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A Review on Synthetic Cathinone and Its Derivatives: Analyses and Legal Status

Ahmad Fahmi Lim Abdullah[a*], Kah Haw Chang[a], Savarana Kumar Jayaram[b], Maimonah Sulaiman[b]

[a] *Forensic Science Programme, School of Health Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan.*
[b] *Department of Chemistry Malaysia, Jalan Sultan, 46661 Petaling Jaya, Selangor.*

ABSTRACT: New psychoactive substances, including synthetic cathinone, had gained popularity within the industry of narcotics. The presence of these synthetic substances as new products in the market requires better information sharing among law enforcement agencies worldwide. Up-to-date information about such substances testing in forensic laboratory is needed. In this review, we highlighted the analyses of synthetic cathinone and its derivatives by various techniques. The legal status of synthetic cathinone and its derivatives of selected countries were discussed.

Keywords: new psychoactive substances, synthetic cathinone, analysis, legal status

Introduction

Recent years, the new psychoactive substances (NPS) are popular within the industry of narcotics. They are abused substances which are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances in both pure and prepared form [1,2]. These chemically modified substances produce similar effects as in stimulants, depressants, hallucinogenic and narcotic drugs [3]. In our previous paper, we reviewed the prevalence and syntheses on the synthetic cathinone [4]. This paper aims to highlight the analyses and legal status of synthetic cathinone and its derivatives, particularly in Malaysia and also some other countries worldwide.

Analysis of synthetic cathinone and its derivatives

Colour spot test

Colour test is presumptive test used to detect the presence of certain drug when combined with the chemical reagents. A research on colour tests suitable for preliminary identification of cathinone and methcathinone were reported by Toole *et al.* (2012) [5]. In testing cathinone and its derivatives, Chen's test can be used to distinguish ephedrine, pseudoephedrine, norephedrine, phenylephedrine, phenylpropanolamine and methcathinone from both amphetamine and methamphetamine which do not react with Chen's test reagent [6]. By Chen's test, the presence of cathinone or methcathinone is shown by a solution gradually turning into yellow or orange colour, while purple colour solution will be formed with the presence of ephedrine and pseudoephedrine. Synthetic cathinone shows no reaction with both Marquis's reagent and Simon's reagent [6,7]. For methcathinone, Simon's test gives a slightly blue solution with spot-or ring-like precipitate with the presence of methcathinone [6]. Yellow coloured products arose from the reaction of cathinone and methcathinone with Liebermann's reagent [5].

Thin Layer Chromatography (TLC)

TLC is one of the most commonly used techniques for the separation and identification of drugs. For synthetic cathinone, the solvent systems of methanol:concentrated ammonia (100:1.5) as well as ethyl acetate:methanol:concentrated ammonia (85:10:5) were reported for the detection of these drugs, giving the R_f values for the drug substances [6]. Methcathinone and cathinone do not interfere or cross react in standard drug abuse screening methods (*i.e.* amphetamine-type stimulants) based on the analysis by TLC with the Toxi-Lab commercial system [8]. The R_f values of cathinone and methcathinone were observed in the range of 0.5, much higher than those reported by ephedrine, amphetamine or methamphetamine. The colour of blanch was observed with concentrated sulfuric acid, suggesting the additional carbonyl group in these aminoketones. The use of Dragendorff's reagent gave the usual brown colour, unique for amines [8].

Immunoassay

The individual enantiomers of methcathinone and racemic cathinone could also be screened in enzyme multiplied immunoassay technique (EMIT), aiming to screen the amphetamine and related amines. Both cathinone and methcathinone showed a 200-400 fold lower affinity for the amphetamine antibodies, with a relative affinity similar to those for ephedrine and pseadoephedrine [8]. However, immunoassay field test for methamphetamine gave false positive reactions with some cathinone derivatives [7].

Gas Chromatography (GC)

GC can separate organic compounds based on the differences in their partitioning behavior between the mobile gas phase and the stationary phase in the column, allowing the analysis of drug substances. A mixture of drug substances of different cathinone derivatives, as well as their isomers can be separated through the GC analysis [8]. After the separation of complex mixture containing the particular drug substance, such as the synthetic cathinone and its derivatives, the mass spectrometric techniques were commonly used for identification and characteristion purposes. Table 1 showed the characteristic peaks of varying derivatives of synthetic cathinone in previously conducted studies. It summaries the possible ion peaks which can be seen in the MS spectrum of a drug substance. In general, the electron ionisation technique of MS gives the characteristic fragmentations of the substance, although the parent ions are hardly to be achieved. On the other hand, the utilisation of chemical ionisation during analysis can give the indication of parent ion determining their molecular weight, and the additional information to that particular drug substance analysed [9-12]. Table 1 illustrates the studies that have been conducted to determine the presence of synthetic cathinone and its derivatives [8-17].

In the MS spectra, all the cathinone and its derivatives are substance with an odd molecular mass based on "nitrogen rule". The presence of a carbonyl bond, located at the α-carbon atom (first carbon atom to the core benzene ring and the second atom adjacent to the nitrogen atom) is the characteristic feature of cathinones. For even molecular mass substances, they could be originated from the groups of benzylpiperazine and tryptamine [13]. Generally, the presence of immonium ions (m/z 16+14n, n= 1,2,3…) and characteristic pair of ions in a m/z 28 distance could indicate the straight chained cathinones [13]. On the other hand, the appearance of main ion at m/z 70+14n (n=1,2,3…) in the spectrum of an odd molecular mass substance could also indicate the presence of cathinones with pyrrolidine ring [13]. Another alternative cleavage reaction in cathinone is the result of the ionisation of an aromatic π-bond with α-cleavage. This reaction leaves behind an acylium ion, and subsequent reaction causes the loss of carbon monoxide from the molecule. The formation of phenyl cations due to the decarbonylation reaction wills subsequently loss the acetylene or an allene radical [13].

