

Review Article

Synthetic Cathinones: A Brief Overview of Overviews with Applications to the Forensic Sciences

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Submitted: 24 February 2017

Accepted: 20 March 2017

Published: 21 March 2017

ISSN: 2378-9476

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Keywords

- α -Aminopropiophenones
- β -Ketoamphetamine
- Forensics
- Khat
- Methcathinone
- Psychoactive bath salts
- Review

Abstract

Catha edulis, the fresh leaves of which (i.e., *khat*) are used for their central stimulant actions, has been known for many hundreds of years. *S*(-)-Cathinone was identified as a centrally-active *khat* constituents > 30 years ago. Although *khat* use was a problem long localized to certain Middle Eastern and certain Eastern African nations, 'synthetic cathinones' (synthetic analogs of cathinone) represent a "new" class of abused substances with growing worldwide appeal. To date, about 150 synthetic cathinones have been identified on the clandestine market, and only a dozen or so have been controlled (U.S. Schedule I). Because these agents do not represent a pharmacologically (i.e., behavioral) or mechanistically homogeneous class of agents, synthetic cathinones are being investigated one agent at a time to understand their actions, mechanisms of action, metabolism, toxicity, and abuse potential - the latter to identify possible modes of overdose treatment and for Scheduling purposes. The available agents might represent only the 'tip of the iceberg'; the potential for many more new synthetic cathinones is very real. Investigation of these agents on an agent-by-agent basis is a daunting task. Attempts are being made to understand these agents as a class, by examination of their structure-activity relationships. Here, we provide an overview of review articles that attempts to shed light on these agents as a class, rather than on an agent-by-agent basis. This article is meant to be a reference resource that might expedite the work of those in this field by directing them to where they can find useful information.

INTRODUCTION

Some of the newest "club dugs" include the *synthetic cathinones*. *S*(-)-Cathinone (1) (Figure 1) was first identified as a phenylalkylamine central nervous system stimulant component of *Catha edulis*, a shrub indigenous to certain Eastern African countries and the Arabian peninsula, in 1975 [1]. Since then, a host of "synthetic cathinones" (cathinone bearing various structural appurtenances) have become popular on the clandestine market as abused substances or substances with abuse potential. For the most part, they are not "controlled substances" (i.e., illegal). A Medline search (January 3, 2017; search terms: "cathinone or cathinones or methcathinone") revealed that in the decade following the discovery of cathinone, 70 scientific papers were published on the topic. An average of seven papers per year does not suggest major scientific interest in this topic. A similar number of papers were published in each of the next two decades (i.e., 99 and 71 papers, respectively). Today, there are nearly 1,000 scientific papers that include at least one of the above search terms. And, it should be noted that articles describing a specific

synthetic cathinone analog under its current "street name" or chemical name might not have been captured in our search. Also, our search did not include "*khat*" (note: a separate search for "*khat not cathinone*" conducted on the same day, identified an additional 460 citations). Hence, our count of published articles on cathinone and cathinone analogs is likely an underestimate of what has been actually published. An up-tick in scientific interest in synthetic cathinones coincided with Iverssen's 2010 letter to the British Home Office on the appearance of synthetic cathinones on the European clandestine market [2]. The availability and use of new synthetic cathinones is a growing worldwide drug abuse problem [3]. Synthetic cathinones are now "fashionable" agents of abuse - something novel.

Some of the best recognized synthetic cathinones (i.e., those most popular in the current scientific literature and on the clandestine market) include methcathinone (MCAT; **2**), mephedrone (**3**), methylenedioxypyrovalerone (MDPV; **4**), and α -pyrrolidinovalerophenone (α -PVP; **5**; "*flakka*") (Figure 1). But, this is just a very small sampling of the approximately 100-150

