IDENTIFICATION OF CANNABIMIMETIC MDMB(N)-073F METABOLITES IN URINE BY METHOD OF GAS CHROMATOGRAPHY WITH MASS SPECTROMETRIC DETECTION

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Background. At the beginning of 2019, the use of a new representative of synthetic cannabimimetics of the methylbutanoate indazole carboxamides group, MDMB(N)-073F, was recorded in a number of regions in the Russian Federation. Characteristic features of the pharmacological effect, the clinical picture of MDMB(N)-073F poisoning have not been studied, the psychoactive effects produced by MDMB(N)-073F remain unexplored. In this regard, the study of the new cannabimimetic metabolism is an important aspect in establishing the fact of taking MDMB(N)-073F during expert studies of biological objects.

The aim of the research is identifying metabolites of synthetic MDMB(N)-73F cannabimimetics in real urine samples using solid-phase extraction (SPE) and gas chromatography (GC) with mass spectrometric detection (GC-MS).

Materials and methods. 10 urine samples were collected from March 15 to March 29, 2019. 8 urine samples were taken from the medical examination offices of the city of Yekaterinburg and the Sverdlovsk region from the persons examined for intoxication; 2 urine samples were obtained from the patients of the Sverdlovsk regional center of acute poisoning upon enrolment to the toxic-intensive care unit with a preliminary diagnosis of “acute poisoning by synthetic cannabimimetics”. In the research, SamplIQ EVIDEX-200 mg – 3 ml (Agilent, USA) cartridges were used for the sample preparation; β-glucuronidase Type HP-2, From Helix Pomatia, 100000 U/ml (Sigma-ALDRICH CHEMI, Germany) was used for enzymatic hydrolysis. Gas chromatography – mass spectrometry with the use of Agilent 7820 gas chromatograph with Agilent 5975 mass selective detector (Agilent, USA) was used as an instrumental method of the analysis.

Results. The metabolites that make it possible to establish the fact of taking MDMB(N)-073F cannabimimetics via urine screening procedure to detect the presence of narcotic and medicinal substances with the use of solid-phase extraction and gas chromatography methods with mass spectrometry, have been described. The major metabolites MDMB(N)-073F in the urine of smoking mixtures consumers have been identified. The metabolism of MDMB(N)-073F has been found to be mainly due to hydrolysis of the ester group, hydroxylation, oxidative defluorination and N-dealkylation. Most of the resulting metabolites are excreted in the urine in the conjugated form.

Conclusion. Gas chromatographic and mass spectrometric characteristics of some derivatives of the main metabolites of the new synthetic MDMB(N)-073F cannabimimetic have been obtained. This data can be used in the practice of forensic chemical and chemical toxicological analysis.

Keywords: MDMB(N)-073F, cannabimimetics, metabolism, enzymatic hydrolysis, solid-phase extraction (SPE), gas chromatography – mass spectrometry
ИДЕНТИФИКАЦИЯ МЕТАБОЛИТОВ КАННАБИМИМЕТИКА MDMB(N)-073F В МОЧЕ МЕТОДОМ ГАЗОВОЙ ХРОМАТОГРАФИИ С МАСС-СПЕКТРОМЕТРИЧЕСКИМ ДЕТЕКТИРОВАНИЕМ

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В начале 2019 года в ряде областей Российской Федерации появился новый представитель синтетических каннабимиметиков группы метилбутаноатиндазолкарбоксамидов – MDMB(N)-073F. Особенности фармакологического действия, клиническая картина отравлений MDMB(N)-073F не изучены, психоактивные эффекты, производимые MDMB(N)-073F, являются неисследованными. В этой связи изучение метаболизма нового каннабимиметика является важным аспектом в установлении факта приема MDMB(N)-073F при экспертных исследованиях биологических объектов.