Liquid Chromatography (LC)

Cathinone, methcathinone, dimethcathinone, ethcathinone and diethylcathinone (diethylpropion) can be separated by reversed-phase LC using a phenyl bonded stationary phase and an acidic (pH 3) mobile phase [8]. The compounds elute according to increasing hydrophobic surface area, and thus the primary amine (cathinone) was first eluted. The presence of cathinones and their related ephedrines in whole blood samples were also simultaneous determined using LC-MSMS by Sorensen (2011) [18]. The compounds identified included cathinone, methcathinone, ethcathinone, amfepramone, mephedrone, flephedrone, methedrone, methylone, butylone, cathine, morephedrine, pseudoephedrine, methylephedrine and methylpseudoephedrine in both live and post-mortem human blood samples [18]. Jankovics *et al.* (2011) developed an LC-MS-MS method to screen six different methcathinone analogs, namely mephedrone, butylone, MDPV, flephedrone, methylone and methedrone, besides 4-methyl-ethyl cathinone (4-MEC) [19].

Table 1: Previous studies on the determination of the presence of synthetic cathinone and its derivatives

Substance	Peak (m/z)	Ion	Observations	Ref
Cathinone	44	$CH_3-CH=N^+H_2$	The side chain in cathinone molecule derivatives determines the fragmentation pattern, either with an aliphatic amine or a pyrrolidine ring. The formation of the cations which appeared as the base peaks was due to the dissociation of the C−C bond between α and β carbon atoms	[13]
	105	$C_6H_5-C\equiv O^+$	Formation of benzoyl cations due to cleavage of the β-ketone moiety	
	77, 51, 39	$C_6H_5^+$, $C_4H_3^+$, $C_3H_3^+$	The formation of phenyl cations (m/z 77) as the product of decarbonylation, subsequently loss of acetylene (C_2H_2) to form the fragment ions with m/z 51, or the loss of allele diradical (C_3H_2) to form fragment ions at m/z 39	
Ephedrone (Methcathinone)	163	Molecular ion	Parent molecule	[8,13]
	58	$CH_3-CH=N^+H-CH_3$	Loss of the C_6H_5CO from the parent molecule	
	161	Molecular ion	Decomposition products (conjugated or unconjugated imine of methcathinone) with the loss of hydrogen from the nitrogen atom to produce 2 mass unit lower than methcathinone	
	56	$CH_3-C\equiv N^+-CH_3$ or $CH_3-CH=N^+=CH_2$	The difference within the side chain imine fragment (conjugated imine or unconjugated imine) in the loss of C_6H_5CO.	
	105	$C_6H_5-C\equiv O^+$	Formation of benzoyl cations due to cleavage of the β-ketone moiety	
	77, 51, 39	$C_6H_5^+$, $C_4H_3^+$, $C_3H_3^+$	The formation of phenyl cations (m/z 77), subsequently loss of acetylene (m/z 51), or the loss of allele diradical (m/z 39)	
Dimethcathinone	177	Molecular ion	Parent molecule	[8]
	72	$CH_3-CH=N^+H-CH_2CH_3$	Loss of C_6H_5CO from the parent molecule	
	170, 70	-	Decomposition products	
Mephedrone (Methylmethcathinone)	177	Molecular ion	Parent molecule	[14,15]
			Isomeric molecule (elution of 2 < 3 < 4 of individual isomers)	
	58	$CH_3-CH=N^+H-CH_3$	Appeared as the base peak due to the formation of the immonium ions via the amine-initiated α-cleavage of the benzylic bonds	
	119	$CH_3-C_6H_4-C\equiv O^+$	Formation of 4-methylbenzoyl cations due to the α-cleavage	
	91	$CH_3-C_6H_4^+$	Formation of methylphenyl cations due to subsequent loses of CO from 4-methylbenzoyl cations	
	65	$C_5H_5^+$	Subsequent loses of acetylene from methylphenyl cation	
	162	$C_6H_4^+CO-CH(CH_3)NH-CH_3$	Amine-initiated α-cleavage, resulting in the loss of α-methyl group	
	56, 42		Secondary decomposition of immonium ions ($CH_3-CH=N^+H-CH_3$) by the loss of H_2	
Fluoromethcathinone	181	Molecular ion	Parent molecule. Note that the 2-fluoromethcathinone was firstly eluted followed by 3- and 4-fluoromethcathinone in a GC analysis, but the MS data shows no significant differences between the three isomers	[16]
	123	$(C_7H_4FO)^+$	Formation of fluorophenyl cations	

