

# Psychoactive Bath Salts and Neurotoxicity Risk

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## **Abstract**

*Synthetic cathinones are new designer drugs that possess hallucinogenic and psychostimulant properties, designed to mimic the effects of illegal substances such as cocaine, amphetamines and 3,4-methylenedioxymethamphetamine (ecstasy) and to produce rewarding effects by circumventing existing laws and penalties. Synthetic cathinones, also entitled as 'bath salts', have become popular particularly among young people since mid-2000s. Similar to other psychomotor stimulants, synthetic cathinones have potential to increase monoamine concentration in synaptic cleft by targeting plasma membrane transporters of dopamine, norepinephrine and serotonin. Because of their structural similarities to amphetamines, it has been suggested that synthetic cathinones may have a similar neurotoxicity profile with their amphetamine congeners. Therefore, it has been hypothesized that synthetic cathinones may induce neurotoxicity on monoamine nerve endings in the striatum, hippocampus, and cortex. By now, with regard to synthetic cathinone neurotoxicity, parameters such as monoamine depletion, biosynthetic enzyme inhibition, cytotoxicity, generation of reactive oxygen species, pro-oxidation status and the ability to induce neuroinflammation were investigated both in vitro/in vivo experimental studies. Compared with amphetamines, synthetic cathinones seem to be more moderate than their amphetamine congeners in terms of neurotoxic effects. Many synthetic cathinone users take these substances simultaneously with other drugs such as benzodiazepines, amphetamines, ecstasy, tetrahydrocannabinol (THC) and ethanol so as to modify toxicity. Hence, it is important to understand the underlying mechanism of early neurotoxic effects in case of poly-substance use. In this review, it is aimed to summarize synthetic cathinones' abuse liability, legal status, mechanism of action and particularly their neurotoxic effects.*

**Key words:** psychoactive, hallucinogen, bath salts, synthetic cathinones, neurotoxicity

## Psikoaktif Banyo Tuzları ve Nörotoksisite Riski

### Özet

Sentetik katinonlar, mevcut yasa ve cezaları atlatabilmek amacıyla, kokain, amfetamin ve 3,4-metilendioksimetamfetamin (ekstazi) gibi yasadışı maddelerin etkilerini taklit etmek ve benzer ödüllendirici etkiler yaratmak üzere geliştirilmiş halüsinojenik ve psikostimulan özellikte yeni tasarım maddelerdir. "Banyo tuzları" olarak da bilinen sentetik katinonlar, 2000'li yılların ortalarından itibaren özellikle genç bireyler arasında popüler hale gelmeye başlamıştır. Diğer psikomotor uyarıcılara benzer şekilde, sentetik katinonlar da, dopamin, norepinefrin ve serotoninin plazma membran taşıyıcılarını hedef alarak sinaptik aralıktaki monoamin konsantrasyonunu arttırmaktadır. Amfetaminlere olan yapısal benzerlikleri nedeniyle, sentetik katinonların amfetamin homologları ile benzer nörotoksisite profiline sahip olabileceği düşünülmüştür. Bu nedenle, sentetik katinonların striatum, hipokampus ve kortekste monoamin sinir uçları üzerinde nörotoksisiteyi indükleyebileceği hipotezi öne sürülmüştür. Şimdiye dek sentetik katinonların nörotoksisitesi ile ilgili olarak yapılan in vitro/in vivo deneysel çalışmalarda, monoamin depleasyonu, biyosentetik enzim inhibisyonu, sitotoksisite, reaktif oksijen türlerinin oluşumu, pro-oksidasyon durumu ve nöroinflamasyon indükleme yeteneği gibi parametreler incelenmiştir. Sentetik katinonların nörotoksik etkiler açısından amfetamin homologlarından daha ılımlı olduğu görülmektedir. Ancak pek çok sentetik katinon kullanıcısının bu maddeleri benzodiazepinler, amfetaminler, ekstazi, tetrahidrokannabinol (THC) ve etanol gibi diğer ilaç ve uyuşturucu maddeler birlikte alması, nörotoksik etkileri modifiye edebilmektedir. Bu nedenle, çoklu madde maruziyeti durumundaki erken nörotoksik etkilerin anlaşılması önemlidir. Bu derlemede, sentetik katinonların suistimal potansiyeli, yasal statüsü, etki mekanizması ve özellikle nörotoksik etkileri hakkında bilgi verilmesi amaçlanmıştır.

