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REVIEW ARTICLE

A narrative review of the neuropharmacology of synthetic cathinones—Popular alternatives to classical drugs of abuse

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Abstract

Objective: To review the literature on the neuropharmacology of synthetic cathinones.

Methods: A comprehensive literature search was carried out across multiple databases (mainly PubMed, World Wide Web, and Google Scholar) using relevant keywords.

Results: Cathinones exhibit a broad toxicological profile, mimicking the effects of a wide variety of 'classic drugs' such as 3,4-methylenedioxymethamphetamine (MDMA), methamphetamine and cocaine. Even small structural changes affect their interactions with key proteins. This article reviews existing knowledge of the mechanisms of action of cathinones at the molecular level, and key findings from research on their structure-activity relationship. The cathinones are also classified according to their chemical structure and neuropharmacological profiles.

Conclusions: Synthetic cathinones represent one of the most numerous and widespread groups among new psychoactive substances. Initially developed for therapeutic purposes, they quickly started to be used recreationally. With a rapidly increasing number of new agents entering the market, structure-activity relationship studies are valuable for assessing and predicting the addictive potential and toxicity of new and potential future substances. The neuropharmacological properties of synthetic cathinones are still not fully understood. A full elucidation of the role of some key proteins, including organic cation transporters, requires detailed studies.

KEYWORDS
monoamine transporters, neuropharmacology, NPS, organic cation transporters, SAR, synthetic cathinones

1 | INTRODUCTION

Cathinone (2-amino-1-phenylpropan-1-one) is an alkaloid naturally occurring in the khat shrub (*Catha edulis*) (Figure 1) (Kalix, 1984). As a β-ketone analogue of amphetamine, cathinone is called a 'natural amphetamine' due to its similar structure and stimulating effect (Kalix, 1992). Ephedrone (2-[methylamino]-1-phenyl-propan-1-one), an N-methyl derivative of cathinone first synthesised in 1928 by oxidising ephedrine (2-[methylamino]-1-phenylpropan-1-ol), is considered to be the first synthetic cathinone (SC) (Hyde et al., 1928). At present, SCs are one of the most important groups among the new psychoactive substances (NPSs), which are designed to resemble and provide a cheaper alternative to 'classic drugs' (EMCDDA, 2019). The European Monitoring Centre of Drugs and Drug Addiction's (EMCDDA) report indicates that at the end of 2021, out of the 880 monitored NPSs, as many as 162 were SCs, while in 2020 in Europe,

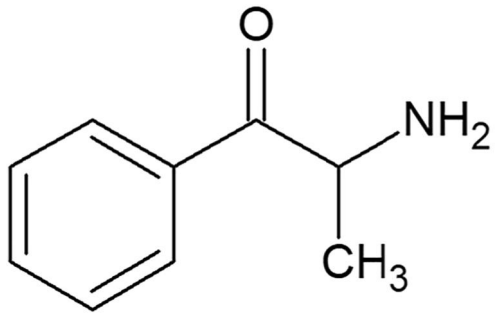

FIGURE 1 Chemical structure of cathinone.

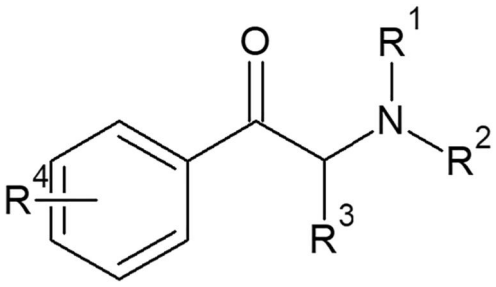

FIGURE 2 General structure of synthetic cathinones.

about two-thirds of the NPS seized material (more than 3 tons) were cathinone derivatives (EMCDDA, 2022). Meanwhile, globally, a total of 201 SCs were reported to the United Nations Office of Drugs and Crime's early earning advisory (UNODC EWA) at the end of 2021 (UNODC, 2022). Most of them are produced in China and other Asian countries and enter the market without any toxicological or pharmacological testing (EMCDDA, 2020). Such a product may contain many active substances of the same group or being a mixture of compounds of different chemical nature, which may lead to unintentional poisoning (German et al., 2014; Guirguis et al., 2017). There are numerous reports in the literature of severe and even fatal intoxications by SCs(Kraemer et al., 2019; la Maida et al., 2021; Loi et al., 2015; Pieprzyca et al., 2022). The number of new derivatives available on the market may continue to increase, therefore studying the properties of each individual structure and obtaining its complete toxicological profile is a laborious, time-consuming, and inefficient process. Research is ongoing to enable prediction of the pharmacological profiles of newly developed and potential future derivatives. This paper will review the chemical structure of SCs and the characteristics of their neuropharmacological action. It will also summarise the current knowledge on the activity of SCs depending on their chemical structure.

2 | CHEMICAL STRUCTURE OF SYNTHETIC CATHINONES

Chemically, all SCs are cathinone derivatives. They resemble amphetamine derivatives except that there is a carbonyl group in the β-position of the aminoalkyl chain. All possible derivatives are formed by attaching substituents to the basic cathinone structure at several typical positions (Figure 2) (Valente et al., 2014).

Structurally, cathinone derivatives can be classified into four groups (Table 1). Most of the initially synthesised ones (including those with therapeutic properties - bupropion [2-{tert-butylamino}-1-{3-chlorophenyl}propan-1-one] and diethylpropion [2-diethylamino-1-phenylpropan-1-one]) can be classified into the simplest group I. These are N-alkylated derivatives at the R1 position and/or at the R2 position. This group may contain substitution with an alkyl (usually methyl or ethyl) or halogen group at the R4 position (Figure 3). The SCs from group II are similar in structure to 3,4-methylenedioxymethamphetamine (MDMA), a popular amphetamine derivative. They are distinguished by a 3,4-methylenedioxy substituent at the R4 position (Figure 3). The SCs from group III have a pyrrolidine ring in place of the amino group and, similarly to the first group, their aromatic ring is sometimes substituted with alkyl or halogen groups (Figure 4). The last group is a combination of groups II and III. The SCs of this group are characterised by both the substitution of the aromatic ring with a 3,4-methylenedioxy group and the possession of a pyrrolidine ring (Valente et al., 2014). Groups III and IV are often referred to jointly as 'pyrovalerone derivatives' or 'pyrovalerones'. The derivatives of all groups have different alkyl chain lengths at the R3 position (Figure 4). There are also several derivatives that cannot be assigned to any of the groups. These are substances formed by replacing a phenyl group with another (thiophene or naphthyl) ring (Figure 3) (Gambaro et al., 2016; Valente et al., 2014). It is worth noting that the carbon atom to which the amino group is attached is the stereogenic centre of the molecule, but the vast majority of SCs products exist in racemic form (Simmons et al., 2018).

