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# Effect fingerprinting of new psychoactive substances (NPS): What can we learn from *in vitro* data?

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ABSTRACT

The use of new psychoactive substances (NPS) is increasing and currently > 600 NPS have been reported. However, limited information on neuropharmacological and toxicological effects of NPS is available, hampering risk characterization.

We reviewed the literature on the *in vitro* neuronal modes of action to obtain effect fingerprints of different classes of illicit drugs and NPS. The most frequently reported NPS were selected for review: cathinones (MDPV, α-PVP, mephedrone, 4-MEC, pentedrone, methylone), cannabinoids (JWH-018), (hallucinogenic) phenethylamines (4-fluoroamphetamine, benzofurans (5-APB, 6-APB), 2C-B, NBOMes (25B-NBOMe, 25C-NBOMe, 25I-NBOMe)), arylcyclohexylamines (methoxetamine) and piperazine derivatives (mCPP, TFMPP, BZP).

Our effect fingerprints highlight the main modes of action for the different NPS studied, including inhibition and/or reversal of monoamine reuptake transporters (cathinones and non-hallucinogenic phenethylamines), activation of 5-$HT_2$receptors (hallucinogenic phenethylamines and piperazines), activation of cannabinoid receptors (cannabinoids) and inhibition of NDMA receptors (arylcyclohexylamines). Importantly, we identified additional targets by relating reported effect concentrations to the estimated human brain concentrations during recreational use. These additional targets include dopamine receptors, α- and β-adrenergic receptors, $GABA_A$receptors and acetylcholine receptors, which may all contribute to the observed clinical symptoms following exposure.

Additional data is needed as the number of NPS continues to increase. Also, the effect fingerprints we have obtained are still incomplete and suffer from a large variation in the reported effects and effect sizes. Dedicated *in vitro* screening batteries will aid in complementing specific effect fingerprints of NPS. These fingerprints can be implemented in the risk assessments of NPS that are necessary for eventual control measures to reduce Public Health risks.

*Abbreviations:* 2C-B, 2,5-Dimethoxy-4-bromophenethylamine; 4-FA, 4-Fluoroamphetamine; 4-MEC, 4-Methylethcathinone; 4-MMC, 4-Methylmethcathinone, a.k.a. mephedrone; 5-APB, 5-(2-Aminopropyl)benzofuran; 6-APB, 6-(2-Aminopropyl)benzofuran; 5-HT, Serotonin; 25B-NBOMe, 4-Bromo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine; 25C-NBOMe, 4-Chloro-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine; 25I-NBOMe, 4-Iodo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine; α-PVP, 1-Phenyl-2-(1-pyrrolidinyl)-1-pentanone, a.k.a. Flakka; ACh, Acetylcholine; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BPF, Brain partitioning factor; BZP, 1-Benzylpiperazine; CB, Cannabinoid; COMT, Catechol-*O*-methyltransferase; DA, Dopamine; $EC_{50}$, Drug concentration that induces a half-maximal response; EMCDDA, European Monitoring Centre for Drugs and Drug Addiction; EU, European Union; EWS, Early Warning System; GABA, γ-Aminobutyric acid; GPCR, G-protein coupled receptor; (h)DAT, (human) Dopamine reuptake transporter; (h)NET, (human) Norepinephrine reuptake transporter; (h)SERT, (human) Serotonin reuptake transporter; $IC_{50}$, Drug concentration that inhibits the response by 50%; JWH-018, 1-pentyl-3-(1-naphthoyl) indole; MAO-A, Monoamine oxidase A; mACh-R, Muscarinic acetylcholine receptor; mCPP, 1-(3-Chlorophenyl)piperazine; MDMA, 3,4-Methylenedioxymethamphetamine; MDPV, 3,4-Methylenedioxypyrovalerone; MXE, Methoxetamine ((RS)-2-(ethylamino)-2-(3-methoxyphenyl)cyclohexanone; nACh-R, Nicotinic acetylcholine receptor; NE, Norepinephrine; NMDA, *N*-methyl-D-aspartate; NPS, New psychoactive substance; PCP, 1-(1-Phenylcyclohexyl)piperidine, a.k.a. phencyclidine; TFMPP, 1-(3-Trifluoromethyl)phenylpiperazine; THC, Tetrahydrocannabinol; UNODC, United Nations Office on Drugs and Crime; VGCCs, Voltage-gated calcium channels

