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OXFORD UNIVERSITY PRESS | Journal of Analytical Toxicology

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Journal:	*Journal of Analytical Toxicology*
Manuscript ID	Draft
Manuscript Type:	Article
Date Submitted by the Author:	n/a
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Keywords:	NPS, hair analysis, epidemiology, fentanyl, ketamine

Introduction

New psychoactive substances (NPS) are designer drugs which have progressively become a global issue, with over 100 countries and regions throughout the world having reported the emergence or at least the presence of a new psychoactive molecule on their territory (1,2). In recent years, the availability and the consequent consumption of NPS have proliferated at an unprecedented rate, alarming the public health actors and challenging the clinical and forensic toxicological laboratories to develop effective analytical methods. Among the newly synthetized compounds, synthetic cannabinoids, synthetic cathinones, phenethylamines, piperazines, and tryptamines are the most popular. Furthermore, more recently, there has been an outbreak of new synthetic opioids (3) and designer benzodiazepine derivatives (4). In this scenario, most NPS disappear after a short time, others seem to establish a niche market and only a few are used by large populations.

At least until few years ago, most of laboratories performing drug testing in conventional and nonconventional biological matrices for clinical and forensic purposes did not include screening procedures for NPS in their routine protocols in the context of workplace drug testing, driving re-licensing, roadside control, and withdrawal programs (5). As a matter of fact, most of the current analytical methods are generally based on the targeted detection of a limited and well-defined list of compounds to monitor, usually chosen on the base of the national or international reports, or alerts from national warning system. Therefore, it becomes difficult for laboratories to stay up to date because of the continued entry in the market of newly synthesized products, and the consequent low availability (and cost) of reference analytical standards. Furthermore, many of the new compounds are very potent, and low doses ingested will lead to traces concentrations in biological matrices, especially in hair (6).

Nevertheless, the forensic toxicologist community reacted promptly, and rapidly several procedures for NPS detection in the keratin matrix have been proposed (7-9). Then, hair analysis has often been used to try to infer about NPS diffusion in selected populations (10-12). Certainly, the longer detection window of hair is a big advantage for prevalence studies. Even sporadic exposures occurred several weeks before the hair sampling can be identified,

while this would not be possible with urine and blood. Therefore, the exposure, voluntarily or not, to a certain NPS occurred in the weeks prior the sampling, can be identified by means of hair analysis. While this approach has been promisingly applied in several countries (13-16), data from the analysis of biological samples in the Italian territory to evaluate the real NPS consumption are still rare. For this reason, an extensive epidemiological study was carried out by means a UPLC-MS/MS method for the determination of 115 NPS on 847 keratin specimens, collected from suspected drug users in different locations in Northern Italy.

Materials and Methods

Chemicals and reagents

LGC Standards (LCG Standard S.r.l. Sesto San Giovanni, Milan, Italy) and Cayman Chemical (Ann Arbor, Michigan 48108 USA) provided all the NPS standard, which were diluted in methanol to prepare the calibrators: ketamine, norketamine, 2-fluorodeschloroketamine, deschloro-N-ethylketamine, clonazolam, flualprazolam, etizolam, bentazepam, cinazepam, diclazepam, 4-AcO-DiPT, 5-MeO-DPT, 5-MeO-DALT, 5-MeO-MiPT, 5-MeO-DMT, N,N-DMT, 4-OH-DET, ritalinic acid, isotonitazene, alpha-ethyltryptamine, ethylphenidate, 5-MeO-AMT, 5-APB, 6-APB, MMB-2201, MDMB-CHMICA, AB-CHMINACA, UR-144, 5-EAPB, 6-MAPB, 5-MAPB, MDPBP, MPHP, 3-4 MDPHP, α-PHP, AP-237, 2-methyl-AP-237, APP-FUBINACA, AB-FUBINACA, ADB-FUBINACA, 5F-ADB, PX1, PX2, THJ-018, 5-F-PB-22, 5F-NNEI-2, CUMYL-PeGACLONE, 5F-CUMYL-PINACA, 5-chloro AB-PINACA, 5-fluoro CUMYL-PeGACLONE, 5-fluoro MDMB-7-PAICA, MDMB-4en-PINACA, 5-fluoro MDMB-PICA, 5-fluoro CUMYL-7-PAICA, furanylfentanyl, para-fluoro furanylfentanyl, furanylnorfentanyl, furanylethylfentanyl, methoxyacetylfentanyl, methoxyacetylnorfentanyl, cis-3-methylnorfentanyl, trans-3-methylnorfentanyl, fentanyl, norfentanyl, B-phenylfentanyl, phenylfentanyl, phenylacetylfentanyl, acetylfentanyl, acetylnorfentanyl, butyrylfentanyl, isobutyrylfentanyl, butyrylfentanyl carboxy metabolite, valerylfentanyl carboxy metabolite, cyclopropylfentanyl, butyrylnorfentanyl, alfentanyl, carfentanyl, ocfentanyl, β-hydroxythiofentanyl, despropionyl-para-fluorofentanyl, 4-ANPP,

ethylone, butylone, eutylone, methylone, methedrone, N-ethylpentylone, MDPV, 3,4-dimethylmethcathinone, dimethylcathinone, ethcathinone, methcathinone, AM-2233, naphyrone, pravadoline, pentylone, 4-fluoro methcathinone, JWH-081, JWH-398, JWH-210, AM-2201, JWH-122, JWH-019, JWH-007, JWH-016, JWH-203, JWH-251, AM-694, 5F-AKB48, JWH-098, JWH-147, RCS-8, JWH-018, JWH-302, RCS-4.

LCG Standards (LCG Standard S.r.l. Sesto San Giovanni, Milan, Italy) provided MDMA-D5, MDEA-D5, cocaine-D3, methadone-D3, Δ^9-THC-D3, fentanyl-D5, zolpidem-D6 and CBD-D3 as solution in methanol to prepare the mixture of deuterated internal standards.

Solvents used for hair washes included dichloromethane Honeywell Riedel de Haën™ (Germany) analytical grade (≥99.9%) and methanol Honeywell Riedel de Haën™ (Germany) LC-MS CHROMASOLV™. The M3® Reagent used for hair extractions, and the liquid chromatography mobile phases were provided by Comedical® (Comedical S.r.l. Trento, Italy).

Instrumentation and Software

The UPLC-MS/MS system consisted of a *Waters XEVO TQ-XS* triple quadrupole mass spectrometer (Wexford, Ireland) operated in multiple reaction monitoring (MRM) mode and an electrospray ionization (ESI) in positive mode. The Ultra Performance Liquid Chromatography system consisted of a *Waters ACQUITY UPLC® I-Class* (Wexford, Ireland) with binary pump, autosampler, column oven and a degasser.

Elution was performed on a Waters Atlantis™ Premier BEH C18 AX Van Guard™ FIT (2.1*100 mm, 2.5 µm particle size) Column 1/pk with pre-column, which was kept at 50°C. The chromatographic method involves the injection of 1 µL of sample with a run time of 10.00 min, a flow rate of 0.400 mL/min, and the equilibration time of 0.1 min. The autosampler was set at 8°C.

Gradient elution was performed with mobile phase A (based on water) and mobile phase B (based on organic solvent) belonging to the Comedical M3® Line. The gradient trend of 10 minutes was as follows: 0 min 10% phase B, 3 min 35% phase B, 5 min 85% phase B, 7 min 100% phase B and from 7.25 min to 10 min gradient returns to 10% phase B.

Data processing was executed using MassLynx™ V4.2 SCN1007 and TargetLynx™ XS software.

The instrumental parameters were: 0.003 s for InterChannel Delay e InterScan Delay; 2 for the number of smooths and ±3 for the window size (scans) to reduce the noise of a curve. In addition, 20 points were acquired to obtain each peak.

Analysis of hair samples

Hair belonging to subjects between 18-40 years old from treatment and withdrawal services (SerD) and driving re-licensing commissions treated by our lab, were selected as samples. Samples were collected between 2020 and 2021. In total, 847 samples of keratin matrix (hair, pubic hair and chest hair) were analyzed. Among the selected subjects, 753 were male and 94 were female.

Either the proximal (0-3 cm) or distal (3-6 cm) segments were analyzed, according to the incoming request for analysis. All samples donors produced informed consent to the hair collection and analysis.

Hair wash and extraction procedure

Hair samples were washed twice with 10 mL of dichloromethane and then twice with 10 mL of methanol. The samples were then dried on a heating plate at 45°C. The hair strands were chopped up, 25 mg were weighed for each sample and then transferred to the test tubes.

M3® reagent (500 µL) was added to each sample, together with the mixture of deuterated internal standards (5 µL). The test tubes were placed in a centrifuge for 10 minutes and then in a stove at 100°C for one hour for hydrolysis. The test tubes were cooled to room temperature and then again placed in centrifuge for 5 minutes. Finally, 200 µL of extract were transferred into the glass vials for the UPLC-MS/MS analysis, in which 1 µL of the extract was injected.

Validation experiments

The international guidelines and articles of references for the validation of analytical methods in mass spectrometry were followed (17-19).

The following parameters were validated for each compound: calibration, LOQ, LOD, accuracy, precision, recovery, matrix effect and process efficiency.

