ca. 20-25 min bei herkömmlicher Auswertung. Des Weiteren konnten mit der halbautomatischen Auswertung Substanzen gefunden werden, die mit manueller nicht gefunden werden konnten. Zusammenfassend lässt sich sagen, dass die neu entwickelte U+UhySPEAc der etablierten U+UhyAc leicht unterlegen ist. Sie könnte jedoch vor allem bei nur geringem vorhandenem Probenvolumen eine brauchbare Alternative darstellen. Der Wechsel von manueller auf halbautomatische Auswertung könnte in der täglichen Routinearbeit nicht nur die Zeiten für die Auswertung senken, sondern auch das Auffinden überlagerter Peaks erheblich erleichtern.

2 SUMMARY

The aim of the presented study was to first develop a method for systematic toxicological analysis (STA) of urine samples based on acid hydrolysis, mixed-mode solid-phase extraction (reversed-phase C8 and strong cation exchange), and acetylation (U+UhySPEAc). This method was then to be compared with an established STA method for urine samples based on acid hydrolysis, liquid-liquid extraction, and acetylation (U+UhyAc). For this purpose, leftover urine samples from 100 psychiatric patients were used, that had previously been subject to routine analysis. The samples were worked up with both procedures and analyzed by gas chromatography-mass spectrometry (GC-MS). Data evaluation was performed semi-automatically with the deconvolution software AMDIS 32. The results obtained with both methods were compared with each other and with those obtained by manual data evaluation during routine analysis of the same samples. Both the U+UhySPEAc and the U+UhyAc method covered a wide spectrum of analytes. The U+UhySPEAc yielded considerably cleaner extracts as the U+UhyAc method. The U+UhyAc method was clearly superior to the U+UhySPEAc method with respect to analysis time and also had some advantages with respect to sensitivity of detection and analyte spectrum. The higher sensitivity could be explained by the larger sample volume used in the U+UhyAc method. Semi-automated data evaluation using AMDIS 32 not only ensured more objective results but also reduced the time needed for data evaluation to about 5-10 min as compared to about 20-25 min needed for conventional manual data evaluation. Moreover, semi-automated data allowed detection of compounds that could not be detected manually. In summary, it can be said that the newly developed method has disadvantages as compared to the U+UhyAc method. However, it could be a useful alternative in cases, where only small sample volumes are available. Switching from manual to semi-automated data evaluation could not only reduce analysis in routine analysis, but also considerably facilitate finding peaks co-eluting with other compounds.

3 GENERAL PART

3.1 INTRODUCTION

3.1.1 General aspects of toxicological screening analysis

Systematic toxicological analysis (STA), i.e. comprehensive screening analysis for drugs, poisons and/or their metabolites in biological samples, is a routine task in various areas of analytical toxicology, most notably in clinical and forensic toxicology, work place drug testing and doping control.[1,2] In emergency departments, toxicological screening analysis are usually requested when the question appears:"Do the symptoms relate to the ingestion of a drug or other toxin (poison), to disease or to trauma?". It provides useful information in cases of multi-drug intoxication, masked intoxications, asymptomatic overdoses etc. Moreover, it can provide guidance for the choice of care and increase the confidence of the treating physician in doing the right thing.[3-5]

Besides emergency medicine STA can be a useful tool in other disciplines of medicine: Patients addicted to alcohol, drugs or medicaments have to be monitored, as far as the compliance has to be supervised. Moreover, it can be used to detect co-medication surreptitiously taken by patients without the treating physician's knowledge increasing the risk of negative effects from drugs with a narrow therapeutical range and drug-drug interactions.[3] Finally, toxicological analysis plays an important role in the exclusion relevant drug effects in the determination of clinical brain death.[6,7]

Besides clinical routine, the presence or absence of xenobiotics in human biosamples plays an important role in forensic medicine, where the presence of xenobiotics may inhibit the capability to safely drive a vehicle, have affect on court sentences, e.g. in cases of certifiably insanity because of intoxication, or even explain the cause of death. Moreover, occupational and environmental medicine is becoming increasingly important and the potential of an efficient toxicological analysis in these disciplines is evident. Finally, toxicological analysis is of a great significance in doping control.

3.1.2 Choice of biosample

The detectability and the quantification of specific drugs, poisons and/or their metabolites depend on the choice of the biosample used for analysis. Common biosamples are blood, plasma/serum, and urine. Blood is the biosample of choice when quantification of the xenobiotics is needed, but has the disadvantages that blood concentrations are often relatively low and that the detection window is comparatively short (hours to a few days). For qualitative drug screening, urine is better suited. It is easily available in rather large quantities and sampling is usually non-invasive. Hence, no physician is needed to collect urine in contrast to collecting blood, e.g. in a stop-and-search operation of the police. A further important advantage of urine are the generally higher concentrations of drugs/poisons and/or their metabolites in comparison to blood due to concentration of urine in the kidneys.[8,9] Moreover, the identification of a certain drug in urine is often easier because of the presence of a potentially broad range of metabolites. Urine is therefore still the sample of choice for toxicological screening analysis, especially in clinical toxicology. However, in post-mortem forensic toxicology or in case of an acute overdose leading to rapid death, urinalysis may not be appropriate, because of the fact, that the xenobiotics and/or their metabolites might not yet have appeared in urine.[1]

A bigger challenge for the analyst is certainly meconium, oral fluid, sweat, fingernails or hair, the so-called alternative matrices. Disadvantages of these alternative matrices are rather low concentrations of some drugs/drug classes and that analytical method for these matrices are generally only available for particular drugs or drug classes.[1,10] Advantages are the often longer detection windows in comparison to blood or even urine. This is particularly true for hair analysis, where drugs can be detected for months, depending on the length of the hair samples.

3.1.3 Methods for toxicological analysis in urine

As the experience in hospitals often shows, physicians must not only focus on xenobiotics knowingly ingested by the intoxicated/poisoned patient, but rather consider the potential presence of thousands of other relevant toxicants. An ideal STA procedure should therefore allow sensitive and selective detection of all these

relevant compounds. In addition, it should have a short turnaround time, be easy to handle and constantly available at reasonable cost. Several techniques have been proposed for toxicological screening analysis, but so far none fulfilling all these criteria.

The simplest techniques to screen for drugs in urine are the immunoassay-based bedside or point-of-care tests. They are generally easy to perform even by untrained personnel and have short turnaround times of usually about 15 min. As already mentioned above, the major drawbacks of these bedside tests is that they cover only a very limited number of drugs/drug classes which also play a role in workplace drug testing such as amphetamines, barbiturates, cannabinoids, cocaine, benzodiazepines, and opiates. Some bedside tests additionally cover methadone and tricyclic antidepressants. However, many other toxicologically relevant compounds such as paracetamol, diphenhydramine or tramadol can principally not be detected by these devices.[11] For these reasons, interpretation of the results of bedside tests requires considerable knowledge about the analyte spectrum of test, knowledge that untrained medical personnel usually does not have. Furthermore, bedside tests only provide preliminary results that have to be confirmed by more selective methods, particularly when medico legal issues are involved.[12]

More comprehensive STA can be performed with so-called hyphenated techniques, in which chromatographic systems with high separation power are linked to detection systems with high identification power. Gas chromatography (GC) has the highest separation power, but is not applicable for polar, non-volatile or thermolabile compounds. Liquid chromatography (LC) has a lower separation power, but also allows separation of polar, non-volatile and thermolabile compounds. GC-MS, especially in the electron ionization full scan mode, is still the method of choice for comprehensive screening providing best separation power, specificity and universality, although requiring derivatization.[1] LC with diode array detection (DAD) is also often used for screening, but its separation power and its specificity are still inferior to those of GC-MS. Finally, LC-MS has shown to be an ideal supplement.[1] DAD cannot be used in connection with GC, whereas MS(/MS) can be linked to both GC and LC. Mass spectra generally have a higher identification than UV/VIS spectra. However, there is an important difference between electron ionization (EI) mass spectra obtained in GC-MS and electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) mass spectra or product ion spectra obtained in

LC-MS(/MS). In EI, the fragmentation pattern of certain molecule is always the same so that libraries with reference spectra can be used for identification of compounds via mass spectra recorded on different GC-MS apparatus, while the ESI or APCI mass spectra and even product ion spectra as recorded in LC-MS(/MS) may differ considerably depending on the type of apparatus. A drawback of all these hyphenated techniques is that the respective apparatus can only be operated by well-trained lab personnel and that the analysis can only be performed in specialized laboratories. In addition the turnaround of these techniques is considerably longer than that of the bedside tests, which is a disadvantage in emergency toxicology. The costs for one screening procedure should also be kept in mind. The immunoassay-based tests are relatively cheap in absolute costs, but not in relative cost considering the limitations concerning their analyte spectrum. LC-DAD and GC-MS are rather cost-effective techniques, considering the wide analyte spectrum covered by these techniques, while LC-MS(/MS) apparatus are still very expensive.

Considering all of the above-mentioned aspects it is not surprising that GC-MS which allows screening of a wide spectrum of analytes, the best separation power and a standardized high identification power at reasonable cost is still the gold standard STA,[1,10,13,14] also recent developments in LC-MS(/MS) look promising.

3.1.4 Sample preparation for GC-MS analysis of urine

As mentioned above, GC-MS is only amenable to non-polar, volatile, and thermostable compounds. Furthermore, the analytes must be dissolved in an organic solvent. Therefore, samples preparation of urine samples for GC-MS involves several steps namely conjugate cleavage, extraction and derivatization.

Xenobiotics can only be renally excreted if they are hydrophilic. Therefore, in the human body lipophilic drugs or poisons are usually biotransformed to more hydrophilic metabolites.[8,9] Metabolic reactions can be divided into phase I and phase II reaction. Phase I reactions such as dealkylation, hydroxylation or ester hydrolysis make the molecules somewhat more hydrophilic. More importantly, they activate the molecules for phase II reactions. In these phase II reactions, the phase I metabolites are linked to activated sulfuric acid or glucuronic acid. Some xenobiotics such as some steroids, opiates or benzodiazepines already carrying hydroxyl groups can be directly conjugated without previous phase I metabolism.[9,15] The resulting phase II

metabolites then carry the highly hydrophilic sulfate or glucuronide moieties, so that they are sufficiently hydrophilic for excretions in urine or bile.

Due to their hydrophilic properties phase II conjugates cannot be extracted from the aqueous urine with organic solvents. Therefore, sulfate and glucuronide conjugates must be cleaved to the less polar parent compounds or phase I metabolites prior to extraction. Several methods for cleavage of conjugates have been described in the literature, most importantly acid hydrolysis[1,10] or enzymatic hydrolysis, either in solution[16] or with immobilized enzymes.[17]

For the cleavage of acetalic and acylalic glucuronides and sulfuric esters with acid hydrolysis urine samples are generally refluxed with concentrated hydrochloride acid.[18] Low costs, simplicity and speed are the advantages of this procedure. However, a important drawback of this rather aggressive workup is the possible formation of artifacts, e.g. in case of buprenorphine or benzodiazepines,[19,20] or complete destruction of some analytes, e.g. diuretics. Finally, breakdown products of bile pigments, which may be formed during the procedure, may interfere with extraction and analysis.[17] Enzymatic hydrolysis using preparations of glucuronidase, arylsulfatase or combinations of those is a more gentle procedure for conjugate cleavage. However, it is rather time-consuming and expensive. Systematic comparisons have shown that both cleavage procedure are effective, but that acid hydrolysis has advantages in emergency toxicology because it is more rapid.[16]

After the cleavage of conjugates, the next in sample preparation for GC-MS analysis is extraction. One possibility to achieve this is liquid-liquid extraction (LLE). This sample work-up procedure has been and is still very common in STA. Extraction pH and choice of extraction solvent are the key parameters in LLE. With the exception of ion pair extraction, only neutral, i.e. unionized, compounds can be extracted from aqueous matrices with organic solvents. Hence, basic compounds are generally extracted at basic pH values while acidic compounds are preferably extracted at acidic pH values. Dichloromethane-isopropanol-ethylacetate, toluene-ethylacetate, dichloromethane-isopropanol-heptane or dichloromethane-diethylether-ethylacetat are examples which have been used as solvent mixtures. Only a small difference exist in terms of their extraction power, although a higher background will be given by the polar solvents.[21] A remarkable advantage of LLE is, that with one extracting procedure a broad range of substances could be found, from benzodiazepines over NSAIDs to designer drugs or opiates and many more classes of drugs.[18] Another

advantage is that LLE is a low-cost and simple procedure. Complications with extracting columns like in solid-phase extraction can be avoided. However, LLE has not only advantages. The use of large volumes of more or less hazardous solvents, matrix interferences and emulsion formation are some of the disadvantages of the LLE.[13,21,22] The fact that LLE is not simple to automate is another disadvantage, especially when large series of samples have to be analyzed.

For that reason, SPE which can more easily be automatized, has become more and more interesting in STA. Chemically modified silica, polystyrene-divinylbenzene resin (SDB) and diatomaceous earth are most common types of sorbents. Diatomaceous earth is basically LLE, but it is often included in SPE methods. Because of its large pores diatomaceous earth increases the surface of adsorbed aqueous liquids, e.g. urine, so that they can be effectively extracted with organic solvents without the need of shaking. The most commonly used SPE sorbents today are silica-based which retain the analytes by different mechanisms depending on the modification of the silica.[13] Reversed-phase silica sorbents in which silanol groups of silica back-bone are partially derivatized with alkyl chains (e.g. C8 or C18) mainly retain the analytes by hydrophobic interactions. They can effectively retain hydrophobic compounds, but are less applicable for extraction of more polar compounds. Modified silica sorbents with ion exchange properties retain charged analytes by ion-ion interactions. Cation exchange sorbents interact with positively charged ions, e.g. protonated amines, while anion exchange sorbents interact with negatively charged compounds, e.g. deprotonated carboxylic acids. Thus, acidic or basic drugs can be effectively extracted with ion exchange sorbents, depending on the pH value of the sample. Different retention mechanism can also be combined in so-called mixed-mode sorbents in which different chemical modifications are present in one sorbent.[13] As alternative to silica-bases SPE columns, polymer based columns are available on the market. Basically, these polymer based sorbents have similar retention properties as silica-based sorbents, but are chemically more stable tolerating extreme pH values. Newer methods in SPE like solid-phase disc extraction (SPEC) or solid-phase micro extraction (SPME) look promising, too.[23,24]

Because of the aim of STA to achieve extraction of as many substances as possible with one single procedure, mixed-mode sorbents combining reversed-phase and cation-exchange properties have been used for this purpose.[13] A model of silica-based mixed-mode sorbent and its retention principles is shown in Fig. 1. The silanol

groups are partially derivatized with C8 alkyl chains and partially with cation exchange substituents (phenylsulfonic acid).