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## 1. Introduction

The use of illicit drugs is high; around 5% of the adult population worldwide used an illicit drug in the last year (World Drug Report, 2016). The prevalence of last year illicit drug use in specific populations can be much higher compared to the overall adult population. For example, the prevalence of last year drug use in Dutch young adults (15-35 years) who went to clubs, parties or festivals in the last year, was reported to be 61% for ecstasy, 52% for cannabis, 33% for speed and 27% for cocaine (Monshouwer, van der Pol, Drost, & van Laar, 2016). Cannabis, cocaine, ecstasy (active substance often 3,4-methylenedioxymethamphetamine (MDMA)) and amphetamines are also worldwide the most frequently used illicit drugs (EMCDDA, 2016b).

While the use of these common illicit drugs appears to decrease slightly (World Drug Report, 2015), more and more new psychoactive substances (NPS) are entering the drug market. NPS are a chemically diverse class of substances that often induce effects comparable to common illicit drugs. NPS are also known as synthetic drugs, legal highs, bath salts, research chemicals and are even advertised as plant fertilizers. The most commonly used definition of NPS is *'a new narcotic or psychotropic drug, in pure form or in preparation, that is not controlled by the United Nations drug conventions, but which may pose a public health threat comparable to that posed by substances listed in these conventions'* (EMCDDA, 2016a). These conventions date back to 1961 and 1971 and the term 'new' does not necessarily refer to newly developed drugs, since several NPS were first synthesized as pharmaceutical candidates already 40 years ago. 'New' rather refers to substances that have recently (re)emerged on the drug market and have not been scheduled under the drug conventions (UNODC, 2013).

Currently, over 700 different NPS have been reported to monitoring centers worldwide and around 5% of the European population has used a NPS during the last year (World Drug Report, 2017). While NPS use appears comparable to the use of common illicit drugs, the last year prevalence of use for NPS differs strongly between European countries, for example, it was 31% in Poland and only 1% in Switzerland (Global Drug Survey, 2015). Also, for specific NPS and specific populations, the last year prevalence of use is as high as that of common illicit drugs. For example, the last year use of 4-fluoroamphetamine (4-FA) among Dutch young adults (15-35 years) who went to clubs, parties or festivals in the last year, was 25% (Monshouwer et al., 2016).

When a NPS enters the drug market, the positive as well as the adverse effects are initially often unknown. Notably, around 10% of all drug-related emergency department visits in Europe involved NPS exposure (EMCDDA, 2015a). Moreover, the European Union (EU) Early Warning System (EWS) for NPS has issued 34 public health alerts since 2014 to warn for severe health risks of specific NPS (EMCDDA, 2016b). For example, synthetic cannabinoids were linked to more than 200 emergency department visits within one week in Poland (EMCDDA, 2016b) and methylenedioxypyrovalerone (MDPV) resulted in nearly 100 deaths and over 200 intoxications at the time of risk assessment by the EU-EWS (EMCDDA, 2015a).

Legal approaches to control NPS vary per country. Some countries, such as the United States and Canada, have implemented legal instruments using a 'generic approach' (controlling a family of substances that are precisely defined) or an 'analogue approach' (based on chemical similarity to an already controlled substance) to control substances not explicitly mentioned in the legislation (UNODC, Legal responses). On the other hand, many countries perform a risk assessment of each individual NPS that has been related to severe adverse effects or fatalities. However, the yearly stream of NPS reported for the first time to monitoring centers in Europe (EMCDDA), 98 in 2015, and worldwide (UNODC) seems never-ending and regulators can hardly keep up. In addition, the legal status of a specific NPS may not reduce its use and the associated health risks remain.