3 | MECHANISM OF ACTION OF SYNTHETIC CATHINONES

The intake of a cathinone affects neurotransmission in the brain that is dependent on monoamines (dopamine [DA], norepinephrine [NE], and serotonin [5-HT]), resulting in a psychostimulatory effect similar to that of amphetamine (Dal Cason et al., 1997; Kalix, 1992). This effect is primarily due to the ability of the stimulants to interact with membrane proteins present in neurons, which are called monoamine transporters (MATs) (Amara & Sonders, 1998; Rothman & Baumann, 2003; Simmler, 2018). There are three main types of MATs in the central nervous system: dopamine transporter (DAT), norepinephrine transporter (NET), and serotonin transporter (SERT). The role of these specialised proteins is to reuptake neurotransmitters from the synaptic cleft (released during signal transmission) back into the neuron. Under physiological conditions, this reuptake is the main mechanism that inactivates signalling (Amara & Sonders, 1998; Rothman & Baumann, 2003). Another important group of proteins involved in monoamine transport within the neuron are vesicular

TABLE 1 General structures of chemical groups of synthetic cathinones.

	R1/R2	R3	R4	Typical derivatives
Group I	Alkyl	Alkyl	Alkyl and/or halogen	Cathinone, mephedrone, bupropion, diethylpropion, ethcathinone, flephedrone
Group II	Alkyl	Alkyl	3,4-methylenedioxy	Methylone, ethylone, butylone, pentylone, ephylone
Group III	Pyrrolidinyl	Alkyl	Alkyl and/or halogen	α-PPP, α-PBP, α-PVP, α-PHP, pyrovalerone
Group IV	Pyrrolidinyl	Alkyl	3,4-methylenedioxy	MDPV, MDPPP, MDPBP

monoamine transporters (VMATs). VMATs are membrane proteins of synaptic vesicles and are responsible for the recapturing of monoamines from the cytoplasm into the vesicle. The interaction of MATs and VMATs determines the proper circulation and reuse of neurotransmitters (Figure 5). Many stimulants work by interacting with MAT and VMAT proteins (Amara & Sonders, 1998; Rothman & Baumann, 2003).

The interaction of SCs with MAT proteins may vary. Even small structural changes have a large impact on both potency and protein selectivity and therefore individual SCs exhibit different pharmacological effects, require different doses to induce a psychoactive response, and show different addictive potential (Glennon & Dukat, 2017; Luethi & Liechti, 2020). SCs can interact with MATs in two different ways. Some SCs act as inhibitors (blockers) by attaching to and blocking MATs. An increase in neurotransmitter concentration in the synaptic cleft is due to blockage of reuptake. Other SCs act as substrate-type releasers for MATs. These substrates are able to pass through MATs into the cell. In addition to competitive inhibition of reuptake, substrates reverse the standard direction of neurotransmitter flow. This can be facilitated by interaction with the VMAT protein. As a result of this interaction, the accumulation of neurotransmitters in synaptic vesicles is impaired, and subsequently the excess monoamines present in the cytosol are released from the cell by MATs. This creates a mechanism of monoamine release into the synaptic cleft that differs from the vesicular release. Whether an SC acts as a substrate-type releaser or blocker, the effect is similar—an increase in extracellular monoamine concentration and thus increased stimulation of the postsynaptic neuron (Figure 5) (Eshleman et al., 2013; Simmler, 2018; Simmler et al., 2013; Sitte & Freissmuth, 2015).

The pharmacological effects of most SCs are mainly due to an increase in extracellular concentrations of endogenous monoamines. Compared to amphetamines, SCs are less likely to interact with monoamine receptors (Eshleman et al., 2013; Rickli et al., 2015; Simmler, 2018; Simmler et al., 2014). For example, amphetamine-derived hallucinogens often interact directly with serotonin receptors activating them. In the case of SCs with serotonergic properties, their effects are not due to direct activation of receptors, but rather to indirect action by increasing endogenous 5-HT in the extracellular space. Some of them (especially the para-substituted ones) have the ability to bound to serotonin receptors, but they typically do not act as their functional agonists or antagonists and their influence on the final pharmacological effect is negligible due to their low binding affinities (Eshleman et al., 2013; Rickli et al., 2015; Simmler et al., 2014). There are, however, derivatives (including 2,3-dimethylmethcathinone [1-{2,3-dimethylphenyl}-2-{methylamino} propan-1-one] and mephedrone [2-methylamino-1-{4-methylphenyl} propan-1-one]), that in an in vitro activity test (calcium mobilisation assay) showed significant activation of hallucinogenic 5-HT_{2A} receptors equivalent to or stronger than MDMA (Luethi et al., 2018). These findings are consistent with observations of hallucinogenic properties induced in mephedrone users (Schifano et al., 2011). On the other hand, for other derivatives (α-PPP [1-phenyl-2-{1-pyrrolidinyl}-1-propanone] and 4-MePPP [1-{4-methylphenyl}-2-{1-pyrrolidinyl}-1-propanone]) micromole binding and antagonistic activity against the human 5-HT_{2A} receptor was demonstrated by in vitro radioligand competition binding assay and inositol monophosphate (IP-One) assay, and this for α-PPP was corroborated by in vivo studies (reduction of head-twitch response in mice induced by the 5-HT2A receptor agonist) (Chen et al., 2019). In another study involving α-PPP and 4-MePPP, as well as another two derivatives MPHP (1-[4-methylphenyl]-2-[1-pyrrolidinyl]-1-hexanone) and MDPPP (1-[3,4-methylenedioxyphenyl]-2-[1-pyrrolidinyl]-1-propanone), significant micromole binding to the human 5-HT_{2A} receptor was confirmed by radioligand binding assay, and was demonstrated by calcium assay that despite the binding, these SCs failed to activate these receptors (Kolaczynska et al., 2021). In addition, some SCs such show weak affinity for α_{1A}- and α_{2A}-adrenergic receptors, which are responsible for the sympathomimetic effects (Kolaczynska et al., 2021; Luethi et al., 2018). And on the other hand, α-PHP (1-phenyl-2-(pyrrolidin-1-yl)-hexan-1-one) in in vitro studies interacts antagonistically with another target by blocking human muscarinic receptors M_1 and M_2 and therefore has the potential to cause anticholinergic signs and symptoms (Chen & Canal, 2020). Interestingly, no in vitro studies to date have shown affinity for D_1, D_2 or D_3 receptors for any of the SCs, so their dopaminergic effects arise solely from their interaction with DAT (Kolaczynska et al., 2021; Luethi et al., 2018; Rickli et al., 2015; Simmler, 2018).