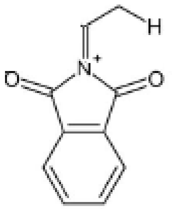
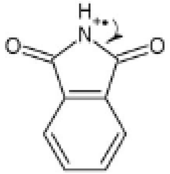
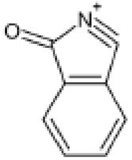
	58	$(C_3H_8N)^+$	Appeared as base peaks as a result of the formation of immonium ions	
	95	$(C_6H_4F)^+$	Formation of fluorobenzyloxy cations	
	56	-	Additional peak observed in 2-fluoromethcathinone, due to the structural difference or an artifact of the observed degradation.	
Methedrone	58	$CH_3{-}CH{=}N^+H{-}CH_3$	Appeared as the base peak due to the formation of the immonium ions via the amine-initiated α-cleavage of the benzylic bonds	[13]
	135	$CH_3{-}O{-}C_6H_4{-}C{\equiv}O^+$	Formation of 4-methoxybenzoyl cations due to the α-cleavage	
	107	$CH_3{-}\ O{-}C_6H_4^+$	Formation of methoxyphenyl cations due to subsequent loses of CO from 4-methoxybenzoyl cations	
Methylone	58	$CH_3{-}CH{=}N^+H{-}CH_3$	Appeared as the base peak due to the formation of the immonium ions via the amine-initiated α-cleavage of the benzylic bonds	[13]
	149	$C_7H_5O_2{-}C{\equiv}O^+$	Formation of 3,4-methyenedioxybenzoyl cations due to the α-cleavage	
	121	$C_7H_5O_2^+$	Formation of 3,4-methyenedioxyphenyl cations due to subsequent loses of CO from 3,4-methyenedioxybenzoyl cations	
Flephedrone	58	$CH_3{-}CH{=}N^+H{-}CH_3$	Appeared as the base peak due to the formation of the immonium ions via the amine-initiated α-cleavage of the benzylic bonds	[13]
	123	$C_6H_4F{-}C{\equiv}O^+$	Formation of 4-fluorobenzoyl cations due to the α-cleavage	
	95	$C_6H_4F^+$	Formation of 4-fluorophenyl cations due to subsequent loses of CO from 4-fluorobenzoyl cations	
3,4-dimethylmethcathinone(3,4-DMMC)	58	$CH_3{-}CH{=}N^+H{-}CH_3$	Appeared as the base peak due to the formation of the immonium ions via the amine-initiated α-cleavage of the benzylic bonds	[13]
	133	$CH_3(CH_3)C_6H_4{-}C{\equiv}O^+$	Formation of 3,4-dimethylbenzoyl cations due to the α-cleavage	
	105	$CH_3(CH_3)C_6H_4^+$	Formation of 3,4-dimethylphenyl cations due to subsequent loses of CO from 3,4-dimethylbenzoyl cations	
Ethcathinone	72	$CH_3{-}CH{=}N^+H{-}C_2H_5$	The formation of the iminiun ions which appeared as the base peaks was due to the dissociation of the C−C bond between α and β carbon atoms	[13]
	44	$C_2H_6N^+$	Hydrogen transfer of second carbon atom adjacent to nitrogen leads to the elimination of ethane (moderate intensity)	
	105	$C_6H_5{-}C{\equiv}O^+$	Formation of benzoyl cations due to cleavage of the β-ketone moiety	
	77, 51, 39	$C_6H_5^+$, $C_4H_3^+$, $C_3H_3^+$	The formation of phenyl cations (m/z 77), subsequently loss of acetylene (m/z 51), or the loss of allele diradical (m/z 39)	
Buphedrone	72	$C_2H_5{-}CH{=}N^+H{-}CH_3$	The formation of the iminiun ions which appeared as the base peaks was due to the dissociation of the C−C bond between α and β carbon atoms	[13]
	44	$C_2H_6N^+$	Hydrogen transfer of second carbon atom adjacent to nitrogen leads to the elimination of ethane (low intensity)	
	57	-	Elimination of methyl radical, and practically unobservable for other common cathinones, except butylone	
	105	$C_6H_5{-}C{\equiv}O^+$	Formation of benzoyl cations due to cleavage of the β-ketone moiety	