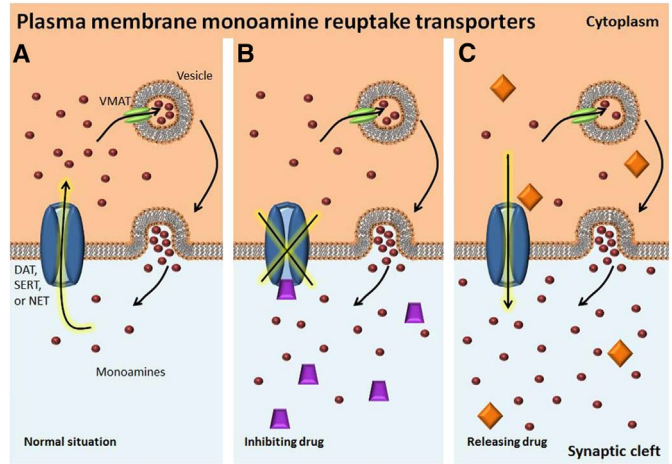


**Fig. 1. Plasma membrane monoamine reuptake transporters (DAT, SERT and NET).** Cytosolic monoamines are stored in vesicles by the vesicular membrane monoamine transporter (VMAT). Upon neuronal stimulation, these monoamines are released into the synaptic cleft through fusion of the vesicles with the cell membrane (exocytosis). Presynaptic plasma membrane dopamine, serotonin or norepinephrine reuptake transporters (DAT, SERT and NET, respectively) are responsible for the reuptake of released monoamines following exocytosis. This normalizes the extracellular monoamine concentration (A). However, drugs that inhibit monoamine reuptake transporters prevent efficient clearance of the synaptic cleft and thus increase extracellular monoamine levels (B). Drugs that induce reversal of monoamine reuptake transporters may increase extracellular monoamine levels even further as they induce efflux of monoamines, even in the absence of vesicle fusion (C).

Risk assessments on NPS include data on occurrence (e.g., seizures), acute intoxications, deaths, animal experiments and *in vitro* data on specific mechanisms of action. The primary mode of action of illicit drugs like MDMA, amphetamine and cocaine involves inhibition and/or reversal of monoamine transporters such as the dopamine (DA), norepinephrine (NE) and serotonin (5-HT) reuptake transporters (DAT, NET and SERT respectively, Fig. 1) (Fleckenstein, Volz, Riddle, Gibb, & Hanson, 2007; Gowrishankar, Hahn, & Blakely, 2014; Korpi et al., 2015; Rietjens, Hondebrink, Westerink, & Meulenbelt, 2012; Torres, Gainetdinov, & Caron, 2003; Verrico, Miller, & Madras, 2007; Williams & Galli, 2006). Exposure to these illicit drugs therefore results in increased extracellular brain levels of monoamines. These increased neurotransmitter levels can lead to both the desired and adverse behavioral and clinical effects. For example, increased NE levels can result in cardiovascular effects (e.g., tachycardia and hypertension) and hyperthermia (Greene, Kerr, & Braitberg, 2008). Increased DA levels are related to reinforcing and behavioral-stimulating effects of drugs (Kimmel, Carroll, & Kuhar, 2001; Volkow, Fowler, Wang, Baler, & Telang, 2009). Also, drugs that primarily affect DAT have a high abuse liability (Howell & Kimmel, 2008; Koob & Volkow, 2010). Finally, increased serotonin levels can result in entactogenic effects, as well as adverse effects, such as the potentially life-threatening serotonin syndrome (Mugele, Nañagas, & Tormoehlen, 2012).