Another feature that distinguishes SCs from amphetamines is their negligible interaction with the trace amine associated receptor 1 (TAAR1). Activation of this receptor reduces the activity of dopaminergic neurones, thereby reducing psychostimulatory effects and addictive potential (Miller, 2011; Simmler et al., 2016). Amphetamines are potent agonists of this receptor, making them likely to self-inhibit their stimulating effects. In contrast, SCs show negligible activity towards TAAR1 (Kolaczynska et al., 2021; Rickli et al., 2015; Simmler et al., 2014, 2016). The two exceptions are 2,4-dimethylmethcathinone (1-[2,4-dimethylphenyl]-2-[methylamino]propan-1-one) and 2,3-dimethylmethcathinone, which in radioligand binding

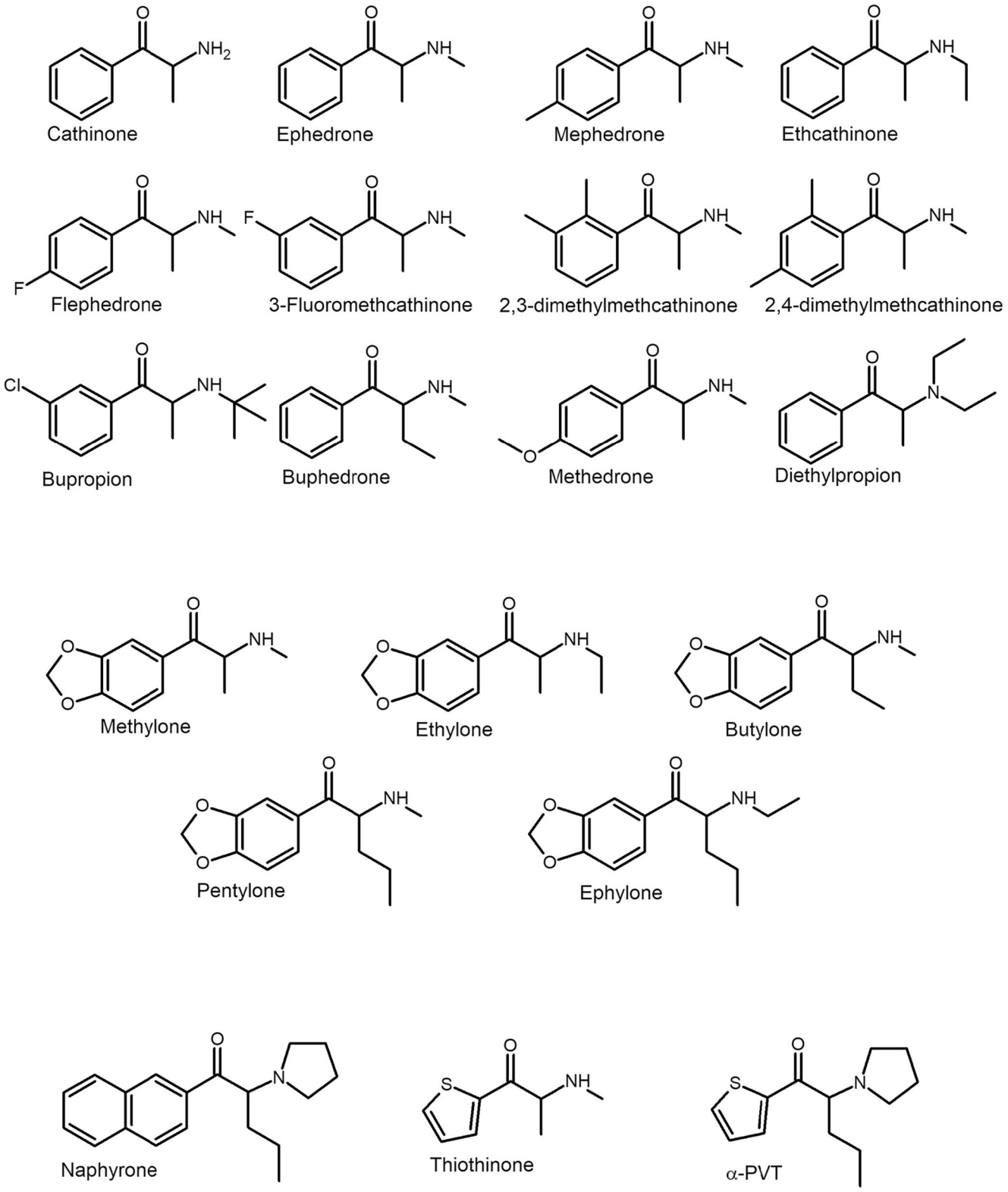

FIGURE 3 Chemical structures of cathinone derivatives of I, II and 'other' group.

assay have shown high affinity for rat and mouse TAAR1 receptor (Luethi et al., 2018). It is worth noting, however, that for TAAR1 there is considerable species variability in its interaction with ligands, and it is possible that the in vitro activity of these SCs may not translate into activity in the human body (Simmler et al., 2016). The lack of self-regulation by TAAR1 may partly explain the higher addictive potential of SCs compared to amphetamines (Miller, 2011; Simmler et al., 2013).