Цель исследования – выявление метаболитов синтетического каннабимиметика MDMB(N)-073F в реальных образцах мочи с использованием твердофазной экстракции (ТФЭ) и газовой хроматографии с масс-спектрометрическим детектированием (ГХ-МС).

Материалы и методы. 10 образцов мочи были собраны в период с 15 по 29 марта 2019г. 8 проб мочи были доставлены из кабинетов медицинского освидетельствования г. Екатеринбурга и Свердловской области от лиц, освидетельствованных на состояние опьянения; 2 образца мочи были получены от пациентов Свердловского областного центра острого отравления при поступлении в токсико-реанимационное отделение с предварительным диагнозом «острое отравление синтетическими каннабимиметиками». В исследовании для подготовки проб применялись патроны для ТФЭ SampliQ EVIDEX – 200 мг – 3 мл (Agilent, США), для ферментативного гидролиза использовалась β-глюкуронидаза, Type HP-2, From Helix Pomatia, 100000 ЕД/мл (Sigma-ALDRICH CHEMI, Германия), в качестве инструментального метода анализа – газовая хроматография – масс-спектрометрия с использованием газового хроматографа Agilent 7820 с масс-селективным детектором Agilent 5975 (Agilent, США).

Результаты и обсуждение. Описаны метаболиты, позволяющие установить факт употребления каннабимиметика MDMB(N)-073F в процедуре скрининга мочи на наличие наркотических и лекарственных веществ с применением методов твердофазной экстракции и газовой хроматографии с масс-спектromетрией. Выполнена идентификация основных метаболитов MDMB(N)-073F в моче потребителей курительных смесей. Установлено, что метаболизм MDMB(N)-073F, главным образом, обусловлен гидролизом сложноэфирной группы, гидроксилированием, окислительным дефторированием и N-деалкилированием; большая часть образующихся метаболитов выводится с мочой в конъюгированном виде.

Заключение. Получены газохроматографические и масс-спектрометрические характеристики некоторых производных основных метаболитов нового синтетического каннабимиметика MDMB(N)-073F, которые могут быть полезны в практике судебно-химического и химико-токсикологического анализа.

Ключевые слова: MDMB(N)-073F, каннабимиметики, метаболизм, ферментативный гидролиз, твердофазная экстракция, газовая хроматография – масс-спектрометрия

INTRODUCTION

Legislative efforts in the field of control over the traffic of narcotic drugs and psychotropic substances, made over the last years, have reduced the scale of the emergence of the “designer drugs” series, but the trend towards the periodic emergence of new representatives of synthetic cannabininetics remains. Synthetic cannabininetics (SCs) are the most diversely represented...
group of psychoactive substances on the illegal drug market. Over the past few years, several “generations” of synthetic cannabimimetics have changed.

Thus, according to the chemical structure, the majority of SCs identified in 2014–2015, were found in the following groups: naphthoylindoles, 1-amino-1-oxobutane indazole carboxamides and methyl butane-indindazole carboxamides [1].

At the beginning of 2019, a new representative of synthetic cannabimimetics of the methylbutanoate indazole carboxamides group, MDMB(N)-073F, which is a 4-fluorine derivative of the previously encountered MDMB(N)-073 [2], was recorded in a number of regions in the Russian Federation.

According to the Decree of the Government of the Russian Federation No. 1097 (dated October 12, 2015), a synthetic cannabimimetic MDMB(N)-073F is covered by List I of narcotic drugs, psychotropic substances and their precursors, which are controlled by the government [3]. Based on the chemical structure, MDMB(N)-073F is a derivative of 2-(1-buty1-1H-indazol-3-carboxamido) acetic acid.

The features of the pharmacological effect, the clinical picture of MDMB(N)-073F poisoning have not been studied, the psychoactive effects produced by MDMB(N)-073F remain unexplored. In this regard, the study of new cannabimimetic metabolism seems relevant in the practice of expert institutions engaged in chemical-toxicological and forensic-chemical analysis of the objects.