	77, 51, 39	$C_6H_5^+$, $C_4H_3^+$, $C_3H_3^+$	The formation of phenyl cations (m/z 77), subsequently loss of acetylene (m/z 51), or the loss of allele diradical (m/z 39)	
4-methylethylcathinone (4-MEC)	72	$CH_3{-}CH{=}N^+H{-}C_2H_5$	The formation of the iminiun ions which appeared as the base peaks was due to the dissociation of the C−C bond between α and β carbon atoms	[13]
	119	$CH_3{-}C_6H_4{-}C{\equiv}O^+$	Formation of 4-methylbenzoyl cations due to the α-cleavage	
	91	$CH_3{-}C_6H_4^+$	Formation of methylphenyl cations due to subsequent loses of CO from 4-methylbenzoyl cations	
N,N-dimethylmethcathinone (DMMC)	72	$CH_3{-}CH{=}N^+(CH_3){-}CH_3$	The formation of the iminiun ions which appeared as the base peaks was due to the dissociation of the C−C bond between α and β carbon atoms	[13]
	105	$C_6H_5{-}C{\equiv}O^+$	Formation of benzoyl cations due to cleavage of the β-ketone moiety	
	77, 51, 39	$C_6H_5^+$, $C_4H_3^+$, $C_3H_3^+$	The formation of phenyl cations (m/z 77), subsequently loss of acetylene (m/z 51), or the loss of allele diradical (m/z 39)	
Ethylone	72	$CH_3{-}CH{=}N^+H{-}C_2H_5$	The formation of the iminiun ions which appeared as the base peaks was due to the dissociation of the C−C bond between α and β carbon atoms	[13]
	44	$C_2H_6N^+$	Hydrogen transfer of second carbon atom adjacent to nitrogen leads to the elimination of ethane (moderate intensity)	
	149	$C_7H_5O_2{-}C{\equiv}O^+$	Formation of 3,4-methyenedioxybenzoyl cations due to the α-cleavage	
	121	$C_7H_5O_2^+$	Formation of 3,4-methyenedioxyphenyl cations due to subsequent loses of CO from 3,4-methyenedioxybenzoyl cations	
Butylone	72	$C_2H_5{-}CH{=}N^+H{-}CH_3$	The formation of the iminiun ions which appeared as the base peaks was due to the dissociation of the C−C bond between α and β carbon atoms	[13]
	44	$C_2H_6N^+$	Hydrogen transfer of second carbon atom adjacent to nitrogen leads to the elimination of ethane (low intensity)	
	57	-	Elimination of methyl radical, and practically unobservable for other common cathinones (significant difference from ethylone)	
	149	$C_7H_5O_2{-}C{\equiv}O^+$	Formation of 3,4-methyenedioxybenzoyl cations due to the α-cleavage	
	121	$C_7H_5O_2^+$	Formation of 3,4-methyenedioxyphenyl cations due to subsequent loses of CO from 3,4-methyenedioxybenzoyl cations	
Pentedrone	191	Molecular ion	Parent ion	[12,13]
	86	$C_5H_{12}N^+$ @ $CH_3NH^+{=}CH{-}C_3H_7$	Immonium ions	
	57	$C_4H_9^+$	Decomposition of immonium ions with the loss of $-CH_2NH$	
	44	$C_2H_6N^+$	Decomposition of immonium ions with the loss of $-C_3H_6$ (propene)	
	105	$C_6H_5{-}C{\equiv}O^+$	Formation of benzoyl cations due to cleavage of the β-ketone moiety	
	77, 51, 39	$C_6H_5^+$, $C_4H_3^+$, $C_3H_3^+$	The formation of phenyl cations (m/z 77), subsequently loss of acetylene (m/z 51), or the loss of allele diradical (m/z 39)	
	148	$(C_9H_{10}NO)^+$	Formation of immonium ions due to the loss of a propyl radical from the alkyl side chain of the molecule	

	86	Isopentedrone $C_5H_{12}N^+$	Immonium ions formed after alpha cleavage	[12]
	120	Isopentedrone	N-methylbenzylimmonium ions due to alpha cleavage	
	42	Isopentedrone	Ketene radical cations from the keto side chain after the rearrangement and elimination of ethane and methylbenzylamine or via the elimation of benzne from the immonium ion (m/z 120)	
Pentylone	235	Molecular ion	Parent molecule	[12]
	86	$C_5H_{12}N^+$	Immonium ions	
	57	$C_4H_9^+$	Decomposition of immonium ions with the loss of $-CH_2NH$	
	44	$C_2H_6N^+$	Decomposition of immonium ions with the loss of $-C_3H_6$ (propene)	
	149	$C_7H_5O_2-C\equiv O^+$	Formation of 3,4-methyenedioxybenzoyl cations due to the α-cleavage	
	121	$C_7H_5O_2^+$	Formation of 3,4-methyenedioxyphenyl cations due to subsequent loses of CO from 3,4-methyenedioxybenzoyl cations	
	164	Isopentylone	Formation of N-methyl-3,4-methylenedioxybenzylimmonium ion as base peak due to the methylene moiety of the molecule	
	42	Isopentylone	Ketene radical cations from the keto side chain after the rearrangement and elimination of ethane and methylbenzylamine or via the elimation of benzne from the immonium ion	
Diethylpropion (diethylcathinone)	205	Molecular ion	Parent molecule	[8,12]
	100	$CH_3-CH=N^+(CH_2CH_3)CH_2CH_3$	Loss of the C_6H_5CO from the parent molecule	
	98, 42	$CH_2=C=N^+(CH_2CH_3)CH_2CH_3$	Enamine fragment (m/z 98) contains two N-ethyl groups that can be rearranged to eliminate ethylene, resulting in m/z 42 ions.	
	105	$C_6H_5-C\equiv O^+$	Formation of benzoyl cations due to cleavage of the β-ketone moiety	
	77, 51, 39	$C_6H_5^+$, $C_4H_3^+$, $C_3H_3^+$	The formation of phenyl cations (m/z 77), subsequently loss of acetylene (m/z 51), or the loss of allele diradical (m/z 39)	
Bupropion	44	$C_2H_6N^+$	The secondary ionization processes are very fast leading to the elimination of iso-butene (2-methylpropene), appeared as the base peak	[13]
Pyrrolidin-1-ynpropiophenone (PPP)	98	$C_4H_8N^+=CH-CH_3$	The base peak due to the formation of cations with the dissociation of the C−C bond between α and β carbon atom	[13]
	70, 55, 42, 41	-	Degradation of the pyrolidinium cation and lead to the formation of characteristic ions at m/z 70, 55, 42 and 41. Pyrrolidium cation (m/z 70) is formed by the inductively-driven loss of ethane (or its homologs) and the remaining ions correspond to the endocyclic chain of the pyrolidine ring, propyl and propene cations.	
	105	$C_6H_5-C\equiv O^+$	Formation of benzoyl cations due to cleavage of the β-ketone moiety	
	77, 51, 39	$C_6H_5^+$, $C_4H_3^+$, $C_3H_3^+$	The formation of phenyl cations (m/z 77), subsequently loss of acetylene (m/z 51), or the loss of allele diradical (m/z 39)	
4-methyl-pyrrolidin-1-ynpropiophenone (MPPP)	98	$C_4H_8N^+=CH-CH_3$	The base peak due to the formation of cations with the dissociation of the C−C bond between α and β carbon atom	[13]
	70, 55, 42,	-	Characteristic ions for cathinone with a pyrolidine ring in the side chain, with a general	