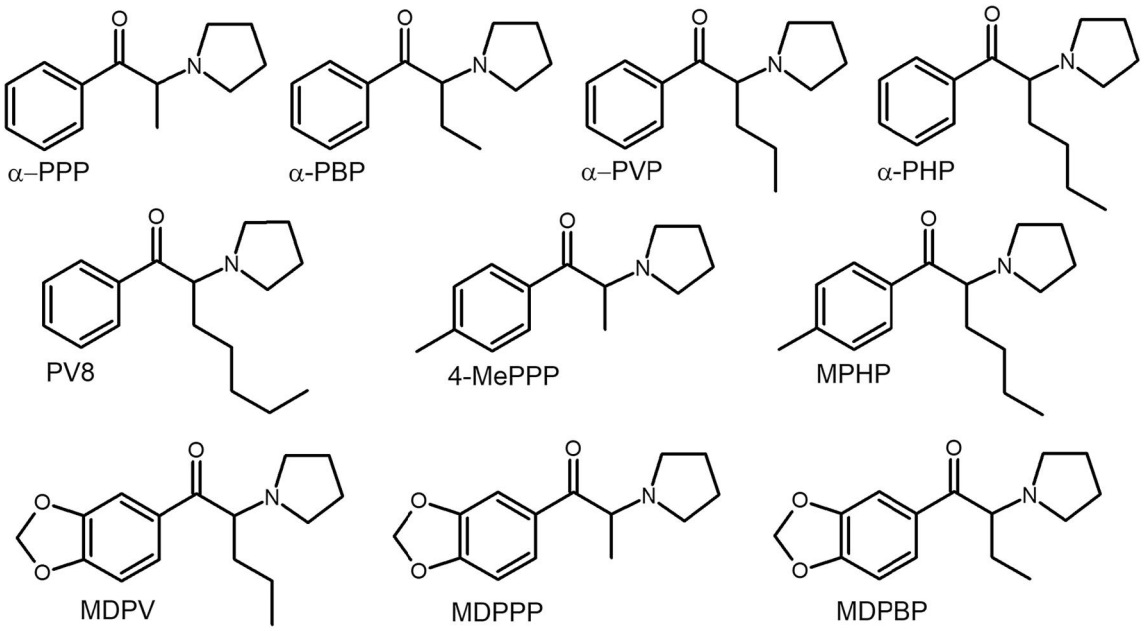

FIGURE 4 Chemical structures of cathinone derivatives of III and IV group.

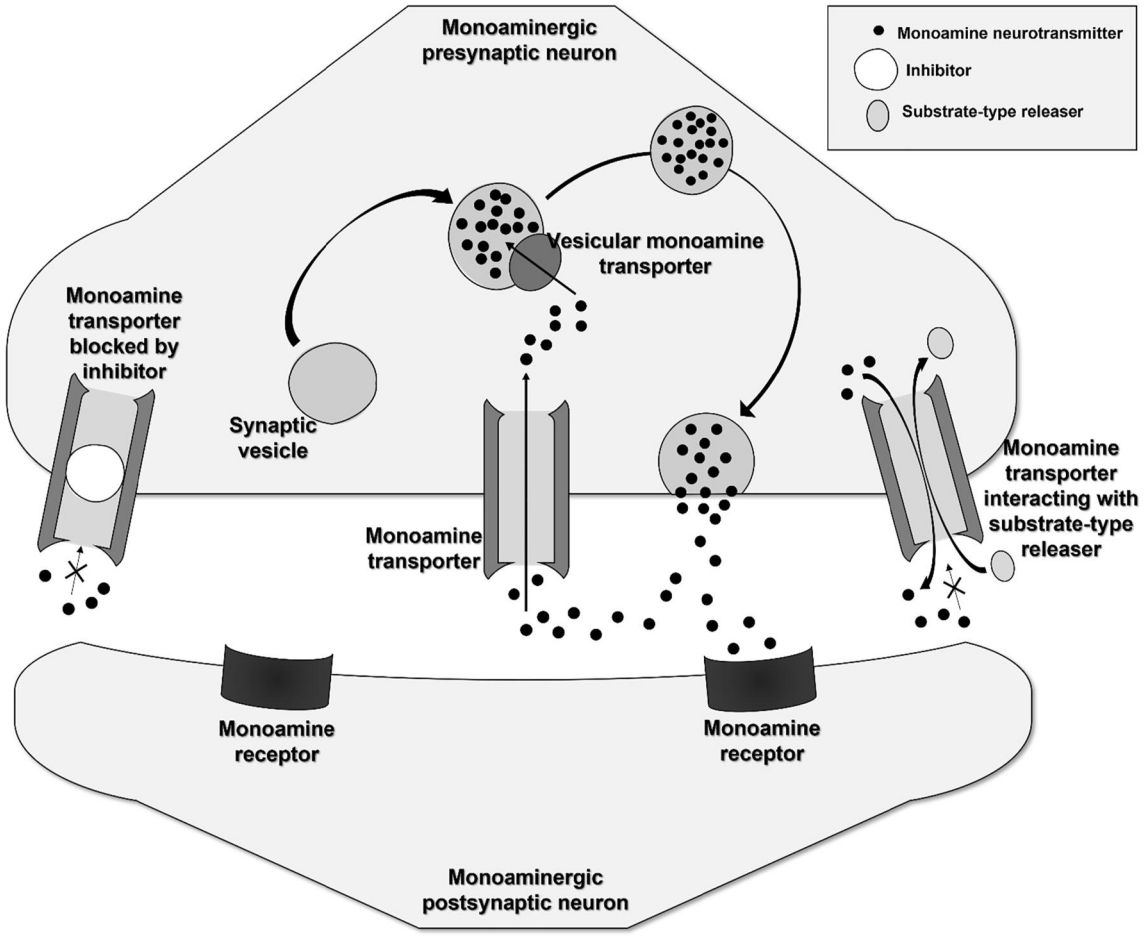

FIGURE 5 Synapse of monoaminergic neuron. Proper circulation of monoamine neurotransmitters is ensured by the coordinated work of monoamine transporter (MAT) and vesicular monoamine transporter proteins. Substrate-type releasers and inhibitors (blockers) disrupt the proper functioning of the MAT protein resulting in increased concentration of monoamines in the synaptic cleft.

An interesting neurochemical issue is the interaction between compounds acting as blockers and substrates. Substrates (e.g. mephedrone) use MAT proteins to release neurotransmitters, while inhibitors (e.g. MDPV [1-{1,3-benzodioxol-5-yl}-2-{pyrrolidin-1-yl} pentan-1-one]) prevent the transport of any compounds through MATs. It follows that simultaneous use of a substrate and a blocker should result in an antagonistic mechanism that lowers the mutual potency. Paradoxically, MDPV and mephedrone occur together in mixtures, and in addition they reinforce each other's effects, resulting in very strong stimulation. Simultaneous use of both SCs is reported by users, and studies in rodents involving simultaneous administration of the drugs have shown a significant increase in locomotor activity and additive effect compared to administering these drugs alone (Allen et al., 2019; Benturquia et al., 2019). Initially, on the basis of in vitro studies that examined the electrical currents conducted by DAT expressed in *Xenopus laevis* oocytes, the synergistic action of these two SCs was explained as follows: first, mephedrone was thought to induce reverse transport of monoamines through their transporters, and only then did MDPV prevent the reuptake of the released monoamines by blocking MATs (Cameron, Kolanos, Solis et al., 2013; Cameron, Kolanos, Verkariya et al., 2013). However, even at very low concentrations, MDPV shows such strong affinity for MATs that mephedrone is unlikely to be able to reverse monoamine transport in its presence; additionally, observations of locomotor activity in rats indicated only an additive interaction of these SCs(Baumann, Partilla, Lehner et al., 2013; Benturquia et al., 2019; Mayer et al., 2019). The explanation for this phenomenon can be found in the action of organic cation transporter (OCT) proteins. OCTs are a family of proteins responsible for endothelial transport of small, organic, hydrophilic, and positively charged molecules, including neurotransmitters and xenobiotics (Couroussé & Gautron, 2015). OCT3 is a protein present in the dopaminergic regions of the central nervous system, where it promotes DA reuptake when it is inhibited for high affinity transporters (DAT) (Couroussé & Gautron, 2015). Monoamines can also be released by OCTs. This bidirectional transport means that OCTs may play a significant role in the mechanisms of xenobiotics that stimulate the central nervous system, but a full explanation of their role requires a detailed study (Angenoorth et al., 2021; Gasser, 2019; Jensen et al., 2020; Koepsell, 2021; Maier et al., 2021). Ex vivo studies on superior cervical ganglia cells enriched in NET and OCT3 showed that in the presence of MDPV blocking MAT proteins, mephedrone causes neurotransmitter efflux through OCT3, which is insensitive to the inhibitory effects of MDPV. The release of monoamines through OCT3, a low-affinity transporter, presumably explains the paradoxical synergistic effects of inhibitors and substrates (Mayer et al., 2019).