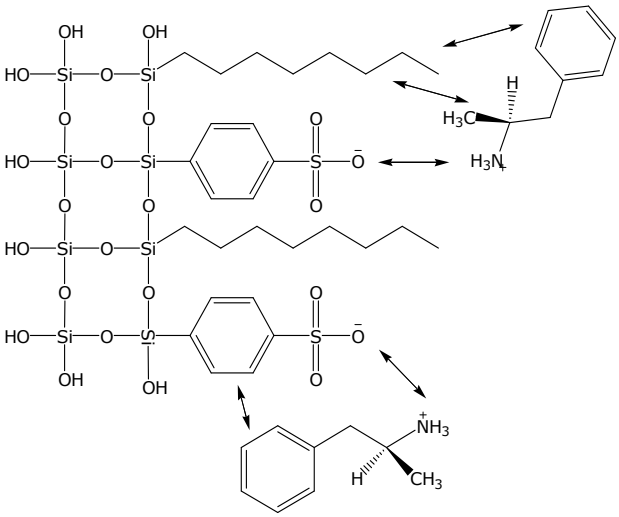

Fig.1: Structure of a mixed-mode bonded silica and its interactions with amphetamine.

SPE columns with such mixed-mode phases are produced and distributed by a number of manufacturers e.g. TSC, Elut Certify, Isolute HCX, etc. Acidic and neutral substances can be retained by this mixed-mode silica at a suitable pH by hydrophobic interactions with the alkyl chains and the basic substances can be retained by interactions with the cation exchange groups.[13,25]

Generally, SPE with such mixed-mode columns involves several steps: sample pretreatment, column conditioning, sample application, pH adjustment, column drying, elution of the acidic/neutral fraction (fraction A), column wash, elution of the basic fraction (fraction B), evaporation. The effectiveness of extraction is determined by the properties of the analytes, namely sample pretreatment, pH, the solvents used for eluting and washing and finally the flow rate during the different steps. Many different approaches for performing these steps have been published.[13,19-21,25-27]

3.1.5 Evaluation of GC-MS Data

The acquired GC-MS data files can either be evaluated manually or by semi-automatically using deconvolution software. Manual evaluation involves a first general screen of the total ion chromatograms (TIC) which can be followed by a screening for specific drug classes employing previously described user-defined

macros,[1] which extract characteristic fragment ions from the total ion current thus indicating the possible presence of the respective drugs and/or metabolites. Such macros are available for the following drug classes: psychotropics, barbiturates, benzodiazepines, stimulants/hallucinogens, designer drugs, opioids, analgesics, anticonvulsants, antidepressants, butyrophenone neuroleptics, cardiovascular drugs, sedative hypnotics and phenothiazine neuroleptics.[1] Unambiguous identification can finally be achieved by computer assisted comparison of the peak underlying mass spectra with those of a reference library, e.g. the MPW_2007 mass spectral library.[28] In semi-automatic data evaluation, peaks present in the TIC are first separated from the background by devonvolution and subsequently identified by automatic library search. However, the results still have to be reviewed by experienced and well-trained personnel.

3.2 AIM OF THE STUDY

The first aim of the present study was the comparison of two different workup procedures for GC-MS analysis of urine samples with respect to their advantages and disadvantages in daily routine clinical toxicology application. The first workup procedure was based on acid hydrolysis, LLE, and acetylation (U+UhyAc), which is currently used in the Department of Experimental and Clinical Toxicology of Saarland University. The second was based on acid hydrolysis, mixed-mode SPE, and acetylation (U+UhySPEAc).
The second aim was the comparison of manual data evaluation versus semi-automated data evaluation.

The approach was as follows:

1) Adapting and optimizing an existing mixed-mode SPE method for extraction of urine samples after acid hydrolysis
2) Sample workup of 100 routine urine samples by acid hydrolysis, dividing the sample according to the needs of the two methods, followed by
    a) LLE, acetylation and GC-MS (U+UhyAc)
    b) optimized SPE, acetylation, and GC-MS (U+UhySPEAc).

3) Semi-automated evaluation of all acquired GC-MS files and setup of a database with the results
4) Systematic comparison of the data obtained using the two extraction methods.
5) Systematic comparison of the data obtained with manual routine and semi-automated data evaluation.

4 EXPERIMENTAL PROCEDURES/MATERIAL AND METHODS

4.1 CHEMICALS AND REAGENTS

Acetic anhydride, ammonium sulfate, and pyridine were obtained from Fluka (Steinheim, Germany). Sodium hydroxide pellets and aqueous ammonia (25% m/v) were obtained from Riedel-de Haen (Seelze, Germany). Bond Elute Certify cartridges (sorbent mass: 130 mg, reservoir volume: 3 ml) were obtained from Varian (Darmstadt, Germany). All other chemicals were obtained from Merck (Darmstadt, Germany). All chemicals were of analytical grade or highest available grade.

4.2 BIOLOGICAL SAMPLES/DATA

Untreated human urine samples (n=100) submitted from psychiatric hospitals to the Department of Experimental and Clinical Toxicology for routine for clinical toxicological analysis were used in the presented study. Routine analysis had been completed on all samples and only the leftover samples scheduled for disposal were used. Selection of urine samples was based on the results of routine analysis to cover a wide range of drugs and/or metabolites. The urine samples were stored at –20 °C and were defrosted just before starting the extraction procedures.

4.3 SAMPLE PREPARATION

4.3.1 Acid hydrolysis of urine samples (U+Uhy)

A 6 ml portion of urine was divided in two equal parts. One part, 3 ml urine, was mixed with 1.2 ml of hydrochloric acid (37%, m/v) and refluxed for 15 min. Then, the sample was cooled and adjusted to pH 8-9 with 2.4 ml of aqueous ammonium sulfate solution (30%) and 1.8 ml of sodium hydroxide (10 M). The pH was checked with indicator test paper. Thereafter, 3 ml of neat urine was mixed with the hydrolyzed urine. Two milliliters of this sample mixture were taken for further preparation with solid-phase extraction and the remaining 9.4 ml were taken for liquid-liquid extraction.

4.3.2 Liquid-liquid extraction (LLE)

The samples were extracted according to references.[29,30] To the 9.4 ml of the sample 5 ml of extraction solvent mixture (ethyl acetate-dichloromethane-isopropanol, 3:1:1 v/v/v) were added. The sample was vigorously shaken for 20 s and subsequently centrifuged for 2 min (1000 x *g*). The organic phase was transferred into a glass flask and evaporated to dryness (70 °C, reduced pressure).

4.3.3 Solid-phase extraction (SPE)

The 2 ml of the sample was centrifugated (2 min, 1000 x *g*). The supernatant was loaded on Bond Elute Certify cartridges previously conditioned with 1 ml of methanol and 1 ml of dionized water. The solvents were passed through the column under light vacuum. After the sample had passed through by gravity or, if needed, under light vacuum (flow-rate not above 2ml/min), the column was washed with 4 ml of hydrochloric acid (0.01 M), dried under reduced pressure, centrifuged (2 min, 1000 x g). Then, column was washed with 3 ml of distilled water, dried under reduced pressure, centrifuged (2 min, 1000 x g). The analytes were eluted from the column with 2 ml of methanol and 1 ml of methanol-aqueous ammonia 25% (98:2 v/v) by gravity in one glass flask and evaporated to dryness (70 °C, reduced pressure).

4.3.4 Acetylation of LLE and SPE extracts

To the dry residues of both procedures, 100 µl of derivatization reagent (acetic anhydride-pyridine, 3:2 v/v) was added and derivatization was performed under microwave irradiation (400 W, 5 min).[31] After evaporation of excess reagent (70 °C, reduced pressure), the residue of the LLE extract was reconstituted in 100 µl of methanol and the residue of the SPE extract was reconstituted in 50 µl of methanol and in each case were 2 µl injected into the GC-MS system.

4.4 GC-MS ANALYSIS

4.4.1 Apparatus

For analyzing the samples, a Hewlett Packard (Agilent, Waldbronn, Germany) HP 6890 Series GC system combined with an HP 5972 Series mass selective detector, an HP 6890 Series injector and an HP Chem Station G1701AA version A.03.00 was used. The GC conditions were as follows: splitless injection mode; column, HP-1 capillary (12 m x 0.2 mm I.D.), cross-linked methyl silicone, 330 nm film thickness; injection port temperature, 280°C; carrier gas, helium; flow-rate, 1 ml/min; column temperature, programmed from 100-310°C at 30°/min, initial time 3 min, final time 8 min. The MS conditions for the screening procedure were as follows: full scan mode (m/z 50-550 u); EI mode: ionization energy, 70 eV; ion source temperature, 280°C.

4.4.2 Semi-automated evaluation of GC-MS data

Semi-automated evaluation of the acquired GC-MS files was performed using the deconvolution software AMDIS 32 version 2.1 (National Institute of Standards and Technology, Gaithersburg MD, USA) with the following settings: minimal match factor, 35; type of analysis, simple; scan direction, high to low; instrument type, quadrupole; adjacent peak subtraction, two; resolution, high; sensitivity, very high; shape requirements, medium. The target library used for peak identification was based on the MPW_2007 library. The results were listed in Microsoft Excel tables.

4.5 COMPARATIVE STUDIES

4.5.1 Comparison of the results obtained with U+UhyAc and U+UhySPEAc

The results for the U+UhyAc and UhySPEAc methods were systematically compared. In case of discrepant findings, the results were re-checked specifically searching for the respective analytes by extraction of characteristic ions from the total ion chromatogram (TIC). This was done using Standalone Data Analysis software.

4.5.2 Comparisons of the results of the U+UhyAc method in the present study with those obtained in routine analysis

The findings as obtained with the U+UhyAc method in the present study were compared to those from routine toxicological screening as given in the report of the toxicologists on duty. The latter data had been acquired under routine conditions using the routine U+UhyAc method[18] and manual data evaluation by experienced toxicologist on duty using Standalone Data Analysis software version c.03.00 (Hewlett-Packard, Böblingen, Germany). Manual data evaluation consisted of a manual screening of the total ion chromatograms and a screening for specific drug classes employing previously described user-defined macros,[1] which extract characteristic fragment ions from the total ion current thus indicating the possible presence of the respective drugs and/or their metabolites. Such macros were available for the following drug classes: psychotropics, barbiturates, benzodiazepines, stimulants/hallucinogens, opioids, analgesics, anticonvulsants, antidepressants, butyrophenone neuroleptics, cardiovascular drugs, sedative hypnotics and phenothiazine neuroleptics.[1] Unambiguous identification was achieved by computer assisted comparison of the peak underlying mass spectra with those of the MPW_2007 mass spectral library.[28]

In case of discrepant findings, the results were re-checked specifically searching for the respective analytes by extraction of characteristic ions from the TIC. This was done using Standalone Data Analysis software. Furthermore, the purity of the corresponding mass spectra as obtained by deconvolution with AMDIS 32 and with manual background subtraction with Standalone Data Analysis to assess whether discrepancies might have resulted from the mode of evaluation, i.e. semi-automated vs. manual evaluation.

5 RESULTS

5.1 RESULTS OF SAMPLE ANALYSIS

All detected drugs and their metabolites as detected by the two procedures are listed in the order of the case numbers in the table in the Appendix 1, which includes the sample number, the names of the detected parent drug, the entry numbers of the mass spectra found in the MPW_2007 library,[28] and finally, the respective MPW library entry names.

5.1.1 Results obtained with U+UhyAc method

Sample preparation by the U+UhyAc method typically took 30-35 min including derivatization. The 25 compounds most frequently detected by this method and the frequency of their occurrence are shown in Fig. 2.

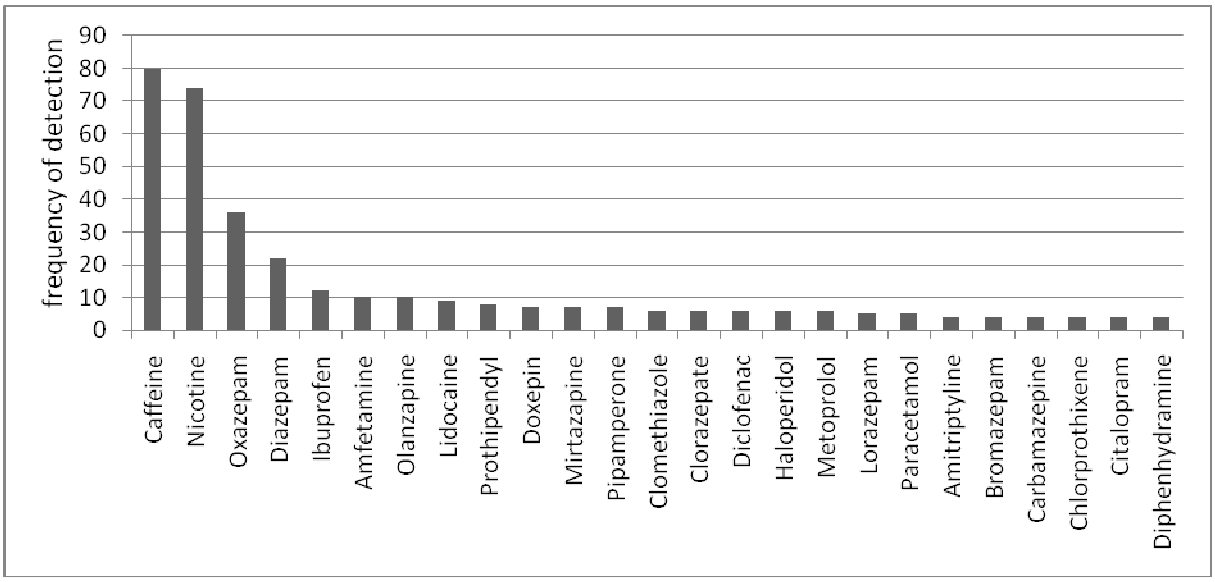

Fig. 2: The 25 most frequently detected drugs with U+UhyAc

5.1.2 Results obtained with U+UhySPEAc method

Sample preparation by the U+UhySPEAc method typically took 55 min including derivatization. The 25 compounds most frequently detected by this method and the frequency of their occurrence are shown in Fig. 3.