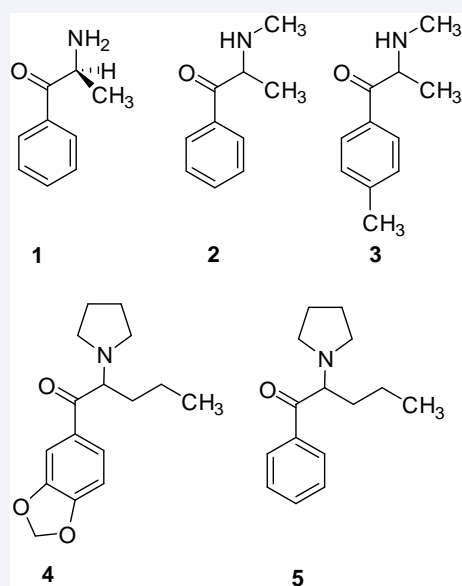


Figure 1 Chemical structures of S (-) cathinone (1) and several structurally-related synthetic cathinones as their racemates: methcathinone (2), mephedrone (3), MDPV (4), and α -PVP (5).

or so synthetic cathinones identified on the illicit market by law enforcement officials [4]. The term “*psychoactive bath salts*” has been used in conjunction with these agents. *Bath salts* initially contained one or more of these agents, alone, or in combination with other synthetic cathinones or with amphetamine-derived (sometimes known and sometimes novel) agents [5]; but, newer synthetic cathinone (and amphetamine) analogs now are supplanting these. One problem is that many structural variants of cathinone and amphetamine are theoretically possible. A few of these agents have been described in the patent literature over the years as synthetic precursors for one potential therapeutic target or another, but were never pharmacologically examined themselves, or for their therapeutic potential as, for example, appetite suppressants or antidepressants, but never made it to the clinic for one reason or another [4,5].

Today, *bath salts* might refer to almost anything, and the term is used quite frivolously (but, *bath salts* commonly contains at least one cathinone analog as a constituent). The prevalence of the use/abuse of synthetic cathinones is difficult to discern because they are alternately referred to, and sometimes classified as, “amphetamine-type stimulants” (ATSS), a category that includes amphetamine, methamphetamine, MDMA (3,4-methylenedioxymethamphetamine, also known as, for example, “XTC” and “Molly”), and other agents [3]. Synthetic cathinones are also sometimes classified as “new psychoactive substances” (NPS) - “*substances of abuse... that are not controlled under the Single Convention on Narcotic Drugs of 1961 or the 1971 Convention, but that may pose a public health threat. In this context, the term “new” does not necessarily refer to new inventions but to substances that have recently become available*” [3]. However, NPS also include other, non-cathinone related agents (e.g. novel hallucinogens, synthetic cannabinoids). ATS and NPS appellations are useful from a legal standpoint, but offer no scientific aid in investigating these agents [5].

Certain synthetic cathinones are now specifically controlled (U.S. Schedule I) by name, and include all the agents shown in Figure (1). Perhaps the most accurate information on synthetic cathinones, as a class of agents, will be with literature searches using the term “synthetic cathinones” rather than “ATSS” or “NPS”. Better yet, a specific chemical name should be employed in searching for a given agent. Unfortunately, searching for information about these agents using their “street names” often produces unreliable results because products with a common street name might contain different ingredients, or the same agents (or combinations) might be known by different names [5]. Indeed, Kesha et al. [6], have compiled a list of 98 street names that refer to bath salts ingredients. And, our guess is that many of these preparations have never been examined regarding their exact composition.

The pace at which new synthetic cathinones, and their ever-changing “street” nomenclature, are appearing on the clandestine market is taxing the ability of science and law enforcement to characterize and regulate these substances. In fact, so many synthetic cathinones have appeared (and a vastly greater number of agents are potentially possible), that it is becoming nearly impractical (i.e., too costly and/or too laborious) to study them on an agent-by-agent basis. We concede (and have suggested [5]) that an agent-by-agent investigation will be required to *thoroughly* understand an individual agent (e.g., pharmacology, behavioral actions, mechanism(s) of action, toxicity, metabolism, long-term effects). Nevertheless, we provide here a brief compendium of selected review articles that might assist those in the forensic (and other) sciences to quickly appreciate what is currently happening in this field and to identify specific references in which they might find useful state-of-the-art information (Table 1). Almost all references in Table (1) are to review articles or to manuscripts immanently germane to this area, and many deal with detection and detection techniques. Although not entirely devoted to synthetic cathinones, a recent 27-chapter book on novel drugs of abuse covers topics very pertinent to forensic scientists [7].