Over five days, the six levels of calibrators (L0 to L5) and the three levels of quality controls (QC1, QC2 and QC3) were analyzed. The concentrations of the calibrators were in the range 0.01 – 4.0 ng/mg, and the quality controls in the range 0.015-3.0 ng/mg, depending on the analytes.

The number of repetitions for each day is detailed as follows. Day 1: each calibrator was prepared in quadruple; day 2: each calibrator in duplicate and three quality controls in triple, injected three times; day 3: each calibrator in duplicate and the three quality controls in triple; day 4: each calibrator in duplicate and the three quality controls in triple; day 5: three levels of quality controls in triple under three different conditions of analyte addition for recovery and matrix effect assessment (pre, post and blank).

Calibration was achieved on day 1 through quadruple repetition of all calibrators and on days 2 and 3 through duplicate repetitions. The ratio of analyte area/IS area was plotted against the five concentrations values, excluding blanks. For each line, the values of slope, intercept and R^2 were calculated.

LOD (Limit of Detection) and LOQ (Limit of Quantification) were obtained by the four repetitions of the calibrator L0 (blank) on day 1, then the average value was added with three times and ten times the standard deviation, respectively.

Accuracy, precision, recovery, matrix effect, and process efficiency were obtained from signals of the three quality controls repeated in triple. The average value for each compound, at the three levels, was calculated.

For accuracy, the relative percent error ERR% was calculated from the three repetitions of the three quality controls performed on days 2, 3, and 4. The acceptability limit for accuracy was set at 20% as ERR%.

Precision was assessed by means of the relative percent standard deviation or the coefficient of variation (RSD% or CV%). As per the accuracy, precision was calculated from three repetitions of the three quality controls analyzed on days 2, 3, and 4. The acceptability limit for precision was set at 10% for the RSD%.

On day 5, the three quality controls were analyzed for recovery, matrix effect, and process efficiency. In the former case, calibrators were prepared with the keratin matrix, M3® reagent and standards at the appropriate concentrations and then incubated in a stove (series 1). In the second case, only the matrix was incubated with M3® reagent and standards were added after the extraction (series 2). In the last case, only the standards were added to the M3® reagent, without the matrix. Then, the three series were used to calculate the percentage values for recovery, matrix effect, and process efficiency (17). The closer these parameters are to 100%, the more efficient the process.

Results & Discussion:

The present method proved effective for the individual detection of all 115 target analytes and 8 deuterated internal standards. The chromatographic run was completed in 10 minutes, including the final re-equilibration time, which qualifies this procedure as adequate with the efficiency requirement needed for routine application. All compounds eluted in the first 7.0 minutes. Even when co-elution of chromatographic peaks was observed, the multiple reaction monitoring acquisition allowed separate quantifications of the coeluting substances by means of their peculiar differences in parent and fragment ion values. The retention times and the mass transitions for the compound acquisitions are presented as Supplementary Materials (Table S1 and S2).

Table S3 reports the results obtained from the calibration process. Considering the high number of screened compounds over a wide range of concentration, it was chosen to adopt a simple calibration model with a linear equation. When dealing with NPS in hair, the priority is to correctly identify the molecule and to assess a prior exposure to it. In case an accurate quantification is needed, or when cut-offs or interpretation criteria will be described in, for example, a consensus document, other appropriate alternatives to evaluate calibration models will have to be explored (20).

The LOD values (see Table 1) were below 3 pg/mg, with 107 out of 115 compounds detectable as low as 1 pg/mg or less. The obtained LOD values are compatible with the very low expected concentration of NPS in hair obtained from clinical and forensic cases (9). In fact, high-potency NPS are usually taken at low doses, thus the chance to find detectable

levels in hair even under the favorable circumstance that the drug has high affinity toward the keratin matrix is reduced (6). Furthermore, drug users are often exposed to different molecules along a certain period, because i) they like to experiment different compounds and compare their effects, and ii) the dynamic black market of NPS is continuously changing, so it is less likely to have repeated intakes of the same substance.

Intra-day precision and accuracy for all 115 target analytes are reported in Table 2. Noteworthy, the presented method allowed precise and accurate calculation at three different concentration levels, as recommended by most validation protocols. Only few exceptions, especially at the lowest concentration, exceeded the value of 25%.

The extraction recovery was also found to be adequate (data not shown), while ME and PE are presented in Tab S4.

Real samples

In the analysis of real samples, the LODs were set as the minimum criterion to identify positive samples. Overall, 56 samples resulted positive for ketamine, 35 for norketamine, 6 for fentanyl, 3 for norfentanyl, 3 for 4-ANPP, 3 for MDMB-4en-PINACA, 2 for N,N-DMT, 2 for 5-chloro AB-PINACA, 1 for α-PHP and 1 for methcathinone.

Ketamine was the most frequently detected compound. Among the 56 positive samples, 35 presented also the main metabolite norketamine. Among the latter 35 samples, 21 had ketamine above the value of 0.2 ng/mg, which is considered the cut-off to discriminate between sporadic and frequent users (21). For 26 samples, the ratio norketamine/ketamine was above 0.1, suggesting a direct intake rather than passive exposure (22). Ketamine is considered as belonging to the group of NPS (23), and we consider alarming the number of positive samples in the selected population. This trend of huge ketamine diffusion for recreational purposes has been observed in other Countries (24).

Other detected compounds of interest are fentanyl and MDMB-4en-PINACA. The first is well known to be the main agent of the opioids epidemics in Northern America (25). Among the six samples positive to fentanyl, three were also positive to norfentanyl, suggesting a direct intake of the drug (26,27). Quite remarkably, one sample was collected from a subject undergoing through driving relicensing, which normally does not include testing for NPS or

synthetic opioids. It is therefore possible that this subject decided to use fentanyl because of its non-detectability during routinary toxicological tests, and possibly abstained from the use of traditional drugs, such as heroin. A second noteworthy case involved a subject which tested positive also to cocaine and heroin. However, in this case, it is impossible to discriminate whether fentanyl was taken alone or as a cocaine or heroin cutting agent.

Three samples were positive to MDMB-4en-PINACA. Two likely scenarios account to explain the presence of this synthetic cannabinoid (SCRA) in Italy: in the first, SCRA are taken to experiment alternative sensations or to escape the regular screening tests (28, 29). In the second, which seems very plausible for MDMB-4en-PINACA, cannabis-derived products containing either high or low THC levels are adulterated with SCRA (30).

Other sporadic findings included N,N-DMT, 5-chloro AB-PINACA, α-PHP and methcathinone. A summary of the results is presented in Table 3.

Conclusions: Epidemiological studies are needed to understand the real diffusion of psychoactive drugs, especially the most recent ones. In this study, we focused on a high-risk population, and we exploited the large detection window provided by hair. Nevertheless, NPS were detected in a small part of samples (8.4%). This result seems in contrast with the high number of materials which are commonly seized by the police (31) or detected in the wastewater (32) around the Italian territory, yet it is congruent with similar investigation based on hair analysis (33). Future studies will be performed to expand the investigated population, especially in terms of age and origin.

Hair analysis is still a valid tool to understand trends and patterns of drug use. Given adequate hair length, hair testing can detect exposure to drugs within wide timeframes—much wider than with urine, blood, and saliva. However, very recent exposure and infrequent use can be difficult to discover, thus the possible combination of hair analysis with other sources of information should be possibly implemented.

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***Table 1**: LOD and LOQ values of each NPS.*

	NPS	LOD (pg/mg)	LOQ (pg/mg)
1	Ketamine	0.3	0.9
2	Norketamine	0.1	0.2
3	2-fluorodeschloroketamine	0.1	0.1
4	Deschloro-N-ethylketamine	0.1	0.1
5	Clonazolam	0.2	0.6
6	Flualprazolam	0.1	0.4
7	Etizolam	0.1	0.5
8	Bentazepam	0.1	0.1
9	Cinazepam	0.9	2.9
10	Diclazepam	0.5	1.6
11	4-AcO-DiPT	0.3	0.9
12	5-MeO-DPT	0.2	0.8
13	5-MeO-DALT	0.1	0.1
14	5-MeO-MiPT	0.4	1.5
15	5-MeO-DMT	1.6	5.3
16	N.N-DMT	0.1	0.1
17	4-OH-DET	0.9	3.1
18	Ritalinic acid	0.7	2.2
19	Isotonitazene	0.1	0.4
20	Alpha-ethyltryptamine	0.1	0.3
21	Ethylphenidate	0.1	0.2
22	5-MeO-AMT	0.2	0.6
23	5-APB	0.1	0.1
24	6-APB	0.3	1.1
25	MMB-2201	0.1	0.1
26	MDMB-CHMICA	0.1	0.3
27	AB-CHMINACA	0.3	1.1
28	UR-144	0.4	1.3
29	5-EAPB	0.1	0.4
30	6-MAPB	0.1	0.3
31	5-MAPB	0.3	0.8
32	MDPBP	0.5	1.5
33	MPHP	0.1	0.2
34	3-4 MDPHP	0.1	0.2
35	α-PHP	0.1	0.2
36	AP-237	0.1	0.1
37	2-methyl-AP-237	0.1	0.1
38	APP-FUBINACA	1.1	3.7
39	AB-FUBINACA	0.1	0.4
40	ADB-FUBINACA	0.7	2.2
41	5F-ADB	0.1	0.5
42	PX1	0.1	0.4