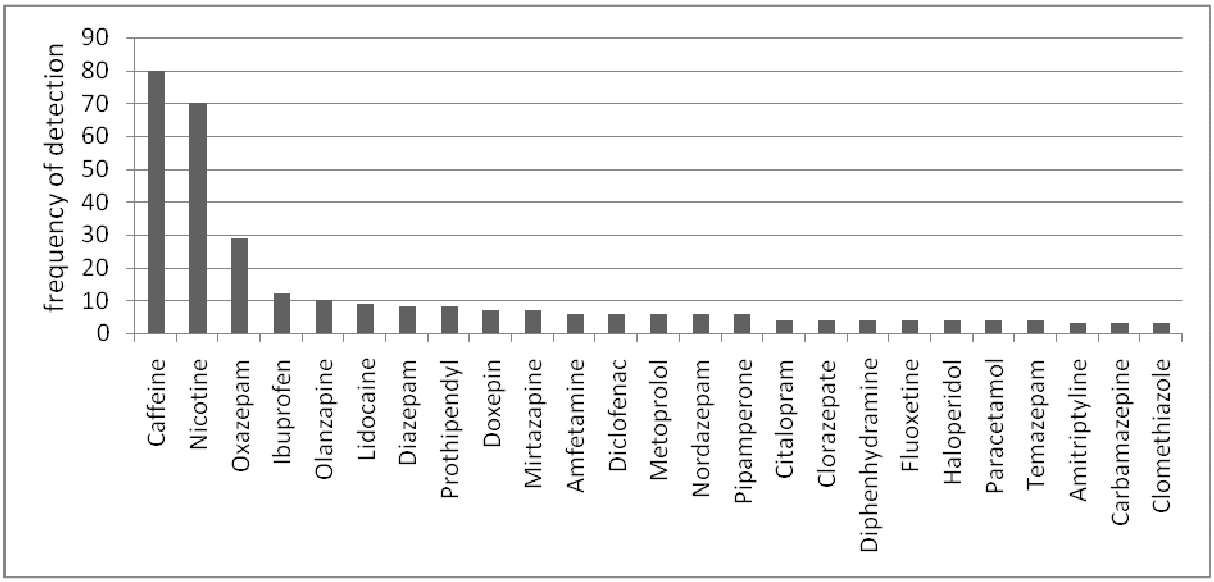

Fig. 3: The 25 most frequently detected drugs with U+UhySPEAc

5.2 COMPARATIVE STUDIES

5.2.1 Comparison of the results obtained with U+UhyAc and U+UhySPEAc

The extracts obtained with the U+UhySPEAc method were considerably cleaner and lead to lower noise levels than those of the U+UhyAc method. Discrepant findings between the two methods and the frequency of their occurrence are shown in Fig. 4. Findings only made by U+UhySPEAc but not by U+UhyAc are shown on the left and findings only made by U+UhyAc are shown on the right. Discrepant nicotine findings are not included because of minor toxicological relevance.

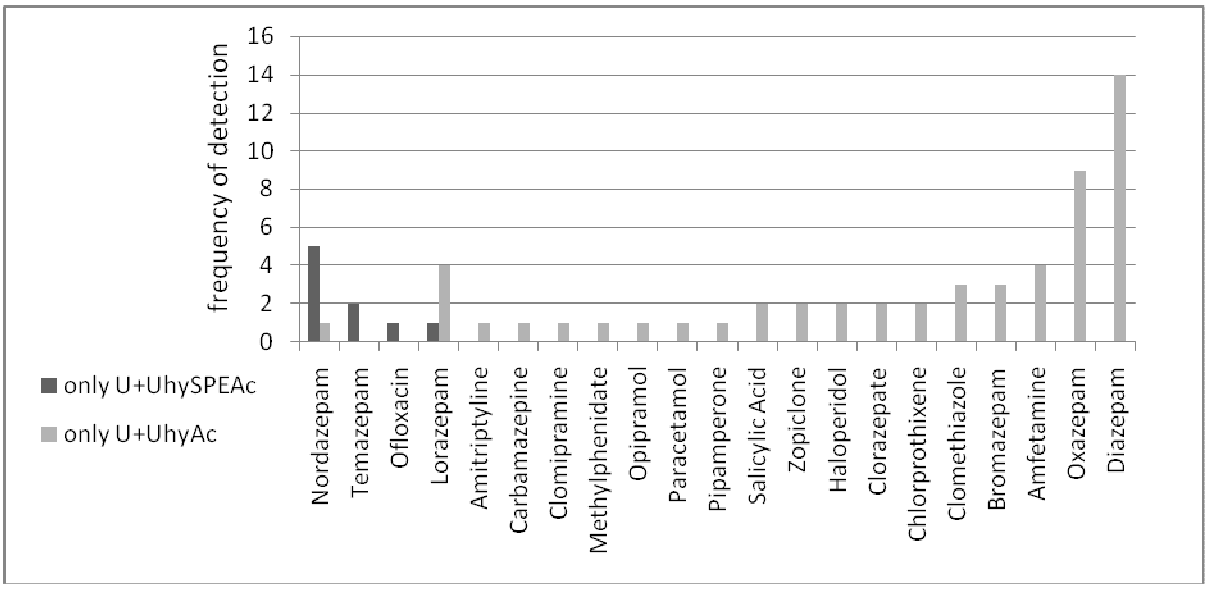

Fig. 4: Differences of detected drugs with the respective methods (without nicotine)

5.2.2 Comparisons of the results of the present study with those obtained in routine analysis

Fig. 5 provides an overview of discrepancies between the results obtained in the present study using semi-automated data analysis and the results from routine analysis using manual data evaluation as listed in the reports of the respective cases. In all cases, additional findings were made with semi-automated data evaluation, while no compounds were listed in the medical reports which were not found by semi-automated data analysis.

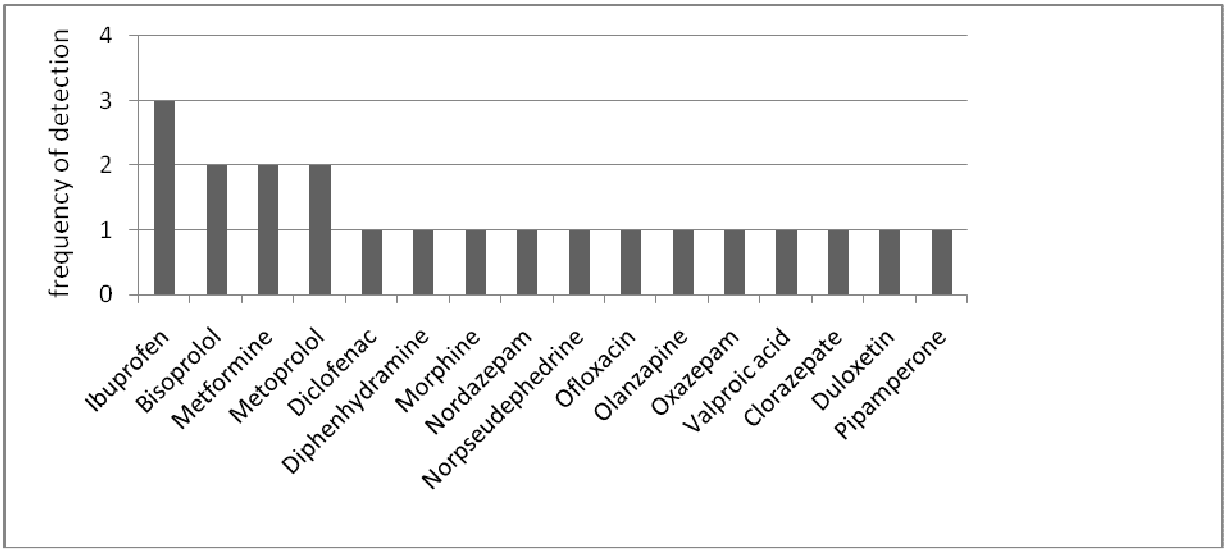

Fig. 5: Drugs which were only found with semi-automated data analysis using AMDIS 32 and the frequency of their occurrence.

Table 2 gives a more detailed account of the discrepant findings listing the case number, the parent drugs and/or metabolites for which discrepant findings were observed, their entry numbers in the MPW Library and their MPW Library Name. When re-checking the discrepancies, the respective compounds could only be detected with difficulties even after searching with characteristic ions and sometimes not at all.

Table 2: Case number (patient ID), name of the detected parent drug, entry numbers of the mass spectra found in the MPW library, respective MPW library entry names.

Case No.	Detected Drug	AMDIS 32 MPW ENTRY NUMBER U+UhyAc	MPW LIBRARY NAME
69524	Ibuprofen	1941	Ibuprofen P231
	Ibuprofen	1942	Ibuprofen ME P274
	Ibuprofen	3380	Ibuprofen-M (HO-) -H2O ME P265
	Ibuprofen	3381	Ibuprofen-M (HO-) isomer-1 ME P330
	Ibuprofen	3382	Ibuprofen-M (HO-) -H2O P226
69547	Bisoprolol	2791	Bisoprolol 2AC P1040
	Bisoprolol	2932	Bisoprolol-M (phenol) P245
	Morphine	225	Morphin 2AC @ P915
	Morphine	474	Morphine @ P539
	Morphine	2341	Heroin-M (3-acetyl-morphine) P744
	Morphine	525	Heroin-M (6-acetyl-morphine) P744
69567	Valproic acid	1019	Valproic acid P123
	Valproic acid	4670	Valpromide P122
69681	Metformine	6311	Metformine artifact-1 P133
69705	Ofloxacin	4691	Ofloxacin -CO2 P697
	Ibuprofen	1942	Ibuprofen ME P274
69816	Metoprolol	1133	Metoprolol 2AC P850
	Norpseudephedrine	1154	d-Norpseudoephedrine @ P129
69855	Olanzapine	4675	Olanzapine P676
69952	Pipamperone	179	Pipamperone P937
	Pipamperone	5586	Pipamperone-M (dihydro-) -H2O P881
70037	Ibuprofen	1942	Ibuprofen ME P274
	Ibuprofen	6386	Ibuprofen-M (HO-) isomer-2 ME P331
70054	Duloxetin	928	Duloxetine-M (1-naphthol) @ P123
	Duloxetin	932	Duloxetine-M (1-naphthol) AC @ P188
	Duloxetin	933	Duloxetine-M (4-HO-naphthol)2AC @ P355
	Duloxetin	7465	Duloxetine-M/artifact -H2O AC P207
70055	Metoprolol	1133	Metoprolol 2AC P850
70132	Diphenhydramine	731	Diphenhydramine P403
	Diphenhydramine	735	Diphenhydramine-M (nor-) AC P529
	Diphenhydramine	2047	Diphenhydramine-M (nor-) P348
	Diphenhydramine	2049	Diphenhydramine-M (deamino-HO-) P301
	Diphenhydramine	2079	Diphenhydramine-M AC P470
	Bisoprolol	2791	Bisoprolol 2AC P1040
70217	Metformine	6311	Metformine artifact-1 P133
	Metformine	6510	Metformine artifact-1 AC P207

	Oxazepam	273	Oxazepam HYAC @ P480
	Oxazepam	300	Oxazepam artifact-1 @ P342
	Oxazepam	301	Oxazepam-M artifact-2 @ P397
	Oxazepam	419	Oxazepam HY @ P308
	Oxazepam	1257	Oxazepam artifact-3 P604
	Diclofenac	716	Diclofenac -H2O @ P498
	Clorazepate	1751	Clorazepate-M isomer-2 HY2AC @ P762
	Clorazepate	2112	Clorazepate-M (HO-) HY @ P365
	Clorazepate	2125	Clorazepate-M isomer-1 HY2AC @ P762
	Clorazepate	3143	Clorazepate-M (HO-) HYAC @ P556
	Nordazepam	463	Nordazepam @ P468

6 DISCUSSION

In the Department of Experimental and Clinical Toxicology in Homburg/Saar, STA of urine samples is currently based on acid hydrolysis, LLE, acetylation (U+UhyAc), GC-MS analysis in the full-scan mode and manual data evaluation supported by user-defined macros facilitating searching for the most important drugs/drug classes.[18] This procedure has proven its versatility in many years of routine application, being relatively fast thanks to acid hydrolysis, applicable for a wide spectrum of analytes thanks to derivatization, and very specific with respect to analyte identification thanks to full-scan MS analysis. However, the procedure also has a few disadvantages, namely that some analytes are destroyed during acid hydrolysis, that the obtained extracts are fairly “dirty”, that automatizing the extraction procedure is very difficult and that manual data evaluation is time-consuming.

In attempt to overcome the first two disadvantages, an alternative STA procedure employing enzymatic hydrolysis and mixed-mode SPE was recently developed and compared to the established U+UhyAc method.[16] Indeed, good results were obtained with this new method. The extracts were considerably cleaner and the analyte spectrum was largely similar to that of U+UhyAc. However, even at elevated temperatures of 50°C enzymatic hydrolysis had to be performed for 90 min in order to achieve more or less complete conjugate cleavage.[16] For these reasons, one aim of the presented study was to do develop a STA method based on rapid acid hydrolysis and mixed-mode SPE to obtain a rapid and automatizable method leading to rather clean extracts. The newly developed method was then to be systematically compared to the conventional U+UhyAc method using 100 urine samples from daily routine work containing a wide spectrum of analytes.

The development of the SPE method was based on an already existing SPE method.[16,32-38] Early in method development, it was tried to buffer the samples after acid hydrolysis to a slightly acidic pH around 5.8 to achieve a similar extraction as in the previously described method. Several buffering procedures were tested, but it proved to be almost impossible to achieve a reproducible pH in the slightly acidic range. Therefore, it was finally decided to buffer the samples in the same way as in the U+UhyAc method and to perform SPE at the resulting pH of 8-9. Besides this, the washing step after extraction had to be modified to remove residues of buffer salts from the extraction cartridge prior to analyte elution. Without removal of these salt

residues the performance of the GC-MS apparatus decreased tremendously even after only a few sample injections. Specifically, the volume of 0.01 M hydrochloric acid in the first washing step was increased from 1 ml to 4 ml and a second washing step with 3 ml of purified water was introduced prior to elution. These modifications resolved the problem of decreasing GC-MS performance, but increased the time needed for samples extraction considerably. The final SPE method took 55 min including acid hydrolysis and acetylation and thus more than 20 min more than the conventional U+UhyAc workup.

This final method was then systematically compared to the established U+UhyAc method. For this purpose, urine samples from psychiatric patients submitted for routine STA were used. The samples were used after routine analysis had been completed. They were selected based on the drugs listed in the routine toxicology reports to cover a wide range of analytes from acidic drugs such as ibuprofen over more or less neutral compounds such as paracetamol and benzodiazepines to basic drugs such as tricyclic antidepressants or butoyrophenone-type neuroleptics.

To control for any differences that might arise from acid hydrolysis, a sufficient amount of samples was first hydrolyzed and only thereafter devided for further workup by U+UhyAc and U+UhyAc. The amount taken for U+UhyAc (9.4 ml) approximately corresponds to the 5 ml or urine routinely used for U+UhyAc, while the amount of 2 ml taken for SPE corresponds to approximately 1 ml of urine sample. Larger amounts of urine are difficult to handle with the used SPE cartridges because of limited capacity of the 130 mg of SPE sorbent and because of the viscosity of some urine samples limiting the flow through the extraction cartridges and hence leading to long extraction times. To account at least partly for the five-fold higher sample volume in U+UhyAc as compared to U+UhySPEAc, the extracts of the latter method were reconstituted in only half the volume of reconstitution volume. Hence, the concentration factor for U+UhyAc was only 2.5 times as high as in U+UhySPEAc. Besides the different extraction properties, this lower sample volume is probably also at least partly responsible for the cleaner extracts obtained by U+UhySPEAc (see below).