THE AIM of work is to identify metabolites of synthetic cannabimimetics MDMB(N)-073F in real urine samples using solid-phase extraction and gas chromatography with mass spectrometric detection.

MATERIALS AND METHODS

Equipment
- Gas chromatograph Agilent 7820 (capillary column HP-5MS, inner diameter 0.25 mm, length 30 m, thickness of film 0.25 µm) (Agilent, USA);
- mass-selective detector Agilent 5975 (Agilent, USA);
- 12 position SPE Vacuum Manifold System (Supelco);
- low vacuum pump (KNF lab LABOPORT, France);
- thermal block PE-4030 (Ekros, Russia);
- single-channel vaporizer PE-2300 (“Ecros”, Russia);
- microshaker PE-2 (“Ecros”, Russia);
- microwave Supra MWS-1824SW (Russia);
- solid-phase extraction cartridges SampliQ EVIDEX (200 mg-3 ml) (Agilent, USA);
- semi-automatic dispensers with 4–40, 40–200 µl and 0.2–1, 1–5 ml range.

Materials
- Bis-trimethylsilyl-trifluoroacetamide (BSTFA) containing 1% trimethylchlorosilane; β-glucuronidase, Type HP-2, From Helix Pomatia, 100,000 U / ml (Sigma-AL-DRICH CHEMI, Germany). The chemicals used in the study are of the “chemically pure” brand. The storage of the urine samples before the study was carried out at + 4°C.

Sample preparation
10 urine samples were collected from March 15 to March 29, 2019. 8 urine samples were taken from the medical examination offices of the city of Yekaterinburg and the Sverdlovsk region from the persons examined for intoxication; 2 urine samples were obtained from the patients of the Sverdlovsk regional center of acute poisoning upon enrolment to the toxic-intensive care unit with a preliminary diagnosis of “acute poisoning by synthetic cannabimimetics”.

The preparation of urine samples using enzymatic hydrolysis was carried out in the following way: 50 µl of each of alcohol solutions of inner standards (ethylmorphine hydrochloride (0,02 mg/ml), N-ethylbenzylamine (0,01 mg/ml) and hexenal (0,2 mg/ml) were added to 1 ml of urine samples. Next, for one parallel of urine samples, their preliminary preparation was carried out. Hereby, enzymatic hydrolysis was used. 250 µl of 1/15 M phosphate buffer (pH 6) and 25 µl of β-glucuronidase were added to the urine sample, then the vial was corked up and exposed to 45°C for 2 hours.

2 ml 1/15 M phosphate buffer (pH 4,8) was added to the urine samples without and after hydrolysis. The contents of the vials were centrifuged at 3000 rpm for 10 minutes, the centrifugate was separated from the residue.

For extraction, SPE cartriges SampliQ EVIDEX (200 mg/3 ml) with a mixed phase were used. Conditioning of a sorbent was conducted via successive transfer of 2 ml of 95% ethanol and 2 ml of 1/15 M phosphate buffer (pH 4,8) through the cartridge. After that, the sample was downloaded at the speed of 1 ml/min.

Flushing was conducted in a successive manner: 1 ml of 1/15 M phosphate buffer (pH 4,8) and 1 ml of 10% ethanol. Drying the cartridge was carried out in vacuum for 20 minutes. Eluate I was derived via double transfer of 2 ml of n-hexane – ethylacetate (2:1) conception through the cartridge. Elute II was derived via double transfer of 2 ml of dichloromethane – 2-propanol – 25% ammonia (2:1:0.1) conception. Eluates I and II were vaporized in a nitrogen flow at 45°C.

