

## A Review on Synthetic Cathinone and Its Derivatives: Prevalence and Syntheses

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**ABSTRACT:** New psychoactive substances, also labeled as designer drugs had gained popularity in the recent years within the industry of narcotics as “legal” alternatives to the internationally controlled drugs. We review on the prevalence of synthetic cathinone and its derivatives from various sources. Syntheses of synthetic cathinone and its derivatives particularly ephedrone, mephedrone and methylone were discussed. Newer derivatives will emerge into the recreational drug markets and information gathering and sharing are therefore important. Possible synthesis pathways of these clandestine products must be understood by forensic analysts prior to their analyses.

**Keywords:** controlled drugs, synthetic cathinone, derivatives, prevalence, syntheses

### Introduction

New psychoactive substances (NPS), also labeled as designer drugs had gained popularity in the recent years within the industry of narcotics as “legal” alternatives to the internationally controlled drugs. NPS’ are substances of abuse, either in pure form or preparation, which are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but still may pose public health threat [1,2]. These substances carry the properties and effects similar to those known illicit stimulants, depressants, hallucinogenic and narcotic drugs, but with chemically modified to evade the illicit drug control in endless variety of analogs [3] of designer drugs or termed as ‘legal highs’, ‘herbal high’, and ‘bath salts’ in the market [4]. An alarming rise in NPS was noted globally (UNODC, 2013) with a total of 81 NPS being reported in 2013 as compared to 73 in the previous year by European Monitoring Centre for Drugs and Drug Addiction [5].

Since the beginning of 1980s, ketamine was noticed in the United States and being known as the oldest NPS which was the spread to Europe in 1990s. The family of phenethylamines and piperazines appeared in the illicit market through 1990s and at the beginning of the 2000s, respectively. Since 2004, synthetic cannabinoids were noticed,

followed by synthetic cathinones in more recent years [1,6]. The plant-based substances with the characteristics of NPS make up to the total of six main groups of substances in the market [1,4]. Note that substances which contained the recently identified NPS but do not fit into any aforementioned groups were grouped as miscellaneous substances [1].

The psychoactive cathinone is the principle active ingredient originally found in the leaves of *Catha edulis* plant, commonly known as khat. Cathinone and its derivatives are closely related to phenethylamine family, and differ with the presence of  $\beta$ -keto group on the side chain of the phenethylamines [1,7,8]. Amphetamine and methamphetamine also belong to the family of phenethylamine but are more potent than cathinone and its derivatives. Similar to amphetamines, cathinone is a central nervous system stimulant with euphoria and increased alertness effects [2,4,7-9]. Cathinone is also known with its sympathomimetic effects, including tachycardia and hypertension [2,8,9] and are associated with negative side effects including increased heart rate, breathing difficulties, loss of appetite, deterioration of memory, hallucinations when abused [4,7]. The aim of this paper is to provide a review on the prevalence and syntheses of synthetic cathinone and its derivatives. A second part of the review covers the legal status and analyses of these compounds

### Prevalence of synthetic cathinones

NPS mimic the effect of those ‘traditional’ controlled drugs. Their history and information for either short or long term health effects are still lacking. UNODC conducted a survey that revealed 87% of the 80 responding countries and territories noticed the appearance of NPS in their drug markets [1]. As many as 31 and 19 countries from Europe and Asia, respectively, have all reported the NPS appearance. The worldwide spread of NPS was followed by 11 countries from the Americas, seven countries from the Africa, and 2 countries from Oceania (UNODC, 2013a). Ketamine (83%) and plant-based substances (83%) were recorded with the highest number of respondent countries or territories, followed by piperazines (77%) and synthetic cannabinoids (75%) [1]. Synthetic cannabinoids, phenethylamines and cathinones have gained popularities in Europe [5]. Between 2008 and 2013, synthetic cannabinoids and synthetic cathinones recorded the highest number of reports world among all the NPS groups at 28% and 25%, respectively [2]. The single most widespread substances were JWH-018 and JWH-073 among synthetic cannabinoids, as well as mephedrone, methylone and MDPV among the synthetic cathinones [4]. All NPS groups have reported their emergence in all the regions, except Africa with no synthetic cathinones and phenethylamines have been reported [1]. Synthetic cannabinoids which were rarely known before 2008, have become the most frequently reported NPS group in 2010 [1]. Before 2009, the synthetic cathinone and its derivatives, Figure 1, were not widely known, but have made their largest appearance on the market in that year [1,8].