The mixed-mode (reversed-phase C8 and strong cation exchange) SPE columns used in this study were chosen, because they can retain a wide spectrum of analytes. Neutral and weakly acidic drugs are retained by the hydrophobic part of the SPE column. This part of the sorbent can also retain the unionized fraction of some

weakly acidic drugs such as ibuprofen or diclofenac. After washing with hydrochloric acid, basic compounds were positively charged and thus retained by the cation exchange sorbent. For strongly acidic compounds such as diuretics this kind of extraction seems not suitable, because they are negatively charged at the given pH and thus neither retained by the hydrophobic nor by the ion-exchange part of the sorbent. The first wash step with hydrochloric acid was performed to wash unretained matrix compounds from the sorbent and to protonate basic drugs which are then retained by strong interaction with the ion exchange sorbent. As already mentioned, the second wash step with unionized water was to wash out the excess hydrochloric acid. The first elution with methanol eluted neutral and weakly acidic drugs from the lipophilic part of the sorbent. In the second step with methanol-aqueous ammonia (98:2 v/v) basic drugs were deprotonated by ammonia and could thus be eluted from the cation exchange sorbent.

Comparison of the total ion chromatograms showed that the extracts obtained with the SPE procedure tended to be cleaner than those obtained with the U+UhyAc. This was particularly impressive for the selected ion chromatograms extracted by the user-defined macros with Standalone Data Analysis. They contained only few matrix peak which considerably facilitated screening for and identification of the respective drug classes.

Semi-automated data evaluation using the AMDIS software had the advantage that the data files were compared with maximum objective, because exactly the same criteria were used for peak deconvolution and library searching. The settings of the deconvolution were selected in a way to sensitively detect even small peaks and the minimum match quality for library searching was chosen at rather value of 35 to avoid overlooking peaks with less clean mass spectra because of co-elution with other compounds. A further advantage of semi-automated data evaluation was that the time needed for evaluation of one data file was approximately 5-10 min and thus considerably shorter than the 15-20 min needed for manual data evaluation.

As can be seen from Fig. 2 and from the Appendix, the detected compounds represent a typical spectrum of drugs one would expect in a population of psychiatric in-patients. Caffeine, nicotine and their metabolites were by far the most frequently detected compounds with both procedures, but will not be considered further because of their limited toxicological relevance. In the following, the results for all other drugs will be discussed in detail for which discrepancies between U+UhyAc and

U+UhySPEAc findings were observed (Fig. 4). Only four drugs were more frequently reported with the U+UhySPEAc method, namely nordazepam, temazepam, ofloxacine and lorazepam. For nordazepam and temazepam, which are both metabolites of diazepam, this is probably more a reporting than an actual detection issue. During hydrolysis, most benzodiazepines are (more or less completely) hydrolyzed to the respective benzophenones. In the case of nordazepam the resulting benzophenone is 2-amino-4-chloro-benzophenone which is identical to the benzophenone formed by hydrolysis of oxazepam and usually reported as the latter. The seeming additional findings of nordazepam can be explained as follows: In all these additional findings, unhydrolyzed nordazepam was detected by U+UhySPEAc and therefore reported as nordazepam. In the respective U+UhyAc no unhydrolyzed nordazepam was detected, but the respective benzophenone which was reported as oxazepam rather than nordazepam. A similar situation is given for temazepam which is hydrolyzed to the same benzophenone as diazepam. In U+UhySPEAc, unhydrolyzed temazepam was detected and reported as temazepam, while in U+UhyAc only the respective benzophenone was detected and therefore reported as diazepam. In summary, these discrepant findings are therefore not discrepant but only due to the fact that the unhydrolyzed benzodiazepines are better detected by U+UhySPEAc. The additional ofloxacine and lorazepam findings are single occurrences and might therefore be coincidental findings which cannot be reasonably interpreted.

Several compounds were more frequently detected with U+UhyAc (Fig. 4). At least part of these additional findings was most likely attributable to the higher concentration factor of the U+UhyAc method (see above). In addition to this, the more frequent findings of diazepam, oxazepam and bromazepam indicate that the benzophenones resulting from acid hydrolysis are more sensitively detected with the U+UhyAc method. The less frequent detection of salicylic acid with the U+UhySPEAc method can be explained with the high polarity of this drug. At the used extraction, salicylic is present in the samples in its ionized form and therefore too polar to be extracted with the reversed-phase part of the sorbent. The less frequent detection of basic drugs such as zoplicone, haloperidol, chlorprothixene, and amphetamine by U+UhySPEAc is somewhat surprising considering that similar SPE procedures had previously proven very versatile for extraction of basic drugs from biological matrices. However, maybe effective extraction cannot fully compensate the lower

concentration factor of the U+UhyAc method. Moreover, competition between cations from the buffer and the analytes at the cation exchange sorbent may also contribute to this observation.

Comparing the results obtained in the present study with the reports of the initial routine analysis of the same samples it can be seen that there are few differences. In all of these cases, more compounds were detected by semi-automated evaluation. To find possible reasons why these drugs had not been detected during routine analysis, the respective data files were re-evaluated by manually searching for the specific compound. In most cases, the respective drugs could hardly be found even with such specific searching. The reason was that manual evaluation allowed only background subtraction so that it was very difficult to obtain clean enough mass spectra for library searching. This clearly indicates that the peak deconvolution of AMDIS is a powerful tool in GC-MS analysis of rather dirty extracts.

It can be stated that both procedures cover a wide range of toxicologically relevant compounds and are therefore applicable for STA. The results obtained with both methods are essentially similar and considerable differences were only observed for the minority of the detected compounds. Advantages of the U+UhyAc procedure are the faster and simpler sample preparation, which is particularly important in emergency toxicology, and the lower costs. Advantages of the U+UhySPEAc procedure are cleaner extracts, which facilitate evaluation of GC-MS data, and the smaller sample volume required for analysis. This can be a big advantage in cases of post-mortem screening or renal failure. Disadvantages of U+UhySPEAc are the comparatively high costs of SPE columns and the comparatively long analysis time. In conclusion, the results of the presented study show that there is no reason to switch from the established U+UhyAc method to the U+UhySPEAc method in daily routine work. Semi-automated data evaluation proved to be very versatile and powerful tool in this study. In some cases it was clearly superior to manual data evaluation and should therefore become a useful tool also in routine analysis.

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8 ABBREVIATIONS

APCI	Atmospheric Pressure Chemical Ionization
DAD	Diode Array Detection
EI	Electron Ionization
ESI	Electrospray Ionization
GC	Gas Chromatographic
GC- MS	Gas Chromatographic-Mass Spectrometry
LLE	Liquid-liquid Extraction
MS	Mass Spectrometry
MPW	Maurer Pfleger Weber Mass spectral library[18,28]
SDB	Polystyrene-divinylbenzene Resin
SPE	Solid-phase Extraction
SPEC	Solid-phase Disc Extraction
SPME	Solid-phase Micro Extraction
STA	Systematic Toxicological Analysis
TIC	Total Ion Chromatogram
U+UhyAc	Acid hydrolysis/Liquid-liquid extraction/Acetylation
U+UhySPEAc	Acid hydrolysis/Solid-phase extraction/Acetylation
UV/VIS	Ultraviolet/Visible

9 APPENDIX 1

Table 1: Case number (patient ID), name of the detected parent drug, entry numbers of the mass spectra found in the MPW library, respective MPW library entry names.

Case No.	Detected Drug	MPW ENTRY NUMBER		MPW LIBRARY NAME
		U+UhySPEAc	U+UhyAc	
69506	Caffeine	191	191	Caffeine P204
	Naloxone	361	361	Naloxone AC P916
	Venlafaxine	5267	5267	Venlafaxine AC P713
	Venlafaxine	5269	5269	Venlafaxine-M (O-demethyl-) AC P642
	Venlafaxine	7185	7185	Venlafaxine-M -H2O AC P549
69511	Caffeine	191	191	Caffeine P204
	Diclofenac	716	716	Diclofenac -H2O @ P498
	Diclofenac	1212	1212	Diclofenac-M (HO-) -H2O iso-2 AC @ P782
	Diclofenac		2321	Diclofenac-M (HO-) -H2O iso-1 AC @ P782
	Diclofenac		2322	Diclofenac-M/artifact @ P863
	Diclofenac		2324	Diclofenac -H2O ME @ P567
	Fenofibrat	1940	1940	Fenofibrate P884
	Fenofibrat	3039	3039	Fenofibrate-M (HOOC-) ME P767
	Lidocaine	1061	1061	Lidocaine P321
	Lidocaine	1066	1066	Lidocaine-M (deethyl-) AC P372
	Lidocaine	2585	2585	Lidocaine AC P498
	Oxazepam	273	273	Oxazepam HYAC @ P480
	Oxazepam	300	300	Oxazepam artifact-1 @ P342
	Oxazepam	301	301	Oxazepam-M artifact-2 @ P397
	Oxazepam	419	419	Oxazepam HY @ P308
	Oxazepam	1257		Oxazepam artifact-3 P604
69514	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
	Tilidine	259	259	Tilidine-M (bis-nor-) AC P548
	Tilidine		260	Tilidine-M (nor-) AC P621
69524	Diazepam		272	Diazepam HY @ P358
	Diazepam	621		Diazepam-M (HO-) AC @ P816
	Doxepin	31	31	Doxepin-M (nor-HO-) isomer-2 2AC P901
	Doxepin	332	332	Doxepin P513
	Doxepin	333	333	Doxepin-M (N-oxide) -(CH3)2NOH P320
	Doxepin	335	335	Doxepin-M -(CH3)2NOH AC P575
	Doxepin	337	337	Doxepin-M (nor-) AC P649
	Doxepin	338	338	Doxepin-M (nor-HO-) isomer-1 2AC P901
	Doxepin	4470		Doxepin artifact P244
	Ibuprofen	1941	1941	Ibuprofen P231
	Ibuprofen	1942	1942	Ibuprofen ME P274
	Ibuprofen	3380	3380	Ibuprofen-M (HO-) -H2O ME P265

	Ibuprofen	3381	3381	Ibuprofen-M (HO-) isomer-1 ME P330
	Ibuprofen	3382	3382	Ibuprofen-M (HO-) -H2O P226
	Ibuprofen	3385		Ibuprofen-M (HO-) MEAC P508
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
	Oxazepam	273	273	Oxazepam HYAC @ P480
	Oxazepam		419	Oxazepam HY @ P308
	Pipamperone	179	179	Pipamperone P937
	Pipamperone		5586	Pipamperone-M (dihydro-) -H2O P881
	Tilidine	259	259	Tilidine-M (bis-nor-) AC P548
	Tilidine	260	260	Tilidine-M (nor-) AC P621
69542	Aripiprazol	7123	7123	Aripiprazole-M (N-dealkyl-) AC P477
	Caffeine	191	191	Caffeine P204
	Clozapine	320	320	Clozapine P739
	Clozapine	322	322	Clozapine-M (nor-) AC P861
	Clozapine	323	323	Clozapine-M (nor-) 2AC P1006
	Clozapine		2604	Clozapine AC P913
	Clozapine		6766	Clozapine-M/artifact P945
	Fluoxetine	4338	4338	Fluoxetine-M (nor-) AC P792
	Fluoxetine	5342	5342	Fluoxetine-M (nor-) HY2AC P324
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
69547	Amitriptyline	37	37	Amitriptyline P503
	Amitriptyline	42	42	Amitriptyline-M -H2O AC @ P629
	Amitriptyline	46	46	Amitriptyline-M -H2O -(CH3)2NOH @ P307
	Amitriptyline	1873	1873	Amitriptyline-M -H2O AC @ P558
	Bisoprolol	2791	2791	Bisoprolol 2AC P1040
	Bisoprolol		2932	Bisoprolol-M (phenol) P245
	Caffeine	191	191	Caffeine P204
	Clomipramine		318	Clomipramine-M (nor-HO-) 2AC P1018
	Clomipramine		1176	Clomipramine-M (nor-) AC P818
	Lidocaine	1061	1061	Lidocaine P321
	Lidocaine		1063	Lidocaine-M (deethyl-) P231
	Lidocaine		2585	Lidocaine AC P498
	Morphine	225	225	Morphin 2AC @ P915
	Morphine	474	474	Morphine @ P539
	Morphine	2341	2341	Heroin-M (3-acetyl-morphine) P744
	Morphine	525	525	Heroin-M (6-acetyl-morphine) P744
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Oxycodone		247	Oxycodone AC P873
	Oxycodone	583	583	Oxycodone P689
	Oxycodone	1191	1191	Oxycodone-M (nor-dihydro-) 2AC P976
	Oxycodone	1192		Oxycodone-M (nor-dihydro-) 3AC P1078
	Oxycodone		7167	Oxymorphone AC @ P821
	Promethazine		381	Promethazine P535

	Promethazine	382	382	Promethazine-M (nor-) AC P675
	Promethazine	383	383	Promethazine-M (HO-) AC P817
	Promethazine	384	384	Promethazine-M (nor-HO-) 2AC P919
69567	Caffeine	191	191	Caffeine P204
	Chlorprothixene		313	Chlorprothixene-M isomer-1 AC P935
	Chlorprothixene		436	Chlorprothixene-M @ P541
	Chlorprothixene		3733	Chlorprothixene-M isomer-2 AC P935
	Chlorprothixene		3734	Chlorprothixene-M AC P762
	Diclofenac	716	716	Diclofenac -H2O @ P498
	Diclofenac	1212	1212	Diclofenac-M (HO-) -H2O iso-2 AC @ P782
	Diclofenac		2321	Diclofenac-M (HO-) -H2O iso-1 AC @ P782
	Diclofenac		4469	Diclofenac @ P588
	Diclofenac		6467	Diclofenac-M (HO-) -H2O @ P578
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
	Melperone	174	174	Melperone P436
	Melperone	175	175	Melperone-M (dihydro-) AC P652
	Melperone	176	176	Melperone-M (dihydro-) -H2O P369
	Melperone	6511	6511	Melperone-M (dihydro-oxo-) -H2O P427
	Valproic Acid	1019	1019	Valproic acid P123
	Valproic Acid	4670	4670	Valpromide P122
	Zopiclone		7801	Zopiclone-M/artifact @ P361
69633	Caffeine	191	191	Caffeine P204
	Duloxetine	7465	7465	Duloxetine-M/artifact -H2O AC P207
	Duloxetine		933	Duloxetine-M (4-HO-naphthol)2AC @ P355
	Haloperidol		181	Haloperidol-M -2H2O @ P191
	Haloperidol		182	Haloperidol-M -H2O AC P322
	Haloperidol	340	340	Haloperidol P936
	Haloperidol	523	523	Haloperidol -H2O P873
	Haloperidol		524	Haloperidol-M (N-dealkyl-) AC @ P393
	Lorazepam		290	Lorazepam HYAC @ P647
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
	Olanzapine	4675	4675	Olanzapine P676
	Olanzapine	4676	4676	Olanzapine AC P862
	Prothipendyl		385	Prothipendyl P539
	Prothipendyl	386	386	Prothipendyl-M (ring) @ P219
	Prothipendyl	387	387	Prothipendyl-M (bis-nor-) AC P610
	Prothipendyl	389	389	Prothipendyl-M (nor-) AC P679
	Oxazepam		273	Oxazepam HYAC @ P480
69640	Caffeine	191	191	Caffeine P204
	Citalopram	4452	4452	Citalopram P732
	Citalopram	4454	4454	Citalopram-M (bis-nor-) AC P797
	Citalopram	4455	4455	Citalopram-M (nor-) AC P854
	Diazepam		272	Diazepam HY @ P358