43	PX2	0.2	0.5
44	THJ-018	0.1	0.1
45	5-F-PB-22	0.1	0.1
46	5F-NNEI-2	0.2	0.5
47	CUMYL-PeGACLONE	1.3	4.5
48	5F-CUMYL-PINACA	0.1	0.1
49	5-chloro AB-PINACA	2.7	9.1
50	5-fluoro CUMYL-PeGACLONE	0.2	0.8
51	5-fluoro MDMB-7-PAICA	0.1	0.4
52	MDMB-4en-PINACA	0.1	0.1
53	5-fluoro MDMB-PICA	0.1	0.2
54	5-fluoro CUMYL-7-PAICA	0.1	0.2
55	Furanylfentanyl	0.1	0.4
56	Para-fluoro furanylfentanyl	0.1	0.1
57	Furanylnorfentanyl	0.1	0.2
58	Furanylethylfentanyl	0.1	0.2
59	Methoxyacetylfentanyl	0.1	0.4
60	Methoxyacetylnorfentanyl	0.4	1.3
61	Cis-3-methylnorfentanyl	0.1	0.1
62	Trans-3-methylnorfentanyl	0.1	0.2
63	Fentanyl	0.1	0.2
64	Norfentanyl	0.1	4.0
65	B-phenylfentanyl	0.2	0.6
66	Phenylfentanyl	0.1	0.3
67	Phenylacetylfentanyl	0.1	0.2
68	Acetylfentanyl	0.1	0.1
69	Acetylnorfentanyl	1.7	5.5
70	Butyrylfentanyl	0.2	0.5
71	Isobutyrylfentanyl	0.1	0.2
72	Butyrylfentanyl carboxy metabolite	0.1	0.1
73	Valerylfentanyl carboxy metabolite	0.1	0.1
74	Cyclopropylfentanyl	0.1	0.1
75	Butyrylnorfentanyl	0.2	0.7
76	Alfentanyl	0.1	0.1
77	Carfentanyl	0.1	0.1
78	Ocfentanyl	0.3	1.1
79	β-hydroxythiofentanyl	0.1	0.3
80	Despropionyl-para-fluorofentanyl	0.1	0.1
81	4-ANPP	0.1	0.1
82	Ethylone	0.5	1.6
83	Butylone	0.1	0.5
84	Eutylone	0.1	0.4
85	Methylone	0.1	0.2
86	Methedrone	3.1	10.4
87	N-ethylpentylone	1.8	6.0

88	MDPV	0.1	0.5
89	3.4-dimethylmethcathinone	0.2	0.7
90	Dimethylcathinone	0.6	2.1
91	Ethcathinone	0.5	1.7
92	Methcathinone	0.3	1.0
93	AM-2233	0.1	0.2
94	Naphyrone	0.1	0.3
95	Pravadoline	0.1	0.1
96	Pentylone	1.2	4.0
97	4-fluoro methcathinone	0.1	0.2
98	JWH-081	0.1	0.1
99	JWH-398	0.1	0.1
100	JWH-210	0.1	0.1
101	AM-2201	0.1	0.1
102	JWH-122	0.1	0.2
103	JWH-019	0.1	0.1
104	JWH-007	0.1	0.1
105	JWH-016	0.1	0.1
106	JWH-203	0.5	1.5
107	JWH-251	0.9	3.2
108	AM-694	0.1	0.1
109	5F-AKB48	0.2	0.5
110	JWH-098	0.1	0.1
111	JWH-147	0.1	0.5
112	RCS-8	0.1	0.1
113	JWH-018	0.1	0.1
114	JWH-302	0.2	0.7
115	RCS-4	0.5	1.8

***Table 2**: ERR% values for accuracy and RSD% values for precision calculated for each NPS.*

	NPS	Average ERR%			Average RSD%		
		QC1	QC2	QC3	QC1	QC2	QC3
1	Ketamine	7.4	3.7	4.6	8.9	2.3	3.8
2	Norketamine	15.8	4.8	7.1	26.6	6.2	6.6
3	2-fluoro deschloroketamine	6.6	8.7	5.1	5.4	2.3	4.2
4	Deschloro-N-ethylketamine	11.1	7.9	6.2	4.3	2.0	3.5
5	Clonazolam	16.1	8.3	6.1	10.0	1.7	3.9
6	Flualprazolam	18.0	8.7	7.6	11.5	1.3	4.3
7	Etizolam	18.2	7.5	8.0	12.8	1.8	4.2
8	Bentazepam	18.2	8.6	7.9	8.7	1.4	3.5
9	Cinazepam	12.0	4.9	3.4	4.9	4.2	5.6
10	Diclazepam	26.3	6.4	9.9	25.5	3.4	5.5
11	4-AcO-DiPT	10.4	12.2	5.1	1.0	3.0	2.6
12	5-MeO-DPT	12.6	9.7	6.2	6.2	2.9	2.8
13	5-MeO-DALT	13.1	9.5	7.0	6.0	2.0	3.5
14	5-MeO-MiPT	8.2	6.7	4.7	2.2	1.6	1.6
15	5-MeO-DMT	10.1	7.4	5.5	8.3	3.0	3.1
16	N.N-DMT	10.7	9.5	6.5	5.1	1.2	1.3
17	4-OH-DET	31.6	12.5	5.6	10.4	5.2	7.6
18	Ritalinic acid	17.7	5.7	5.7	20.8	4.5	6.3
19	Isotonitazene	13.7	9.5	5.7	9.4	1.0	4.5
20	Alpha ethyltryptamine	29.5	6.1	9.9	42.5	6.5	10.4
21	Ethylphenidate	13.7	8.2	5.8	8.3	2.7	3.2
22	5-MeO-AMT	21.7	2.1	6.6	20.0	2.3	5.9
23	5-APB	15.8	6.3	12.0	13.5	4.3	6.6
24	6-APB	25.1	4.8	10.8	31.4	5.3	9.3
25	MMB-2201	10.3	11.9	5.9	14.9	5.9	4.7
26	MDMB-CHMICA	10.9	10.7	5.4	15.3	6.1	4.8
27	AB-CHMINACA	14.2	11.8	6.8	21.1	8.3	4.6
28	UR-144	11.6	9.7	7.1	13.1	3.3	6.6
29	5-EAPB	22.3	10.2	8.9	20.4	4.9	6.0
30	6-MAPB	10.8	11.1	13.6	16.4	13.7	15.8
31	5-MAPB	10.9	9.1	5.0	7.5	3.1	4.0
32	MDPBP	8.1	6.5	4.7	1.0	2.0	1.5
33	MPHP	15.5	13.7	14.2	8.6	3.0	11.4
34	3-4 MDPHP	14.4	13.5	11.9	7.1	2.2	8.9
35	α-PHP	10.5	4.3	3.8	6.2	2.2	1.7
36	AP-237	18.5	6.8	7.5	17.8	3.8	4.2
37	2-methyl-AP-237	18.0	14.6	14.0	12.3	3.2	12.4
38	APP-FUBINACA	14.7	9.3	8.0	19.9	3.4	5.4
39	AB-FUBINACA	13.2	10.3	6.0	19.9	8.5	5.5
40	ADB-FUBINACA	20.5	9.2	14.0	27.0	6.9	14.0
41	5F-ADB	11.0	10.9	5.0	15.2	6.5	4.1
42	PX1	8.5	10.5	6.2	10.6	3.5	3.4