In addition, extracellular brain monoamines levels can also be increased via indirect effects of (illicit) drugs. Increased stimulatory input (e.g., activation of glutamate receptors) or decreased inhibitory input (e.g., inhibition of GABA receptors) can increase the output of monoaminergic neurons. Targets other than reuptake transporters are less frequently investigated, but MDMA and amphetamine have been

reported to also affect GABA- and acetylcholine (ACh)-receptor function and voltage-gated calcium channels (VGCCs; Hondebrink, Meulenbelt, Meijer, Van Den Berg, & Westerink, 2011; Hondebrink, Meulenbelt, Rietjens, Meijer, & Westerink, 2012). Activation of the GABA receptor is linked to sedative effects, whereas ACh receptor antagonists can cause an increased heart rate and reduce synaptic transmission and muscle contraction. On the other hand, ketamine primarily inhibits the glutamate N-methyl-D-aspartate (NMDA) receptor (Monteggia & Zarate, 2015), inducing hallucinations and the feeling of dissociation. Thus, in addition to the well-known effects on monoamine reuptake transporters, illicit drugs can exert their (clinical) effects through numerous additional targets, including neurotransmitter receptors and ion channels. However, for the rapidly increasing number of NPS this is less well studied.

In the past years, an increasing number of studies described effects of NPS on a multitude of targets. However, literature is scattered and pharmacological profiles are lacking. A summary of the effects of a specific NPS, a 'fingerprint', could aid risk characterization. This review therefore aims to compare the effects of common illicit drugs and NPS, based on chemical similarity (for example amphetamine versus 4-fluoroamphetamine and ketamine versus methoxetamine) on specific neuronal molecular targets. NPS were selected based on continued presence on the drug market. For hazard characterization purposes, drugs were divided into groups based on chemical structure, i.e. cathinones (mephedrone, 4-MEC, pentedrone, methylone, MDPV and α-PVP), cannabinoids (THC and JWH-018), non- or mild hallucinogenic phenethylamines (amphetamine, 4-FA, MDMA, 5-APB and 6-APB), hallucinogenic phenethylamines (2C-B, 25B-NBOMe, 25C-NBOMe and 25I-NBOMe), arylcyclohexylamines (ketamine and methoxetamine (MXE)) and piperazines (BZP, TFMPP and mCPP).

## 2. Methods

### 2.1. Literature search

A PubMed search for English-written literature published up to 1 October 2017 was performed. The search strategy combined search terms for specific neuronal targets with NPS that were most frequently notified to the EU-EWS (EMCDDA, 2016b). These included cathinones, cannabinoids, phenethylamines, hallucinogenic phenethylamines, arylcyclohexylamines and piperazines (Fig. 2). In total, the search strategy resulted in 9276 hits. Based on titles, 1314 abstracts were considered potentially relevant. Thorough screening of these abstracts, resulted in 496 articles that were suitable and consistent with the aims of this review (see Supplemental methods for the full search strategy and an overview of the resulting hits). For other common illicit drugs (THC, amphetamine and MDMA) that were considered relevant for comparison with NPS, data was gathered using selected articles and reviews, in addition to relevant articles derived from the search strategy, rather than using a full search strategy. Unfortunately, not all existing (negative) data is available via Pubmed. To further complete the effect fingerprints, we encourage scientists to submit their data on cellular and molecular neurotoxic effects of NPS via the 'submit NPS data' option in the contact form on www.neurotoxicology.nl.