Mechanism(s) of Action

How do these synthetic cathinones act? Not a simple question. For the most part, synthetic cathinones act, variously, as substrates (i.e., as releasing agents) and/or as blockers (i.e., as uptake inhibitors) at dopamine, norepinephrine and/or serotonin transporters (DAT, NET, SERT, respectively). That is, dopamine, norepinephrine, and serotonin neurons possess membrane-spanning proteins (i.e., transporters) that regulate the concentration of synaptic neurotransmitter. Releasing agents, presumably by transporter reversal, increase synaptic neurotransmitter concentrations, whereas uptake inhibitors prevent their reuptake into presynaptic neurons and, thereby, also increase the synaptic concentration of a neurotransmitter. Consequently, the behavioral, and underlying mechanistic, actions of cathinone analogs, are not homogeneous and can vary from agent to agent depending upon its specific chemical composition (i.e., chemical structure), and depend on its function (release, uptake inhibition) and DAT/NET/SERT selectivity [5].

Thirty years ago, cathinone and methcathinone were found to act as amphetamine-like releasing agents at DAT [8].

Subsequently, *S*(-)-methcathinone, the behaviorally more potent optical isomer of methcathinone, was shown to act as a releasing agent at DAT, NET, and SERT with a potency and selectivity similar to *S*(+)-methamphetamine (i.e., DAT ≈ NET >> SERT) [9].

At the beginning of the *bath salts* era, two of the most prominent synthetic cathinones were mephedrone and MDPV. Mephedrone was found to act primarily (but not exclusively) as a releasing agent at DAT whereas MDPV was an uptake inhibitor at the same transporter [10-14]. That is, mephedrone and MDPV behave in an opposite manner at DAT (and NET). Like amphetamine and methamphetamine, mephedrone is a DAT releasing agent whereas, like cocaine, MDPV is an uptake inhibitor at DAT. Given a combination (i.e., ingestion) of both, mephedrone could increase synaptic concentrations of dopamine whereas MDPV then blocks its reuptake [5]. Because MDPV is at least 30- to 50-fold more potent than cocaine as a DAT uptake inhibitor, the combination of mephedrone and MDPV is likely akin to ingestion of methamphetamine followed by ingestion of cocaine - but, in a more potent fashion [12].

Synthetic cathinones can act as releasing agents at DAT, NET, and/or SERT, as uptake inhibitors at one or more of these same three transporters, or behave in a “hybrid” manner (i.e., acting as a releasing agent at one or two of these transporters, but as a reuptake inhibitor at one or more of the others) (Figure 2). Certain agents might also act somewhat selectively - as releasing agents at one or more of the two transporters while being inactive (or very nearly so) at another(s) (Figure 2). This implies a very complex mechanism(s) of action for the synthetic cathinones as a class. The mechanism(s) of action of a few synthetic cathinones has/have been investigated in detail; the mechanisms of action of most synthetic cathinones are still under investigation. To reiterate and re-emphasize a comment made above: *the behavioral and underlying mechanistic actions of synthetic cathinones are not homogeneous and can vary from agent to agent* [5]. Fortunately, some trends are beginning to emerge.