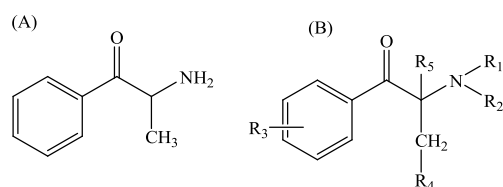


Figure 1: Chemical structure of cathinone (A) and general structure of synthetic cathinones (B) (Source: Valente *et. al.* [8])

Synthetic cathinones were reported in the illicit market in 2005 [10] and more than 30 substances have been identified in the licit and

illicit drug markets to date [8]. Prior to 2008, synthetic cathinones have been reported Finland, Germany, Hungary and the Netherlands from European Countries, as well as Japan and Hong Kong China from Asia Countries. These drug substances were also appeared in Australia before 2008, and in New Zealand in 2008. Canada and Mexico reported the emergence of synthetic cathinones in the local market before 2008, but their first appearance in the United States was recorded in 2009. Until 2011, this NPS group was starting to be popular in South America [1].

The recreational use of synthetic cathinone is not a new issue, as the consumption of ephedrone, a derivative of synthetic cathinone, was reported in the ex-Soviet Union in 1970s and in the United States in 1990s [7]. The term ‘legal high’ labeled on synthetic cathinone and its derivatives usually misleads the drug users who intended to have the cocaine and MDMA-like psychostimulant effects, especially among young people [7]. A synthetic cathinone user frequently believes that these substances are safe to consume, as the commercially information could mislead those users in terms of their safety and health effect [7-9]. The prices of these substances are also far more affordable, especially for young people, compared to those ‘traditional’ drug substances [7,10].

The peak of synthetic cathinone was reported in 2010 probably due to the reduction of purity of cocaine and MDMA in 2009 [7-9]. For instance, a remarkable decrease in the purity of cocaine from 60% to 22% was seen in UK [9-11] while the composition of tablets containing MDMA decreased from more than 90% to less than 50% of active ingredient in the Netherlands [9]. Some replacement of opioids by the synthetic stimulants, especially the synthetic cathinones, was reported in countries facing heroin shortage [5,10]. The reason of shifting from heroin injection to cathinone consumption remained unknown, but it might be linked to the easy availability and high quality of these new drugs [5].

Due to the continuous search for new, legal, less expensive and more powerful highs by drug users, the synthesis of novel cathinone derivatives became a fruitful industry, leading to a fast emergence of new alternative substances every year. This situation causes the increase of the prevalence of synthetic cathinone users, as they are not responsible for

the legal consequences due to their consumptions [7].

### Syntheses of synthetic cathinone and its derivatives

Highly skilled chemist in clandestine drug laboratories can produce cathinones in endless variations [3] especially via the addition of diverse substitutes at different locations of the molecule [8]. The situations have challenged the law enforcement authorities to control these drug substances carrying varying chemical composition, potency and the type of synthetic ingredients.

#### *Ephedrone (Methcathinone)*

Methcathinone (or also known as ephedrone) was the first synthetic cathinones [7,8], synthesized by Hyde *et al.* (1928) during their experiment to synthesise ephedrine homologs [8,9]. In some instances, this designer drug is also called CAT, Jeff or Mulka [12]. This N-alkylated cathinone was primarily used in medical and therapeutic perspective as an anti-depressant. However, due to its strong additive potential and cocaine-like stimulant properties (twice as potent as cathinone), it has been misused and abused [7,8,12,13].

Ephedrone was reported as a significant drug of abuse in ex-Soviet Union, starting 1970s, and its first known appearance in the United States was in 1989 [14]. The synthesis of ephedrone is simple and inexpensive via oxidizing reaction of readily available pharmaceuticals containing ephedrine and pseudoephedrine with an oxidizing agent in the presence of acid solution [8,10,15-18].