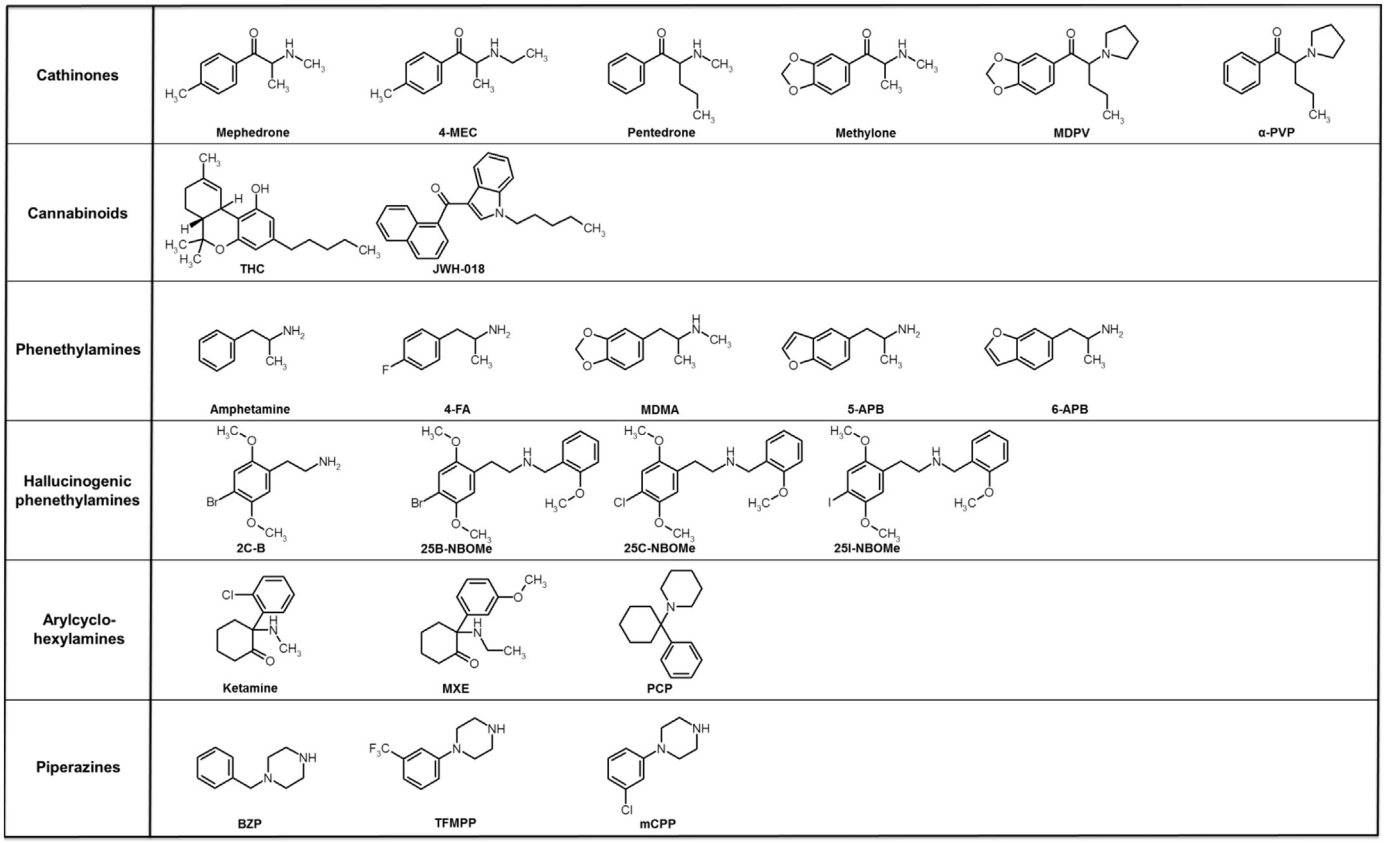


**Fig. 2. Chemical structures of drugs included in this review grouped by drug classes.** Different cathinones, cannabinoids, phenethylamines, hallucinogenic phenethylamines, arylcyclohexylamines and piperazines were included. See list of abbreviations for full names.

### 2.2. Targets

Effect concentrations of drugs obtained from literature are reported per target (e.g., transporter inhibition, receptor activation) and displayed in Tables 1-3, Figs. 3, 4, 6-8, 11, 12 (single target, multiple NPS), and Supplemental Figs. 1-24 (single drug, all targets). Data are reported in Box plots showing the lowest and highest reported effects concentrations, the median and the interquartile range (IQR 25-75%) using GraphPad Prism (version 6.05). All reported effect concentrations are included in the Box plots as single data points. Effect concentrations mentioned in the main text represent the most potent reported concentrations, as reported in Table 1. When maximal effect sizes were reported, a threshold of 5% was applied for the effect to be classified as an (ant)agonistic effect and to include the reported $IC_{50}$ or $EC_{50}$ value in the results. References used for the data presented in the figures are included in the legends. References of all data points that are presented in supplemental figures, are only included in the supplemental material.