4 | NEUROPHARMACOLOGICAL PROFILES OF SYNTHETIC CATHINONES

SCs can be divided into three main groups in terms of their relative inhibitory potency and the nature of interactions with MATs (Simmler et al., 2013, 2014). The effects produced by each group are compared to the neuropharmacological effects of classic, well-studied psychoactive substances: cocaine, MDMA, methamphetamine, and pyrovalerone. These reference substances have been the subject of extensive research for a long time, and the relationships between their in vitro properties and their effects on the organism as well as the induced clinical effect are well-known for them. Using an approach in which SCs are tested in parallel with known reference compounds, it is possible to achieve, based on the similarity obtained, a good estimate of how the in vitro properties of SCs translate into actual pharmacological properties. Most of the cathinone derivatives show similarly potent NET inhibition, therefore the main differentiating factor is the interaction with dopaminergic and serotoninergic systems (Eshleman et al., 2017; Simmler, 2018). Stimulation of individual systems translates into specific risks associated with the use of these substances (Table 2). SERT inhibitors are known to be entactogenic and induce serotonin syndrome. Noradrenergic stimulation results in sympathomimetic cardiac stimulation, and dopaminergic agitation strongly influences the addictive potential and reinforcing properties (Gannon, Baumann, et al., 2018; Simmler, 2018).

The effects produced by the SCs of the first group resemble both MDMA and cocaine. MDMA stimulates the release of 5-HT while inhibiting SERT and NET reuptake and is less potent in relation to DAT. It is therefore a good reference compound for SCs that have a particularly strong effect on the serotonergic and noradrenergic systems (Eshleman et al., 2017; Simmler et al., 2013, 2014). Cocaine acts entirely as a reuptake blocker, hence its action is not accompanied by neurotransmitter efflux through MATs. Blockage occurs with a similar potency for all three transporters (Rothman & Baumann, 2003). Therefore, the group of cathinones similar in action to both cocaine and MDMA are distinguished by their ability to release 5-HT, which results in signs and symptoms similar to those after the use entactogenic MDMA, while uptake inhibition of DAT and NET also results in the effects similar to those after taking cocaine (Simmler et al., 2013, 2014). Typical representatives of this group are methylone and mephedrone, which in in vivo discriminative-stimulus studies on rats and squirrel monkeys completely substituted in MDMA-trained individuals (Dolan et al., 2018; Wakeford et al., 2021). Other compounds in this group include, among others,

TABLE 2 Effects of stimulation of different monoaminergic systems (Assi et al., 2017; Liechti, 2015; Simmler, 2018; Soares et al., 2021).

Stimulated monoamine system	Clinical and toxic effects
Dopaminergic	Psychostimulant effects, high abuse and addiction potential, euphoria, locomotor activation, psychosis
Noradrenergic	Sympathomimetic effects, cardiostimulation and psychostimulation
Serotonergic	Entactogenic effects, hyperthermia, hyponatremia, hallucinations, seizures, reduced potential for addiction

ethylone (1-[1,3-benzodioxol-5-yl]-2-[ethylamino]propan-1-one) and butylone ([1,3-benzodioxol-5-yl]-2-[methylamino]butan-1-one) (Eshleman et al., 2017; Simmler, 2018).

Methamphetamine is a substrate for MATs and causes the release of DA and NE and, to a lesser extent, 5-HT. Therefore, the SCs of the second group, which are similar in action to methamphetamine, have a high addictive potential due to strong dopaminergic stimulation and produce similar toxic effects to those of methamphetamine and amphetamine (Rothman & Baumann, 2003; Simmler et al., 2013). These compounds are usually unsubstituted on the aromatic ring (or substituted with fluorine) and do not contain a pyrrolidine ring. A typical SC resembling methamphetamine in its effects is its β-ketone analogue: methcathinone. Methcathinone produces increased extracellular levels of DA in the rodent striatum, fully substitutes for the discriminative stimulus effects of methamphetamine in rodents and nonhuman primates and causes a dose-dependent increase in horizontal locomotor activity in rats. This effect however, is weaker when compared to pyrrolidine derivatives (Gatch et al., 2015; Wakeford et al., 2021; Wojcieszak et al., 2019). In addition to methcathinone, derivatives such as, cathinone, flephedrone (1-[4-fluorophenyl]-2-[methylamino]propan-1-one), ethcathinone (2-ethylamino-1-phenyl-propan-1-one), 3-fluoromethcathinone (1-[3-fluorophenyl]-2-[methylamino]propan-1-one), and buphedrone (2-[methylamino]-1-phenylbutan-1-one) belong to this group (Simmler, 2018; Simmler et al., 2014).