43	PX2	12.7	8.9	5.6	17.7	4.2	5.1
44	THJ-018	10.8	8.5	6.8	13.4	4.8	4.1
45	5-F-PB-22	16.1	9.5	7.9	10.2	3.7	3.3
46	5F-NNEI-2	8.8	10.8	5.9	10.4	4.4	3.2
47	CUMYL-PeGACLONE	13.4	10.5	8.0	17.3	13.7	11.3
48	5F-CUMYL-PINACA	9.0	11.3	6.2	9.1	5.6	2.5
49	5-chloro AB-PINACA	6.8	9.9	5.1	11.3	9.0	2.5
50	5-fluoro CUMYL-PeGACLONE	13.2	10.6	10.9	18.0	13.4	15.4
51	5-fluoro MDMB-7-PAICA	21.4	8.2	4.7	23.1	11.4	4.3
52	MDMB-4en-PINACA	/	/	/	/	/	/
53	5-fluoro MDMB-PICA	16.9	9.2	8.1	9.6	4.3	2.8
54	5-fluoro CUMYL-7-PAICA	12.0	9.7	5.5	16.0	6.6	3.2
55	Furanylfentanyl	15.0	13.4	12.9	5.6	2.5	10.7
56	Para-fluoro furanylfentanyl	16.6	14.3	13.3	9.8	2.5	11.4
57	Furanylnorfentanyl	12.4	9.4	5.7	5.9	1.3	3.3
58	Furanylethylfentanyl	14.8	7.2	6.7	9.0	1.9	2.8
59	Methoxyacetylfentanyl	19.4	8.3	7.2	16.3	4.4	5.1
60	Methoxyacetylnorfentanyl	10.5	5.7	4.6	10.9	1.8	2.8
61	Cis-3-methylnorfentanyl	14.1	8.8	7.1	11.0	3.4	4.8
62	Trans-3-methylnorfentanyl	16.2	9.5	7.8	13.5	3.6	4.9
63	Fentanyl	18.9	29.2	13.3	4.6	2.2	9.9
64	Norfentanyl	14.5	10.3	7.1	11.5	2.5	4.7
65	B-phenylfentanyl	11.3	9.5	5.5	4.9	0.6	2.6
66	Phenylfentanyl	16.2	15.1	12.7	9.0	2.9	11.0
67	Phenylacetylfentanyl	12.1	7.7	5.6	3.3	0.7	3.2
68	Acetylfentanyl	15.3	13.8	12.4	5.7	2.6	10.5
69	Acetylnorfentanyl	13.6	3.8	6.8	11.6	2.4	4.9
70	Butyrylfentanyl	9.5	7.9	7.0	4.6	1.4	1.5
71	Isobutyrylfentanyl	11.6	7.7	5.8	4.6	0.9	2.1
72	Butyrylfentanyl carboxy met.	19.3	14.2	13.9	13.0	3.4	12.7
73	Valerylfentanyl carboxy met.	17.1	13.8	13.7	8.8	2.9	11.7
74	Cyclopropylfentanyl	14.4	14.5	12.9	6.7	3.5	10.4
75	Butyrylnorfentanyl	15.2	9.6	7.3	13.4	3.3	5.7
76	Alfentanyl	15.3	14.3	13.7	7.8	2.6	11.5
77	Carfentanyl	16.1	13.6	13.3	9.5	2.8	10.9
78	Ocfentanyl	18.3	14.9	13.3	10.0	3.1	11.2
79	β-hydroxythiofentanyl	16.8	14.8	12.9	8.3	1.9	11.1
80	Despropionyl-para-fluorof.	13.9	13.5	12.6	5.7	2.7	9.7
81	4-ANPP	17.6	14.4	14.0	10.7	2.8	12.0
82	Ethylone	12.7	2.9	4.4	11.9	2.0	5.6
83	Butylone	4.8	7.0	4.3	5.0	1.8	4.4
84	Eutylone	4.4	4.0	3.4	4.2	1.5	3.0
85	Methylone	10.1	1.8	3.3	7.2	2.5	5.1
86	Methedrone	36.1	24.5	6.2	14.2	8.3	6.2
87	N-ethylpentylone	8.0	3.5	4.4	7.4	1.8	2.8

88	MDPV	25.6	15.2	1.5	4.8	1.4	1.2
89	3.4-dimethylmethcathinone	49.1	36.8	9.3	11.5	10.2	2.6
90	Dimethylcathinone	44.2	35.5	15.1	16.6	6.2	6.2
91	Ethcathinone	60.2	43.2	27.3	22.2	18.2	4.8
92	Methcathinone	16.0	12.3	2.0	5.4	5.5	1.6
93	AM-2233	24.9	14.2	1.6	3.4	1.6	1.4
94	Naphyone	31.6	17.5	1.2	4.0	0.9	1.1
95	Pravadoline	19.1	15.1	3.5	7.6	1.7	3.5
96	Pentylone	31.2	13.4	5.1	13.9	6.5	6.8
97	4-fluoro methcathinone	40.4	18.4	4.0	12.2	4.0	5.6
98	JWH-081	26.4	16.1	5.5	7.9	1.1	5.8
99	JWH-398	22.5	15.9	5.7	7.1	2.7	6.6
100	JWH-210	23.0	18.1	6.6	7.7	1.5	7.1
101	AM-2201	28.5	13.1	2.5	8.7	5.0	3.5
102	JWH-122	28.7	17.3	5.9	9.4	3.0	6.2
103	JWH-019	30.2	17.5	5.8	7.4	2.4	6.2
104	JWH-007	26.6	18.3	5.9	10.3	2.4	6.9
105	JWH-016	26.9	5.7	4.1	11.4	6.3	5.6
106	JWH-203	28.8	14.5	2.3	11.3	5.0	3.2
107	JWH-251	26.8	11.1	3.1	10.2	5.3	5.6
108	AM-694	16.1	13.5	4.6	7.3	4.6	2.4
109	5F-AKB48	10.4	7.9	7.5	13.9	3.4	7.4
110	JWH-098	27.5	16.3	6.0	8.4	2.4	6.7
111	JWH-147	27.2	16.1	4.8	9.3	1.6	6.0
112	RCS-8	29.8	17.5	4.9	4.5	2.5	4.2
113	JWH-018	27.0	14.9	3.3	16.2	6.9	4.7
114	JWH-302	25.8	12.8	2.8	10.8	5.5	3.7
115	RCS-4	21.1	13.1	3.4	7.9	5.7	2.6

Table 3. Summary of the analytical findings.

Sample number	Age	Gender	Finding	Concentration (pg/mg)	Positive to ketamine
1	23	M	Metcathinone	90	NO
2	35	M	α-PHP	500	NO
3	25	M	N,N-DMT	790	YES
4	24	M	Fentanyl	2	NO
5	40	M	5-chloro AB-PINACA	32	NO
6				30	NO
7	39	F	Fentanyl	3200	NO
			Norfentanil	460	
			4-ANPP	340	
8			Fentanyl	5700	NO
			Norfentanyl	1300	
			4-ANPP	610	
9	35	M	N,N-DMT	40	NO
10	38	M	Fentanyl	8	NO
11	34	F	Fentanyl	5	NO
12	37	F	MDMB-4en-Pinaca	0.4	NO
13	25	M	Fentanyl	450	NO
			Norfentanyl	90	
			4-ANPP	5	
14	28	M	MDMB-4en-Pinaca	0.9	NO
15	33	F	MDMB-4en-Pinaca	0.2	NO

***Table S1**: list of molecules in the method with their respective precursor ions. fragment ions 1 and 2. cone potential and collision energy (parameters of acquisition method).*

	NPS	PRECURSOR ION (Da)	FRAGMENT ION 1 E 2 (Da)	CONE POTENTIAL (V)	COLLISION ENERGY (eV)
1	Ketamine	238.20	125.10	20.00	25.00
			220.20	20.00	15.00
2	Norketamine	224.10	125.00	20.00	25.00
			207.10	20.00	10.00
3	2-fluorodeschloroketamine	222.20	109.10	25.00	26.00
			163.10	25.00	14.00
4	Deschloro-N-ethylketamine	218.20	91.00	25.00	32.00
			145.10	25.00	20.00
5	Clonazolam	354.10	308.00	25.00	22.00
			278.00	25.00	36.00
6	Flualprazolam	327.10	223.00	25.00	42.00
			292.00	25.00	24.00
7	Etizolam	343.10	314.10	30.00	22.00
			138.00	30.00	32.00
8	Bentazepam	297.10	166.10	25.00	26.00
			139.00	25.00	36.00
9	Cinazepam	466.90	348.90	30.00	14.00
			320.90	30.00	28.00
10	Diclazepam	321.10	153.60	25.00	32.00
			226.60	25.00	30.00
11	4-AcO-DIPT	303.10	114.00	15.00	18.00
			160.00	15.00	28.00
12	5-MeO-DPT	275.20	174.00	14.00	16.00
			114.00	14.00	14.00
13	5-MeO-DALT	271.20	110.00	4.00	14.00
			174.00	24.00	18.00
14	5-MeO-MiPT	247.10	174.00	10.00	16.00
			86.00	10.00	14.00
15	5-MeO-DMT	219.20	159.20	40.00	24.00
			130.20	40.00	48.00
16	N.N-DMT	189.30	117.10	28.00	28.00
			91.00	28.00	42.00
17	4-OH-DET	233.10	86.10	16.00	14.00
			160.00	16.00	18.00
18	Ritalinic acid	220.10	84.10	20.00	20.00
			56.00	20.00	46.00
19	Isotonitazene	411.10	100.00	25.00	22.00
			72.00	25.00	46.00
20	Alpha-ethyltryptamine	189.20	130.10	20.00	14.00
			77.10	20.00	44.00

21	Ethylphenidate	248.30	84.10	34.00	20.00
			91.10	34.00	40.00
22	5-MeO-AMT	205.10	147.00	22.00	20.00
			173.00	22.00	22.00
23	5-APB	176.20	91.00	26.00	28.00
			77.00	26.00	38.00
24	6-APB	176.20	91.00	22.00	26.00
			77.00	22.00	40.00
25	MMB-2201	363.30	231.90	34.00	12.00
			143.90	34.00	38.00
26	MDMB-CHMICA	385.20	240.20	34.00	14.00
			144.10	34.00	40.00
27	AB-CHMINACA	357.40	241.20	38.00	28.00
			145.00	38.00	46.00
28	UR-144	312.20	125.00	18.00	22.00
			55.00	18.00	36.00
29	5-EAPB	204.15	131.00	24.00	20.00
			91.00	24.00	30.00
30	6-MAPB	190.15	159.00	22.00	10.00
			131.00	22.00	18.00
31	5-MAPB	190.30	131.10	26.00	18.00
			159.20	26.00	10.00
32	MDPBP	262.30	112.20	30.00	24.00
			161.20	30.00	20.00
33	MPHP	260.20	105.00	10.00	22.00
			189.00	10.00	16.00
34	3-4 MDPHP	290.20	140.10	30.00	26.00
			135.00	30.00	26.00
35	α-PHP	246.20	91.00	25.00	28.00
			105.00	25.00	24.00
36	AP-237	273.20	117.00	25.00	10.00
			91.00	25.00	46.00
37	2-methyl-AP-237	287.00	117.00	25.00	12.00
			91.00	25.00	48.00
38	APP-FUBINACA	417.30	109.00	20.00	40.00
			253.00	20.00	24.00
39	AB-FUBINACA	369.30	253.00	36.00	24.00
			109.00	36.00	40.00
40	ADB-FUBINACA	383.20	253.00	25.00	25.00
			109.00	25.00	42.00
41	5F-ADB	378.30	233.00	45.00	24.00
			318.00	45.00	14.00
42	PX1	396.30	232.00	36.00	26.00
			144.00	36.00	44.00