**Anahtar Kelimeler:** psikoaktif, halüsinojen, banyo tuzları, sentetik katinonlar, nörotoksisite

## Introduction

Synthetic cathinones are a subgroup of new psychoactive substances (NPS) that possess hallucinogenic and psychostimulant properties and designed to mimic the effects of illegal substances such as cocaine, 3,4-methylenedioxymethamphetamine (MDMA) and other amphetamines by circumventing existing laws.<sup>1</sup> NPS or in the other term 'designer drugs' are and intentionally mislabeled and marketed as bath salts, fertilizers - although there is no such a purpose - plant food, laboratory chemicals or reagents and marked as 'not for human consumption' or 'not tested for danger/toxicity' to avoid criminal liability.<sup>2,3</sup> Synthetic cathinones are one of the most commonly found psychoactive substances in these designer drug mixtures.<sup>1</sup> Bath salts contain one or more synthetic cathinone derivates. Most popular bath salt constituents are 4-methylcathinone (mephedrone), 3,4-methylenedioxymethcathinone (methylone), 3,4-methylenedioxypropylvalerone (MDPV). In point of fact, these compounds have no legitimate use as a bath additive in these products.<sup>4</sup>

Synthetic cathinones are usually a white, amorphous or crystalline powder, used by oral, rectal routes, injection or inhalation (Synthetic Cathinones (Bath Salts): An emerging domestic treat, US dept of Justice, 2014). Some synthetic cathinone derivates also can be smoked or used as "vapor" in e-cigarette-like devices.<sup>5</sup> Synthetic cathinones, also entitled as 'bath salts', have become popular particularly among young individuals since mid-2000s.<sup>4</sup> In recent years, synthetic cathinones have increased in both supply and demand literally in each corner of the world. Because they have known as 'legal alternatives' for illicit drugs, there has been a dramatic increase in the sales. Another reason which made bath salts popular and widespread is the fact that they are easily accessible on the web.<sup>6</sup> Drug trade through the cryptomarket on the web, called "Darknet", allows users to anonymously buy drugs. According to United Nations Office on Drugs and Crime, while drug trafficking over the darknet remains small, there is an increase in drug transactions, of some 50% annually between 2013 and 2016.<sup>7</sup>

Low doses of synthetic cathinones cause euphoria and alertness, however, high doses or chronic use can cause serious adverse effects such as hallucination, psychosis, delirium, hyperthermia, tachycardia, renal failure, ischemia. Similar to other psychomotor stimulants, synthetic cathinones increase monoamine concentration in synaptic cleft by targeting plasma membrane transporters of dopamine (DAT), norepinephrine (NET) and serotonin (SERT). Induction of dopaminergic transmission is suggesting that they have a high potential for addiction. Because of their structural similarities with amphetamines, many synthetic cathinone derivates have been attempted to be developed as anorectic, CNS stimulant or antidepressant, however, addiction problems hindered their clinical use.<sup>8,9</sup>

Synthetic cathinones could physically harm the users, which could also pose public health threats such as violence and irresponsible driving. Due to the health risks posed by bath salts, certain synthetic cathinones such as mephedrone, methylone, and MDPV have rendered illegal in many countries. Even though they have seen as a legal alternative by users, their legal situation rapidly changes and differs among the countries.<sup>10</sup> The illegal inclusion of popular synthetic cathinones in many countries has led to the synthesis of new cathinone derivatives with minor modifications by their functional groups. This leads to a great diversity of product composition even within the same brand.<sup>11</sup> The replacement of synthetic cathinones with newly developed cathinone derivatives causes a major problem in terms of the drug policy. The major problem is theoretically many structural variants of the cathinone are possible.<sup>12</sup> The number of synthetic cathinones reported in 2008 was 8, but increased to 68 by the end of 2014. The cumulative number reported to the European Monitoring Center for Drugs and Drug Addiction (EMCDDA) between 2005 and 2016 is 118. The total number reached 128 by 2017.<sup>13</sup>