Structure-activity Relationships

Investigations of structure-activity relationships (SARs) are aimed at identifying the effect of chemical structure, and its alteration, on a particular pharmacological action by examining trends in the action of a series of related agents [4]. This is a

relatively straight-forward affair when members of a series can be related to each other, particularly by one structural change at a time, and the agents produce their effect through a single mechanism (e.g. activation or blockade of a specific protein target); that is, SAR studies question/identify how chemical structures of an agent influences its action (e.g. affinity, activation, antagonism) at a target protein. With synthetic cathinones, formulation of SAR is much more problematic. Common to the actions of synthetic cathinones is their interaction and action (i.e., function) at three major protein targets: the monoamine transporters (i.e., DAT, NET, SERT). But, they can act as releasing agents and/or as uptake inhibitors at each of the three target proteins (i.e., transporters in this case); see (Figure 2). What structural features are responsible for, or contribute to, the actions of synthetic cathinones to act as substrates/releasing agents or as uptake inhibitors/blockers of monoamine transporters, and what is their effect on an agent’s selectivity profile? The question is complex because we are dealing with the SAR of these agents i) to release neurotransmitter at DAT, NET, and/or SERT (i.e., the release of dopamine, norepinephrine, and serotonin, respectively), ii) to block uptake at DAT, NET, and/or SERT (i.e., to inhibit uptake of dopamine, norepinephrine, or serotonin, respectively), iii) to act via a combination of any of the above (i.e., release at one of more of these transporters vs. uptake inhibition at one or more transporters), and iv) inactivity at one or two of these transporters (resulting in selective or semi-selective agents) (see Figure 2). Each of these actions can, at least in theory, have their own SAR. This requires that each agent be investigated on an agent-by-agent basis. That is, unless some general SAR hypotheses can be formulated and guidelines generated.

Some agents are fairly selective (though most are not), as releasing agents or as uptake inhibitors, but many act at more than one transporter. At this time, i) more is known about the SAR of synthetic cathinones as releasing agents than as uptake inhibitors (and more is known about release of dopamine than norepinephrine and serotonin, at DAT, NET, and SERT, respectively), and ii) more is known about how these agents act at DAT as compared to NET or SERT. Some of this information is summarized in Figure (3).

Releasing agents: Synthetic cathinones bearing a primary

Transporter	Agent A	Agent B	Agent C	Agent D	Agent E	Agent F	Agent G
DAT	↓	↓	↓	↑	↑	↑	↑
NET	↓	↓	↑	↑	↑	↓	↑
SERT	↓	↑	↓	↑	↓	↑	--

Figure 2 In theory, synthetic cathinones (as well as other substances) can have one or more of multiple actions at the major monoamine transporters, DAT, NET, and SERT. ^aSeveral such actions are shown here; other scenarios are possible.

^aAgents might act as releasing agents (i.e., as substrates; ↓) or blockers (i.e., as inhibitors; ↑) of one or more transporters (i.e., Agents A-F). Some agents (e.g. Agent G) might be selective for one or more transporters as a substrate or inhibitor (only one example shown here); other scenarios are possible. Pharmacological action depends upon potency and function at each, as well as their selectivity.

amine (i.e., $R_1 = R_2 = H$; Figure 2) or a secondary amine where $R_1 = -CH_3$ and $R_2 = H$) typically act as releasing agents when R_3 is $-H$ or $-CH_3$. Aryl substitution (i.e., R, Figure 3) can modulate transporter selectivity. For example, methcathinone ($EC_{50} = 12$ nM and 3,869 nM at DAT and SERT, respectively, where EC_{50} is the drug concentration required to produce release that is 50% of maximum) displays > 200-fold selectivity for DAT, whereas mephedrone ($EC_{50} = 49$ nM and 118 nM at DAT and SERT, respectively) displays a little more than 2-fold selectivity; replacement of the 4- CH_3 group of the latter with a $-CF_3$ group ($EC_{50} = 2,700$ nM and 190 nM at DAT and SERT, respectively) results in reversal of selectivity with the latter agent being nearly 15-fold selective for SERT [15]. Clearly, very simple structural changes can have a substantial impact on the potency and selectivity of synthetic cathinones. Furthermore, a behavioral investigation of a series of several such agents (including those just mentioned) revealed that those synthetic cathinones with 4-position substituent's of low steric bulk display greater selectivity as DAT releasing agents, produce abuse-related facilitation of intracranial self-stimulation, and have high abuse potential, whereas those with bulkier 4-position substituent's display greater selectivity as SERT releasing agents, produce abuse-limiting depression of intracranial self-stimulation, and likely have lower clinical abuse potential [16].