	41		formula of $C_nH_{2n}N^+$ of the base ion	
	119	$CH_3{-}C_6H_4{-}C{\equiv}O^+$	Formation of 4-methylbenzoyl cations due to the α-cleavage	
	91	$CH_3{-}C_6H_4^+$	Formation of methylphenyl cations due to subsequent loses of CO from 4-methylbenzoyl cations	
4-methoxy-pyrrolidin-1-ynpropiophenone (MoPPP)	98	$C_4H_8N^+{=}CH{-}CH_3$	The base peak due to the formation of cations with the dissociation of the C−C bond between α and β carbon atom	[13]
	70, 55, 42, 41	-	Characteristic ions for cathinone with a pyrolidine ring in the side chain, with a general formula of $C_nH_{2n}N^+$ of the base ion	
	135	$CH_3{-}O{-}C_6H_4{-}C{\equiv}O^+$	Formation of 4-methoxybenzoyl cations due to the α-cleavage	
	107	$CH_3{-}\ O{-}C_6H_4^+$	Formation of methoxyphenyl cations due to subsequent loses of CO from 4-methoxybenzoyl cations	
3,4-methylenedioxy-pyrrolidin-1-ynpropiophenone (MDPPP)	98	$C_4H_8N^+{=}CH{-}CH_3$	The base peak due to the formation of cations with the dissociation of the C−C bond between α and β carbon atom	[13]
	70, 55, 42, 41	-	Characteristic ions for cathinone with a pyrolidine ring in the side chain, with a general formula of $C_nH_{2n}N^+$ of the base ion	
	149	$C_7H_5O_2{-}C{\equiv}O^+$	Formation of 3,4-methyenedioxybenzoyl cations due to the α-cleavage	
	121	$C_7H_5O_2^+$	Formation of 3,4-methyenedioxyphenyl cations due to subsequent loses of CO from 3,4-methyenedioxybenzoyl cations	
4-methyl-α-pyrrolidino-butyrophenone (MPBP)	231	Molecular ion	Parent molecule	[9,13]
	119	$CH_3{-}C_6H_4{-}C{\equiv}O^+$	Ionization of carbonyl oxygen atom and α-cleavage reactions form *p*-methylbenzoyl cations	
	112	$C_4H_8N^+{=}CH{-}C_2H_5$	α-cleavage reaction of the benzyl bond and produces a base peak immonium ion, and also some isomeric products	
	91	$CH_3{-}C_6H_3^+$	Ionisation of an aromatic π-bond with α-cleavage form tropylium cation	
	202	$(C_{13}H_{16}NO)^+$	Immonium ions formed due to the alternative α-cleavage reaction which break the alkyl bonds by the loss of butyl radicals	
	70, 55, 42, 41	-	Characteristic ions for cathinone with a pyrolidine ring in the side chain, with a general formula of $C_nH_{2n}N^+$ of the base ion	
4-methyl-α-pyrrolidino-hexanophenone (MPHP)	259	Molecular ion	Parent molecule	[9]
	119	$CH_3{-}C_6H_4{-}C{\equiv}O^+$	Ionization of carbonyl oxygen atom and α-cleavage reactions form *p*-methylbenzoyl cations	
	140	$C_4H_8N^+{=}CH{-}C_4H_9$	α-cleavage reaction of the benzyl bond and produces a base peak immonium ion	
	91	$CH_3{-}C_6H_3^+$	Ionisation of an aromatic π-bond with α-cleavage form tropylium cation	
	202	$(C_{13}H_{16}NO)^+$	Immonium ions formed due to the alternative α-cleavage reaction which break the alkyl bonds by the loss of butyl radicals	
	244, 216	$(C_{16}H_{22}NO)^+$, $(C_{14}H_{18}NO)^+$	M-15 α-cleavage fragments with lower intensities	
	70, 55, 42, 41		Characteristic ions for cathinone with a pyrolidine ring in the side chain, with a general formula of $C_nH_{2n}N^+$ of the base ion	