The gradual increase in the number of new derivatives makes difficult to detect synthetic cathinones in biological specimens with routine toxicological tests. Since synthetic cathinones are a new chemical class, they can not be determined by conventional techniques. The low specificity of immunoserological tests causes false-positive results. Qualitative and quantitative analysis of synthetic

cathinones requires more sensitive techniques and equipment such as Gas Chromatography-Mass Spectrometry (GC/MS) or Liquid Chromatography-Mass Spectrometry (LC/MS). Due to the challenges with routine imaging techniques, the rate of use in subpopulations such as military personnel is still increasing in some countries.<sup>14</sup> No global data available, however, the prevalence of mephedrone abuse among European adults aged 16-59 is estimated to have reached 0.5% in 2012-2013.<sup>13</sup> In 2010 and 2011, there were total 362 calls has been made to the Texas Poison Center due to synthetic cathinone intoxication, 84.5% were over 20 years of age, 74% were male patients, 47.8% of those were exposed via inhalation, and 28.7% only oral route.<sup>14</sup>

The most commonly seized synthetic cathinones in Europe were  $\alpha$ -pyrrolidinovalerophenone ( $\alpha$ -PVP), 3-methylmethcathinone (3-MMC), ethylone, 4-chloromethcathinone (4-CMC) and pentedrone in 2015 (European Drug Report 2017, EMCDDA). In recent years, second-generation synthetic cathinone derivative  $\alpha$ -PVP has rapidly gained popularity.  $\alpha$ -PVP or 'flakka' as a street name, is synthetic cathinone derivate that bearing pyrrolidine ring, colloquially called 'Zombie drug' due to unpredictably bizarre and erratic behavior seen in its users. Recently, flakka abuse has seen in Turkey which flakka is approved as an illegal substance.<sup>15,16</sup> Great handicap for  $\alpha$ -PVP abuse is its legal/under control status in some European and United Nations member states, e.g. Belgium, Denmark, Spain, Bulgaria and Japan.<sup>17</sup>

The underlying mechanisms of the behavioral effects of cathinone analogs are not same in all synthetic cathinone compounds; it depends on the chemical composition, function and their selectivity on dopamine/ norepinephrine/serotonin transporters. A growing body of information upon neurotoxicity of synthetic cathinones brings out a need a review for the frequently used synthetic cathinone's neurotoxicity.

### **Chemical Structure and Properties**

Synthetic cathinones are the structural analog of amphetamines and is chemically referred  $\beta$ -ketone analogs because of the carbonyl (=O) group in  $\beta$  carbon. The common pharmacophore group responsible for the biological effect seen in amphetamine, MDMA (ecstasy) and cathinones is phenethylamine, represented in Figure-1.<sup>18</sup>

The substitutional regions of synthetic cathinones are  $\alpha$  and  $\beta$  carbon. The length of the substitution at the N-terminus varies within itself. MDPV and its derivatives differ from other derivates by the presence of the nitrogen-containing pyrrolidine ring.<sup>4</sup> There is no scientific classification of synthetic cathinones, however, substituted cathinones can be classified as pyrrolidine-bearing / not pyrrolidine-bearing derivatives (Figure-2).

MDPV is structurally similar with pyrovalerone, the psychoactive drug used in the treatment of chronic lethargy.<sup>3</sup> Pyrovalerone cathinones (MDPV and  $\alpha$ -PVP) are highly lipophilic compared with other derivates, thus having a high blood-brain barrier (BBB) penetration/transition and a high volume of distribution. This results in longer plasma and tissue half-live.<sup>19</sup> The presence of electrophilic groups such as fluorine and the length of carbon substitution at the N-terminus increase the lipophilic nature of synthetic cathinone analogs.

### **Mechanism of Action**

The underlying mechanism of behavioral and physiological effects of synthetic cathinone derivates is not fully understood yet. In general, synthetic cathinones increase the monoamine concentration in the synaptic cleft. The monoamine increase in the synaptic region mediates the stimulatory and hallucinogenic effects of synthetic cathinones.<sup>4,9,20</sup>