Derivatization and research
Methylation. 500 µl of anhydrous acetone, 40 µl of iodomethane and 20–25 mg of anhydrous potassium carbonate were added to the dry residue of eluate I, the vial was corked up and heated at 60°C for 60 minutes in the thermal block. The vial was then cooled down, the fluid fraction of the reactive concoction was separated and transferred into a clean vial, then vaporized in nitrogen flow at 40°C. The dry residue was dissolved in 100 µl of anhydrous ethylacetate and 1 µl of this solution was put into chromato-mass-spectrometer’s injector.
Acetylation. 40 µl of anhydrous pyridine and 60 µl of acetic anhydride (washing off the vial wallsides) were added to the dry residue of eluate II, the vial was corked up and exposed to microwave emission in the oven at 560 watt for 5 minutes. After cooling down, the vial was opened and the surplus reagents were vaporized in nitrogen flow at ≤ 40°C. The dry residue was dissolved in 100 µl of anhydrous ethylacetate, and 1 µl of this solution was put into the chromato-mass-spectrometer’s injector.

Trimethylsilyl esters acquisition. 100 µl of BSTFA containing 1% of trimethylchlorsilane was added to the dry residue of eluate I or II, the vial was corked up, shaken with the microshaker and heated at 80°C for 60 minutes in the thermal block. The vial was cooled down and 2 µl was put into the chromato-mass-spectrometer’s injector.

Operation mode of gas chromatograph with a mass-selective detector

The speed of the flow of the carrier gas (helium) passing the column was 1.5 ml/min, the flow-splitting was 15:1 with the impulse delay of 1 minute after the sample injection. The temperatures of the injection port and the line connecting to the mass spectrometer were 250°C and 280°C, respectively. The initial temperature of the column was 70°C for 2 minutes; then, the column was heated up to 280°C at the rate of 20 degrees/min and kept at the final temperature for 8 minutes.

The voltage of the multiplier of the mass-spectrometric detector was equal to that of the automatic routine adjustment of the detector. The registration of mass spectrum for acetyl and methyl derivatives in full ion scanning mode was in mass range of 42–450 a.u. The registration of mass spectrum for trimethylsilyl derivatives in full ion scanning mode was in the mass range of 43–650 a.u.

Processing of the chromatograms in order to identify the components of the samples was carried out using MSD ChemStation E.02.01.1177 (Agilent) и AMDIS (The Automatic Mass Spectral Deconvolution and Identification System, NIST) software.

The degree of conjugation of MDMB(N)-073F metabolites was determined for their methyl esters by the ratio of the peak area of the ion with the following m/z values: for M1 and M4 artifact – 219, for M2 – 249, for M3 – 159, for M5 – 245, for M6 – 235, for M7 and for M9 – 189, M8 – 217 ion. For N-methylhexenal (inner standard) in eluate I of urine with and without hydrolysis the ion peak area was 235.

The relative content for their trimethylsilyl esters M1, M10, M4 and artifact M4 was determined by internal normalization with respect to the peak area of the ion with the value of m/z 219 in urine eluate I with enzymatic hydrolysis.

The results of the calculations of physicochemical constants (LogP, KOC) were obtained using the software package ACD/Labs v6.0 (Advanced Chemistry Development Inc., Toronto, Canada).

RESULTS AND DISCUSSION

The chemical name of cannabimimetics is MDMB(N)-073F – 2-[1-(4-fluorobutyl)-1H-indazole-3-carboxamide]-3,3-dimethylbutanoic acid methyl ester; the chemical formula is: C19H26FN3O3; the molecular mass = 363.4 g/mol. Its synonyms are: 4-fluoro MDMB-BINACA, 4F-MDMB-BINACA, 4-fluoro MDMB-BUTINACA.

MDMB(N)-073F is a derivative of the already known compound MDMB(N)-073 [2] and differs from the latter by the presence of fluorine in position 4 of the alkyl substituent of the indazole heterocycle. The chemical structures of cannabimimetics MDMB(N)-073 and MDMB(N)-073F are shown in Fig. 1.