Uptake inhibitors: A tertiary amine (or a bulky secondary amine) and/or an elongated α side chain, as found in MDPV and α -PVP, tend to favor action as uptake inhibitors at DAT (and NET) with reduced potency as uptake inhibitors at SERT, and little to no action as releasing agents [12,17,18]. The effect of aryl substituent's (i.e., R in Figure 3) has not been systematically investigated for DAT uptake inhibitors; however, such substituent's likely play a role in the actions of these agents. For example, as uptake inhibitors, MDPV is more potent at DAT ($IC_{50} = 4.1$ nM, where IC_{50} represents the drug concentration required to inhibit uptake by 50%) than at SERT ($IC_{50} = 3,349$ nM), whereas α -PVP (DAT $IC_{50} = 17.5$ nM) is inactive at SERT [17,18].

SAR and QSAR (quantitative structure-activity relationship) studies are beginning to have an impact [4,5]. Already there are indications of what structures might produce a specific transporter effect. QSAR studies attempt to identify

physicochemical properties of specific substituent's as to how they might contribute to SAR (i.e., what specific property of a substituent influences its action(s): electronic, steric, shape, bulk, length?). However, it is apparent that, although inroads are being made, much more work is needed here in order to accurately forecast the behavioral actions of various synthetic cathinones; that is, many of the newer synthetic cathinones have appended substituent's that variously influence potency, function, and selectivity at DAT, NET, and SERT [4,5], and it is difficult to predict which of the different combinations of substituent's predominate in their overall behavioral effects.

Forensic issues

Forensic scientists might be less interested in mechanisms of action and SAR than in issues such as drug detection (in biological and clandestinely-seized drug samples), detection methods and techniques, drug stability (under different detection procedures), drug metabolism and detection of metabolites (are the metabolites centrally-active? do they lead to/imply a specific illicit drug), adulterants, synthetic by-products, forensic toxicology, use and availability of applicable reference materials, and drug prevalence (i.e., topics discussed in many of the references provided in Table (1) should help here).

However, forensic chemists, forensic pathologists, or forensic toxicologists might sometimes be requested to provide evidence or testify in criminal cases involving "designer drugs", and synthetic cathinones are, by definition, designer drugs. Hence, forensic scientists might wish to be aware of issues beyond, for example, a particular assay method associated with the drug(s) they are examining (and, potential isomeric forms – geometric, stereochemical, or other isomers - some of which are Scheduled, and some which are not).

What is a designer drug? A designer drug is a chemical substance related to a currently controlled substance. The Controlled Substances Act, particularly with regard to "controlled analogs", includes such agents that are "intended for human consumption" [19]. Hence, if an agent is deliberately and explicitly marketed as "not for human consumption", does it fall under this regulation? This has been a problem here. New synthetic cathinones are appearing at a rapid rate and are typically