During synthesis, the benzylic hydroxyl group of the two starting materials is oxidized to the corresponding carbonyl-containing aminoketone [16]. The starting material used can be in free base form or an acid addition salt form, such as hydrochloride or sulfate. The oxidation process was reported to best carried out in an acidic condition and an alkali metal dichromate (*i.e.* sodium dichromate and potassium dichromate) as the oxidizing agent [19]. During the synthesis process, a solution of potassium dichromate in concentrated sulfuric acid is added to a solution of ephedrine or pseudoephedrine in water. Sodium hydroxide makes the reaction mixture alkaline and toluene is used to extract the resulting suspension. Upon filtration and drying, anhydrous ether is added to yield the final

products. The hydrochloride salts are white solids [16].

In most recent report, the precursor either ephedrine or pseudoephedrine is reacted with a solution of potassium permanganate in dilute sulfuric acid, resulting in the common synthesis pathway of methcathinone [10]. In the potassium permanganate oxidation pathway, the precursors are mixed with potassium permanganate, methylene chloride, water and acetic acid, followed by the addition of sodium hydrogen to reduce the precipitated manganese dioxide. Respective sodium hydroxide and sulfuric acid are used to make the aqueous phase alkaline and further separation. The final methcathinone formed light yellow oils after evaporation of methylene chloride [16]. When *N*-methylephedrine instead of ephedrine or pseudoephedrine is used as the precursor, dimethcathinone forms the final product [16].

The *l*- $\alpha$ -methylaminopropiophenone compounds can be produced from *dl*- $\alpha$ -methylaminopropiophenone, or from *l*-ephedrine. The former synthesis pathway involves the reaction of *dl*- $\alpha$ -methylaminopropiophenone with an optically active acid, and separates the mixture of salts by fractional crystallization. In many instance, the products are further converted to an acid addition salt, such as hydrochloride and phosphate [19]. The above pathway is a two-stage for synthesising this product. In one stage method, the reaction between *dl*- $\alpha$ -methylaminopropiophenone and the optically active acid is performed in a solvent and the desired products (*l*- $\alpha$ -methylaminopropiophenone) are isolated directly from the reaction mixture [19]. Camphor sulfonic acids were preferred in the synthesis process as it acts as the most easily separable mixtures of salts [19]. As for solvent, an anhydrous alcohol with a branched chain, such as isopropyl and isobutyl alcohol could be used [19].

Alternatively, ephedrone and its derivatives can be produced from  $\alpha$ -bromopropiophenone [16]. The synthetic reaction involves the displacement of bromine by methylene from  $\alpha$ -bromopropiophenone. Commonly, a solution of  $\alpha$ -bromopropiophenone in methylene chloride is reacted with a stirred solution of appropriate amine hydrochloride and triethylamine in methylene chloride. Adjustment to pH followed by the evaporation of the methylene chloride extract gave the

product oils which could be dissolved in anhydrous ether and hydrochloric gas to produce the hydrochloride salts. In the synthesis pathway, the amine hydrochloride decides the products. Methylamine and ethylamine can yield ephedrone and dimethcathinone respectively when they are used as the starting materials [16].

Ephedrone contains a chiral carbon at the 2-position of the side chain, and thus it can exist in two enantiomeric forms [16]. Each individual isomer of ephedrine and pseudoephedrine can produce homochiral ephedrone via the conservation of configuration (DeRuiter *et al.*, 1994). The precursors can be obtained as specific enantiomers, ensuring the stereoselective synthesis [10]. Therefore, 1*R*,2*S*-ephedrine and 1*R*,2*S*-pseudoephedrine produce *S*-ephedrone, whereas 1*S*,2*R*-ephedrine and 1*R*,2*R*-pseudoephedrine yield *R*-ephedrone [16]. Synthesis methods for methcathinone have been developed and available from the internet using all kind of common chemicals such as battery acid, drain cleaner and Epsom salts [16].