43	PX2	397.30	233.00	26.00	22.00
			145.00	26.00	46.00
44	THJ-018	377.20	248.90	25.00	16.00
			212.90	25.00	24.00
45	5-F-PB-22	377.20	232.20	30.00	12.00
			144.10	30.00	38.00
46	5F-NNEI-2	375.30	232.00	22.00	20.00
			144.00	22.00	42.00
47	CUMYL-PeGACLONE	373.30	255.00	30.00	10.00
			119.00	30.00	24.00
48	5F-CUMYL-PINACA	368.30	250.00	32.00	10.00
			233.00	32.00	18.00
49	5-chloro AB-PINACA	366.00	249.00	36.00	24.00
			145.00	36.00	44.00
50	5-fluoro CUMYL-PeGACLONE	391.20	273.10	30.00	10.00
			119.10	30.00	28.00
51	5-fluoro MDMB-7-PAICA	378.20	233.00	30.00	14.00
			145.00	30.00	44.00
52	MDMB-4en-PINACA	358.20	213.10	25.00	22.00
			298.20	25.00	14.00
53	5-fluoro MDMB-PICA	377.20	232.10	30.00	14.00
			144.10	30.00	40.00
54	5-fluoro CUMYL-7-PAICA	368.20	250.10	30.00	16.00
			119.10	30.00	24.00
55	Furanylfentanyl	375.10	188.00	30.00	20.00
			105.00	30.00	25.00
56	Para-fluoro furanylfentanyl	393.20	188.10	25.00	22.00
			105.10	25.00	40.00
57	Furanylnorfentanyl	271.00	84.20	16.00	18.00
			55.10	16.00	38.00
58	Furanylethylfentanyl	357.20	95.10	25.00	34.00
			178.10	25.00	16.00
59	Methoxyacetylfentanyl	353.30	105.00	30.00	20.00
			188.10	30.00	24.00
60	Methoxyacetylnorfentanyl	249.00	84.10	15.00	14.00
			55.20	15.00	38.00
61	Cis-3-methylnorfentanyl	247.00	98.00	25.00	16.00
			69.20	25.00	30.00
62	Trans-3-methylnorfentanyl	247.00	98.10	25.00	16.00
			69.10	25.00	30.00
63	Fentanyl	337.20	105.20	35.00	38.00
			188.20	35.00	38.00
64	Norfentanyl	233.10	84.25	25.00	20.00
			55.30	25.00	34.00

65	B-phenylfentanyl	413.20	105.10	30.00	42.00
			188.20	30.00	24.00
66	Phenylfentanyl	385.20	105.20	30.00	36.00
			188.30	30.00	20.00
67	Phenylacetylfentanyl	399.30	188.05	46.00	24.00
			105.05	46.00	44.00
68	Acetylfentanyl	323.20	105.00	25.00	36.00
			188.00	25.00	20.00
69	Acetylnorfentanyl	219.20	84.05	25.00	18.00
			55.20	25.00	36.00
70	Butyrylfentanyl	351.20	105.00	30.00	40.00
			188.10	30.00	22.00
71	Isobutyrylfentanyl	351.30	105.10	30.00	42.00
			188.10	30.00	22.00
72	Butyrylfentanyl carboxy metabolite	381.20	105.00	25.00	42.00
			188.10	25.00	30.00
73	Valerylfentanyl carboxy metabolite	395.30	105.25	40.00	44.00
			188.15	40.00	26.00
74	Cyclopropylfentanyl	349.20	105.00	25.00	30.00
			188.10	25.00	25.00
75	Butyrylnorfentanyl	247.10	84.15	25.00	20.00
			55.30	25.00	36.00
76	Alfentanyl	417.10	197.05	24.00	26.00
			268.10	24.00	16.00
77	Carfentanyl	395.20	335.00	22.00	16.00
			113.00	22.00	32.00
78	Ocfentanyl	371.20	105.15	30.00	40.00
			188.15	30.00	24.00
79	β-hydroxythiofentanyl	359.20	192.00	25.00	22.00
			111.00	25.00	38.00
80	Despropionyl-para-fluorofentanyl	299.10	105.10	15.00	38.00
			188.10	15.00	16.00
81	4-ANPP	281.20	105.00	22.00	32.00
			188.00	22.00	14.00
82	Ethylone	222.20	174.20	30.00	20.00
			146.20	30.00	26.00
83	Butylone	222.00	173.90	25.00	20.00
			145.90	25.00	26.00
84	Eutylone	236.20	188.20	25.00	18.00
			174.20	25.00	32.00
85	Methylone	208.10	159.90	30.00	16.00
			131.90	30.00	26.00
86	Methedrone	193.80	161.10	30.00	20.00
			146.00	30.00	28.00

87	N-ethylpentylone	250.20	100.00	25.00	18.00
			174.00	25.00	32.00
88	MDPV	276.10	126.00	30.00	26.00
			134.80	30.00	24.00
89	3.4-dimethylmethcathinone	192.00	158.80	30.00	22.00
			143.90	30.00	28.00
90	Dimethylcathinone	177.70	105.30	30.00	20.00
			72.10	30.00	22.00
91	Ethcathinone	177.70	105.20	30.00	22.00
			72.00	30.00	16.00
92	Methcathinone	163.90	104.80	30.00	22.00
			130.70	30.00	20.00
93	AM-2233	459.00	111.90	45.00	22.00
			97.80	45.00	34.00
94	Naphyrone	282.10	140.90	45.00	26.00
			126.20	45.00	36.00
95	Pravadoline	379.10	134.80	45.00	24.00
			113.90	45.00	32.00
96	Pentylone	236.10	174.90	35.00	22.00
			187.80	35.00	18.00
97	4-fluoro methcathinone	205.00	148.70	35.00	26.00
			102.80	35.00	28.00
98	JWH-081	371.80	185.08	45.00	26.00
			157.90	45.00	40.00
99	JWH-398	376.06	189.06	45.00	26.00
			161.07	45.00	48.00
100	JWH-210	369.80	183.10	45.00	26.00
			214.20	45.00	24.00
101	AM-2201	360.20	154.90	45.00	28.00
			126.90	45.00	40.00
102	JWH-122	326.10	168.80	45.00	26.00
			140.90	45.00	40.00
103	JWH-019	356.10	155.07	45.00	26.00
			228.10	45.00	26.00
104	JWH-007	355.80	155.09	45.00	26.00
			127.09	45.00	48.00
105	JWH-016	341.70	155.10	45.00	24.00
			127.10	45.00	44.00
106	JWH-203	340.40	124.80	45.00	28.00
			187.80	45.00	20.00
107	JWH-251	319.80	214.20	45.00	15.00
			105.90	45.00	22.00
108	AM-694	436.00	230.70	45.00	28.00
			202.70	45.00	40.00

109	5F-AKB48	384.00	134.90	35.00	25.00
			106.90	35.00	45.00
110	JWH-098	385.80	185.10	45.00	26.00
			157.20	45.00	42.00
111	JWH-147	382.10	155.06	45.00	22.00
			127.09	45.00	48.00
112	RCS-8	376.10	120.85	45.00	26.00
			90.85	45.00	40.00
113	JWH-018	342.10	155.00	45.00	34.00
			127.00	45.00	25.00
114	JWH-302	336.10	121.10	45.00	22.00
			214.20	45.00	26.00
115	RCS-4	322.00	134.80	45.00	24.00
			106.80	45.00	40.00
116	MDMA-D5	199.10	165.10	20.00	12.00
117	MDEA-D5	213.10	163.10	20.00	14.00
			105.10	20.00	26.00
118	Cocaine-D3	307.00	84.80	30.00	30.00
			184.70	30.00	20.00
119	Methadone-D3	313.20	105.10	38.00	28.00
120	Δ^9-THC-D3	318.10	123.10	40.00	34.00
121	Fentanyl-D5	342.20	105.20	35.00	38.00
			188.20	35.00	30.00
122	Zolpidem-D6	314.30	235.20	30.00	34.00
123	CBD-D3	318.30	123.20	40.00	32.00

***Table S2**: list of molecules in the method with their respective internal standards associated and their retention times.*