![Figure 1 – Chemical structures of MDMB(N)-073 and MDMB(N)-073F cannabimimetics](image)

The supposed chemical structure of MDMB(N)-073F metabolites, identified during the examinations of urine samples of the individuals who used smoking mixtures, is shown in Fig. 2.

The structures of metabolites were determined on the basis of mass fragmentation of peaks, which were detected on chromatograms obtained in the study of urine samples of drug users. The structures were also determined.
on the basis of literature data on mass fragmentation of metabolites MDMB(N)-073 [2] and 5F-AB-PINACA [4]. In order to establish the properties of functional groups in the structure of metabolites, various types of derivatization were used, as well as their sequential combination.

Fig. 3–16 present the supposed structures and mass-spectra of M1–M10 MDMB(N)-073F metabolite derivatives.

Figure 2 – Supposed chemical structures of cannabimimetic MDMB(N)-073F metabolites
Figure 3 – Mass-spectrum, retention index and structure of methyl ester of M1 metabolite

Figure 4 – Mass-spectrum, retention index and structure of methyl ether of M2.2 metabolite
Figure 5 – Mass-spectrum, retention index and structure of dimethyl derivative M3

Figure 6 – Mass-spectrum, retention index and structure of M4 metabolite artifact
Figure 7 – Mass-spectrum, retention index and structure of dimethyl ester of M5 metabolite

Figure 8 – Mass-spectrum, retention index and structure of methyl ester of M6 metabolite
Figure 9 – Mass-spectrum, retention index and structure of methyl ether of M7 metabolite

Figure 10 – Mass-spectrum, retention index and structure of methyl ether of M8 metabolite
Figure 11 – Mass-spectrum, retention index and structure of trimethyl derivative of M9 metabolite

Figure 12 – Mass-spectrum, retention index and structure of trimethylsilyl ester of M10 metabolite
**Figure 13** – Mass-spectrum, retention index and structure of monomethyl ether of M6 metabolite after acetylation

**Figure 14** – Mass-spectrum, retention index and structure of monomethyl ether of M6 metabolite after treating with BSTFA
Figure 15 – Mass-spectrum, retention index and structure of monomethyl ester of M8 metabolite after acetylation

Figure 16 – Mass-spectrum, retention index and structure of bis-trimethylsilyl ether of M4 Metabolite
As a result of the research of the samples using sequential derivatization by methylation and subsequent acetylation or silylation for M6 and M8 metabolites, a shift in retention time and a change in the nature of mass fragmentation were observed. These factors indicate the presence of alcohol hydroxyl groups in the structure. As the resulting derivatives have a tendency to intramolecular cyclization with the formation of the corresponding artifact during gas chromatographic research, the relative content and degree of conjugation for M4 and M10 metabolites were determined in total after the preparation of methyl derivatives. The content of M10 was determined as an individual compound only after hydrolysis and derivatization with BSTFA.

In the mass spectra of methyl esters of MDMB(N)-073F metabolites, an expressed molecular radical ion is observed. There are general directions of fragmentation typical for methyl esters, with the exception of metabolite M7 and the artifact of metabolite M4, such as [M-59]+ and the cleavage of 2-methylprop-1-ene, generated from the tert-butyl group, forming radical ion [M-56]+.

Common characteristic ions for metabolites M1, M4 – M8 with m/z values of 131, 145, are shown in Fig. 17. For the dimethyl ester of metabolites M2.1, M2.2 (the presence of two isomers is due to the location of the hydroxyl group in the heterocycle of metabolites), there are expressed ions with m/z values of 161 and 175. Hereby the ions with m/z values of 131 and 145 are absent from the mass spectrum.

![Image](image-url)

**Figure 17 – A supposed structure of characteristic ions peculiar to mass fragmentation of MDMB(N)-073F metabolites**

A high degree of cannabimimetic markers conjugation requires performing hydrolysis before their analysis (optimally: enzymatic or alkaline), while lipophilicity of markers makes it possible to extract them using hydrophobic or mixed-type sorbents (a combination of reversed-phase properties and cation exchanger properties). The latter make it possible to define SC markers directly in the urine screening procedure for narcotic and medicinal substances [5].