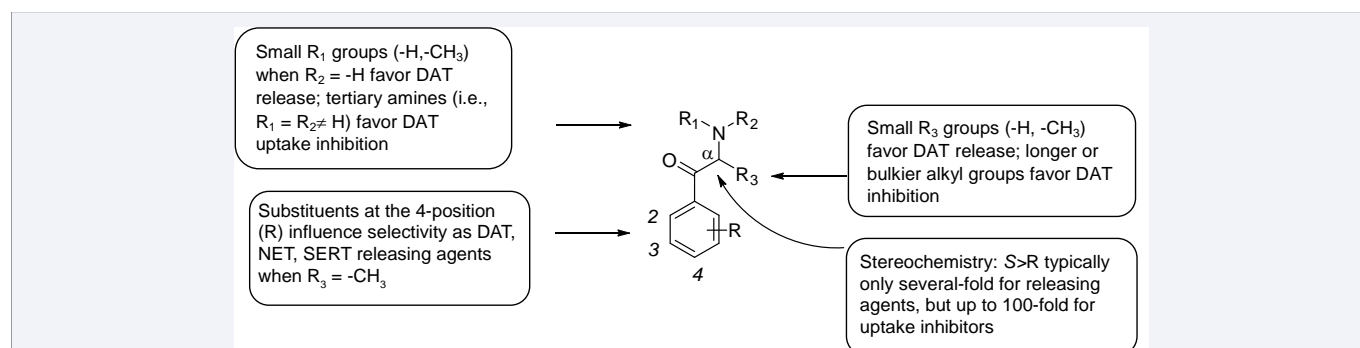


Figure 3 General structure-activity relationships of synthetic cathinones with a primary focus on release or uptake inhibition at the dopamine transporter (DAT). Recognize that different actions are possible: i) release of DA, NE, and/or 5-HT at DAT, NET, and SET, respectively, ii) uptake inhibition at the same three transporters, and iii) different actions (release of one or more) and reuptake inhibition (of one or more) of these neurotransmitters, the latter being termed "hybrid" transporter agents. The information shown here is based on what has been learned so far, but additional studies are required for further elaboration. See (Table 1) for reviews of SAR.

Table 1: Some key review articles covering various aspects of the synthetic cathinones.^a

Topic	Reference
Abuse liability	[23] [24]
Amphetamine analogs, corresponding	[5]
Behavior, animal	[5] [23] [25] [22]
Case reports	[6] [26-30]
Chemical structures	[4] [5] [26]
Degradation, thermal	[31]
Detection techniques	[31] [20] [32-38]
Detection in biological samples	[6] [29] [31] [38-41]
Doses, recreational	[27]
Fatalities and mortality	[26-29] [32]
History	[5] [23] [24] [26]
Mechanism(s) of action	[4] [5] [22] [23]
Nomenclature	[5] [23] [26]
Pharmacokinetics/ Metabolism	[5] [23] [26][30][34] [39] [42][44]
Pharmacology	[32]
Self-administration	[23]
Stability	[35] [36]
Structure-activity relationships (SAR)	[4] [5]
Subjective effects	[25] [26]
Toxicology and toxicity	[24] [22] [26] [27] [31] [32] [34] [38] [43] [44]
Treatment	[43]
Withdrawal	[43]

^a Many of the articles describe more than a single topic, or include topics not specifically listed here. Nevertheless, the references provided are a useful place to begin where a specific topic is of interest.

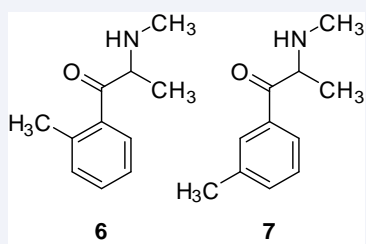


Figure 4 Positional (i.e., geometric) isomers of mephedrone (3; Figure 1): 2-methylmethcathinone (2-MMC; 6) and 3-methylmethcathinone (3-MMC; 7).

marketed as “not for human consumption”. Nevertheless, SAR, neurochemical, and preclinical behavioral studies suggest that many of the new synthetic cathinones possess abuse potential. This problem remains to be solved.

Various drugs of abuse are commonly identified by mass spectrometric (MS) techniques to determine their molecular weight. However, some caution should be exercised here. For example, according to MolPort (<https://www.molport.com/shop/molecular-formula/C10H13NO>, accessed February 13, 2017), there are 2,136 commercially available agents with the empirical formula $C_{10}H_{13}NO$ - the same empirical formula as

methcathinone. It is recommended that gas chromatography-mass spectrometry (GC-MS) be used in combination so that retention times as well as fragment ions and molecular weight be identified [20]. Case in point, mephedrone (i.e., 4-methylmethcathinone; 3, Figure 1), and its two positional isomers, 2-methylmethcathinone and 3-methylmethcathinone (6 and 7, respectively; Figure 4), have identical molecular weights and very similar MS fragmentation patterns (mephedrone is a controlled U.S. Schedule I substance; its isomers, 6 and 7 are not) however, they vary in their GC retention times. Proton NMR can also be used to distinguish between these positional (i.e., geometric) isomers [20].