3,4-methylenedioxy-α-pyrrolidino-butyrophenone (MDPBP)	261	Molecular ion	Parent molecule	[11]
	112	$C_4H_8N^+{=}CH{-}C_2H_5$	α-cleavage reaction of the benzyl bond and produces a base peak immonium ion, similar to MPBP	
	232	$(C_{13}H_{14}NO_3)^+$	Alternative α-cleavage due to the loss of ethyl radical, but in a lower intensity	
	149	$(C_8H_5O_3)^+$	Formation of methylenedioxybenzoyl cation due to ionisation of the carbonyl oxygen and an α-cleavage fragmentation	
	121	$(C_7H_5O_2)^+$	Subsequent loss of carbon monoxide from above ions (m/z 149)	
	70, 55, 42, 41	-	Characteristic ions for cathinone with a pyrolidine ring in the side chain, with a general formula of $C_nH_{2n}N^+$ of the base ion	
Pyrrolidin-1-ynvalerophenone (PVP)	126	$C_4H_8N^+{=}CH{-}C_3H_7$	The base peak due to the formation of cations with the dissociation of the C−C bond between α and β carbon atom	[13]
	70, 55, 42, 41	-	Characteristic ions for cathinone with a pyrolidine ring in the side chain, with a general formula of $C_nH_{2n}N^+$ of the base ion	
	119	$CH_3{-}C_6H_4{-}C{\equiv}O^+$	Formation of 4-methylbenzoyl cations due to the α-cleavage	
	91	$CH_3{-}C_6H_4^+$	Formation of methylphenyl cations due to subsequent loses of CO from 4-methylbenzoyl cations	
3,4-methylenedioxy-pyrovalerone (MDPV)	275	Molecular ion	Parent molecule	[10,13,17]
	126	$C_4H_8N^+{=}CH{-}C_3H_7$	Appeared as the base peak and produced immonium ion, due to the α-cleavage reaction of the benzyl bond	
	232	$(C_{13}H_{14}NO_3)^+$	α-cleavage due to the loss of propyl radical, but in a lower intensity	
	149	$(C_8H_5O_3)^+$	Resulted from ionisation of the carbonyl oxygen and an α-cleavage fragmentation losing the alkyl side chain at the carbonyl group	
	121	$(C_7H_5O_2)^+$	The formation of methylenedioxybenzene fragment due to subsequent loss of carbon monoxide from above ions (m/z 149), exactly the characteristics indicated by MDPV	
	70, 55, 42, 41	-	Characteristic ions for cathinone with a pyrolidine ring in the side chain, with a general formula of $C_nH_{2n}N^+$ of the base ion	
	84	$(C_5H_{10}N)^+$	An even electron ion due to fragmentation/rearrangement of immonium ion (m/z 126)	
	69	$(C_4H_7N)^+$	Hydrogen rearrangement reaction initiated by the carbonyl oxygen of the molecular ion (m/z 276)	
	98, 112, 126, 140, 154	Side chain and amino-group homologs and regioisomers related to MDPV	Immonium cations of homologous and regioisomeric compounds related to synthetic cathinone derivative MDPV, with 14 mass units added for every homologous compound	
	149, 121	$(C_8H_5O_3)^+$, $(C_7H_5O_2)^+$	Fragmentation initiated by radical cation formation at the carbonyl oxygen of molecular ion (m/z 276)	
Naphyrone	126	$C_4H_8N^+{=}CH{-}C_3H_7$	The base peak due to the formation of cations with the dissociation of the C−C bond between α and β carbon atom	[13]
	155	$C_{10}H_7{-}C{\equiv}O^+$	Formation of naphthylbenzoyl cations due to the α-cleavage	

	127	$C_{10}H_7^+$	Formation of naphthylphenyl cations due to subsequent loses of CO from naphthylbenzoyl cations	
α-phthalimidopropiophenone (PAPP)	279	Molecular ion	Parent molecule	[13,15]
	174	 $C_{10}H_8NO_2^+$	Appeared as the base peak due to the formation of the immonium ions via the amine-initiated α-cleavage of the benzylic bonds	
	105	$C_6H_5{-}C{\equiv}O^+$	Formation of benzoyl cations due to cleavage of the β-ketone moiety	
	77	$C_6H_5^+$	Formation of phenyl cation due to subsequent loss of CO	
	51	$C_4H_3^+$	Formation of m/z 51 fragment with the loss of acetylene from phenyl cations	
	147, 130	 	Two-step fragmentation initiated by McLafferty rearrangement via a radical cation on the phthalidimido oxygen followed by subsequent loss of a hydroxyl radical	

24 synthetic cathinones including cathinone, methcathinone, and synthetic cathinones position-3'-substituted (*e.g.* buphedrone and pentedrone), N-alkyl-substituted (*e.g.* diethylcathinone and diethylcathinone), ring-substituted (*e.g.* mephedrone and 4-MEC), methylenedioxy-substituted (*e.g.* methylone and ethylone), and pyrrolidinyl-substituted (*e.g.* MDPV, α-PPP, pyrovalerone and naphyrone), as well as four metabolites (*e.g.* buphedrone ephedrine and normephedrone) were analysed and confirmed using the LC-high resolution mass spectroscopy (LC-HS-MS) [20]. Two product ions were utilised for identification and quantification of synthetic cathinones commonly found in the market [20].

Infrared spectroscopy (IR)

The analysis of GC-MS and Infrared Spectroscopy (IR) is straightforward [7]. The infrared data substantiated the secondary amine hydrochloride moiety (2937, 2696 and 2461 cm^{-1}), which remained unchanged when ephedrine is changed to ephedrone [21]. Additionally, an amide carbonyl stretching was absent in the IR profile, which eliminated the possibility of N-formyl oxidative formation as the typical amine-permanganate oxidations [21]. Carbonyl stretching at 1700 cm^{-1} suggested the presence of benzoyl ketone, and it was further confirmed by splitting of aromatic proton resonance in the hydrogen NMR [21]. The mass spectral of ephedrone confirmed also with the nominal mass ($C_{10}H_{13}NO = 163$), and the amine driven beta bond cleavage is exhibited in the m/z ion of 58 [21].