### 2.3. Estimated drug concentration in the brain

For all drugs, we estimated the concentration in the brain during recreational use according to Zwartsen et al. (2017). Briefly, human recreational serum, blood or plasma levels were obtained from literature and a brain partitioning factor (BPF: [brain] / ([serum], [blood] or [plasma]) was calculated for each drug using human post mortem or animal data. Human recreational serum, blood or plasma levels were multiplied with the corresponding BPF to estimate human brain concentrations resulting from (recreational) drug use. Estimated human brain concentrations were used to provide relevant test concentrations (Table 2).

## 3. Results

### 3.1. Cathinones

#### 3.1.1. Introduction

Cathinone is a naturally occurring β-ketone amphetamine analogue. It is the major active constituent of khat, the leaf from the *Catha edulis* that can be chewed recreationally for its mild amphetamine-like effects. The first synthetic cathinones were produced for medical use almost 100 years ago. In the late 1920s, mephedrone (4-MMC, 4-methylmethcathinone) and ephedrone (methcathinone) were synthesized (see Kelly, 2011 for review). While mephedrone was never marketed as a potential drug, ephedrone was marketed in the 1930s as an antidepressant in the Soviet Republic. Due to heavy abuse, ephedrone was prohibited in the 1990s, but numerous new synthetic derivatives of cathinone have emerged on the recreational drug scene in the last decade. To avoid regulation, these synthetic cathinones were marketed as bath salts, plant food or fertilizer and labelled "not for human consumption" (Prosser & Nelson, 2012).

In 2013, mephedrone, methylone (3,4-methylenedioxymethcathinone), pentedrone (α-ethylaminovalerophenone), 4-MEC (4-methylethcathinone) and the substituted cathinones α-PVP (α-pyrrolidinovalerophenone) and MDPV (3,4-methylenedioxypyrovalerone) were the most seized cathinones in Europe (EMCDDA, 2015a). Also in the US, these six synthetic cathinones were most reported (2010-2013) and represented over 90% of 30.000 synthetic cathinone seizures in the US (Drug Enforcement Administration, 2014). Since 2008, mephedrone is reported every year, showing the persistence of some of these drugs (World Drug Report, 2016).

Although prevalence numbers are not available for most synthetic cathinones, lifetime prevalence of synthetic cathinones use in general varies strongly, from just over 1% in a self-report survey amongst 2349 students at a large university in the Southeastern US (Stogner & Miller, 2013) up to almost 61% for mephedrone use among 560 readers of UK clubbers' magazine (Winstock, 2011; for review see Bretteville-Jensen, Tuv, Bilgrei, Fjeld, & Bachs, 2013). The prevalence derived from such self-report surveys likely underestimates the actual use, also because synthetic cathinones are sometimes sold as MDMA. For example, 11.5% of pills sold as MDMA in the Netherlands in 2009 contained mephedrone (96-155 mg per tablet) as the only pharmacological active compound (Brunt, Poortman, Niesink, & van den Brink, 2011).

#### 3.1.2. Clinical effects

Synthetic cathinones are preferably administered by insufflation or oral uptake and to a lesser extent by smoking or injecting. Administration typically results in stimulant-related subjective effects, including euphoria, intensification of sensory experiences, sexual arousal, reduced appetite and increased alertness, awareness and energy (Glennon, 2014; Zawilska, 2014a).

Synthetic cathinones have been implicated in many intoxications and fatalities worldwide. For example, within eight months after the first appearance of synthetic cathinones in the US, over 1400 intoxications were reported to American poison centers in 47 out of 50 states (Spiller, Ryan, Weston, & Jansen, 2011). Similarly, the number of cathinone-intoxicated patients in a London inner-city emergency department increased from none in 2006 to 82 in 2010 (Wood, Greene, & Dargan, 2013).

The most commonly reported clinical effects include altered mental status (agitation, violent behavior, hallucinations, paranoia), tachycardia, hypertension and hyperthermia (Glennon, 2014; Zawilska, 2014a). Additionally reported severe effects include hyponatremia, acute kidney and liver failure, rhabdomyolysis, compartment syndrome, cardiomyopathy and in severe cases death (Baumann et al., 2017; Zawilska, 2014a).