Application of established SAR might also provide some insight and a unique perspective on how to view novel agents. For example, four of the 2,136 chemical agents with the empirical formula $C_{10}H_{13}NO$ are shown in Figure (5). These compounds might have been hypothetically encountered on the street or as by-products in the synthesis of an abused substance. There is no evidence of abuse (and even very few pharmacological studies) on compounds 8-10. They don't fit any SAR pattern for abused substances with cathinone-like properties [4]. In contrast, on the basis of established SAR [4,5], compound 11 might be expected to be a non-selective releasing agent at both DAT and SERT, but with a potency somewhat less than that of cathinone or methcathinone. Indeed, both optical isomers of 11 were synthesized and evaluated, and the neurochemical (i.e., DAT and SERT release) and behavioral (i.e., rodent intracranial self-stimulation) results were found to be consistent with what might have been expected [21]. So, here is an example of the application of SAR to forecast the action(s) (i.e., abuse potential) and approximate potency of a cathinone analog for which there was no prior scientific data.

Note: 4-Methylcathinone [22] (also known as nor-mephedrone), is a stimulant drug of the cathinone chemical class that has been sold online as a designer drug. It is the *N-des*-methyl metabolite of mephedrone. Little scientific documentation is available about this agent. But now, on the basis of our studies, data are available (see Hutsell et al. [21]).

CONCLUSIONS

The synthetic cathinones, that is - synthetic analogs of naturally-occurring cathinone, also known as β -ketoamphetamine - represent a large and growing class of abused substances.

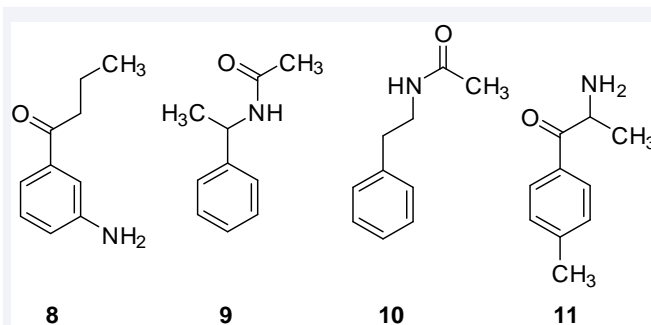


Figure 5 Four of 2,136 commercially available agents with an empirical formula identical to that of methcathinone (i.e. $C_{10}H_{13}NO$).

Similar to amphetamine, certain cathinone analogs act as releasing agents at DAT, NET, and SERT, but, some seem to act through one or more of these major monoamine transporters as releasing agents whereas others act as releasing agents and/or as uptake inhibitors, and with varying potency and selectivity for the transporters with which they interact. Their mechanisms of action are complex, and the pharmacology of the different agents can vary on almost an agent-by-agent basis (although this is to some extent an exaggeration - obviously, certain of these analogs are acting via a relatively common mechanisms, but, many different "mechanisms" are possible). It remains to be determined which agents do what. Efforts are now underway to understand these agents as a class by examining their SAR so as to group them into common-acting categories.

As noted in the article "Recommended Methods for the Identification and Analysis of Synthetic Cathinones in Seized Material": "Attention is . . . drawn to the vital importance of the availability to drug analysts of reference materials and literature on drugs of abuse and the analytical techniques used for their identification" [20]. Here, we provide, in Table (1), a compilation of review articles on the literature of synthetic cathinones and synthetic cathinone abuse, as well as references on analytical/detection techniques that have been employed, and on a number of other cathinone-relevant topics. Best-practices for detection are described. Most references are to "detection" and "sample preparation". But, the references include other information that might be of value, and perhaps of interest, to forensic scientists.

Transporter information, and particularly the results of SAR and QSAR studies with synthetic cathinones, might provide a new way of thinking about how this large class of abused substances act.

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Cite this article

Glennon RA, Dukat M (2017) Synthetic Cathinones: A Brief Overview of Overviews with Applications to the Forensic Sciences. *Ann Forensic Res Anal* 4(2): 1040.