	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
	Oxazepam	273	273	Oxazepam HYAC @ P480
	Prothipendyl	385	385	Prothipendyl P539
	Prothipendyl	386	386	Prothipendyl-M (ring) @ P219
	Prothipendyl	387	387	Prothipendyl-M (bis-nor-) AC P610
	Prothipendyl	388	388	Prothipendyl-M (HO-) AC P821
	Prothipendyl	389	389	Prothipendyl-M (nor-) AC P679
	Prothipendyl	612		Prothipendyl-M (HO-) P619
69678	Citalopram	4452		Citalopram P732
	Citalopram	4454	4454	Citalopram-M (bis-nor-) AC P797
	Citalopram	4455	4455	Citalopram-M (nor-) AC P854
	Diazepam	272	272	Diazepam HY @ P358
	Diazepam		2542	Diazepam HYAC @ P546
	Morphine	225	225	Morphin 2AC @ P915
	Morphine	525	525	Heroin-M (6-acetyl-morphine) P744
	Oxazepam	273	273	Oxazepam HYAC @ P480
	Oxazepam	301		Oxazepam-M artifact-2 @ P397
	Oxycodone	583		Oxycodone P689
	Oxycodone	1189		Oxycodone-M (dihydro-) 2AC P1021
	Oxycodone		1192	Oxycodone-M (nor-dihydro-) 3AC P1078
	Trimethoprim	1004	1004	Trimethoprim P564
	Trimethoprim	1005	1005	Trimethoprim isomer-1 AC P769
	Trimethoprim		1006	Trimethoprim 2AC P934
	Trimethoprim	2576	2576	Trimethoprim isomer-2 AC P769
69680	Caffeine	191	191	Caffeine P204
	Chlorprothixene	312	312	Chlorprothixene P688
	Chlorprothixene	313	313	Chlorprothixene-M isomer-1 AC P935
	Chlorprothixene	436	436	Chlorprothixene-M @ P541
	Chlorprothixene	438	438	Chlorprothixene-M -(CH3)2NOH @ P467
	Chlorprothixene	1259	1259	Chlorprothixene-M (nor-) AC P820
	Chlorprothixene		2641	Chlorprothixene-M/artifact @ P361
	Chlorprothixene		3732	Chlorprothixene-artifact P697
	Chlorprothixene		3734	Chlorprothixene-M AC P762
	Chlorprothixene	3736	3736	Chlorprothixene-M (bis-nor-) AC P753
	Chlorprothixene	4163	4163	Chlorprothixene-M isomer-1 AC P929
	Diazepam		272	Diazepam HY @ P358
	Diazepam		2542	Diazepam HYAC @ P546
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
	Nordazepam	463		Nordazepam @ P468
	Oxazepam	273	273	Oxazepam HYAC @ P480
	Pipamperone	179	179	Pipamperone P937
	Pipamperone	597		Pipamperone-M (HO-) P990
	Pipamperone	598	598	Pipamperone-M (N-dealkyl-) AC P396

	Pipamperone	599	599	Pipamperone-M (HO-) AC P1086
	Pipamperone	1914	1914	Pipamperone artifact P145
	Pipamperone	5586	5586	Pipamperone-M (dihydro-) -H2O P881
69681	Caffeine	191	191	Caffeine P204
	Clopidogrel	5704	5704	Clopidogrel P717
	Fluoxetine	4278	4278	Fluoxetine AC P848
	Fluoxetine	4338	4338	Fluoxetine-M (nor-) AC P792
	Fluoxetine	5342		Fluoxetine-M (nor-) HY2AC P324
	Ibuprofen	1941	1941	Ibuprofen P231
	Ibuprofen	1942	1942	Ibuprofen ME P274
	Ibuprofen	3380	3380	Ibuprofen-M (HO-) -H2O ME P265
	Ibuprofen	3381	3381	Ibuprofen-M (HO-) isomer-1 ME P330
	Ibuprofen	3384		Ibuprofen-M (HOOC-) 2ME P439
	Ibuprofen	3385	3385	Ibuprofen-M (HO-) MEAC P508
	Melperone	174	174	Melperone P436
	Melperone	176	176	Melperone-M (dihydro-) AC P652
	Metformine	6311	6311	Metformine artifact-1 P133
	Metformine	6510		Metformine artifact-1 AC P207
	Metoprolol	1133	1133	Metoprolol 2AC P850
	Metoprolol	1134	1134	Metoprolol -H2O AC P572
	Mirtazapine	4487	4487	Mirtazapine P446
	Mirtazapine	4488	4488	Mirtazapine-M (nor-) AC P581
	Mirtazapine	4489	4489	Mirtazapine-M (nor-HO-) 2AC P849
	Mirtazapine	4490	4490	Mirtazapine-M (HO-) AC P728
	Mirtazapine	4498		Mirtazapine-M (HO-) P523
	Mirtazapine	5261		Mirtazapine-M (oxo-) P511
	Moxonidine	6806	6806	Moxonidine AC P528
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
	Ramipril	4769	4769	Ramipril-M/artifact -H2O P1012
	Ramipril		4770	Ramipril-M/artifact -H2O ME @ P968
69689	Caffeine	191	191	Caffeine P204
	Clomethiazole		1461	Clomethiazole-M -H2O AC P181
	Clorazepate		3143	Clorazepate-M (HO-) HYAC @ P556
	Diazepam	272	272	Diazepam HY @ P358
	Diazepam	2542	2542	Diazepam HYAC @ P546
	Oxazepam	273	273	Oxazepam HYAC @ P480
69705	Caffeine	191	191	Caffeine P204
	Diazepam		272	Diazepam HY @ P358
	Diphenhydramine	731		Diphenhydramine P403
	Diphenhydramine	735	735	Diphenhydramine-M (nor-) AC P529
	Diphenhydramine	1241	1241	Diphenhydramine HYAC @ P294
	Diphenhydramine	1333		Diphenhydramine HY @ P184
	Diphenhydramine		1625	Diphenhydramine-M @ P299
	Diphenhydramine		2079	Diphenhydramine-M AC P470

	Ibuprofen	1942	1942	Ibuprofen ME P274
	Metoclopramide	1125	1125	Metoclopramide P611
	Metoclopramide	1126	1126	Metoclopramide AC P812
	Mirtazapine	4487	4487	Mirtazapine P446
	Mirtazapine	4488	4488	Mirtazapine-M (nor-) AC P581
	Mirtazapine		4489	Mirtazapine-M (nor-HO-) 2AC P849
	Mirtazapine	4490	4490	Mirtazapine-M (HO-) AC P728
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Ofloxacin	4691	4691	Ofloxacin -CO2 P697
	Oxazepam	273	273	Oxazepam HYAC @ P480
	Oxazepam	300	300	Oxazepam artifact-1 @ P342
	Oxazepam	301		Oxazepam-M artifact-2 @ P397
	Oxazepam	419	419	Oxazepam HY @ P308
	Pipamperone	179	179	Pipamperone P937
	Pipamperone	598	598	Pipamperone-M (N-dealkyl-) AC P396
	Pipamperone	599	599	Pipamperone-M (HO-) AC P1086
	Pipamperone		5586	Pipamperone-M (dihydro-) -H2O P881
69743				
	Caffeine	191	191	Caffeine P204
	Clorazepate	2112		Clorazepate-M (HO-) HY @ P365
	Clorazepate		3143	Clorazepate-M (HO-) HYAC @ P556
	Diazepam	272	272	Diazepam HY @ P358
	Diazepam		481	Diazepam @ P532
	Diazepam	2542	2542	Diazepam HYAC @ P546
	Fluoxetine	4278	4278	Fluoxetine AC P848
	Fluoxetine	4338	4338	Fluoxetine-M (nor-) AC P792
	Niotine	692	692	Nicotine-M (cotinine) @ P163
	Niotine		1150	Nicotine P142
69746	Oxazepam	273	273	Oxazepam HYAC @ P480
	Oxazepam	301	301	Oxazepam-M artifact-2 @ P397
	Oxazepam		419	Oxazepam HY @ P308
	Oxazepam	1257		Oxazepam artifact-3 P604
	Paracetamol		188	Paracetamol AC @ P199
	Paracetamol		201	Paracetamol-M (methoxy-) AC @ P283
	Paracetamol	825	825	Paracetamol @ P129
	Paracetamol	6550	6550	Paracetamol-D4 AC P212
	Salicylic Acid		953	Salicylic acid @ P118
	Salicylic Acid		954	Salicylic acid ME @ P130
	Temazepam	2099	2099	Temazepam AC @ P816
	Citalopram	4452	4452	Citalopram P732
	Citalopram	4454	4454	Citalopram-M (bis-nor-) AC P797
69753	Citalopram	4455	4455	Citalopram-M (nor-) AC P854
	Flurazepam	286	286	Flurazepam-M (dealkyl-) HYAC @ P567
	Metformine	6311		Metformine artifact-1 P133
	Metformine	6510	6510	Metformine artifact-1 AC P207

69761	Caffeine	191	191	Caffeine P204
	Mirtazapine	4487	4487	Mirtazapine P446
	Mirtazapine	4488	4488	Mirtazapine-M (nor-) AC P581
	Mirtazapine		4489	Mirtazapine-M (nor-HO-) 2AC P849
	Mirtazapine	4490	4490	Mirtazapine-M (HO-) AC P728
	Mirtazapine	4498	4498	Mirtazapine-M (HO-) P523
	Mirtazapine	5261	5261	Mirtazapine-M (oxo-) P511
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Venlafaxine	5269	5269	Venlafaxine-M (O-demethyl-) AC P642
	Venlafaxine	5276	5276	Venlafaxine-M (nor-) P437
	Venlafaxine		5279	Venlafaxine-M (HO-) isomer-2 P583
	Venlafaxine	7185	7185	Venlafaxine-M -H2O AC P549
69783	Amfetamine		55	Amfetamine AC @ P165
	Amfetamine		1804	Amfetamine-M (4-HO-) 2AC @ P324
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
69816	Cafedrine	772	772	Etofylline AC @ P448
	Cafedrine	1313	1313	Cafedrine -H2O P803
	Cafedrine	1739	1739	Cafedrine -H2O AC P957
	Cafedrine	1886	1886	Cafedrine-M (N-dealkyl-) AC @ P443
	Cafedrine	778	778	Fenetylline P814
	Cafedrine	779		Fenetylline AC P964
	Caffeine	191	191	Caffeine P204
	Fentanyl	788	788	Fentanyl P790
	Fentanyl		7368	Fentanyl-D5 P815
	Lidocaine	1061	1061	Lidocaine P321
	Lidocaine		1064	Lidocaine-M 2AC P277
	Lidocaine		1065	Lidocaine-M 3AC P434
	Lidocaine	1066	1066	Lidocaine-M (deethyl-) AC P372
	Metamizol	183	183	Metamizol-M AC @ P359
	Metamizol	184	184	Metamizol-M (dealkyl-) AC @ P416
	Metamizol	220	220	Metamizol-M (dealkyl-) @ P261
	Metoclopramide	1125	1125	Metoclopramide P611
	Metoclopramide	1126	1126	Metoclopramide AC P812
	Metoprolol	1133	1133	Metoprolol 2AC P850
	Midazolam	296	296	Midazolam-M (HO-) AC P962
	Norpseudephedrine	1154	1154	d-Norpseudoephedrine @ P129
	Paracetamol		188	Paracetamol AC @ P199
	Paracetamol		825	Paracetamol @ P129
69818	Caffeine	191	191	Caffeine P204
	Leflunomide	7372	7372	Leflunomide HYAC @ P223
69829	Amitriptyline	41	41	Amitriptyline-M (nor-) AC @ P640
	Amitriptyline	42	42	Amitriptyline-M -H2O AC @ P629
	Amitriptyline	46	46	Amitriptyline-M -H2O -(CH3)2NOH @ P307
	Amitriptyline	1873	1873	Amitriptyline-M -H2O AC @ P558

	Amitriptyline		1874	Amitriptyline-M -(CH3)2NOH AC @ P564
	Amitriptyline		2541	Amitriptyline-M -(CH3)2NOH AC @ P552
	Caffeine	191	191	Caffeine P204
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
69834	Caffeine	191	191	Caffeine P204
	Carbamazepine	309	309	Carbamazepine-M/artifact @ P200
	Carbamazepine	420	420	Carbamazepine P328
	Carbamazepine	421	421	Carbamazepine-M (acridine) @ P170
	Carbamazepine	422	422	Carbamazepine-M (formyl-acridine) P232
	Carbamazepine	425	425	Carbamazepine-M (HO-ring) AC @ P383
	Carbamazepine	2671	2671	Carbamazepine-M/artifact AC @ P323
	Carbamazepine		2672	Carbamazepine-M (HO-ring) 2AC @ P579
	Diazepam		2542	Diazepam HYAC @ P546
	Olanzapine	4675	4675	Olanzapine P676
	Olanzapine		4676	Olanzapine AC P862
	Oxazepam	273	273	Oxazepam HYAC @ P480
	Oxazepam	419	419	Oxazepam HY @ P308
	Oxcarbazepine	6065	6065	Oxcarbazepine P388
	Oxcarbazepine	6067	6067	Oxcarbazepine enol AC P585
69835	Biperiden	103	103	Biperiden-M (HO-) AC P918
	Caffeine	191	191	Caffeine P204
	Diazepam		272	Diazepam HY @ P358
	Diazepam		2060	Diazepam-M (HO-) HYAC @ P626
	Haloperidol		523	Haloperidol -H2O P873
	Ibuprofen		1941	Ibuprofen P231
	Ibuprofen	1942	1942	Ibuprofen ME P274
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
	Olanzapine	4676	4676	Olanzapine AC P862
	Olanzapine		4677	Olanzapine-M (nor-) 2AC P959
	Oxazepam	273	273	Oxazepam HYAC @ P480
	Prothipendyl		385	Prothipendyl P539
	Prothipendyl	386	386	Prothipendyl-M (ring) @ P219
	Prothipendyl	387	387	Prothipendyl-M (bis-nor-) AC P610
	Prothipendyl		388	Prothipendyl-M (HO-) AC P821
	Prothipendyl	389	389	Prothipendyl-M (nor-) AC P679
	Prothipendyl		1883	Prothipendyl-M (bis-nor-HO-) 2AC P872
	Zopiclone		5316	Zopiclone-M AC P157
69836				
69838	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
	Lorazepam		290	Lorazepam HYAC @ P647
69840	Caffeine	191	191	Caffeine P204
	Nicotine	692	692	Nicotine-M (cotinine) @ P163