	NPS	INTERNAL STANDARD	RETENTION TIME (min)
1	Ketamine	Cocaine-D3	1.96
2	Norketamine	Cocaine-D3	1.98
3	2-fluorodeschloroketamine	MDEA-D5	1.52
4	Deschloro-N-ethylketamine	MDEA-D5	1.75
5	Clonazolam	Methadone-D3	5.16
6	Flualprazolam	Methadone-D3	5.34
7	Etizolam	Methadone-D3	5.51
8	Bentazepam	Methadone-D3	5.32
9	Cinazepam	Methadone-D3	5.71
10	Diclazepam	Methadone-D3	5.68
11	4-AcO-DiPT	Cocaine-D3	2.47
12	5-MeO-DPT	Cocaine-D3	2.58
13	5-MeO-DALT	Cocaine-D3	2.47
14	5-MeO-MiPT	MDEA-D5	1.82
15	5-MeO-DMT	MDMA-D5	1.28
16	N.N-DMT	MDEA-D5	1.11
17	4-OH-DET	MDEA-D5	1.20
18	Ritalinic acid	Zolpidem-D6	3.20
19	Isotonitazene	Methadone-D3	4.56
20	Alpha-ethyltryptamine	Cocaine-D3	2.19
21	Ethylfenidate	Zolpidem-D6	2.9000
22	5-MeO-AMT	MDEA-D5	1.6600
23	5-APB	MDEA-D5	1.8600
24	6-APB	MDEA-D5	1.8500
25	MMB-2201	CBD-D3	5.8000
26	MDMB-CHMICA	CBD-D3	6.5000
27	AB-CHMINACA	CBD-D3	6.0600
28	UR-144	Δ^9-THC-D3	6.7300
29	5-EAPB	Cocaine-D3	2.2500
30	6-MAPB	MDEA-D5	1.9300
31	5-MAPB	MDEA-D5	1.9400
32	MDPBP	MDEA-D5	1.8100
33	MPHP	Fentanyl-D5	3.8400
34	3-4 MDPHP	Fentanyl-D5	3.2000
35	α-PHP	Zolpidem-D6	2.9500
36	AP-237	Zolpidem-D6	3.0850
37	2-methyl-AP-237	Fentanyl-D5	3.7400
38	APP-FUBINACA	CBD-D3	5.7400
39	AB-FUBINACA	CBD-D3	5.6300
40	ADB-FUBINACA	CBD-D3	5.7900
41	5F-ADB	CBD-D3	6.0400

42	PX1	CBD-D3	5.6300
43	PX2	CBD-D3	5.6600
44	THJ-018	CBD-D3	6.5100
45	5-F-PB-22	CBD-D3	5.9500
46	5F-NNEI-2	CBD-D3	6.0900
47	CUMYL-PeGACLONE	CBD-D3	6.4500
48	5F-CUMYL-PINACA	CBD-D3	6.1900
49	5-chloro AB-PINACA	CBD-D3	5.7400
50	5-fluoro CUMYL-PeGACLONE	CBD-D3	6.0450
51	5-fluoro MDMB-7-PAICA	CBD-D3	5.7750
52	MDMB-4en-PINACA	CBD-D3	6.3450
53	5-fluoro MDMB-PICA	CBD-D3	5.9300
54	5-fluoro CUMYL-7-PAICA	CBD-D3	5.8400
55	Furanylfentanyl	Fentanyl-D5	3.7400
56	Para-fluoro furanylfentanyl	Fentanyl-D5	3.8550
57	Furanylnorfentanyl	Cocaine-D3	2.1200
58	Furanylethylfentanyl	Zolpidem-D6	3.0500
59	Methoxyacetylfentanyl	Zolpidem-D6	2.8500
60	Methoxyacetylnorfentanyl	MDMA-D5	1.1700
61	Cis-3-methylnorfentanyl	Cocaine-D3	2.4600
62	Trans-3-methylnorfentanyl	Cocaine-D3	2.4500
63	Fentanyl	Fentanyl-D5	3.6200
64	Norfentanyl	Cocaine-D3	2.0500
65	B-phenylfentanyl	Methadone-D3	4.5800
66	Phenylfentanyl	Fentanyl-D5	4.1300
67	Phenylacetylfentanyl	Methadone-D3	4.4200
68	Acetylfentanyl	Fentanyl-D5	2.9600
69	Acetylnorfentanyl	MDMA-D5	1.2400
70	Butyrylfentanyl	Methadone-D3	4.1000
71	Isobutyrylfentanyl	Methadone-D3	4.0400
72	Butyrylfentanyl carboxy metabolite	Fentanyl-D5	3.0700
73	Valerylfentanyl carboxy metabolite	Fentanyl-D5	3.2800
74	Cyclopropylfentanyl	Fentanyl-D5	3.9000
75	Butyrylnorfentanyl	Cocaine-D3	2.8200
76	Alfentanyl	Fentanyl-D5	4.2100
77	Carfentanyl	Fentanyl-D5	3.9900
78	Ocfentanyl	Fentanyl-D5	3.0400
79	β-hydroxythiofentanyl	Fentanyl-D5	3.0200
80	Despropionyl-para-fluorofentanyl	Fentanyl-D5	3.3000
81	4-ANPP	Fentanyl-D5	3.0800
82	Ethylone	MDEA-D5	1.2300
83	Butylone	MDEA-D5	1.5300
84	Eutylone	MDEA-D5	1.7600
85	Methylone	MDMA-D5	1.0500

86	Methedrone	MDMA-D5	1.3300
87	N-ethylpentylone	Zolpidem-D6	2.4500
88	MDPV	Zolpidem-D6	2.4900
89	3.4-dimethylmethcathinone	Zolpidem-D6	2.2900
90	Dimethylcathinone	MDMA-D5	0.9500
91	Ethcathinone	MDMA-D5	0.9600
92	Methcathinone	MDMA-D5	0.9100
93	AM-2233	Methadone-D3	4.2400
94	Naphyrone	Methadone-D3	4.1600
95	Pravadoline	Methadone-D3	5.2900
96	Pentylone	Cocaine-D3	2.2900
97	4-fluoro methcathinone	MDEA-D5	1.5400
98	JWH-081	Δ^9-THC-D3	6.6300
99	JWH-398	Δ^9-THC-D3	6.9100
100	JWH-210	Δ^9-THC-D3	6.9000
101	AM-2201	CBD-D3	6.1100
102	JWH-122	Δ^9-THC-D3	6.7100
103	JWH-019	Δ^9-THC-D3	6.6200
104	JWH-007	Δ^9-THC-D3	6.7100
105	JWH-016	CBD-D3	6.5400
106	JWH-203	CBD-D3	6.4400
107	JWH-251	CBD-D3	6.3300
108	AM-694	CBD-D3	5.9200
109	5F-AKB48	Δ^9-THC-D3	6.7200
110	JWH-098	Δ^9-THC-D3	6.7000
111	JWH-147	Δ^9-THC-D3	6.9700
112	RCS-8	Δ^9-THC-D3	6.7700
113	JWH-018	CBD-D3	6.5400
114	JWH-302	CBD-D3	6.2400
115	RCS-4	CBD-D3	6.2900
116	MDMA-D5	/	1.3100
117	MDEA-D5	/	1.5800
118	Cocaine-D3	/	2.2600
119	Methadone-D3	/	4.4300
120	Δ^9-THC-D3	/	6.9700
121	Fentanyl-D5	/	3.5900
122	Zolpidem-D6	/	3.0900
123	CBD-D3	/	6.4200

***Table S3**: intercept. slope. R^2 values with the respective standard deviations and the type of concentration of each NPS.*