The third group of SCs, distinguished by the presence of a pyrrolidine ring, is comparable in action to pyrovalerone (1-[4-methylphenyl]-2-[1-pyrrolidinyl]pentan-1-one), a cathinone derivative already known since the 1960s (Goldberg et al., 1973; Simmler, 2018). The SCs of this group are extremely potent DAT and NET blockers, while having low affinity for SERT. In addition, they are considered to be completely incapable of releasing monoamines (Kolaczynska et al., 2021; Simmler et al., 2013). However, recent in vitro studies examining the efflux of radiolabelled monoamines in monoclonal human embryonic kidney (HEK) cell lines enriched in human NET suggest that some of the SCs, particularly a-PPP derivatives, may induce NE release through NET by acting as partial releasing agents (Maier et al., 2021). Pyrovalerones are highly lipophilic and studies in in vitro blood-brain barrier (BBB) models have shown that they cross the BBB more effectively compared to less lipophilic derivatives. However, more recent in vivo studies in rat brain tissue demonstrate the opposite relationship, and in general it is the more polar compounds that cross the BBB more effectively (Fabregat-Safont et al., 2020; Peters et al., 2016; Simmler et al., 2013). Nevertheless, SCs containing a pyrrolidine ring, presumably due to their lipophilicity, and due to high potency against DAT and NET, show high activity already at very low doses, which correlates with user-reported lower doses applied compared to other SCs(Kuropka et al., 2023; Simmler, 2018). SCs of this group have been shown to strongly stimulate rodent locomotor activity mediated by the dopamine D_1 receptor and cause increased levels of DA but, remarkably, also 5-HT in the mouse striatum. In vitro affinity studies indicate that pyrovalerones should not interact with SERT and should not cause 5-HT release, therefore the observed elevated 5-HT concentration can presumably be explained by the functional coupling of dopaminergic and serotonergic systems. In the case of high extracellular DA concentrations, the phenomenon of its uptake by SERT is observed, accompanied by a concomitant SERT-mediated release of 5-HT (Larsen et al., 2011; Simmler, 2018; Wojcieszak Andrzejczak et al., 2020; Wojcieszak et al., 2018). Interestingly, recent studies in mice have shown that SCs possessing a pyrrolidine ring, unlike SCs of the second methamphetamine-like group, cause, in addition to horizontal, also vertical increased dose-dependent locomotor activity. The increased vertical locomotor activity is presumably indicative of particularly potent and selective dopaminergic stimulation and anxiety reduction in contrast to derivatives such as those of the second methamphetamine-like group (Wojcieszak, Andrzejczak, et al., 2020; Wojcieszak et al., 2018, 2019; Wojcieszak, Kuczyńska, & Zawilska, 2020). Popular compounds in this group include, among others, PV8 (1-Phenyl-2-pyrrolidin-1-ylheptan-1-one), MDPV, and α-PVP (1-phenyl-2-[1-pyrrolidinyl]-1-pentanone) (Simmler, 2018; Simmler et al., 2013).

5 | STRUCTURAL DETERMINANTS OF THE ACTIVITY OF SYNTHETIC CATHINONES

The effects of SCs are evaluated and predicted using the structure–activity relationship (SAR) method. Such studies focus on single structural changes to observe trends and relationships in changes in activity towards selected proteins (Glennon & Dukat, 2017). The complexity of SAR studies is influenced by differences in the nature and strength of independent interactions of SCs with three MAT proteins. Some SCs act selectively on only one or two transporters while being inactive on the others, whereas others show a hybrid character by acting as a DAT inhibitor and SERT substrate (Glatfelter et al., 2021; Nadal-Gratacós et al., 2021; Saha et al., 2019).

The most important factors determining whether a derivative acts as a substrate or blocker are the size and the number of the amine substituents. As the size and number of the amine substituents increases, potency of blocking action increases as well (Glennon & Dukat, 2017). Tertiary amines and secondary amines with bulky substituents show strong inhibition of MATs and do not stimulate the release of neurotransmitters into the synaptic cleft. On the other hand, primary amines or secondary amines with small substituents act mainly as substrates and simultaneously cause the release of monoamines (Glennon & Dukat, 2017). However, increasing the size of amine substituents does not always lead to an increase in the inhibitory potency. In radioligand uptake studies on rat synaptosomes, it was shown that in vitro inhibition of DA reuptake by human DAT is stronger when the N-methyl group is replaced by an N-ethyl group, but decreases when the pyrrolidine moiety is replaced by a more bulky piperidine ring or diethyl group. Additionally, these observations were shown to be consistent with molecular docking studies (Duart-Castells et al., 2021; Kolanos, Sakloth, et al., 2015; Nadal-Gratacós et al., 2021). Another factor affecting the inhibitory

potency is the elongation of the alkyl side chain at the α-carbon. Radioligand binding and uptake assays using HEK cell lines transfected with human MATs have shown that lengthening the side chain from one to five carbon atoms increases DAT inhibition by up to 100-fold (Eshleman et al., 2017, 2019; Kolanos, Sakloth, et al., 2015; Saha et al., 2019; Zwartsen et al., 2020). It should be noted, however, that in vivo locomotor activity studies have shown that side-chain elongation increases SC potency in mice only up to a certain point. PV8 and PV9 having 5- and 6-carbon side chains respectively, exhibit weaker potency than the 3-carbon α-PVP, as supported by reports from users of these substances, and such an effect may presumably be due to different pharmacokinetic properties of the more lipophilic and bulkier derivatives (Wojcieszak et al., 2018). Interestingly, in recent years, most of the popular SCs have had an elongated carbon side chain (Kuropka et al., 2023; Majchrzak et al., 2018).

One of the most popular 'first generation' SCs was MDPV, a potent blocker distinguished by the presence of a pyrrolidine ring (Simmler et al., 2013). In 2013, MDPV was 'deconstructed' to assess which substituents and to what extent determine the inhibitory potency towards DAT. For this purpose, the electrophysiological voltage clamp experiment in response to MDPV and its derivatives was used with *Xenopus laevis* oocytes expressing human DAT, as well as a radiolabelled monoamines uptake inhibition assay with HEK cells enriched with human DAT (Kolanos et al., 2013). Studies showed that depriving a derivative of the β-ketone group results in a several-fold decrease in inhibitory potency towards DAT and an increase in potency towards SERT, which is consistent with the observation that amphetamine analogues of SCs are less potent inhibitors of DAT (Kolanos et al., 2013; Simmler, 2018; Simmler et al., 2014). In the case of pyrovalerones, the presence of the 3,4-methylenedioxy group has a negligible effect on their potency towards DAT. Without this group, α-PVP is as potent in vitro DAT blocker as MDPV(Kolaczynska et al., 2021; Kolanos et al., 2013; Rickli et al., 2015). On the other hand, the length of the alkyl chain at the α-carbon has a huge impact on the inhibitory potency of derivative. Shortening of the MDPV side chain by 2 carbon atoms results in more than 25-fold reduction in potency (Kolanos et al., 2013). Replacing the pyrrolidine ring with a less bulky N,N-dimethyl group reduces the inhibitory potency by about 5-fold (Kolanos et al., 2013). Reducing the number of amine substituents from tertiary to secondary and primary also significantly reduces the inhibitory potency of DAT. It is worth noting, however, that both long chain alkyl primary amines as well as short chain alkyl tertiary amines continue to act as MAT blockers, although the strongest effect is shown by tertiary amines simultaneously having an extended carbon side chain. Inverting this relationship, derivatives without N-substituents and without an extended carbon side chain act as MAT substrates (Kolanos et al., 2013; Kolanos, Sakloth, et al., 2015).