69849	Amfetamine	55		Amfetamine AC @ P165
	Amfetamine		1803	Amfetamine-M (4-HO-) AC @ P201
	Amfetamine	5515	5515	Amfetamine AC @ P165
	Caffeine	191	191	Caffeine P204
	Doxepin		31	Doxepin-M (nor-HO-) isomer-2 2AC P901
	Doxepin	333	333	Doxepin-M (N-oxide) -(CH3)2NOH P320
	Doxepin	337	337	Doxepin-M (nor-) AC P649
	Lidocaine	1061	1061	Lidocaine P321
	Lidocaine	1066	1066	Lidocaine-M (deethyl-) AC P372
	Lidocaine	2585	2585	Lidocaine AC P498
	Lidocaine	6784	6784	Lidocaine artifact P313
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
69850	Caffeine	191	191	Caffeine P204
	Nicotine		692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
69854	Caffeine	191	191	Caffeine P204
	Lidocaine	1061	1061	Lidocaine P321
	Lidocaine	1066	1066	Lidocaine-M (deethyl-) AC P372
	Lidocaine		6784	Lidocaine artifact P313
	Midazolam		294	Midazolam P734
	Midazolam	296	296	Midazolam-M (HO-) AC P962
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Oxazepam	273	273	Oxazepam HYAC @ P480
69855	Caffeine	191	191	Caffeine P204
	Haloperidol	340	340	Haloperidol P936
	Lorazepam		290	Lorazepam HYAC @ P647
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
	Olanzapine	4675	4675	Olanzapine P676
	Oxazepam		273	Oxazepam HYAC @ P480
	Prothipendyl	386	386	Prothipendyl-M (ring) @ P219
	Prothipendyl	387	387	Prothipendyl-M (bis-nor-) AC P610
69881	Oxazepam	273	273	Oxazepam HYAC @ P480
69890	Caffeine	191	191	Caffeine P204
	Mirtazapine	4487	4487	Mirtazapine P446
	Mirtazapine	4488	4488	Mirtazapine-M (nor-) AC P581
	Mirtazapine	4490	4490	Mirtazapine-M (HO-) AC P728
	Mirtazapine		4497	Mirtazapine-M (nor-) P385
	Mirtazapine	4498		Mirtazapine-M (HO-) P523
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Promethazine		382	Promethazine-M (nor-) AC P675
	Promethazine		384	Promethazine-M (nor-HO-) 2AC P919
	Promethazine	610		Promethazine-M (nor-sulfoxide) AC P749
	Prothipendyl	386	386	Prothipendyl-M (ring) @ P219
	Prothipendyl	387	387	Prothipendyl-M (bis-nor-) AC P610

	Prothipendyl	389	389	Prothipendyl-M (nor-) AC P679
	Prothipendyl		2275	Prothipendyl-M (HO-ring) AC @ P412
	Quetiapine	6431	6431	Quetiapine AC P1070
	Quetiapine	6432	6432	Quetiapine-M (-COOH) ME P1044
	Quetiapine	6433	6433	Quetiapine-M (N-CH2-COOH) ME P908
	Quetiapine	6434	6434	Quetiapine-M (N-dealkyl-) AC P792
	Quetiapine		6435	Quetiapine-M (N-dealkyl-HO-) 2AC P1001
	Quetiapine	6436	6436	Quetiapine-M (N-dealkyl-) art. AC P639
	Quetiapine	6438	6438	Quetiapine-M (N-dealkyl-) P590
	Quetiapine	6448	6448	Quetiapine P963
69897	Amfetamine		55	Amfetamine AC @ P165
	Bromazepam	127	127	Bromazepam HY @ P494
	Bromazepam	128	128	Bromazepam-M (3-HO-) artifact-1 P537
	Bromazepam	129	129	Bromazepam HYAC @ P701
	Bromazepam		2116	Bromazepam-M (3-HO-) artifact-2 P609
	Bromazepam	2700	2700	Bromazepam-M/artifact P691
	Caffeine	191	191	Caffeine P204
	Flunitrazepam		282	Flunitrazepam HY P484
	Flunitrazepam		283	Flunitrazepam-M (nor-) HY P420
	Flunitrazepam	284	284	Flunitrazepam-M HY2AC P684
	Flunitrazepam	501	501	Flunitrazepam-M (amino-) AC P734
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
69901	Caffeine	191	191	Caffeine P204
	Clomethiazole		452	Clomethiazole-M (1-HO-ethyl-) AC P268
	Clomethiazole		1461	Clomethiazole-M -H2O AC P181
	Clomethiazole		3310	Clomethiazole-M (2-HO-) AC P268
	Clomethiazole	4622		Clomethiazole-M (1-HO-ethyl-) TMS P373
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
	Prothipendyl	386	386	Prothipendyl-M (ring) @ P219
	Prothipendyl	387	387	Prothipendyl-M (bis-nor-) AC P610
	Prothipendyl	389	389	Prothipendyl-M (nor-) AC P679
	Prothipendyl		1883	Prothipendyl-M (bis-nor-HO-) 2AC P872
69910	Diphenhydramine	731	731	Diphenhydramine P403
	Diphenhydramine	735	735	Diphenhydramine-M (nor-) AC P529
	Diphenhydramine	2049		Diphenhydramine-M (deamino-HO-) P301
	Diphenhydramine	4483	4483	Diphenhydramine-M (methoxy-) HY P255
	Metoprolol	1133	1133	Metoprolol 2AC P850
	Metoprolol	1134	1134	Metoprolol -H2O AC P572
	Oxazepam	273	273	Oxazepam HYAC @ P480
	Oxazepam	419		Oxazepam HY @ P308
	Phenprocoumon	4822	4822	Phenprocoumon HY P400
	Tetrazepam	2058	2058	Tetrazepam-M (oxo-) HY P434
69911	Caffeine	191	191	Caffeine P204
	Nicotine	692	692	Nicotine-M (cotinine) @ P163

69925	Caffeine	191	191	Caffeine P204
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
69926	Caffeine	191	191	Caffeine P204
69949	Caffeine	191	191	Caffeine P204
	Clozapine	320	320	Clozapine P739
	Clozapine		322	Clozapine-M (nor-) AC P861
	Diazepam		272	Diazepam HY @ P358
	Duloxetine	7465	7465	Duloxetine-M/artifact -H2O AC P207
	Flunitrazepam		504	Flunitrazepam-M (amino-) HY P355
	Haloperidol		340	Haloperidol P936
	Haloperidol		523	Haloperidol -H2O P873
	Ibuprofen	1942	1942	Ibuprofen ME P274
	Ibuprofen		3381	Ibuprofen-M (HO-) isomer-1 ME P330
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
	Nordazepam	463		Nordazepam @ P468
	Olanzapine	4675	4675	Olanzapine P676
	Olanzapine		4676	Olanzapine AC P862
	Oxazepam	273	273	Oxazepam HYAC @ P480
	Oxazepam	419		Oxazepam HY @ P308
	Pipamperone	179	179	Pipamperone P937
	Promethazine	381	381	Promethazine P535
	Promethazine	382	382	Promethazine-M (nor-) AC P675
	Promethazine		383	Promethazine-M (HO-) AC P817
	Promethazine		384	Promethazine-M (nor-HO-) 2AC P919
	Promethazine	608	608	Promethazine-M (nor-HO-) P543
	Promethazine	609		Promethazine-M (HO-) P616
	Promethazine	610		Promethazine-M (nor-sulfoxide) AC P749
	Promethazine		1319	Promethazine-M (bis-nor-) AC @ P605
69952	Caffeine	191	191	Caffeine P204
	Methylphenidate		1119	Methylphenidate AC P490
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Pipamperone		179	Pipamperone P937
	Pipamperone		5586	Pipamperone-M (dihydro-) -H2O P881
69971	Amfetamine		1804	Amfetamine-M (4-HO-) 2AC @ P324
	Caffeine	191	191	Caffeine P204
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
	Ofloxacin	4691		Ofloxacin -CO2 P697
	Oxazepam		273	Oxazepam HYAC @ P480
69973	Amitriptyline		41	Amitriptyline-M (nor-) AC @ P640
	Amitriptyline		42	Amitriptyline-M -H2O AC @ P629
	Caffeine	191	191	Caffeine P204
	Nicotine	692	692	Nicotine-M (cotinine) @ P163

	Nicotine	1150	1150	Nicotine P142
	Oxazepam		419	Oxazepam HY @ P308
69974	Bromazepam		129	Bromazepam HYAC @ P701
	Caffeine	191	191	Caffeine P204
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
69980	Caffeine	191	191	Caffeine P204
	Diazepam		272	Diazepam HY @ P358
	Diazepam		2542	Diazepam HYAC @ P546
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
	Olanzapine	4675	4675	Olanzapine P676
	Olanzapine	4676	4676	Olanzapine AC P862
	Olanzapine	4677	4677	Olanzapine-M (nor-) 2AC P959
	Oxazepam	273	273	Oxazepam HYAC @ P480
	Oxazepam	301		Oxazepam-M artifact-2 @ P397
	Prothipendyl	386	386	Prothipendyl-M (ring) @ P219
	Prothipendyl	387	387	Prothipendyl-M (bis-nor-) AC P610
	Prothipendyl		389	Prothipendyl-M (nor-) AC P679
69997	Amfetamine		54	Amfetamine @ P115
	Amfetamine	55		Amfetamine AC @ P165
	Amfetamine	1803	1803	Amfetamine-M (4-HO-) AC @ P201
	Amfetamine	5515	5515	Amfetamine AC @ P165
	Amfetamine		5907	N-Hydroxy-Amfetamine AC P201
	Diazepam	272	272	Diazepam HY @ P358
	Diazepam		621	Diazepam-M (HO-) AC @ P816
	Naloxone	3720	3720	Naloxone-M (dihydro-) 3AC P1121
	Naloxone	4316		Naltrexone-M (methoxy-) AC P1048
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
	Oxazepam	273	273	Oxazepam HYAC @ P480
	Oxazepam	301		Oxazepam-M artifact-2 @ P397
	Tetrazepam	303	303	Tetrazepam isomer-1 HY P374
	Tetrazepam	304	304	Tetrazepam-M (HO-) isomer-1 HYAC P647
	Tetrazepam	305	305	Tetrazepam-M (HO-) isomer-2 HYAC P647
	Tetrazepam	616	616	Tetrazepam P552
	Tetrazepam	617		Tetrazepam-M (HO-) isomer-1 HY P442
	Tetrazepam	620	620	Tetrazepam-M (HO-) isomer-2 AC P831
	Tetrazepam	919	919	Tetrazepam-M (HO-) isomer-2 HY P442
	Tetrazepam	2059	2059	Tetrazepam isomer-2 HY P374
	Tetrazepam		2061	Tetrazepam-M isomer-2 HY2AC P900
	Tetrazepam	2064	2064	Tetrazepam-M (nor-HO-) HY2AC P783
	Tetrazepam	2087	2087	Tetrazepam-M (HO-) isomer-3 HYAC P647
	Tetrazepam	2088	2088	Tetrazepam-M (HO-) isomer-4 HYAC P648
	Tetrazepam	2092	2092	Tetrazepam-M (nor-) ALHY P322

	Tilidine	259	259	Tilidine-M (bis-nor-) AC P548
	Tilidine	624	624	Tilidine P482
	Tilidine	630	630	Tilidine-M (phenylcyclohexenone) P160
	Tilidine	1219	1219	Tilidine-M/artifact AC P249
	Tilidine	1220	1220	Tilidine-M/artifact-2AC P474
69998	Caffeine	191	191	Caffeine P204
	Carbamazepine	309	309	Carbamazepine-M/artifact @ P200
	Carbamazepine	420	420	Carbamazepine P328
	Carbamazepine	421	421	Carbamazepine-M (acridine) @ P170
	Carbamazepine	422	422	Carbamazepine-M (formyl-acridine) P232
	Carbamazepine		423	Carbamazepine-M (HO-methoxy-ring)@ P339
	Carbamazepine	425	425	Carbamazepine-M (HO-ring) AC @ P383
	Carbamazepine	2506	2506	Carbamazepine-M AC @ P521
	Carbamazepine	2511	2511	Carbamazepine-M (HO-ring) @ P241
	Carbamazepine	2671	2671	Carbamazepine-M/artifact AC @ P323
	Carbamazepine		2672	Carbamazepine-M (HO-ring) 2AC @ P579
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
	Oxcarbazepine	6065	6065	Oxcarbazepine P388
	Oxcarbazepine	6066	6066	Oxcarbazepine artifact ME P333
	Oxcarbazepine	6067	6067	Oxcarbazepine enol AC P585
	Paroxetine	5263	5263	Paroxetine-M isomer-2 2AC P1053
	Paroxetine	5265	5265	Paroxetine AC P923
70001	Clomipramine	122	122	Clomipramine-M (HO-) isomer-2 AC P928
	Clomipramine	315	315	Clomipramine P686
	Clomipramine	316	316	Clomipramine-M (ring) P303
	Clomipramine	317	317	Clomipramine-M (HO-) isomer-1 AC P927
	Clomipramine	318	318	Clomipramine-M (nor-HO-) 2AC P1018
	Clomipramine	1176	1176	Clomipramine-M (nor-) AC P818
	Clomipramine		4159	Clomipramine-M (HO-ring) AC P546
	Flurazepam	286	286	Flurazepam-M (dealkyl-) HYAC @ P567
	Flurazepam	512		Flurazepam-M (dealkyl-) HY @ P373
	Flurazepam	5735		Flurazepam-M/artifact AC P545
	Lidocaine	57		Lidocaine-M (dimethylaniline) AC @ P142
	Lidocaine	1061	1061	Lidocaine P321
	Lidocaine	1066	1066	Lidocaine-M (deethyl-) AC P372
	Lidocaine	2585	2585	Lidocaine AC P498
	Lidocaine	6784	6784	Lidocaine artifact P313
	Metamizol	183	183	Metamizol-M AC @ P359
	Metamizol	184	184	Metamizol-M (dealkyl-) AC @ P416
	Metamizol	3333	3333	Metamizol-M 2AC @ P547
	Ticlopidine	996	996	Ticlopidine P433
	Ticlopidine		6475	Ticlopidine-M (HO-) isomer-1 AC P717
	Trimipramine	410	410	Trimipramine P587
	Trimipramine	411	411	Trimipramine-M (HO-) AC P856