#### ***Mephedrone (Methylmethcathinone)***

Mephedrone, first synthesized in 1929 [1,9], is the most commonly reported synthetic cathinone [2]. The use of mephedrone, or also known as 4-methylmethcathinone (4-MMC), was reported in the illicit markets in Israel in 2007 and transmitted to other countries and regions including Australia, Scandinavia, Ireland and United Kingdom [20]. Mephedrone was sold illegally as alternative to cocaine and ecstasy [8,21]. In the market, mephedrone was known as “meow meow”, “M-CAT” or “TopCat” [8]. Mephedrone differs from cathinone with methylation of the amino group and the benzene ring. Structurally related to amphetamine and methamphetamine, it is likely to act similarly to these drug substances [1,22].

The misuse of this drug substance has emerged rapidly in a relatively short time with notably arising in the popularity among drug users [23]. In many instances, mephedrone has been specifically synthesized to other derivatives, to avoid the existing drug misuse laws. It is of concern that despite the banning of mephedrone, little may indeed prevent the suppliers from using the same marketing approach for novel and shortly forthcoming compounds [23].

In both the licit and illicit markets, mephedrone is commonly sold in powder, pill or capsule forms [1,8,23,24]. Being white powder as mephedrone hydrochloride salt, it is a yellowish liquid with its free base form at ambient temperature [8,22,24,25]. The production of mephedrone was reported to be relatively easy via the bromination of 4-methylpropiophenone (1-(4-methylphenyl)-1-propanone) followed by the reaction of the resulting 4-methylbromopropiophenone (1-(4-methylphenyl)-2-bromo-1-propanone) with methylamine or by oxidation of 4-methylephedrine in a two-step process [2,22-24]. The reaction is then quenched with gaseous or aqueous hydrochloride providing the crystallised hydrochloride salt [22]. This is the simplest choice as the starting materials are often commercially available or easily synthesised [22]. This synthetic route is flexible, where a number of cathinone derivatives can be manufactured by slightly modification to the precursor (*i.e.* 4-methylpropiophenone and methylamine) [2]. For example, changing in the position and/or the identity of the alkyl group of 4-methylpropiophenone can produce different known cathinone compounds. 3-methylpropiophenone can produce 3-methylmethcathinone, and 4-ethylpropiophenone can manufacture 4-ethylmethcathinone [2]. In a similar manner, the replacement of methylamine with ethylamine can produce ethcathinone. In more instances, the substituting of methylamine with another amine enables the manufacturing of a series of ethcathinone [2].

If the substituted ephedrine analogue (4-methylephedrine) is available, then its oxidation with, for example, potassium permanganate is also a feasible method that does not require a professional laboratory. This method, similar to the one used for the clandestine synthesis of methcathinone, requires reacting the precursor with a solution of potassium permanganate in diluted sulphuric acid. The precursor can be obtained in a specific enantiomeric form thereby ensuring that the synthesis is stereoselective [22]. Alternative synthetic methods, though more cumbersome, have been described in the literature such as the Hartung-Munch procedure involving isonitrosopropiophenone, as well as the preparation of related compounds. More synthetic routes for mephedrone may exist [22].

### **Methylone**

Methylone was included in the first generation of synthetic cathinone in the mid-2000s [21] and appeared to be the most common drug substance among the derivatives of synthetic cathinones in European countries, along with mephedrone [1]. Marketed under the brand name of “Explosion”, methylone was popular in the Netherlands, Canada, Japan, Australia and New Zealand [8,18,20], and became one of the first products sold via the Internet and at smartshops [8,20,25].

Methylone was synthesized in 1991 and patented as an anti-depressant and anti-Parkinsonism agent but was not ended with its initial market purpose in the following years [8]. Oral intake of this drug substance is more common, in which the effect is elicited within 15 to 30 minutes and for duration of 3 hours [8,25]. Methylone poisoning was reported either in single consumption [26], as well as in combination with other psychoactive ingredients [8].

Methylone is the benzylic ketone analogue of MDMA and due to its similar psycho-stimulant potency close to MDMA, it was misused and abused [8]. Instead of alkylation, a 3,4-methylenedioxy group was added to the benzyl ring. In the case of methylone, for example, 2-bromo-3,4-methylenedioxypropiofenone can be prepared by reacting 3,4-methylenedioxypropiofenone with bromine. These precursor substances are readily available and none of them is under international control [10].

