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Identification and analytical properties of new synthetic cannabimimetics bearing 2,2,3,3-tetramethylcyclopropanecarbonyl moiety

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ABSTRACT

By means of gas chromatography with mass spectrometry detector (GC–MS), liquid chromatography–mass spectrometry (LC–MS) and nuclear magnetic resonance spectroscopy (NMR), structure of a series from a novel class of synthetic cannabimimetics bearing 2,2,3,3-tetramethylcyclopropanecarbonyl moiety was established. It was found that this fragment could undergo thermal ring-opening into isomeric structures. The title compounds under action of hydrochloric acid can transform into new compounds which structure is discussed in the paper. The compounds identified could be referred to a new class of 'designer drugs' and are in illegal turnover in Russia and Belarus since the summer of 2011. Analytical data obtained in the paper will make possible reliable identification of such new 'designer drugs' during forensic examination.

1. Introduction

Cannabimimetics have become very popular for non-medical usage as psychoactive drugs since 2008 [1,2]. This was especially favored by active development of a network of websites and online trading platforms, which distribute so-called 'legal' plant mixtures and chemicals. Numerous occurrences of these 'designer drugs' were detected in many countries including Russia and Belarus. These compounds are basically indole derivatives such as 3-naphthoylindoles, 3-phenylacetylindoles, 3-benzoylindoles and 3-adamantoylindoles [3–19].

Constant including of such indole derivatives into national black lists of illegal drugs has lead to occurrence of new class of synthetic cannabimimetics, modifications of 3-(2,2,3,3-tetramethylcyclopropanecarbonyl)indole (**1**) (Table 1), first in Russia and later in Belarus.

In June 2011, FDCS officers in Ekaterinburg have made a test purchase of a sample of smoking mixture in a kiosk selling 'legal' smoking and aromatizing mixes. The sample was found to contain a cannabimimetic 'JWH-210' which is forbidden in Russia. Further search has revealed packets with plant mixes and a packet with a powder which was later identified as (1-pentyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (**2**) (our symbolic notation 'TMCP-018'). According to [20,21] the compound acts as a selective full agonist of the cannabinoid receptors CB_2 and CB_1. Later smoking mixes containing 'TMCP-018' became extremely widely spread in Russia with a maximum in February 2012: only in Ekaterinburg there were 2–5 seizures daily.

Bioactivity and methods of synthesis of derivatives of 3-(2,2,3,3-tetramethylcyclopropanecarbonyl)indole compounds are described in the patents and the other literature [20–23]. According to these references 3-(2,2,3,3-tetramethylcyclopropanecarbonyl)indole derivatives possess strongly pronounced physiological activity similar to Δ^9-tetrahydrocannabinol. NMR spectra of some compounds are also described in the literature, but there is no other spectral analytical data, which could enable reliable identification of these new classes of drugs.

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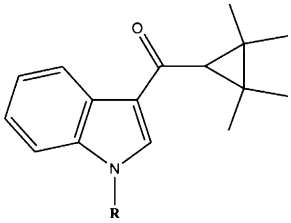
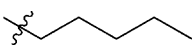
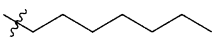
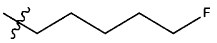
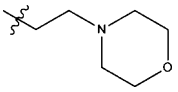
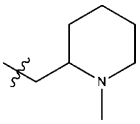
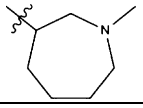
Table 1
Chemical structure of substances **1**–**7**.



No.	Short name	R	Chemical names
1	TMCP-H	H	(1*H*-Indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone
2	TMCP-018		(1-Pentyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone
3	TMCP-020		(1-Heptyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone
4	TMCP-2201		[1-(5-Fluoropentyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone
5	TMCP-200		[1-(2-Morpholin-4-ylethyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone
6	TMCP-1220		[1-(1-Methylpiperidin-2-ylmethyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone
7	TMCP-1220-azepane		[1-(1-Methylazepan-3-yl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone

We have identified that since the summer 2011 most popular compounds, from the class, were: 'TMCP-018' (**2**), parent 3-(2,2,3,3-tetramethylcyclopropanecarbonyl)indole (**1**) and the other derivatives thereof (**3**–**7**), as well as {*N*-[3-(2-methoxyethyl)-4,5-dimethylthiazol-2(3*H*)-ylidene]-2,2,3,3-tetramethylcyclopropanecarboxamide} (**8**) ('A-836,339'), a thiazolidene analog of the compounds under discussion (Fig. 1). Also there were cases of occurrence the products of thermal and acidic transformation of compounds **1**–**7**, in illegal turnover.

For the other identified compounds, the we give symbolic notations following structural analogy with known synthetic cannabimimetics of 'JWH' and 'AM' series: 'TMCP-020' – (1-heptyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (**3**), 'TMCP-2201' – [1-(5-fluoropentyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone (**4**), 'TMCP-200' – [1-(2-morpholyn-4-ylethyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)-methanone (**5**), 'TMCP-1220' – [1-(1-methylpyperidin-2-ylmethyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone (**6**), 'TMCP-1220-azepane' – [1-(1-methylazepan-3-yl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone (**7**).

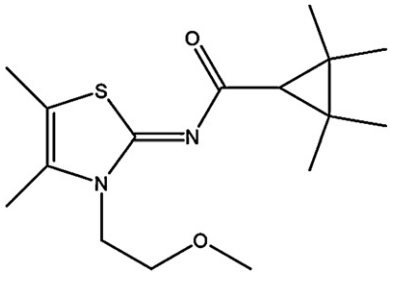


Fig. 1. Chemical structure of 'A-836,339' (substance **8**).

These compounds were detected in numerous real evidences both in pure powders and in smoke mixtures. These compounds are often found in plant mixes in a combination with the other known cannabimimetics of 'JWH' and 'AM' series.

We have found that strained cyclopropyl ring in compounds **1**–**7** tends to undergo ring-opening into isomers **9**–**15**, at thermal treatment (>150 °C) (Table 2). We suggested that similar process takes place during any part of preparation and use of illegal herbal products, adulterated with synthetic cannabimimetics **1**–**7** where overheating is possible: synthesis, application of compounds to a plant matrix, drying from solvents and smoking. Actually, analysis of some samples of criminal smoke mixtures has revealed not only original cannabimimetics **1**–**7** but also thermally stable isomers **9**–**15** thereof – as major components. Moreover, the samples from some seized smoking tools were found to contain isomers **9**–**15** only. This brought us to a suggestion that the latter possess strong psychoactivity.

In some criminal samples, we have found a compound with presumable structure of (*E*)-1-pentyl-3-[4,4,5,5-tetramethyldihydrofuran-2(3*H*)-ylidene]-3*H*-indol-1-ium chloride (**16**) (Fig. 2, symbolic notation 'TMCP-018 acidic'), which – as we have shown later in the experiment – could be prepared under action of hydrochloric acid onto 'TMCP-018'. The acidic recyclization of α-carbonylcyclopropyl found is similar to the process described in the literature [24].

In current paper, we give analytical properties of above-mentioned compounds obtained by means of GC–MS, LC–MS and NMR spectroscopy which would help official experts to determine