Despite its great usefulness, caution should be exercised when drawing conclusions from SAR studies. These studies are carried out in vitro or on rodents, which may interfere with the direct translation of the results of research into the actual action of these drugs in the human body. It is also important to bear in mind the impact of interactions with other proteins such as VMATs and OCTs. Furthermore, studies may not take into account pharmacokinetic factors affecting the activity of these compounds such as absorption, metabolism and the ability to cross the BBB(Eshleman et al., 2019; Glennon & Dukat, 2017).

A useful parameter for comparing the mode of action of SCs is the relative selectivity ratio of DAT uptake inhibition potency to SERT uptake inhibition potency (Table 3). The DAT/SERT ratio, calculated as 1/DAT IC_{50}:1/SERT IC_{50}, takes a wide range of values where high values indicate greater selectivity for DAT, and low values for SERT (Liechti, 2015; Luethi & Liechti, 2020; Simmler et al., 2013). A DAT/SERT selectivity ratio <0.1 indicates an MDMA-like (MDMA's DAT/SERT = 0.08) entactogenic effect, and a high value of this ratio (>10) is associated with a strong addictive potential and methamphetamine-like (methamphetamine's DAT/SERT = 22) psychostimulant effect (Liechti, 2015; Luethi & Liechti, 2020; Simmler et al., 2013, 2014). The highest value of this coefficient is found in highly addictive pyrovalerones, where it can reach several thousand (Gannon, Baumann, et al., 2018; Liechti, 2015). The DAT/SERT ratio is close to one in SCs showing moderate addiction potential and cocaine-like effects (cocaine's DAT/SERT = 3.1) (Liechti, 2015; Luethi & Liechti, 2020; Simmler et al., 2013).

In some cases, the DAT/SERT ratio has limited applicability because some derivatives may exhibit different properties at a comparable DAT/SERT ratio values. SCs with similar values may have different substrate/blocker performance characteristics. Methylone analogues differing in alkyl chain length have similar DAT/SERT ratios, however chain lengthening causes DAT substrates to change their nature into blockers while retaining their activity as substrates for SERT (Eshleman et al., 2013, 2017; Saha et al., 2019). Both pentylone and butylone induce increased in vivo concentrations of DA and 5-HT in the extracellular space in the nucleus accumbens in rats. Pentylone, however, acts primarily as a DAT blocker and results in greater DA levels compared to 5-HT, while butylone, which has a side chain one carbon atom shorter, is primarily a potent SERT substrate and results mainly in increased 5-HT relative to DA. As a result, pentylone's effects are similar to those of the dopaminergic methamphetamine and, in rats, exhibits stronger locomotor activity stimulation, while butylone's effects are more similar to the entactogenic MDMA and displays less reinforcing effects (Dolan et al., 2018; Javadi-Paydar et al., 2018; Saha et al., 2019).

Stereoisomerism also has a major impact on the action of SCs. In the case of SCs with a pyrrolidine ring such as MDPV and α-PVP, their S stereoisomers are many times more potent than the *R* stereoisomers (Glennon & Dukat, 2017; Kolanos, Partilla, et al., 2015; Nelson et al., 2019). In rat studies (S)-α-PVP displayed at doses 30 times lower than (R)-α-PVP the same increased locomotor activity and cardiovascular effects and demonstrated in microdialysis studies the same increased extracellular dopamine concentration in the nucleus accumbens (Schindler et al., 2020). Accordingly, equally large differences were shown for MDPV enantiomers where (S)-MDPV caused many times stronger locomotor activity in rats, as well as

TABLE 3 DAT/SERT selectivity ratio data for synthetic cathinones.

Name	R_1	R_2	R_3	R_4	Chemical group	Selectivity DAT/SERT	Data from
Cathinone	-H	-H	-methyl	-	-	>10	1
Ephedrone	-methyl	-H	-methyl	-	1	140	2
Mephedrone	-methyl	-H	-methyl	-4-methyl	1	5	3
3-Methylmethcathinone	-methyl	-H	-methyl	-3-methyl	1	10	4
4-Ethylmethcathinone	-methyl	-H	-methyl	-4-ethyl	1	0.1	5
Buphedrone	-methyl	-H	-ethyl	-	1	25	6
Pentedrone	-methyl	-H	-propyl	-	1	50	2
4-Methylpentedrone	-methyl	-H	-propyl	-4-methyl	1	3	4
4-Methyl-N-ethylpentedrone	-ethyl	-H	-propyl	-4-methyl	1	6	4
N-Propyl pentedrone	-propyl	-H	-propyl	-	1	330	4
4-Chloropentedrone	-methyl	-H	-propyl	-4-Cl	1	1	4
N-Ethylhexedrone	-ethyl	-H	-butyl	-	1	100	4
Mexedrone	-methyl	-H	-methoxymethyl	-	1	2	4
Brephedrone	-methyl	-H	-methyl	-4-Br	1	1	2
Clephedrone	-methyl	-H	-methyl	-4-Cl	1	3	2
Flephedrone	-methyl	-H	-methyl	-4-F	1	>36	3
3-Fluoromethcathinone	-methyl	-H	-methyl	-3-F	1	60	2
Ethcathinone	-ethyl	-H	-methyl	-	1	10	7
4-Chloroethcathinone	-ethyl	-H	-methyl	-4-Cl	1	0.4	4
4-MEC	-ethyl	-H	-methyl	-4-methyl	1	0.2	2
Methedrone	-methyl	-H	-methyl	-4-methoxy	1	0.1	7
N,N-Dimethylcathinone	-methyl	-methyl	-methyl	-	1	>10	7
2,3-Dimethylmethcathinone	-methyl	-H	-methyl	-2-methyl, -3-methyl	1	0.2	8
2,4-Dimethylmethcathinone	-methyl	-H	-methyl	-2-methyl, -4-methyl	1	0.02	8
3,4-Dimethylmethcathinone	-methyl	-H	-methyl	-3-methyl, -4-methyl	1	0.1	8
Methylone	-methyl	-H	-methyl	−3,4-methylenodioxy	2	6	3
Dimethylone	-methyl	-methyl	-methyl	−3,4-methylenodioxy	2	>4	4
Ethylone	-ethyl	-H	-methyl	−3,4-methylenodioxy	2	0.3	2
Butylone	-methyl	-H	-ethyl	−3,4-methylenodioxy	2	9	3
Dibutylone	-methyl	-methyl	-ethyl	−3,4-methylenodioxy	2	>32	4
Pentylone	-methyl	-H	-propyl	−3,4-methylenodioxy	2	5	2
Dipentylone	-methyl	-methyl	-propyl	−3,4-methylenodioxy	2	11	4
N-Ethylpentylone	-ethyl	-H	-propyl	−3,4-methylenodioxy	2	8	4
Pyrovalerone	-Pyrrolidinyl		-propyl	-4-methyl	3	>100	1
α-PVP	-Pyrrolidinyl		-propyl	-	3	2900	2
4-F-PVP	-Pyrrolidinyl		-propyl	-4-F	3	360	4
4-Cl-PVP	-Pyrrolidinyl		-propyl	-4-Cl	3	80	4
4-MeO-PVP	-Pyrrolidinyl		-propyl	-4-methoxy	3	40	2
α-PPP	-Pyrrolidinyl		-methyl	-	3	350	2
4-Me-PPP	-Pyrrolidinyl		-methyl	-4-methyl	3	20	2