Similar with other psychomotor stimulants, synthetic cathinones target plasma membrane transporters of dopamine (DA), norepinephrine (NE) and serotonin (5-HT), respectively.<sup>4</sup> Two distinct mechanisms

mediate the increase of monoamine concentration in the synaptic cleft. In the first mechanism, as in amphetamines, it stimulates non-exocytic neurotransmitter release (secretory agents/substrates) by inhibiting the vesicular monoamine transporter-2 (VMAT2) and reversing the transporter influx. Substrates can stimulate neurotransmitter release from the cytosolic pool or synaptic vesicles. Monoamine neurotransmitters are packed into synaptic vesicles with the VMAT2. Since VMAT2 functions as a proton-monoamine antiporter, the change in the intravesicular pH value disrupt the ability of VMAT2 to carry monoamines, thereby inhibits vesicular storage of monoamines. Substrates such as MDMA alter the pH gradient required for VMAT2-mediated monoamine accumulation. In the second mechanism, as in cocaine, they inhibit the uptake of neurotransmitters from the synaptic cleft by inhibiting plasma membrane transporters which are responsible for the uptake of NE and 5-HT as well as DA (reuptake inhibitors/blockers).<sup>20,21</sup> Substrates and blockers differ in terms of their acute and chronic effects.<sup>4</sup> Substrates can cause permanent damage to monoamine neurons by the loss of functional transporters and neurotransmitter depletion.<sup>22</sup>

Synthetic cathinones may act as an inhibitor or as a substrate [as an inhibitor on single transporter/ more than one transporters or as a substrate on single transporter/ more than one transporters] on dopamine transporter (DAT), norepinephrine transporter (NET) and/or serotonin transporter (SERT).<sup>12</sup> The underlying mechanism of physiological and behavioral effects of synthetic cathinones differs from agent to agent depending on chemical composition, function (secretory agent or reuptake inhibitor) and DAT / NET / SERT selectivity. This shows that synthetic cathinone analogs have a complex mechanism. Mephedrone is a non-selective substrate and stimulates the non-exocytotic release of NE, 5-HT, and DA. MDPV is the potent blocker of DAT and NET, and also has a slight effect on the SERT.<sup>4,23</sup> Therefore, mephedrone and MDPV act via different mechanisms. When administered in combination, while MDPV blocks their re-uptake, mephedrone increases the concentration of neurotransmitters in the synaptic cleft. MDPV is 30-50 times more potent as a DA reuptake inhibitor than cocaine. Therefore, the combined use of mephedrone and MDPV resembles the effects of methamphetamine following cocaine intake - but with a more potent trend.<sup>12</sup>

Up to now, a few synthetic cathinone compounds' mechanisms of action has been defined in detail. Many synthetic cathinone derivatives are still in the process of research. Although researchers have some progress on the structure-activity relationship of synthetic cathinones, further research is needed to predict the behavioral effects of new derivatives.

## Neurotoxicity

Due to synthetic cathinones differ in terms of their mechanism and potential for causing changes of the extracellular concentrations of DA, NE, and 5-HT, their mood swing effects, toxicity and dependence potentials are also divergent. Therefore, each synthetic cathinone toxicity should be assessed separately.<sup>8,24</sup>

The neurotoxicity induced by amphetamines has been studied well in human and animals. In these studies, several parameters such as neuroinflammation inducing ability, oxidative stress, cytotoxicity, neurotransmitter system dysregulation, changes in monoamine transporter levels and receptors were evaluated.<sup>25</sup>

Methamphetamine is one of the most well-known compounds for its neurotoxic effects at the dopamine nerve endings in the striatum. It has been demonstrated that MDMA causes long-term 5-HT depletion on monoamine nerve endings. Amphetamine neurotoxicity includes inhibition of biosynthetic enzymes of monoamines i.e; tryptophan hydroxylase (TPH-2) and tyrosine hydroxylase (TH), DAT and SERT inactivation, diminished VMAT2 function, degeneration and apoptosis in unmyelinated axons at the nerve endings, prolonged DA and 5-HT depletion.<sup>26</sup>

Because of their structural similarities to amphetamines, it has been suggested that synthetic cathinones may have a similar neurotoxicity profile with their amphetamine congeners. Hence, synthetic

cathinones may cause neurotoxicity at the monoamine nerve endings in the striatum, hippocampus, and cortex.<sup>27</sup> Parameters such as monoamine depletion, biosynthetic enzyme inhibition, cytotoxicity, generation of reactive oxygen species (ROS) and the ability to induce neuroinflammation of synthetic cathinones were compared with amphetamines. Researchers have reached the conclusion that synthetic cathinones are more moderate than their amphetamine congeners in terms of these toxic effects.<sup>25</sup>