	NPS	AVERAGE INTERCEPT±DS	AVERAGE SLOPE±DS	AVERAGE R^2±DS
1	Ketamine	0.048±0.055	2.704±0.112	0.999±0.001
2	Norketamine	0.141±0.107	2.252±0.188	0.995±0.003
3	2-fluorodeschloroketamine	0.014±0.015	1.262±0.076	0.997±0.002
4	Deschloro-N-ethylketamine	0.006±0.007	1.147±0.047	0.999±0.001
5	Clonazolam	0.001±0.001	0.115±0.006	0.999±0.000
6	Flualprazolam	0.003±0.003	0.302±0.018	0.999±0.001
7	Etizolam	0.010±0.009	0.858±0.052	0.999±0.001
8	Bentazepam	0.004±0.004	0.600±0.031	0.999±0.000
9	Cinazepam	0.000±0.000	0.008±0.000	0.998±0.002
10	Diclazepam	0.001±0.000	0.027±0.003	0.996±0.003
11	4-AcO-DiPT	-0.003±0.001	0.427±0.008	0.999±0.000
12	5-MeO-DPT	0.002±0.009	1.751±0.053	0.999±0.000
13	5-MeO-DALT	0.013±0.037	6.163±0.230	0.999±0.000
14	5-MeO-MiPT	0.000±0.001	0.504±0.009	0.999±0.000
15	5-MeO-DMT	0.000±0.001	0.110±0.003	0.999±0.000
16	N.N-DMT	0.000±0.001	0.143±0.002	0.999±0.000
17	4-OH-DET	-0.018±0.013	0.713±0.059	0.997±0.003
18	Ritalinic acid	0.023±0.020	1.157±0.104	0.995±0.004
19	Isotonitazene	0.018±0.022	2.862±0.149	0.999±0.000
20	Alpha ethyltryptamine	0.139±0.103	3.497±0.478	0.989±0.008
21	Ethylphenidate	0.065±0.056	6.207±0.267	0.999±0.001
22	5-MeO-AMT	0.007±0.004	0.235±0.018	0.996±0.002
23	5-APB	0.005±0.004	0.163±0.019	0.990±0.008
24	6-APB	0.007±0.004	0.173±0.017	0.989±0.009
25	MMB-2201	3.683±3.244	258.077±12.078	0.997±0.002
26	MDMB-CHMICA	3.866±3.330	273.783±11.546	0.997±0.002
27	AB-CHMINACA	1.392±1.186	89.816±2.491	0.995±0.004
28	UR-144	2.251±1.669	176.846±6.163	0.997±0.001
29	5-EAPB	0.099±0.089	5.299±0.402	0.996±0.003
30	6-MAPB	0.003±0.012	1.112±0.256	0.996±0.002
31	5-MAPB	0.010±0.010	1.666±0.040	0.997±0.000
32	MDPBP	-0.001±0.001	0.681±0.010	1.000±0.000
33	MPHP	0.014±0.016	1.815±0.125	0.999±0.001
34	3-4 MDPHP	0.003±0.004	0.677±0.028	0.999±0.000
35	α-PHP	0.016±0.011	2.109±0.049	0.999±0.001
36	AP-237	0.117±0.086	6.508±0.397	0.997±0.002
37	2-methyl-AP-237	0.040±0.040	3.226±0.269	0.998±0.002
38	APP-FUBINACA	0.622±0.469	43.876±1.190	0.998±0.001
39	AB-FUBINACA	1.515±1.112	69.256±4.219	0.996±0.003
40	ADB-FUBINACA	0.702±0.690	26.986±3.447	0.994±0.007
41	5F-ADB	2.116±1.663	133.038±5.810	0.997±0.003

42	PX1	0.261±0.209	24.078±0.988	0.997±0.002
43	PX2	0.906±0.699	55.617±2.835	0.997±0.002
44	THJ-018	0.859±0.680	51.985±2.795	0.998±0.002
45	5-F-PB-22	2.337±0.202	312.389±8.207	0.998±0.001
46	5F-NNEI-2	2.082±1.596	178.619±6.362	0.998±0.001
47	CUMYL-PeGACLONE	1.414±0.957	78.121±0.636	0.979±0.012
48	5F-CUMYL-PINACA	0.948±0.953	124.281±3.531	0.998±0.002
49	5-chloro AB-PINACA	0.020±0.011	1.830±0.041	0.995±0.006
50	5-fluoro CUMYL-PeGACLONE	1.295±1.645	91.273±8.306	0.986±0.005
51	5-fluoro MDMB-7-PAICA	1.504±0.898	57.098±1.715	0.992±0.004
52	MDMB-4en-PINACA	-0.089	299.123	0.995
53	5-fluoro MDMB-PICA	2.690±2.388	331.392±8.114	0.999±0.001
54	5-fluoro CUMYL-7-PAICA	2.559±2.033	161.694±6.585	0.997±0.002
55	Furanylfentanyl	0.010±0.012	1.677±0.098	0.999±0.001
56	Para-fluoro furanylfentanyl	0.012±0.012	1.478±0.099	0.999±0.001
57	Furanylnorfentanyl	0.014±0.024	3.747±0.155	0.999±0.001
58	Furanylethylfentanyl	0.019±0.019	2.334±0.096	0.999±0.001
59	Methoxyacetylfentanyl	0.014±0.012	0.985±0.061	0.998±0.002
60	Methoxyacetylnorfentanyl	0.005±0.006	0.886±0.024	0.999±0.001
61	Cis-3-methylnorfentanyl	0.093±0.106	9.227±0.559	0.998±0.001
62	Trans-3-methylnorfentanyl	0.115±0.122	9.914±0.652	0.998±0.002
63	Fentanyl	0.001±0.002	1.967±0.087	0.999±0.000
64	Norfentanyl	0.032±0.052	5.103±0.257	0.999±0.001
65	B-phenylfentanyl	0.005±0.009	2.116±0.068	0.999±0.000
66	Phenylfentanyl	0.025±0.024	2.574±0.179	0.999±0.001
67	Phenylacetylfentanyl	0.001±0.004	1.035±0.038	1.000±0.000
68	Acetylfentanyl	0.010±0.013	1.930±0.103	0.999±0.001
69	Acetylnorfentanyl	0.012±0.010	1.009±0.052	0.998±0.001
70	Butyrylfentanyl	0.005±0.007	1.438±0.0032	0.999±0.000
71	Isobutyrylfentanyl	0.004±0.008	1.640±0.051	0.999±0.000
72	Butyrylfentanyl carboxy met.	0.022±0.020	1.556±0.142	0.998±0.002
73	Valerylfentanyl carboxy met.	0.011±0.013	1.400±0.103	0.999±0.001
74	Cyclopropylfentanyl	0.006±0.009	1.335±0.081	0.999±0.001
75	Butyrylnorfentanyl	0.052±0.061	4.328±0.334	0.997±0.002
76	Alfentanyl	-0.04±0.005	0.682±0.043	0.999±0.001
77	Carfentanyl	0.006±0.008	0.862±0.063	0.999±0.001
78	Ocfentanyl	0.022±0.021	2.175±0.136	0.999±0.001
79	β-hydroxythiofentanyl	0.003±0.003	0.416±0.026	0.999±0.001
80	Despropionyl-para-fluorof.	0.005±0.014	2.217±0.104	0.999±0.000
81	4-ANPP	0.023±0.025	2.408±0.170	0.998±0.001
82	Ethylone	0.003±0.002	0.159±0.011	0.997±0.002
83	Butylone	0.002±0.002	0.270±0.014	0.999±0.001
84	Eutylone	0.001±0.002	0.372±0.011	0.999±0.000
85	Methylone	0.001±0.001	0.134±0.007	0.998±0.001

86	Methedrone	0.000±0.000	0.045±0.002	0.998±0.002
87	N-ethylpentylone	0.004±0.003	0.347±0.015	0.998±0.015
88	MDPV	0.002±0.001	1.383±0.028	0.999±0.000
89	3.4-dimethylmethcathinone	0.001±0.000	0.083±0.002	0.993±0.002
90	Dimethylcathinone	0.000±0.000	0.043±0.003	0.996±0.002
91	Ethcathinone	0.000±0.000	0.038±0.003	0.997±0.002
92	Methcathinone	0.000±0.000	0.255±0.002	0.999±0.000
93	AM-2233	0.000±0.001	0.667±0.014	1.000±0.000
94	Naphyrone	0.000±0.000	0.533±0.010	1.000±0.000
95	Pravadoline	0.003±0.003	1.348±0.069	0.999±0.001
96	Pentylone	0.001±0.001	0.202±0.015	0.995±0.000
97	4-fluoro methcathinone	0.000±0.000	0.030±0.001	0.996±0.000
98	JWH-081	0.441±0.375	208.369±6.090	0.997±0.001
99	JWH-398	0.198±0.193	112.369±3.896	0.998±0.001
100	JWH-210	0.255±0.208	147.824±2.861	0.997±0.001
101	AM-2201	0.298±0.304	158.857±2.823	0.998±0.001
102	JWH-122	0.386±0.374	175.454±4.550	0.996±0.002
103	JWH-019	0.480±0.523	274.463±7.306	0.996±0.001
104	JWH-007	0.518±0.431	176.917±7.524	0.996±0.002
105	JWH-016	3.127±2.051	568.517±39.732	0.996±0.003
106	JWH-203	0.356±0.298	117.930±3.735	0.998±0.001
107	JWH-251	0.060±0.028	16.285±0.795	0.999±0.002
108	AM-694	0.140±0.105	63.513±1.490	0.999±0.001
109	5F-AKB48	3.346±3.017	288.653±10.024	0.997±0.002
110	JWH-098	0.570±0.464	247.787±8.605	0.997±0.001
111	JWH-147	0.502±0.523	246.100±8.763	0.998±0.001
112	RCS-8	0.236±0.283	289.880±5.889	0.998±0.002
113	JWH-018	4.463±3.258	845.179±43.355	0.996±0.003
114	JWH-302	0.265±0.272	123.079±3.742	0.998±0.001
115	RCS-4	0.307±0.318	184.730±5.335	0.998±0.001