(Continues)

TABLE 3 (Continued)

Name	R_1 R_2	R_3	R_4	Chemical group	Selectivity DAT/SERT	Data from
4-Cl-PPP	-Pyrrolidinyl	-methyl	-4-Cl	3	10	4
α-PBP	-Pyrrolidinyl	-ethyl	-	3	860	2
α-PHP	-Pyrrolidinyl	-butyl	-	3	1850	2
4-F-PHP	-Pyrrolidinyl	-butyl	-4-F	3	240	4
4-Me-PHP	-Pyrrolidinyl	-butyl	-4-methyl	3	120	4
PV8	-Pyrrolidinyl	-pentyl	-	3	1850	2
MDPPP	-Pyrrolidinyl	-methyl	−3,4-methylenodioxy	4	30	2
MDPBP	-Pyrrolidinyl	-ethyl	−3,4-methylenodioxy	4	50	2
MDPV	-Pyrrolidinyl	-propyl	−3,4-methylenodioxy	4	110	3
MDPHP	-Pyrrolidinyl	-butyl	−3,4-methylenodioxy	4	160	4
Naphyrone	-Pyrrolidinyl	-propyl	Naphtyl ring	Other	5	3
TH-PVP	-Pyrrolidinyl	-propyl	Tetralin ring	Other	0.1	4
α-PVT	-Pyrrolidinyl	-propyl	Thiophene ring	Other	710	2

Note: Selectivity DAT/SERT = 1/DAT IC50: 1/SERT IC50. IC50 is a concentration of tested drug at which the transporter is inhibited by 50%. Some values have been rounded off. Data: 1—(Simmler et al., 2013), 2—(Eshleman et al., 2017), 3—(Eshleman et al., 2013), 4—(Eshleman et al., 2019), 5—(Rickli et al., 2015) 6—(Liechti, 2015), 7—(Simmler et al., 2014), 8—(Luethi et al., 2018).

increased blood pressure and heart rate than (R)-MDPV(Gannon et al., 2016; Schindler et al., 2016). In addition, a similar difference in self-administration assay under a progressive ratio schedule occurred in potency between (S)-MDPV and (R)-MDPV(Gannon et al., 2017). The impact of stereochemistry is more complex for substances that are transporter substrates. It affects not only their potency but also the selectivity of DAT/SERT inhibition (Glennon & Dukat, 2017). In the case of mephedrone, the stereoisomers do not show much difference in potency as DAT substrates; however, the *R* isomer is selective for DAT, while the S isomer does not show such selectivity and also interacts as a SERT substrate. The selectivity of (R)-mephedrone and its lack of serotonergic properties translates into a more stimulatory profile compared to (S)-mephedrone, which for the *R* stereoisomer in rat studies was reflected in greater locomotor activity, displayed conditioned place preference and greater facilitation of intracranial self-stimulation than for the S stereoisomer (Glennon & Dukat, 2017; Gregg et al., 2015). Nevertheless, it should be noted that SAR studies are mainly performed on racemic mixtures of SCs, as this is the form in which they are sold and used (Simmler, 2018).

For substrate-type releasers, the type of substituent at the aromatic ring, its position, and the ability to withdraw electrons are of great importance (Blough et al., 2019; Bonano et al., 2015; Eshleman et al., 2019). The DAT/SERT selectivity ratio can be controlled by the position of the substituents. In vitro radioligand assay studies on rat synaptosomes have shown that para-substituted derivatives are much more potent on SERT than their ortho- and meta-substituted counterparts (Suyama et al., 2016; Walther et al., 2019). Ortho-derivatives show mainly dopaminergic activity, meta-derivatives show lower DAT/SERT ratios, and para-derivatives are characterised by serotonergic activity (Blough et al., 2019; Grifell et al., 2017; Walther et al., 2019). The DAT/SERT selectivity ratio for the unsubstituted ephedrone is over 300, while methedrone having a methoxy substituent at the para position interacts fourfold more strongly with SERT than with DAT, thus presumably exhibiting entactogenic effects similar to MDMA (Simmler et al., 2014; Suyama et al., 2016; Walther et al., 2019). Disubstituted derivatives and derivatives with sterically expanded substituents at the phenyl ring favour interaction with SERT (Blough et al., 2019). For SCs without a pyrrolidine group, substitution of the aromatic ring with a 3,4-methylenedioxy group favours SERT inhibition (Bonano et al., 2015; Nadal-Gratacós et al., 2021). However, the resulting effect may not always be significant, as pentylone and its analogue lacking the 3,4-methylenedioxy moiety, pentedrone, in rats demonstrate only a small difference in behavioural effects, as locomotor activity, and reinforcing effects determined using the intravenous self-administration technique (Javadi-Paydar et al., 2018). On the other hand, pyrovalerone derivatives with the 3,4-methylenedioxy- group show only a slightly greater in vitro ability to inhibit SERT than those without this group (Kolaczynska et al., 2021).

In conclusion, SAR studies are a valuable tool for assessing the toxicological profiles of SCs. The large number of possible compounds makes systemic studies on the structure-activity relationship a great help in predicting and evaluating the properties of newly developed compounds. The type and strength of interactions between SCs and a particular protein translates into the effects, signs and symptoms, and type of poisoning. The relationships found allow a comparison of the mechanisms of action and toxicities of similar cathinone derivatives and reference compounds based on structure alone.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ETHICS STATEMENT

This article does not contain any studies with human participants or animals performed by any of the author.

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