The neurotoxicity studies of synthetic cathinone compounds are generally directed to mephedrone toxicity.<sup>28-34</sup> The neurotoxicity induced by mephedrone has not been fully elucidated yet. Despite the many evidence that mephedrone is dangerous, how it plays a role in the central nervous system is controversial. While no damage to dopaminergic nerve endings or no change in monoamine levels in synaptic cleft were stated in part of studies with animal models<sup>29,30</sup>; in some other studies, decrease in DAT and SERT function and damage at dopaminergic/serotonergic nerve endings were observed.<sup>28,31</sup>

Many synthetic cathinone users take these substances simultaneously with other drugs such as benzodiazepines, other amphetamines, ecstasy, tetrahydrocannabinol (THC) and ethanol.<sup>35</sup> It is known that 95% of synthetic cathinone users are also alcohol consumers at the same time. How ethanol modifies the neurotoxicity induced by mephedrone remains unknown but researchers found that ethanol exacerbated the decrease in DAT and tyrosine hydroxylase levels in frontal cortex as well as the reduction in SERT and tryptophan hydroxylase levels by 2 fold in CD1 mice. Moreover, this decrease was correlated with a 2-fold increase in lipid peroxidation levels.<sup>33</sup>

In another study with pregnant rats, repeated exposure to mephedrone during pregnancy causes low birth weight and increased risk of stillbirth. Besides, It has been shown that repetitive use of mephedrone is associated with hippocampal damage and disrupts learning and memory processes.<sup>34</sup>

An increase in cytotoxicity and lipid peroxidation parameters by inducing oxidative stress in the frontal cortex was observed after mephedrone application in rats.<sup>32</sup> In addition to brain tissue, mephedrone induces oxidative stress also in kidney, heart, liver, and spleen of mice.<sup>36</sup>

There are also studies about MDPV and methylone neurotoxicity.<sup>27,31,37-41</sup> In a study which comparing methylone and MDPV neurotoxicity with MDMA, the concentration-dependent decrease in cell viability was observed in differentiated and undifferentiated dopaminergic cells (MDPV ~ MDMA > methylone). Differentiated cells were found to be more vulnerable than undifferentiated cells. As a mechanism of neurotoxicity, findings of increased intracellular ROT and NO levels, glutathione depletion, elevated levels of oxidative glutathione, deterioration of mitochondrial membrane potential and intracellular ATP depletion point out oxidative stress and mitochondrial dysfunction, resulting with cell death. Condensed chromatin, pyknotic cell formation, and caspase 3, 8, 9 activations suggest that apoptosis is the mechanism of cell death induced by methylone and MDPV.<sup>37</sup>

Microglia and astrocytes are primary inflammation modulators in the central nervous system. Increased glial-based cytokines in chronic neuroinflammation cause toxic effects in vulnerable neurons. The studies on the neuroinflammation inducing ability of synthetic cathinones are controversial. Some in vivo studies have not found any evidence for astroglial activation in the striatal and cortical regions after mephedrone administration.<sup>31,32,42</sup> However, increased glial-specific marker; glial fibrillary acidic protein (GFAP) immunoreactivity in hippocampus 7 days after mephedrone administration at recreational dose was observed.<sup>43</sup>

In a recent study, it has been found that methylone neurotoxicity is related to posology. Besides, increased immobility in animals indicates depression-like effects.<sup>38</sup> Neurochemical/enzymatic changes in rats following methylone administration at the recreational dose (20 mg/kg) has been tested and hyperthermia developed 30 minutes after dosing. In addition, serotonergic impairment accompanied by astrogliosis in frontal cortex was observed, but no significant neurotoxicity was found on the dopaminergic system. The study was conducted at a high ambient temperature ( $26 \pm 1$  °C) to simulate hot conditions in dance clubs where methylone was used.<sup>39</sup> Time and concentration-dependent reactive oxygen species (ROS) formation, reduction in cellular proliferation rate (only at high concentrations), apoptosis induction and necrosis have been observed in human dopaminergic SH-SY5Y cells regarding

the cytotoxic effects of MDPV.<sup>40</sup> Induction of ROS formation may be the underlying mechanism of the early toxic effects of MDPV.

Various studies have reported the adverse effects of methamphetamine and MDMA on BBB. When comparing the toxic effects of MDPV on BBB with methamphetamine and MDMA, MDPV was found to be more toxic than its amphetamine homologous. MDPV showed cytotoxic effects at all concentrations. There was a decrease in cellular proliferation at 1 mM concentration, an increase in reactive oxygen and nitrogen species at all concentrations, and change in endothelial morphology at  $\geq 0.5$  mM concentrations.<sup>41</sup> These data suggest that synthetic psychostimulants may be toxic to the monoaminergic system as well as to the BBB through different mechanisms.

