International Journal of Mass Spectrometry xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Mass Spectrometry

journal homepage: www.elsevier.com/locate/ijms

Study on the mass fragmentation pathway of the synthetic cannabinoids JWH-018 and JWH-073

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ARTICLE INFO

Article history:
Received 31 October 2014
Received in revised form 15 January 2015
Accepted 22 January 2015
Available online xxx

Keywords:
Mass fragmentation pathway
JWH-018
JWH-073
GC-MS/MS
GC-HRMS

ABSTRACT

Two potent synthetic cannabinoid receptor agonists, JHW-018 and JWH-073, were recently detected as some of the most prominent active agents in abusively used incenses such as 'spice' and other herbal blends. Many countries took legal action to ban or control these substances and some of its analogues, and also the world Anti-Doping Agency prohibited them in elite sports during competition. However, few mass spectrometric fragmentation pathway studies of these compounds exist using a high-resolution mass spectrometer and lack of an assigned fragmentation pathway hindering attempts to detect them. Therefore, there is an urgent need to research the synthetic cannabinoid receptor agonist fragmentation pathways. In this study, we studied the fragmentation pathways of two types of synthetic cannabinoid receptor agonists (JWH-018 and JWH-073) using Gas Chromatography-Tandem Mass Spectrometry (GC-MS/MS) and Gas Chromatography-High Resolution Mass Spectrometry (GC-HRMS). The accurate ion masses from the GC-HRMS and the product ions from the GC-MS/MS were combined and used to obtain the MS fragmentation pathways for these compounds. Most ions were assigned according to the collected high-resolution accurate mass data, and we proposed typical fragmentation pathways of the two types of synthetic cannabinoid receptor agonists. Furthermore, a series of characteristic ions, such as *m/z* 324, 254, 270, and 241, were explained for the first time. These findings are valuable for identifying synthetic cannabinoid receptor agonists and could also provide a theoretical basis for pharmaceutical and metabolites analysis.

1. Introduction

Beginning around 2004, several different herbal blends containing synthetic cannabinoid class chemical agonist compounds began to be sold in the illegal drugs market. These mixtures were sold under a wide variety of names, including 'Spice', 'Yucatan Fire', 'Smoke', 'Sence', 'Skunk', 'Space', 'K2′, 'K2 Citron', 'K2 Blonde', 'K2 Strawberry', 'K2 Pink', 'K3′, and 'K4′. Many such products were reportedly adulterated with synthetic cannabinoids with varying degrees of selectivity and affinity for cannabinoid CB1 and CB2 receptors [1–3]. As most of the products have potentially psychotropic effects, these compounds were also banned in many European countries since 2009 [4]. JWH-018 and JWH-073 were one of the most commonly identified compounds in these herbal products. Fig. 1 includes their structures. They all contained an indole and a naphthalene substructure unit, which might be further identified by Gas Chromatography-Tandem Mass Spectrometry (GC-QQQ) and Gas Chromatography-High Resolution Mass Spectrometry (GC-HRMS).

Most articles on JWH-018 and JWH-073 discussed the metabolites in human urine, and some were identified by GC-MS [5,6]. While the main metabolites are hydroxylate derivatives on the side chain [7–9], they do share a common characteristic structural subunit, which may have a similar mass fragmentation pathway. Few reported examples exist which describe their MS behavior (Scheme 1). However, none of them clearly explain all the characteristic ions, such as *m/z* 324, *m/z* 310, and the *m/z* 167 pathway [6]. Explaining the fragmentation pathway would be very useful for monitoring and identifying the parents and their metabolites. Furthermore, to the best of our knowledge, no detailed fragmentation pathway research on JWH-018 and JWH-073 has been reported to date.

In this study, the fragmentation pathways of JWH-018 and JWH-073 were, for the first time, systematically investigated

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http://dx.doi.org/10.1016/j.ijms.2015.01.007
1387-3806/

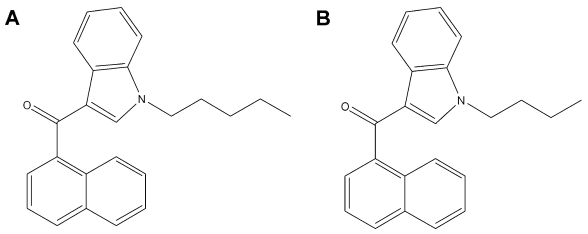
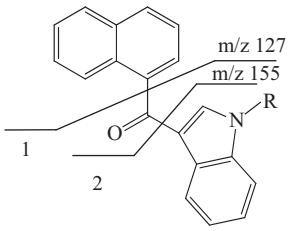
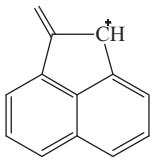


Fig. 1. Chemical structure and common name for (1-pentyl-1H-indol-3-yl)-1-naphthalenyl-methanone (A); (1-butyl-1H-indol-3-yl)-1-naphthalenyl-methanone (B).





m/z 167

Compound	1	2
A(R=C_5H_{11})	214	186
B(R=C_4H_9)	200	172

Scheme 1. The fragmented ions of JWH-018 and JWH-073 have been reported.

using Gas Chromatography-Tandem Mass Spectrometry and Gas Chromatography-High Resolution Mass Spectrometry. Furthermore, this study tried to determine all the major product ions' elemental compositions.