### **3,4-methylenedioxypropiofenone (MDPV)**

MDPV received a large diffusion, especially among young people, causing international alert. It was firstly synthesized as part of stimulant in 1969, which is the methylenedioxy analogue of pyrovalerone synthesised in 1964 [27]. Note that pyrovalerone is a DEA Schedule IV cathinone analog [28]. MDPV was encountered in Japan in 2006 [29] and 2007 in Germany [7,29].

MDPV appears as pyrrolidine derivatives in the synthetic cathinone family with a 3,4-methylenedioxy ring substitution and a N-pyrrolidinyl moiety [8,27]. It can be prepared from the aldehyde piperonal (3,4-methylenedioxybenzaldehyde) via a 4-step synthetic procedure [30]. The alkylmagnesium halides (Grignard reagents) is reacted with the substituted benzaldehyde piperonal (starting material) through a condensation process to

yield the corresponding 3,4-methylenedioxybenzyl alcohol. The benzylalcohols is then oxidised by pyridinium chlorochromate to produce the 3,4-methylenedioxyalkylphenones. Lastly, alpha-bromination of the ketones at the activated methylene carbon gives the alpha-bromoketones and subsequently displaces the bromide ions with the appropriate cyclic secondary amine to form the final products of aminoketone (i.e. MDPV) which are isolated through solvent extraction and recrystallised as the hydrochloric salts [30].

The synthesis of the 2,3-isomers of MDPV was reported by Kavanagh *et al.* (2012) with the 2,3-methylenedioxybenzaldehyde as the starting material. In the study, piperonal (3,4-methylenedioxybenzaldehyde) was used as the starting material for 3,4-isomers, and it was suggested with greater central nervous system stimulant activity [31].

### **Other synthetic cathinone derivatives**

Several other derivatives with minor structural modifications within. N,N-dimethylcathinone or metamfetromone can be synthesised by oxidation of N-methylephedrine (or N-methylpseudoephedrine) [10]. The ring-substituted N-methylcathinone derivatives are best synthesised by reacting the suitably substituted bromopropiophenone with methylamine to give racemic products. The corresponding fluoro  $\alpha$ -bromo-propiophenone (product from the chemical reaction of fluoropropiophenone in dichloromethane and bromine) can be reacted with methylamine ethanol at room temperature, followed by the dissolution of the resulting residue in aqueous hydrochloric acid and extracted with ether. The addition of potassium carbonate made the aqueous phase basic, and the amine was extracted with ether. 4-fluoromethcathinone, as well as 2- and 3-fluoromethcathinone to form the final products [32].  $\alpha$ -pyrrolidinophenones include  $\alpha$ -pyrrolidinopropiophenone (PPP), 4'-methyl- $\alpha$ -pyrrolidinopropiophenone (MPPP), 4'-methoxy- $\alpha$ -pyrrolidinopropiophenone (MOPPP) and 3,4-methylenedioxy- $\alpha$ -pyrrolidinophenone (MDPPP) are produced as part of the clandestine products [33].

### **Conclusion**

Structurally modified cathinone derivatives were primarily synthesised for medical and therapeutically uses, but promptly started being misused and abused. Many cases of

intoxication, and more severe fatalities have been reported throughout the world. Bupropion is the only cathinone derivative as medical perspective for treatment of depression and smoking cessation in the United States and United Kingdom. Although their duration and potency varied between the derivatives, they have reached to the public sold under the label of 'not for human consumption' or under deceptive information on health effect, online and locally as the alternative to ecstasy and cocaine. Over the last few years, a great increase was reported in the popularity of these drugs, with more than 30 cathinone derivatives were identified to date. Mephedrone, methylone and MDPV are the main products of these 'legal highs' so far. However, due to their scheduling as controlled substances, they are gradually modified structurally and presented in the markets as new products. Newer derivatives will emerge into the recreational drug markets and information gathering and sharing are therefore important. Possible synthesis pathways of these clandestine products must be understood by forensic analysts prior to their analyses.

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