Another derivative that has attracted attention in recent years is  $\alpha$ -PVP. Awareness of the case-reports associated with  $\alpha$ -PVP ingestion is increasingly important due to severe toxic effects and fatal intoxications.<sup>5,44-46</sup> Although the exact mechanism of  $\alpha$ -PVP remains unclear, it is known that  $\alpha$ -PVP is designed to cause the brain to become flooded with dopamine. Due to its structural similarity to MDPV,  $\alpha$ -PVP was suggested to be a norepinephrine-dopamine reuptake inhibitor and dopamine releaser and therefore causing an increase in locomotor activity.<sup>47</sup> However, studies which investigating potential neurotoxicity of  $\alpha$ -PVP in the literature is very little. We come across one molecular mechanistic study about  $\alpha$ -PVP.  $\alpha$ -PVP modulates immediate early genes expression such as Arc/Arg3 and c-fos in the frontal cortex, striatum, and hippocampus in that study, thus indicating this drug has an impact on brain homeostasis.<sup>48</sup> Still, more research is needed with regard to neurotoxic effects of  $\alpha$ -PVP on different brain regions.

## Conclusion

Synthetic cathinones represent a broad class of pharmacologically active compounds which can cause numerous effects via different mechanisms. Synthetic cathinones are a global threat with rapidly increasing abuse rates. Due to these substances differ in terms of their mechanism and potency, their mood-altering effect, toxicity and dependence potentials are also divergent. Therefore, each synthetic cathinone compounds should be evaluated separately.

In literature, studies are generally directed to synthetic cathinones' psychostimulant and locomotor stimulant effects, neurocognitive performance and memory, however, neurotoxicity studies are limited. The neurotoxicity of synthetic cathinones has not been fully elucidated yet. Neurotoxic effects of synthetic cathinones on the serotonergic and dopaminergic system are controversial. Differences in experimental design such as temperature and animal species, make difficult to compare the results. In some animal model studies, no damage or changes in monoamine levels were reported at the dopaminergic nerve endings in the striatum, whereas in some other studies decreased DAT and SERT function and damage to dopaminergic/serotonergic nerve endings was observed. Preclinical findings indicate that the adverse effects of synthetic cathinones can often be exacerbated by high temperature and crowded conditions, as in dance club ambiances where the drug is used. For this reason, in some neurotoxicity studies, this high ambient temperature ( $> 26$  °C) have been imitated. It might be said that the neurotoxicity induced by synthetic cathinones is more frequently observed in studies conducted at high temperatures. Since synthetic cathinones are often combined with other cathinone derivatives or non-cathinone compounds such as alcohol, amphetamines, ecstasy, and cocaine, it is important to understand the neurotoxic effects in case of poly-substance use. Further research is needed for the toxicological point of view in order to address the health problems associated with bath salts.