	Trimipramine	412	412	Trimipramine-M (nor-HO-) 2AC P953
	Trimipramine	413	413	Trimipramine-M (nor-di-HO-) 3AC P1095
	Trimipramine	640	640	Trimipramine-M (HO-) P669
	Trimipramine	991	991	Trimipramine-M (nor-HO-) -H2O AC P716
	Trimipramine	2290	2290	Trimipramine-M (nor-) AC P724
	Trimipramine	2676	2676	Trimipramine-M (bis-nor-HO-) 2AC P906
70003	Caffeine	191	191	Caffeine P204
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
	Sertraline	4682	4682	Sertraline -CH5N P483
	Sertraline	5310	5310	Sertraline-M (ketone) P562
70004	Amfetamine	55	55	Amfetamine AC @ P165
	Amfetamine		1804	Amfetamine-M (4-HO-) 2AC @ P324
	Amfetamine		5514	Amfetamine @ P115
	Caffeine	191	191	Caffeine P204
	Clorazepate	2112	2112	Clorazepate-M (HO-) HY @ P365
	Clorazepate	3143	3143	Clorazepate-M (HO-) HYAC @ P556
	Diazepam	272	272	Diazepam HY @ P358
	Diazepam		2060	Diazepam-M (HO-) HYAC @ P626
	Diazepam		2542	Diazepam HYAC @ P546
	Doxepin		333	Doxepin-M (N-oxide) -(CH3)2NOH P320
	Doxepin		334	Doxepin-M (HO-dihydro-) AC P804
	Doxepin		337	Doxepin-M (nor-) AC P649
	Nicotine		692	Nicotine-M (cotinine) @ P163
	Oxazepam	273	273	Oxazepam HYAC @ P480
	Oxazepam	300	300	Oxazepam artifact-1 @ P342
	Oxazepam	301	301	Oxazepam-M artifact-2 @ P397
	Oxazepam	419	419	Oxazepam HY @ P308
	Paroxetine		5263	Paroxetine-M isomer-2 2AC P1053
	Paroxetine	5265	5265	Paroxetine AC P923
	Paroxetine		5309	Paroxetine-M/artifact 2AC P581
	Paroxetine		5343	Paroxetine-M isomer-1 2AC P1053
	Temazepam	2099	2099	Temazepam AC @ P816
	Temazepam	5779		Temazepam artifact-2 @ P468
70033	Caffeine	191	191	Caffeine P204
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
70034	Bromazepam		129	Bromazepam HYAC @ P701
	Clomethiazole		1461	Clomethiazole-M -H2O AC P181
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
70035	Caffeine	191	191	Caffeine P204
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
70036	Caffeine	191	191	Caffeine P204
	Nicotine		692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142

70037	Caffeine	191	191	Caffeine P204
	Ibuprofen	1942	1942	Ibuprofen ME P274
	Ibuprofen		6386	Ibuprofen-M (HO-) isomer-2 ME P331
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
70041	Caffeine	191	191	Caffeine P204
	Clomethiazole		1461	Clomethiazole-M -H2O AC P181
	Clomethiazole		3310	Clomethiazole-M (2-HO-) AC P268
70049	Amfetamine		55	Amfetamine AC @ P165
	Caffeine	191	191	Caffeine P204
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
70051	Caffeine	191	191	Caffeine P204
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
70052	Caffeine	191	191	Caffeine P204
	Ibuprofen		1942	Ibuprofen ME P274
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
70054	Caffeine	191	191	Caffeine P204
	Clozapine		320	Clozapine P739
	Clozapine		322	Clozapine-M (nor-) AC P861
	Clozapine	323	323	Clozapine-M (nor-) 2AC P1006
	Clozapine	2604	2604	Clozapine AC P913
	Clozapine		7802	Clozapine-M/artifact AC P1062
	Diazepam		272	Diazepam HY @ P358
	Diazepam		2542	Diazepam HYAC @ P546
	Duloxetine		928	Duloxetine-M (1-naphthol) @ P123
	Duloxetine		932	Duloxetine-M (1-naphthol) AC @ P188
	Duloxetine		933	Duloxetine-M (4-HO-naphthol)2AC @ P355
	Duloxetine	7465	7465	Duloxetine-M/artifact -H2O AC P207
	Melperone	174	174	Melperone P436
	Melperone	175	175	Melperone-M (dihydro-) -H2O P369
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
	Nordazepam	463		Nordazepam @ P468
	Oxazepam	273	273	Oxazepam HYAC @ P480
	Oxazepam		419	Oxazepam HY @ P308
	Prothipendyl	387	387	Prothipendyl-M (bis-nor-) AC P610
70055	Caffeine	191	191	Caffeine P204
	Citalopram	4452	4452	Citalopram P732
	Citalopram	4454	4454	Citalopram-M (bis-nor-) AC P797
	Citalopram	4455	4455	Citalopram-M (nor-) AC P854
	Clomethiazole		447	Clomethiazole-M (dechloro-HOOC-) P137
	Clomethiazole	451	451	Clomethiazole-M AC P186

	Clomethiazole	452	452	Clomethiazole-M (1-HO-ethyl-) AC P268
	Diclofenac	716	716	Diclofenac -H2O @ P498
	Diclofenac	717	717	Diclofenac ME @ P658
	Diclofenac	1212	1212	Diclofenac-M (HO-) -H2O iso-2 AC @ P782
	Diclofenac	2321	2321	Diclofenac-M (HO-) -H2O iso-1 AC @ P782
	Diclofenac	2322		Diclofenac-M/artifact @ P863
	Diclofenac	4469		Diclofenac @ P588
	Diclofenac	6467	6467	Diclofenac-M (HO-) -H2O @ P578
	Diclofenac	6488		Diclofenac ET P725
	Diclofenac		6490	Diclofenac-M (HO-) -H2O ME @ P647
	Lorazepam	290		Lorazepam HYAC @ P647
	Lorazepam	543		Lorazepam HY @ P441
	Mepivacaine	1085	1085	Mepivacaine P364
	Mepivacaine	1086		Mepivacaine-M (HO-) P432
	Mepivacaine		2968	Mepivacaine-M (nor-) AC P487
	Metoprolol	1133	1133	Metoprolol 2AC P850
	Metoprolol	1134		Metoprolol -H2O AC P572
	Mirtazapine	4487	4487	Mirtazapine P446
	Mirtazapine	4488	4488	Mirtazapine-M (nor-) AC P581
	Mirtazapine	4490	4490	Mirtazapine-M (HO-) AC P728
	Mirtazapine	4498	4498	Mirtazapine-M (HO-) P523
	Mirtazapine		5261	Mirtazapine-M (oxo-) P511
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
	Zopiclone	5315	5315	Zopiclone-M P111
	Zopiclone	5316	5316	Zopiclone-M AC P157
	Zopiclone	6557		Zopiclone-M AC P187
	Zopiclone	7801	7801	Zopiclone-M/artifact @ P361
70063	Caffeine	191	191	Caffeine P204
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
70069	Caffeine	191	191	Caffeine P204
	Diclofenac	716	716	Diclofenac -H2O @ P498
	Diclofenac		1212	Diclofenac-M (HO-) -H2O iso-2 AC @ P782
	Diclofenac		6490	Diclofenac-M (HO-) -H2O ME @ P647
	Nicotine		692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
70085	Caffeine	191	191	Caffeine P204
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
	Olanzapine	4675	4675	Olanzapine P676
	Olanzapine	4676	4676	Olanzapine AC P862
	Olanzapine		4677	Olanzapine-M (nor-) 2AC P959
	Oxazepam	273	273	Oxazepam HYAC @ P480
70095	Caffeine	191	191	Caffeine P204

70123	Caffeine	191	191	Caffeine P204
	Diclofenac	716	716	Diclofenac -H2O @ P498
	Diclofenac		1212	Diclofenac-M (HO-) -H2O iso-2 AC @ P782
	Diclofenac	6490		Diclofenac-M (HO-) -H2O ME @ P647
	Doxepin		31	Doxepin-M (nor-HO-) isomer-2 2AC P901
	Doxepin	332	332	Doxepin P513
	Doxepin	333	333	Doxepin-M (N-oxide) -(CH3)2NOH P320
	Doxepin	335	335	Doxepin-M -(CH3)2NOH AC P575
	Doxepin	4470		Doxepin artifact P244
	Naloxone		361	Naloxone AC P916
	Naloxone	564		Naloxone 2ET P965
	Naloxone		2982	Naloxone 2AC P1045
	Naloxone		3720	Naloxone-M (dihydro-) 3AC P1121
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Tillidine	259	259	Tilidine-M (bis-nor-) AC P548
	Tillidine	260	260	Tilidine-M (nor-) AC P621
	Tillidine	630	630	Tilidine-M (phenylcyclohexenone) P160
	Tramadol		265	Tramadol-M -H2O 2AC P621
	Tramadol	4435	4435	Tramadol AC P641
	Tramadol	4436	4436	Tramadol artifact P191
	Tramadol	4439	4439	Tramadol-M (HO-) 2 AC P895
	Tramadol	4440	4440	Tramadol-M (N-demethyl-) AC P572
	Tramadol	4441	4441	Tramadol-M 2AC P711
70124	Caffeine	191	191	Caffeine P204
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
	Oxazepam	273	273	Oxazepam HYAC @ P480
	Oxazepam	301		Oxazepam-M artifact-2 @ P397
	Oxazepam		419	Oxazepam HY @ P308
70132	Bisoprolol	2791	2791	Bisoprolol 2AC P1040
	Bufexemac?	6085	6085	Bufexamac-M/artifact (HOOC-) ME P282
	Clomethiazole		450	Clomethiazole-M (2-HO-) P164
	Clomethiazole		1461	Clomethiazole-M -H2O AC P181
	Clomethiazole		3310	Clomethiazole-M (2-HO-) AC P268
	Clomethiazole	6560	6560	Clomethiazole-M P134
	Diphenhydramine	731	731	Diphenhydramine P403
	Diphenhydramine	733		Diphenhydramine-M (di-HO-) P356
	Diphenhydramine	735	735	Diphenhydramine-M (nor-) AC P529
	Diphenhydramine	1333		Diphenhydramine HY @ P184
	Diphenhydramine	2047	2047	Diphenhydramine-M (nor-) P348
	Diphenhydramine	2049	2049	Diphenhydramine-M (deamino-HO-) P301
	Diphenhydramine	2079	2079	Diphenhydramine-M AC P470
	Diphenhydramine	2425		Diphenhydramine-M (HO-) HY2AC @ P533
	Diphenhydramine	4483		Diphenhydramine-M (methoxy-) HY P255
	Doxepin		31	Doxepin-M (nor-HO-) isomer-2 2AC P901

	Doxepin	333	333	Doxepin-M (N-oxide) -(CH3)2NOH P320
	Doxepin	337	337	Doxepin-M (nor-) AC P649
	Doxepin		488	Doxepin-M (HO-) isomer-1 P593
	Doxepin		883	Doxepin-M (HO-) isomer-2 AC P794
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
70138	Caffeine	191	191	Caffeine P204
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
	Oxazepam		273	Oxazepam HYAC @ P480
	Oxazepam		419	Oxazepam HY @ P308
70144	Doxepin		31	Doxepin-M (nor-HO-) isomer-2 2AC P901
	Doxepin	332	332	Doxepin P513
	Doxepin	333	333	Doxepin-M (N-oxide) -(CH3)2NOH P320
	Doxepin		335	Doxepin-M -(CH3)2NOH AC P575
	Doxepin	337	337	Doxepin-M (nor-) AC P649
	Doxepin		338	Doxepin-M (nor-HO-) isomer-1 2AC P901
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
	Paracetamol		188	Paracetamol AC @ P199
	Paracetamol	5046	5046	Paracetamol ME @ P147
	Paracetamol		6550	Paracetamol-D4 AC P212
	Pipamperone	179	179	Pipamperone P937
	Pipamperone	598	598	Pipamperone-M (N-dealkyl-) AC P396
70154	Caffeine	191	191	Caffeine P204
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
	Oxazepam		273	Oxazepam HYAC @ P480
	Oxazepam		419	Oxazepam HY @ P308
70177	Caffeine	191	191	Caffeine P204
	Chlorprothixene		3734	Chlorprothixene-M AC P762
	Chlorprothixene		3741	Chlorprothixene-M 2AC P1086
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
70183				
70184	Caffeine	191	191	Caffeine P204
	Fluoxetine	4278	4278	Fluoxetine AC P848
	Fluoxetine	4338	4338	Fluoxetine-M (nor-) AC P792
	Fluoxetine	5342	5342	Fluoxetine-M (nor-) HY2AC P324
70186	Caffeine	191	191	Caffeine P204
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
70217	Amitriptyline	37	37	Amitriptyline P503
	Amitriptyline	42	42	Amitriptyline-M -H2O AC @ P629
	Amitriptyline	1873	1873	Amitriptyline-M -H2O AC @ P558
	Caffeine	191	191	Caffeine P204

	Chlordiazepoxid	432	432	Chlordiazepoxide artifact (deoxo) P528
	Clorazepate		1751	Clorazepate-M isomer-2 HY2AC @ P762
	Clorazepate		2112	Clorazepate-M (HO-) HY @ P365
	Clorazepate		2125	Clorazepate-M isomer-1 HY2AC @ P762
	Clorazepate		3143	Clorazepate-M (HO-) HYAC @ P556
	Diclofenac	716	716	Diclofenac -H2O @ P498
	Diclofenac	6490		Diclofenac-M (HO-) -H2O ME @ P647
	Metformine	6311	6311	Metformine artifact-1 P133
	Metformine	6510	6510	Metformine artifact-1 AC P207
	Nordazepam		463	Nordazepam @ P468
	Oxazepam	273	273	Oxazepam HYAC @ P480
	Oxazepam	300	300	Oxazepam artifact-1 @ P342
	Oxazepam	301	301	Oxazepam-M artifact-2 @ P397
	Oxazepam	419	419	Oxazepam HY @ P308
	Oxazepam	1257	1257	Oxazepam artifact-3 P604
70219	Caffeine	191	191	Caffeine P204
70220	Caffeine	191	191	Caffeine P204
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
70223	Caffeine	191	191	Caffeine P204
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
70234	Caffeine	191	191	Caffeine P204
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
70261	Caffeine	191	191	Caffeine P204
	Carbamazepine		309	Carbamazepine-M/artifact @ P200
	Ibuprofen	1941	1941	Ibuprofen P231
	Ibuprofen	1942	1942	Ibuprofen ME P274
	Ibuprofen	3380	3380	Ibuprofen-M (HO-) -H2O ME P265
	Ibuprofen	3381	3381	Ibuprofen-M (HO-) isomer-1 ME P330
	Ibuprofen	3383	3383	Ibuprofen-M (HO-) isomer-3 ME P331
	Ibuprofen	3385	3385	Ibuprofen-M (HO-) MEAC P508
	Ibuprofen	6386		Ibuprofen-M (HO-) isomer-2 ME P331
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Opipramol		427	Opipramol-M (N-dealkyl-) AC P889
	Opipramol		578	Opipramol P895
70262				
70264	Bromazepam		129	Bromazepam HYAC @ P701
	Bromazepam		2700	Bromazepam-M/artifact P691
	Caffeine	191	191	Caffeine P204
	Nordazepam	463		Nordazepam @ P468
	Olanzapine		4675	Olanzapine P676
	Olanzapine		4676	Olanzapine AC P862
	Oxazepam	273	273	Oxazepam HYAC @ P480