#### 3.1.3. Mechanism of action

Just like many other NPS and illicit drugs, synthetic cathinones interact with monoamine reuptake transporters in the plasma membrane of neuronal cells to increase brain monoamine levels, resulting in the desired psychological effects. In addition to inhibition of these transporters, some synthetic cathinones can also act as a transporter substrate, thereby entering the neurons to stimulate non-exocytotic release of monoamines through the transporter (Glennon, 2014; Green, King, Shortall, & Fone, 2014; Zawilska, 2014a; Fig. 1). Although monoamine levels can also increase indirectly via the inhibition of the monoamine metabolizing enzymes monoamine-oxidase A (MAO-A) and catechol-*O*-methyltransferase (COMT; Napolitano, Cesura, & Da Prada, 1995), literature reports on effects of synthetic cathinones on MAO-A or COMT are very sparse.

Mephedrone and methylone appear to act as a substrate for DAT, like amphetamine, thereby causing both inhibition and reversal of this transporter at sub- and low micromolar concentrations. Mephedrone and methylone are also efficient in inducing inhibition and reversal of SERT and NET at sub- and low micromolar concentrations. Although limited data is available for pentedrone and 4-MEC, these compounds seem roughly equipotent compared to mephedrone and methylone (see Figs. 3-4).

The substituted cathinones α-PVP and MDPV are very potent inhibitors of DAT and NET, with $IC_{50}$values in the nanomolar range. However, α-PVP and MDPV act as relatively poor SERT inhibitors ($IC_{50}$values in the micromolar range). While some studies indicate that α-PVP and MDPV inhibit monoamine transporters without affecting release via reversal, one study (Baumann et al., 2013) identified MDPV