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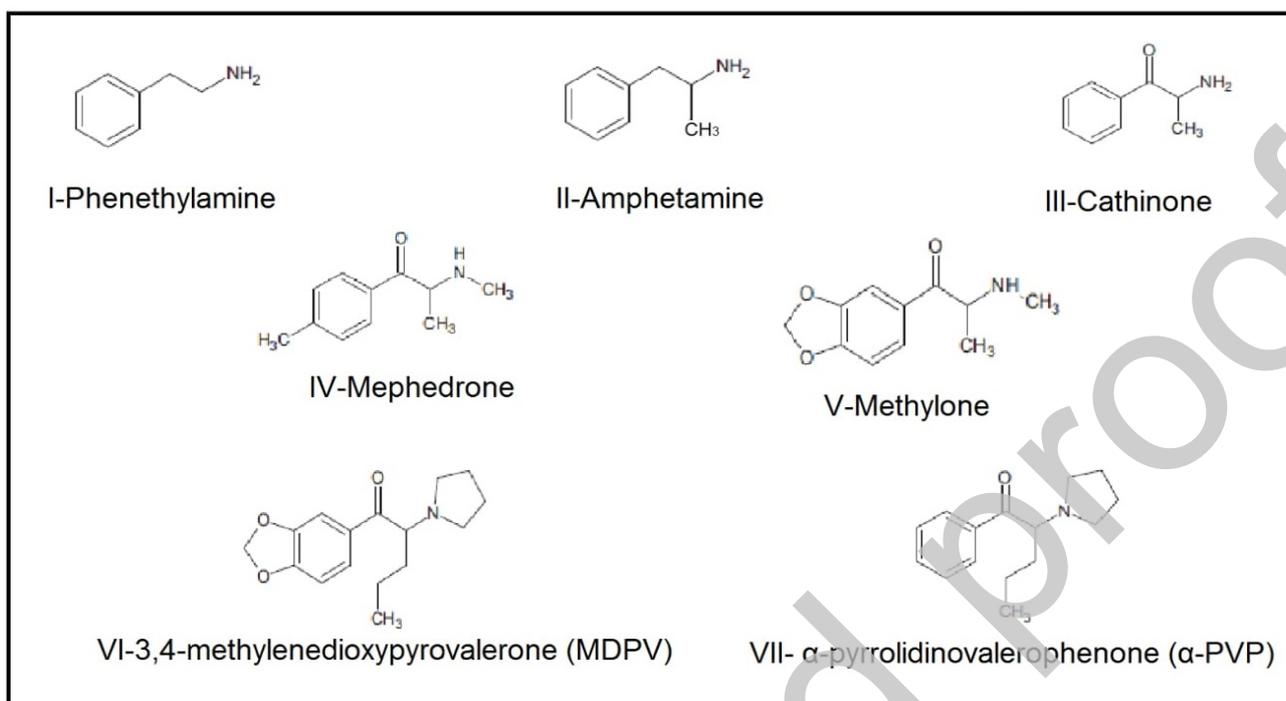


Figure-1: Chemical structure of phenethylamine, amphetamine, cathinone and other synthetic cathinone derivatives <sup>18</sup>

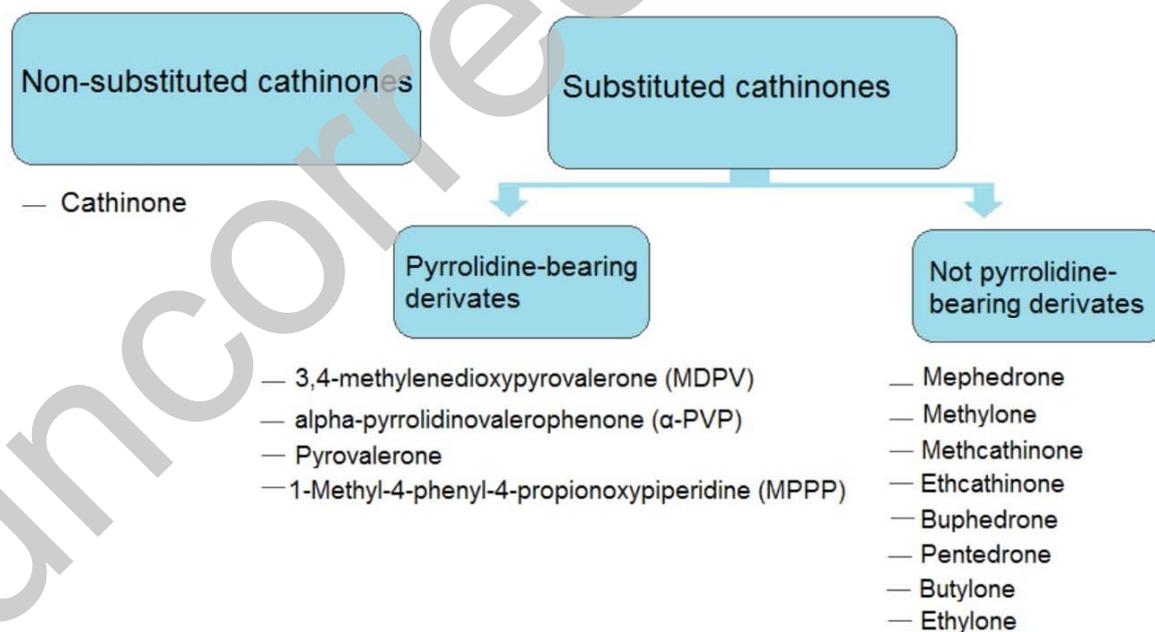


Figure-2: Classification of synthetic cathinone analogues