IR could be used to differentiate the respective pairs of isomers of substituted cathinones on the basis of their IR spectrum [22]. In general, the C–H bending bands in the region of 675-900 cm^{-1} were used to differentiate between substituted aromatic compounds [22]. The carbonyl C=O stretching band was found important in considering the difference in the structure of two pairs of isomers due to the electronic and steric effects. Moreover, the C=C ring vibration bands could be appeared in different wavelength due to the steric effects. These bands appeared at approximately 1605 cm^{-1} in the 3,4-isomers but at approximately 1625 cm^{-1} in 2,3-isomers [22].

In the analysis of pentedrone and pentylone, the alkyl C-H and aryl C-H absorption bands (2800-3000 cm^{-1} and 3060 cm^{-1}) were detected. To differentiate between these molecules, the C=O band are observed at 1680 cm^{-1} for pentedrone free base and 1673 cm^{-1} for pentylone free base respectively [12]. In pentylone alone, the peak at 1253 cm^{-1} dominates the IR spectrum, indicating the C-O absorption of 3,4-methylenedioxy moiety ([12].

IR spectra of MMC isomers were used to differentiate between the three compounds [14]. The carbonyl C=O stretching band for 3-MMC and 4-MMC appeared at approximately 1685 cm^{-1}, differing from 2-MCC at 1696 cm^{-1} due to the steric effect of methyl group nearby [14]. The aromatic ring C=C ring vibration at approximately 1600 cm^{-1} also showed different patterns in all the three isomers. The characteristic of aromatic ring with four adjacent free hydrogen atoms was shown with a strong band at 752 cm^{-1} in 2-MCC. The bands at 894 cm^{-1}, 753 cm^{-1} and 720 cm^{-1} in the spectrum of 3-MCC is the characteristic of having one free hydrogen atom and three adjacent hydrogen atoms [14].

Nuclear magnetic resonance spectroscopy (NMR)

Nuclear magnetic resonance spectroscopy (NMR) allows the elucidation of the stereochemistry of the mephedrone molecule [7]. The ^{1}H NMR spectrum showed the characteristic AA'BB' aromatic system for a 1,4 unsymmetrically substituted aromatic system, a deshielded one-hydrogen quartet, a deshielded three-hydrogen singlet and a slightly desheilded methyl singlet attributed to a methyl attached to an aromatic ring, while the ^{13}C NMR spectrum supported the presence of nine carbons in the molecule [23]. The full spectral analysis also indicated the 2-aminomethyl-propan-1-one side chain of mephedrone, completing the assignment of all resonances [23].

NMR was used to investigate the isomers of substituted cathinones [22], including the butylone, methylone and MDPV. The discrimination of the structural isomers of fluoromethcathinone using ^{1}H NMR spectroscopy ATR-FTIR on the acetone washed samples as well as using ^{19}F NMR for crude samples [16]. Showing sufficient stability of the solution, MDPBP can be characterised by NMR spectrum [11]. The proton spectrum of MDPBP reported the position of the substitution pattern of the aromatic ring, as well as the complex splitting of the higher order system of pyrrolidine ring system [11]. These phenomena are also detected in both the MPHP [9] and MDPV [10]. ^{13}C NMR spectrum of the α-pyrrolidinophenones also proved the structure [11]. In general, the two-dimensional NMR allows the verification of the structure of alkyl side chain and determination of methylenedioxy position in the aromatic ring [10].

Legal status of synthetic cathinone and its derivatives

Initially, the term 'NPS' generally referred to those substances fall outside the global drug control system. However, the increasing concerns on the risks and impacts of these substances to the public health as well as the domestic and transnational security have urged the adaptation of the governments, in many regions and countries on the globe. Following health risks assessment, and its impacts to the personnel and the society, the particular substance shall be decided by the Commission on Narcotic Drugs or the World Health Organization to be added to the schedules, transferred from one schedule to another, or removed from any schedule, as provided for in the 1961 Convention and the 1971 Convention [1].

Since 2009, the number of recreational substances containing synthetic cathinones was on the rise and became to be popular drugs of abuse. The development of new drugs has grabbed the attention of the public and the law enforcement agencies. Information on the patterns and the level of abuse of synthetic cathinones needs to be compiled. From 2005 to 2011, over 150 psychoactive substances were registered under EMCDDA, from which 34 of them are synthetic cathinones [7]. In 2013, more than 50 of synthetic cathinone derivatives were reported, indicating the huge increase in the development of new drugs [24].

Cathinone and its derivatives are often referred as 'legal highs'. Their legal status differs greatly from country to country, and even between states. Until today, their legal status changes with rapid development of new synthetic products, as well as the new findings on possible risks for the public safety. In order to circumvent legislation control, synthetic cathinones were commonly advertised as 'bath salts', 'plant food', or even 'hoover freshner' and labeled as 'not for human consumption' [3,25-28].