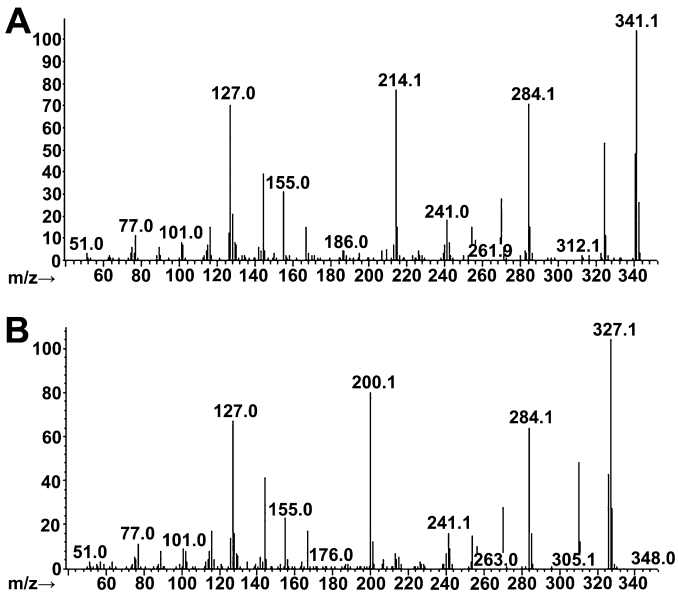


Fig. 2. The full scan spectrum of JWH-018 (A) and JWH-073 (B).

2. Materials and methods

2.1. Chemicals and reagents

JWH-018 and JWH-073 were purchased from Cerilliant. Methanol was HPLC grade and provided by Merck. All other reagents were purchased from Alfa Aesar in the highest available purity and were used as such.

Table 1
List of JWH-018 and JWH-073.

No.	Name	Common name	Formula	Accuracy molecular weight (mono-isotopic)
1	JWH-018	(1-Pentyl-1H-indol-3-yl)-1-naphthalenyl-methanone	$C_{24}H_{23}ON$	341.1774
2	JWH-073	(1-Butyl-1H-indol-3-yl)-1-naphthalenyl-methanone	$C_{23}H_{21}ON$	327.1618

Table 2
Calculated and measured exact masses for the product ions of selected compounds by GC-HRMS.

No.	Compound	Ion species	Element component	Measured mass (Da)	Calculated mass (Da)	RDB	Error (Delta mmu)
1	JWH-018	M	C24H23O1N1	341.1787	341.1774	14	1.284
		M-OH	C24H22N1	324.1746	324.1747	14.5	−0.076
		M-C4H9	C20H14O1N1	284.1084	284.1070	14.5	1.409
		M-C5H11	C19H12O1N1	270.0925	270.0913	14.5	1.159
		M-C5H11O	C19H12N1	254.0961	254.0964	14.5	−0.326
		M-C5H9O	C19H14N1	256.1122	256.1121	13.5	0.124
		M-C6H12O	C18H11N1	241.0893	241.0886	14	0.699
		M-C10H7	C14H16O1N1	214.1222	214.1226	7.5	−0.441
		M-C11H7O	C13H16N1	186.1282	186.1277	6.5	0.474
		M-C12H16N	C12H7O1	167.0492	167.0491	9.5	0.059
		M-C13H16N	C11H7O1	155.0484	155.0491	8.5	−0.741
		M-C15H17	C9H6O1N1	144.0442	144.0444	7.5	−0.190
		M-C14H16ON	C10H7	127.0530	127.0542	7.5	−1.227
2	JWH-073	M	C23H21O1N1	327.1618	327.1618	14	0.034
		M-OH	C23H20N1	310.1578	310.1590	14.5	−1.226
		M-C3H7	C20H14O1N1	284.1073	284.1070	14.5	0.309
		M-C4H9	C19H12O1N1	270.0929	270.0913	14.5	1.559
		M-C4H9O	C19H12N1	254.0956	254.0964	14.5	−0.826
		M-C4H7O	C19H14N1	256.1132	256.1121	13.5	1.124
		M-C5H10O	C18H11N1	241.0887	241.0886	14	0.099
		M-C10H7	C13H14O1N1	200.1068	200.1070	7.5	−0.191
		M-C11H14N	C12H7O1	167.0500	167.0491	9.5	0.859
		M-C12H14N	C11H7O1	155.0495	155.0491	8.5	0.359

Please cite this article in press as: Y. Xing, et al., Int. J. Mass Spectrom. (2015), http://dx.doi.org/10.1016/j.ijms.2015.01.007