	NPS	Average ME%			Average PE%		
		QC1	QC2	QC3	QC1	QC2	QC3
1	Ketamine	97,8	88,8	90,8	96,3	92,7	99,0
2	Norketamine	109,7	89,6	96,1	129,2	88,5	97,7
3	2-fluorodeschloroketamine	99,7	88,7	100,5	95,8	92,1	99,6
4	Deschloro-N-ethylketamine	99,5	87,3	87,6	121,9	90,5	95,8
5	Clonazolam	103,2	91,5	92,6	121,8	96,1	102,4
6	Flualprazolam	100,7	92,1	91,4	121,6	95,1	100,6
7	Etizolam	100,5	85,6	87,9	124,0	90,7	95,7
8	Bentazepam	96,7	86,7	89,0	107,1	83,8	90,2
9	Cinazepam	116,2	108,9	108,8	41,5	32,3	34,7
10	Diclazepam	97,8	87,7	85,0	114,4	92,1	88,7
11	4-AcO-DiPT	109,7	98,4	94,5	100,7	71,2	82,5
12	5-MeO-DPT	104,3	93,1	90,5	125,1	93,2	103,2
13	5-MeO-DALT	106,4	91,5	89,3	121,5	92,9	100,9
14	5-MeO-MiPT	98,7	90,0	89,9	116,5	91,5	99,7
15	5-MeO-DMT	106,5	94,6	90,1	123,1	96,1	99,6
16	N,N-DMT	99,9	87,5	86,7	123,0	87,9	94,0
17	4-OH-DET	105,9	94,2	90,7	104,9	54,5	69,3
18	Ritalinic acid	98,6	89,6	88,5	120,8	93,1	96,9
19	Isotonitazene	101,2	91,3	91,9	128,4	95,1	104,3
20	Alpha-ethyltryptamine	100,9	86,7	87,7	102,2	76,3	84,5
21	Ethylphenidate	103,0	93,4	93,1	125,9	89,8	97,7
22	5-MeO-AMT	85,1	73,6	78,9	69,6	52,4	62,9
23	5-APB	89,6	77,9	75,8	102,2	79,4	80,7
24	6-APB	91,9	81,1	77,1	100,6	81,4	82,7
25	MMB-2201	89,3	82,9	82,8	107,8	84,5	89,6
26	MDMB-CHMICA	79,8	75,3	75,7	96,6	75,0	77,8
27	AB-CHMINACA	77,5	72,1	81,6	90,3	73,0	86,9
28	UR-144	67,6	61,1	61,0	77,6	59,8	59,3
29	5-EAPB	102,5	90,0	87,9	121,1	89,8	97,6
30	6-MAPB	99,8	91,7	88,3	122,4	88,5	97,0
31	5-MAPB	102,6	87,0	84,9	124,8	83,9	95,3
32	MDPBP	100,9	88,6	89,6	114,1	87,8	96,9
33	MPHP	106,5	96,2	92,2	121,9	91,7	97,1
34	3-4 MDPHP	104,3	92,1	93,1	128,9	92,3	100,5
35	α-PHP	104,2	91,1	91,0	110,4	83,5	86,0
36	AP-237	102,5	92,6	92,8	126,6	96,3	103,5
37	2-methyl-AP-237	105,9	95,9	96,2	133,8	102,2	108,6
38	APP-FUBINACA	86,2	85,0	96,8	107,5	88,7	100,5
39	AB-FUBINACA	96,6	104,2	101,1	126,8	103,4	110,6
40	ADB-FUBINACA	87,9	84,3	91,8	109,3	96,7	118,1
41	5F-ADB	83,6	77,8	79,2	100,0	79,0	82,6
42	PX1	111,4	104,9	101,0	135,5	107,2	112,3
43	PX2	105,6	98,6	98,6	121,8	103,8	112,6
44	THJ-018	69,1	67,2	72,7	79,5	66,2	70,7

45	5-F-PB-22	56,8	50,7	55,3	59,4	50,6	53,1
46	5F-NNEI-2	79,7	76,5	81,8	94,6	77,9	83,3
47	CUMYL-PeGACLONE	89,3	72,2	66,5	91,8	75,4	76,9
48	5F-CUMYL-PINACA	79,1	74,0	74,9	91,5	72,9	78,7
49	5-chloro AB-PINACA	88,8	82,6	94,7	110,5	87,5	101,6
50	5-fluoro CUMYL-PeGACLONE	90,6	74,9	79,9	111,1	73,1	77,9
51	5-fluoro MDMB-7-PAICA	82,1	72,9	77,0	94,9	77,5	81,2
52	MDMB-4en-PINACA	/	/	/	/	/	/
53	5-fluoro MDMB-PICA	55,5	50,1	54,9	58,1	50,8	52,8
54	5-fluoro CUMYL-7-PAICA	85,5	77,6	80,7	99,7	81,0	86,6
55	Furanylfentanyl	102,8	91,0	90,7	127,4	95,1	101,8
56	Para-fluoro furanylfentanyl	104,1	91,8	91,7	130,3	97,0	102,5
57	Furanylnorfentanyl	106,9	93,1	93,5	118,5	87,8	100,1
58	Furanylethylfentanyl	105,1	91,6	90,1	123,7	93,8	101,5
59	Methoxyacetylfentanyl	105,4	93,5	91,3	125,1	98,1	103,3
60	Methoxyacetylnorfentanyl	108,7	100,0	105,4	123,1	94,9	111,7
61	Cis-3-methylnorfentanyl	102,4	90,0	88,7	112,9	84,1	93,8
62	Trans-3-methylnorfentanyl	102,2	90,8	89,1	113,9	84,1	94,2
63	Fentanyl	110,4	92,5	88,6	136,6	96,2	100,5
64	Norfentanyl	102,3	90,1	89,4	116,7	85,8	95,9
65	B-phenylfentanyl	104,8	96,6	95,3	132,9	98,9	107,8
66	Phenylfentanyl	102,1	94,1	93,6	132,4	95,8	103,8
67	Phenylacetylfentanyl	105,1	93,6	90,2	123,3	97,0	102,0
68	Acetylfentanyl	104,1	90,9	89,5	123,0	92,2	101,4
69	Acetylnorfentanyl	104,5	90,8	90,6	114,0	87,7	96,5
70	Butyrylfentanyl	101,9	96,0	98,6	138,2	96,8	103,0
71	Isobutyrylfentanyl	102,8	92,1	90,1	123,9	96,8	102,1
72	Butyrylfentanyl carboxy met.	105,0	92,3	90,6	123,4	93,4	102,2
73	Valerylfentanyl carboxy met.	102,6	91,5	89,8	120,8	92,7	99,2
74	Cyclopropylfentanyl	102,4	94,6	93,1	131,2	96,5	103,9
75	Butyrylnorfentanyl	105,1	91,3	87,6	120,9	86,4	94,1
76	Alfentanyl	104,1	90,5	88,3	126,0	92,0	99,8
77	Carfentanyl	101,7	90,8	89,9	124,0	94,4	101,3
78	Ocfentanyl	104,0	89,1	90,9	127,1	93,2	101,7
79	β-hydroxythiofentanyl	103,2	89,8	89,4	123,5	92,5	100,4
80	Despropionyl-para-fluorof.	105,3	92,8	92,3	125,2	95,2	103,9
81	4-ANPP	105,5	93,7	92,7	127,2	96,6	104,2
82	Ethylone	103,9	91,8	91,6	40,4	26,8	26,2
83	Butylone	97,2	92,7	92,1	79,2	55,4	57,1
84	Eutylone	101,1	89,8	89,3	79,7	59,3	60,3
85	Methylone	101,1	92,7	90,3	40,1	25,9	25,8
86	Methedrone	106,0	88,7	80,1	75,3	43,0	39,1
87	N-ethylpentylone	105,3	90,5	90,5	76,9	54,6	56,9
88	MDPV	107,5	100,6	96,0	139,4	96,9	100,3
89	3,4-dimethylmethcathinone	100,3	92,7	89,1	38,0	20,8	18,8

90	Dimethylcathinone	102,0	89,5	85,5	127,3	74,5	76,1
91	Ethcathinone	93,5	71,5	83,5	76,2	71,8	74,8
92	Methcathinone	95,2	94,0	98,6	88,3	94,6	94,7
93	AM-2233	103,2	96,0	91,3	150,5	94,9	97,8
94	Naphyrone	108,3	101,5	95,6	140,4	85,3	88,5
95	Pravadoline	102,7	97,7	94,8	146,3	97,2	100,8
96	Pentylone	106,0	96,1	91,6	83,2	54,3	51,3
97	4-fluoro methcathinone	92,0	92,6	85,3	92,7	97,2	92,4
98	JWH-081	75,5	71,6	71,3	100,9	70,9	68,1
99	JWH-398	56,5	51,0	50,6	71,4	49,5	45,8
100	JWH-210	51,6	47,4	48,7	66,9	45,1	42,2
101	AM-2201	76,9	75	74,7	103,5	74	72,5
102	JWH-122	73,7	69,0	67,0	97,3	66,9	64,3
103	JWH-019	77,2	71,7	69,0	102,2	69,1	67,2
104	JWH-007	70,3	68,1	67,5	94,4	67,2	63,8
105	JWH-016	73,1	62,4	60,4	98,1	62,0	59,9
106	JWH-203	83,3	76,1	74,6	111,8	73,5	72,7
107	JWH-251	73,2	67,6	64,1	105,1	66,1	63,0
108	AM-694	49,1	48,1	53,0	61,4	47,0	48,8
109	5F-AKB48	73,2	66,5	67,8	84,8	66,1	67,0
110	JWH-098	79,1	75,9	73,4	105,8	74,1	70,2
111	JWH-147	69,3	92,9	61,6	92,8	60,9	57,3
112	RCS-8	69,6	63,8	62,6	90,1	61,9	58,9
113	JWH-018	79,8	73,3	73,4	107,4	73,9	71,7
114	JWH-302	75,6	70,8	69,9	99,6	70,3	67,7
115	RCS-4	59,9	55,7	59,4	76,2	55,5	55,8