	Oxazepam	300	300	Oxazepam artifact-1 @ P342
	Oxazepam	301	301	Oxazepam-M artifact-2 @ P397
	Oxazepam	419	419	Oxazepam HY @ P308
	Oxazepam	1257		Oxazepam artifact-3 P604
	Venlafaxine		5266	Venlafaxine P504
	Venlafaxine	5269	5269	Venlafaxine-M (O-demethyl-) AC P642
	Venlafaxine		5272	Venlafaxine-M isomer-2 2AC P943
	Venlafaxine		5273	Venlafaxine-M (nor-) AC P642
	Venlafaxine	5276	5276	Venlafaxine-M (nor-) P437
	Venlafaxine	7185	7185	Venlafaxine-M -H2O AC P549
70274	Caffeine	191	191	Caffeine P204
	Diazepam	272	272	Diazepam HY @ P358
	Diazepam		2542	Diazepam HYAC @ P546
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
	Oxazepam	273	273	Oxazepam HYAC @ P480
	Oxazepam	300	300	Oxazepam artifact-1 @ P342
	Oxazepam	419	419	Oxazepam HY @ P308
74002	Amfetamine	54	54	Amfetamine @ P115
	Amfetamine		55	Amfetamine AC @ P165
	Amfetamine	1803		Amfetamine-M (4-HO-) AC @ P201
	Amfetamine	1804	1804	Amfetamine-M (4-HO-) 2AC @ P324
	Caffeine	191	191	Caffeine P204
	MDMA	4243	4243	MDMA-M isomer-2 2AC P512
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
74011	Ambroxol	20	20	Ambroxol 2AC @ P1127
	Ambroxol	21	21	Ambroxol-M/artifact AC P695
	Ambroxol	2228	2228	Ambroxol 3AC P1165
	Ambroxol	5131	5131	Ambroxol-M (HOOC-) ME @ P646
	Caffeine	191	191	Caffeine P204
	Clorazepate	2112	2112	Clorazepate-M (HO-) HY @ P365
	Clorazepate	3143	3143	Clorazepate-M (HO-) HYAC @ P556
	Diazepam		272	Diazepam HY @ P358
	Diazepam		619	Diazepam-M (HO-) @ P614
	Diazepam		621	Diazepam-M (HO-) AC @ P816
	Diazepam		2060	Diazepam-M (HO-) HYAC @ P626
	Diazepam		2542	Diazepam HYAC @ P546
	Haloperidol		182	Haloperidol-M -H2O AC P322
	Haloperidol	523	523	Haloperidol -H2O P873
	Haloperidol		524	Haloperidol-M (N-dealkyl-) AC @ P393
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
	Nordazepam	463		Nordazepam @ P468
	Oxazepam	273	273	Oxazepam HYAC @ P480

	Oxazepam	300		Oxazepam artifact-1 @ P342
	Oxazepam	301		Oxazepam-M artifact-2 @ P397
	Oxazepam	419		Oxazepam HY @ P308
	Temazepam	417		Temazepam @ P614
	Temazepam	2099		Temazepam AC @ P816
74021	Diphenhydramine	731	731	Diphenhydramine P403
	Diphenhydramine	735	735	Diphenhydramine-M (nor-) AC P529
	Diphenhydramine	2047	2047	Diphenhydramine-M (nor-) P348
	Diphenhydramine	2079	2079	Diphenhydramine-M AC P470
	Lorazepam		290	Lorazepam HYAC @ P647
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
	Paracetamol	188	188	Paracetamol AC @ P199
	Paracetamol	825	825	Paracetamol @ P129
	Paracetamol	6550	6550	Paracetamol-D4 AC P212
74033	Amfetamine	54	54	Amfetamine @ P115
	Amfetamine	55	55	Amfetamine AC @ P165
	Amfetamine	1804		Amfetamine-M (4-HO-) 2AC @ P324
	Caffeine	191	191	Caffeine P204
	Ibuprofen	1941		Ibuprofen P231
	Ibuprofen	1942	1942	Ibuprofen ME P274
	Ibuprofen	3380	3380	Ibuprofen-M (HO-) -H2O ME P265
	Ibuprofen	3381	3381	Ibuprofen-M (HO-) isomer-1 ME P330
	Ibuprofen	3382	3382	Ibuprofen-M (HO-) -H2O P226
	Ibuprofen	3383		Ibuprofen-M (HO-) isomer-3 ME P331
	Ibuprofen	3385	3385	Ibuprofen-M (HO-) MEAC P508
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
74041	Caffeine	191	191	Caffeine P204
	Diazepam		2542	Diazepam HYAC @ P546
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
	Oxazepam		419	Oxazepam HY @ P308
74079	Caffeine	191	191	Caffeine P204
	Enalapril	3199	3199	Enalapril -H2O P878
	Metoprolol	1133	1133	Metoprolol 2AC P850
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
	Trimipramine		410	Trimipramine P587
	Trimipramine	411	411	Trimipramine-M (HO-) AC P856
	Trimipramine	412	412	Trimipramine-M (nor-HO-) 2AC P953
	Trimipramine	413	413	Trimipramine-M (nor-di-HO-) 3AC P1095
	Trimipramine	640	640	Trimipramine-M (HO-) P669
	Trimipramine	2290	2290	Trimipramine-M (nor-) AC P724
	Trimipramine		2293	Trimipramine-M (di-HO-) 2AC P1042

	Trimipramine		1218	Desipramine-M (HO-ring) AC @ P393
	Trimipramine	2292	2292	Desipramine-M (di-HO-ring) 2AC @ P670
74086	Lidocaine	725	725	Lidocaine-M (dimethylaniline) @ P107
	Lidocaine		1061	Lidocaine P321
	Lidocaine	1064	1064	Lidocaine-M 2AC P277
	Lidocaine	1065	1065	Lidocaine-M 3AC P434
	Lidocaine	1066	1066	Lidocaine-M (deethyl-) AC P372
	Metoprolol	1133	1133	Metoprolol 2AC P850
	Midazolam	295	295	Midazolam-M (HO-) P810
	Midazolam	296	296	Midazolam-M (HO-) AC P962
74111	Ambroxol	19	19	Ambroxol @ P938
	Ambroxol	20	20	Ambroxol 2AC @ P1127
	Ambroxol	21	21	Ambroxol-M/artifact AC P695
	Ambroxol		2227	Ambroxol -H2O 2AC P1102
	Ambroxol		2228	Ambroxol 3AC P1165
	Ambroxol	5131	5131	Ambroxol-M (HOOC-) ME @ P646
	Caffeine	191	191	Caffeine P204
	Diazepam		272	Diazepam HY @ P358
	Diazepam		2542	Diazepam HYAC @ P546
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
	Oxazepam	273	273	Oxazepam HYAC @ P480
	Oxazepam	301		Oxazepam-M artifact-2 @ P397
	Oxazepam	419	419	Oxazepam HY @ P308
74112	Caffeine	191	191	Caffeine P204
	Chlorprothixene	312	312	Chlorprothixene P688
	Chlorprothixene	313		Chlorprothixene-M isomer-1 AC P935
	Chlorprothixene	436	436	Chlorprothixene-M @ P541
	Chlorprothixene	438	438	Chlorprothixene-M -(CH3)2NOH @ P467
	Chlorprothixene	1258	1258	Chlorprothixene-M AC P827
	Chlorprothixene	1259	1259	Chlorprothixene-M (nor-) AC P820
	Chlorprothixene		2641	Chlorprothixene-M/artifact @ P361
	Chlorprothixene	3734	3734	Chlorprothixene-M AC P762
	Chlorprothixene	3736	3736	Chlorprothixene-M (bis-nor-) AC P753
	Chlorprothixene		4160	Chlorprothixene-M isomer-1 AC P747
	Chlorprothixene	4162	4162	Chlorprothixene-M/A (sulfoxide) P762
	Diazepam		272	Diazepam HY @ P358
	Lidocaine		1064	Lidocaine-M 2AC P277
	Lidocaine	1066	1066	Lidocaine-M (deethyl-) AC P372
	Oxazepam		273	Oxazepam HYAC @ P480
74119	Biperiden	101	101	Biperiden P673
	Biperiden	103	103	Biperiden-M (HO-) AC P918
	Caffeine	191	191	Caffeine P204
	Diazepam		272	Diazepam HY @ P358
	Diazepam		2542	Diazepam HYAC @ P546

	Haloperidol		181	Haloperidol-M -2H2O @ P191
	Haloperidol	182	182	Haloperidol-M -H2O AC P322
	Haloperidol		340	Haloperidol P936
	Ibuprofen	1941	1941	Ibuprofen P231
	Ibuprofen	1942	1942	Ibuprofen ME P274
	Lidocaine	1061	1061	Lidocaine P321
	Lidocaine	1066	1066	Lidocaine-M (deethyl-) AC P372
	Lidocaine	2585	2585	Lidocaine AC P498
	Mirtazapine	4487	4487	Mirtazapine P446
	Mirtazapine	4488	4488	Mirtazapine-M (nor-) AC P581
	Mirtazapine		4489	Mirtazapine-M (nor-HO-) 2AC P849
	Mirtazapine	4490	4490	Mirtazapine-M (HO-) AC P728
	Oxazepam		273	Oxazepam HYAC @ P480
	Oxazepam	419		Oxazepam HY @ P308
74120	Carbamazepine	309	309	Carbamazepine-M/artifact @ P200
	Carbamazepine	420	420	Carbamazepine P328
	Carbamazepine	421	421	Carbamazepine-M (acridine) @ P170
	Carbamazepine	422	422	Carbamazepine-M (formyl-acridine) P232
	Carbamazepine		423	Carbamazepine-M (HO-methoxy-ring)@ P339
	Carbamazepine	425	425	Carbamazepine-M (HO-ring) AC @ P383
	Carbamazepine	2506	2506	Carbamazepine-M AC @ P521
	Carbamazepine	2671	2671	Carbamazepine-M/artifact AC @ P323
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
	Oxcarbazepine	6065	6065	Oxcarbazepine P388
	Oxcarbazepine	6066	6066	Oxcarbazepine artifact ME P333
	Oxcarbazepine	6067	6067	Oxcarbazepine enol AC P585
	Pipamperone	179	179	Pipamperone P937
	Pipamperone		599	Pipamperone-M (HO-) AC P1086
	Pipamperone		5586	Pipamperone-M (dihydro-) -H2O P881
74133	Caffeine	191	191	Caffeine P204
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
	Panthenol		1509	Panthenol 3AC P765
	Ibuprofen	1941	1941	Ibuprofen P231
	Ibuprofen	1942	1942	Ibuprofen ME P274
74136	Salicylic Acid		1443	Acetylsalicylic acid @ P173
	Salicylic Acid		953	Salicylic acid @ P118
	Salicylic Acid		954	Salicylic acid ME @ P130
	Caffeine	191	191	Caffeine P204
	Diazepam		272	Diazepam HY @ P358
	Doxepin	31	31	Doxepin-M (nor-HO-) isomer-2 2AC P901
	Doxepin	333	333	Doxepin-M (N-oxide) -(CH3)2NOH P320
	Doxepin	335	335	Doxepin-M -(CH3)2NOH AC P575
	Doxepin	337	337	Doxepin-M (nor-) AC P649

	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
	Oxazepam		273	Oxazepam HYAC @ P480
	Trimipramine	411	411	Trimipramine-M (HO-) AC P856
	Trimipramine	412	412	Trimipramine-M (nor-HO-) 2AC P953
	Trimipramine	640	640	Trimipramine-M (HO-) P669
74154	Amfetamine	54	54	Amfetamine @ P115
	Amfetamine	55	55	Amfetamine AC @ P165
	Amfetamine		1803	Amfetamine-M (4-HO-) AC @ P201
	Amfetamine	1804	1804	Amfetamine-M (4-HO-) 2AC @ P324
	Caffeine	191	191	Caffeine P204
	Clorazepate		1751	Clorazepate-M isomer-2 HY2AC @ P762
	Clorazepate	2112	2112	Clorazepate-M (HO-) HY @ P365
	Clorazepate	3143	3143	Clorazepate-M (HO-) HYAC @ P556
	Diazepam	272	272	Diazepam HY @ P358
	Diazepam		2542	Diazepam HYAC @ P546
	Ibuprofen	1941	1941	Ibuprofen P231
	Ibuprofen	1942	1942	Ibuprofen ME P274
	Ibuprofen	3380	3380	Ibuprofen-M (HO-) -H2O ME P265
	Ibuprofen	3381	3381	Ibuprofen-M (HO-) isomer-1 ME P330
	Ibuprofen	3384		Ibuprofen-M (HOOC-) 2ME P439
	Ibuprofen	3385	3385	Ibuprofen-M (HO-) MEAC P508
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
	Nordazepam	463	463	Nordazepam @ P468
	Oxazepam	273	273	Oxazepam HYAC @ P480
	Oxazepam	300		Oxazepam artifact-1 @ P342
	Oxazepam	301	301	Oxazepam-M artifact-2 @ P397
	Oxazepam	419	419	Oxazepam HY @ P308
	Temazepam	2099		Temazepam AC @ P816
74164	Caffeine	191	191	Caffeine P204
	Lorazepam		289	Lorazepam artifact-2 @ P483
	Lorazepam	290	290	Lorazepam HYAC @ P647
	Lorazepam	543	543	Lorazepam HY @ P441
	Lorazepam	2526		Lorazepam artifact-1 P550
	Lorazepam		2527	Lorazepam-M (HO-) artifact AC P830
	Metamizol	183	183	Metamizol-M AC @ P359
	Metamizol	219	219	Metamizol-M (bis-dealkyl-) @ P224
	Metamizol	3333	3333	Metamizol-M 2AC @ P547
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine		1150	Nicotine P142
	Olanzapine	4675	4675	Olanzapine P676
	Olanzapine	4676	4676	Olanzapine AC P862
74739	Aripiprazol	7123	7123	Aripiprazole-M (N-dealkyl-) AC P477
	Caffeine	191	191	Caffeine P204

	Mirtazapine	4487	4487	Mirtazapine P446
	Mirtazapine	4488	4488	Mirtazapine-M (nor-) AC P581
	Mirtazapine	4489	4489	Mirtazapine-M (nor-HO-) 2AC P849
	Mirtazapine	4490	4490	Mirtazapine-M (HO-) AC P728
	Mirtazapine	4498		Mirtazapine-M (HO-) P523
	Nicotine	692	692	Nicotine-M (cotinine) @ P163
	Nicotine	1150	1150	Nicotine P142
	Olanzapine	4675	4675	Olanzapine P676
	Olanzapine	4676	4676	Olanzapine AC P862
	Olanzapine		4677	Olanzapine-M (nor-) 2AC P959
	Paracetamol		188	Paracetamol AC @ P199
	Paracetamol		825	Paracetamol @ P129
	Paracetamol	2383	2383	Paracetamol-M (HO-methoxy-) AC @ P339
	Paracetamol	6550	6550	Paracetamol-D4 AC P212

10 DANKSAGUNG

Die vorliegende Dissertation entstand unter Anleitung von Herrn Professor Dr. Dr. h.c. Hans H. Maurer in der Abteilung Experimentelle und Klinische Toxikologie der Fachrichtung 2.4 Experimentelle und Klinische Pharmakologie und Toxikologie der Universität des Saarlandes in Homburg/Saar.

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