In the United States, the Controlled Substances Act described the federal drug policy under which the manufacturing, importation, possession, use and distribution of the drug substances is regulated. A substance's medical value, harmfulness and potential of abuse decided the schedule of that particular substance [1]. In 1993, cathinone was placed into Schedule I of the Controlled Substance Act, whereas cathine was categorised as Schedule IV substance in 1988 [29]. Khat may be included as the Schedule I substance, when the cathinone was detected. However, the legal status of khat is frequently being challenged, particularly among the immigrants living the countries where khat is illegally controlled [28]. Ephedrone was the first cathinone derivative being included in the Schedule I in 1994 under the Controlled Substance Act [25,29]. Both ephedrine and pseudoephedrine were also the chemicals regulated under the Act, as they are the precursors for the manufacturing of ephedrone [29]. Currently, the United States and Canada banned khat. This plant substance was also considered illegal in Ireland, France, Denmark, Germany, Sweden, Norway and most recently Netherlands. Khat remains legal in the United Kingdom, Portugal, Australia and most Eastern Africa countries [28].

Following the report of several cases of intoxication and deaths related to the consumption of mephedrone in European countries, EMCDDA conducted a risk assessment report on this substance. Mephedrone was subsequently classified as a Class B Controlled Drug under the United Kingdom Misuse of Drug Act and was banned, along with other cathinone derivatives on April 2010 [24,27]. The naphthyl analogues of cathinones, the second generation of this group were also placed in the Class B of the Misuse of Drug Act [25]. In the United States, methylone was temporarily controlled in 2011 along with mephedrone and MDPV, by placing these substances into Schedule I [3,30]. In the following year, mephedrone and MDPV were among the group of synthetic drugs placed in Schedule I. In April 2013, DEA issued the final rule and placed methylone and its salt, isomers and salts of its isomers permanently into Schedule I of Controlled Substance Act [3].

The scheduling of new substance is often a lengthy process, due to the requiring of the health risk assessment and also the legislative amendments. Moreover, the NPS groups are non-controlled substances on the basis of their nature [31]. Under the Controlled Substance Act, the temporary scheduling of new substances to prevent the imminent hazard to the safety of the public is possible. The Analogue Act in the United States has provided the law enforcement authorities to investigate and prosecute those who illegally manufacturing and distributing the dangerous drug substances [3]. The Act allowed the NPS to be treated as scheduled drug substances to extend for human consumption [3]. Synthetic cathinones, including mephedrone, methylone and MDPV and their salt and isomers, were placed into Schedule I of the Act and subjected to temporary control in October 2011 [1,32]. These drug substances were controlled in terms of their possession and sale for one year, while the further evaluation was undertaken [32].

In some countries, analogue or generic system which allowed the control of groups of substances or similar substances to those individually listed, without the need for appeal to legislation reform was generated [33]. An analogue system was introduced in the United Kingdom in 2010 to ban synthetic cathinones. In the same year, Italy also banned a group definition of cathinones under a generic system [1]. Hungary and Ireland also have the generic systems respectively to ban NPS in their own countries [1]. Norway, Germany, Denmark, Croatia, the Netherlands, Russian Federation, Ghana, Saudi Arabia, China, Australia and the United States have also their own analogue systems, or also known as emergency scheduling in some countries, to introduce temporary bans on NPS after indentified the risk factors of these drug substances [1]. Austria, New Zealand and Romania have also issued specific NPS legislation to control these substances [31]. According to the report from UNODC on the basis of questionnaire conducted on NPS, some respondent countries used the Poison Acts to control these drug substances, including Albania, Bahrain, Brunei Darussalam, Bulgaria and Thailand [1]. The use of consumer safety regulations was also reported from Bahrain, Bulgaria, Croatia, Hungary, Israel, Italy, Nepal, Poland, Portugal, Romania, Russian Federation, Togo and the United Kingdom to primarily focus in the controlling of the sale of NPS [1].

The approaches to regulations of different countries are varied. Monitoring was reported in providing good information for evidence-based decisions making, to respond to the rapid changes that encompassing the supply and demand of NPS, including synthetic cathinone and its derivatives. Despite mephedrone, methylone and MDPV were scheduling as controlled substances within the United States or elsewhere, illegal synthetic cathinones frequently appear in psychoactive products in the illicit markets, labeled as ‘bath salts’. Moreover, the law is always a step behind and the illicit manufacturers and illegal markets are able to respond quickly to the changes in the legal status of these recreational drugs. New cathinone derivatives within the same class that currently non-controlled will continue to emerge in the recreational market [3,26,28]. Concerns over their uses and regulations must therefore be viewed seriously and appropriate measures taken promptly.

Conclusion

Over the last few years, a great increase was reported in the popularity of synthetic cathinone and its derivatives with mephedrone, methylone and MDPV remain the main products of these ‘legal highs’. Following their scheduling as controlled substances, these compounds were gradually modified structurally and presented in the markets as new recreational products yearly. Besides their significant place in the illicit market, another worrying phenomenon is that these synthetic substances have been reported to be synthesized in the home environment, made from readily available pharmaceuticals like ephedrine and pseudoephedrine. The unprofessional nature of this manner of drug synthesis would certainly associate with additional health risks. The law enforcement agencies and forensic laboratories are facing great challenge on the detection of such substances. Modified structurally, and their presence as new products in global market complicate the situation and therefore the information sharing between governmental agencies around the world is important especially on the trends of these drugs, their regulatory status and forensic analyses.

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Additional information and reprint request:
Ahmad Fahmi Lim Abdullah
E-mail: fahmilim@usm.my
Forensic Science programme
School of Health Sciences
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan
Phone: +609-7677596
Fax: +609-7677515