The use of SPE in the sample preparation made it possible to perform fractionation of substances into substances of acidic and alkaline nature. All identified MDMB(N)-073F metabolites were detected in eluate I.

The calculations of physicochemical constants LogP and $K_{ow}$, the results of determining the degree of conjugation, the relative content of MDMB(N)-073F cannabimimetic and its metabolites in the studied urine samples are shown in the table 1.

A study of ten urine samples of MDMB(N)-073F cannabimimetics consumers showed that the majority of metabolites are excreted from the body in conjugated form. Unchanged cannabimimetic MDMB(N)-073F was not detected in the examined urine samples.

As it follows from the relative content of metabolites in the urine samples, the main metabolite of MDMB(N)-073F cannabimimetic is M1, which is the product of MDMB(N)-073F ester bond hydrolysis. Due to the expressed nature of the studied objects, metabolite M1 can be used as a marker of cannabimimetic MDMB(N)-073F.

Metabolites M10, M4 and their derivatives are the removable and form an artifact during the GC / MS study due to intramolecular cyclization (Fig. 6).

Metabolites M8 and M9 are common for MDMB(N)-073F and MDMB(N)-073 cannabimimetics [2]. The only identified MDMB(N)-073F metabolite with preservation of the ester bond at the level of sensitivity of the applied methods, was metabolite M10. The latter was identified in five urine samples with a relative content from 0.82% to 8.00% (median 2.72%). Other MDMB(N)-073F metabolites have no diagnostic value due to their low content in urine.
**Table 1 – Characteristic of MDMB(N)-073F cannabimimetic and its major metabolites**

| Compound      | Log P | Kos (pH=4.8) | Conjugation (median, %) | Relative content* |
|---------------|-------|--------------|-------------------------|------------------|
| MDMB(N)-073F | 2.89  | 893.54       | n.d.                    | –                |
| M1            | 2.39  | 19.05        | 100                     | –                |
| M2.1          | 1.65  | 6.05         | 10                      | 0.13 – 2.14      |
| M2.2          | 1.65  | 6.05         | 10                      | 0.14 – 0.68      |
| M3            | 1.29  | 4.70         | 10                      | 2.96 – 14.80     |
| M4**          | 1.44  | 3.74         | 10                      | 1.66 – 10.11     |
| M5            | 1.32  | 8.88         | 10                      | 1.47 – 12.77     |
| M6***         | 1.13 – 1.28 | 3.90 – 4.57 | 10                      | 0.18 – 1.33      |
| M7            | 2.39  | 27.04        | 9                       | 0.07 – 0.98      |
| M8            | 1.23  | 4.51         | 10                      | 0.14 – 0.75      |
| M9            | 0.55  | 1.66         | 10                      | 0.11 – 6.06      |
| M10           | 2.09  | 324.71       | 5                       | 0.82 – 8.00      |

Note:
* The content of M1 is taken as 100%, the relative value of other metabolites was calculated according to the ratio of the areas of chromatographic peaks, formed by the most intense ions in their spectra. n.d. – not detected, n.c. – not calculated.
** The relative content and conjugation were determined in total for metabolites M4 and M10.
*** The values of LogP and $K_v$ vary depending on the location of the hydroxyl group in the alkyl chain.

**CONCLUSIONS**

On the basis of the gas chromatography-mass spectrometry method, its main metabolites have been identified in the urine samples of MDMB(N)-073F consumers. The physicochemical parameters have been calculated, mass spectral and chromatographic characteristics of some derivatives of the main MDMB(N)-073F metabolites have been obtained. The main metabolic pathways of MDMB(N)-073F have been defined; most of the produced metabolites are excreted in the urine as conjugates.

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**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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