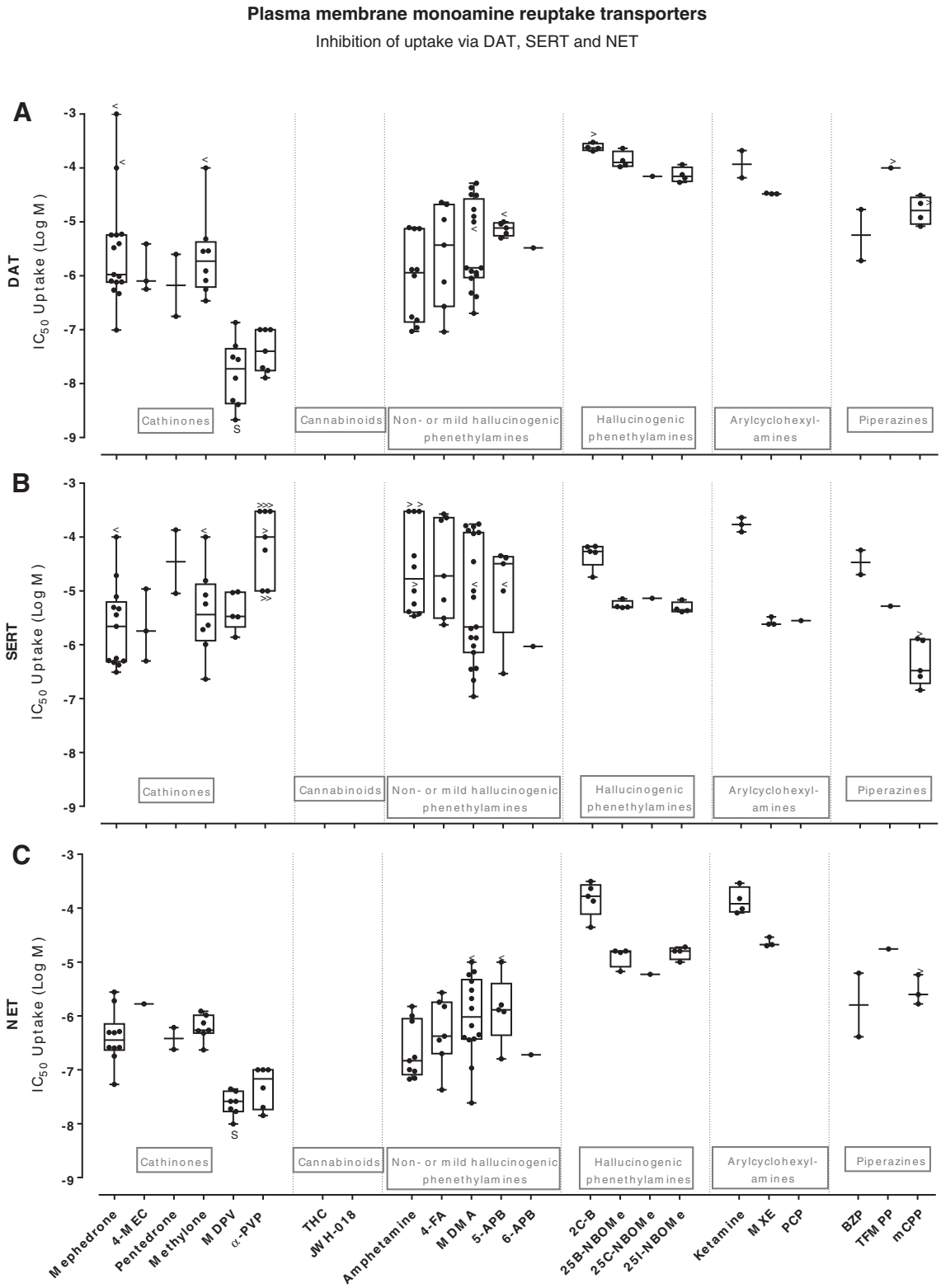


**Fig. 3. Inhibition of monoamine reuptake transporters by different classes of drugs.** Graphs depict $IC_{50}$ values for inhibition of monoamine reuptake for DAT (A), SERT (B) and NET (C). > : effect size smaller than 50% at this concentration, < : effect size larger than 50% at this concentration ($IC_{50}$ not specified) at this concentration, S: S-enantiomer of the drug. References: Cathinones: (Baumann et al., 2013; Cameron, Kolanos, Solis, Glennon, & De Felice, 2013; Eshleman et al., 2013; Hadlock et al., 2011; Martínez-Clemente, Escubedo, Pubill, & Camarasa, 2012; Mayer et al., 2016; Pifl, Reither, & Hornykiewicz, 2015; Saha et al., 2015; Rickli, Hoener, & Liechti, 2015; Simmler et al., 2013; McLaughlin et al., 2017; Iversen, White, & Treble, 2014; Lõpez-Arnau, Martínez-Clemente, Pubill, Escubedo, & Camarasa, 2012; Simmler, Rickli, Hoener, & Liechti, 2014; Eshleman et al., 2017; Cozzi, Sievert, Shulgin, Jacob, & Ruoho, 1999; Nagai, Nonaka, & Kamimura, 2007; Sogawa et al., 2011; Kolanos, Partilla, et al., 2015; Kolanos, Solis, Sakloth, Defelice, & Glennon, 2013; Kolanos, Sakloth, et al., 2015; Marusich et al., 2014; Zwartsen et al., 2017; Luethi et al., in press). Cannabinoids: No data. Non- or mild hallucinogenic phenethylamines: (Simmler et al., 2013; Marona-Lewicka, Rhee, Sprague, & Nichols, 1995; Iversen et al., 2014; Baumann et al., 2013; Rickli, Hoener, et al., 2015; Holmes & Rutledge, 1976; Crespi, Mennini, & Gobbi, 1997; Eshleman et al., 2017; Nagai et al., 2007; Hadlock et al., 2011; Pifl et al., 2015; Eshleman et al., 2013; Cozzi et al., 1999; Verrico et al., 2007; Shimshoni, Winkler, Golan, & Nutt, 2017; Rickli, Kopf, Hoener, & Liechti, 2015; Montgomery et al., 2007; Zwartsen et al., 2017). Hallucinogenic phenethylamines: (Rickli, Luethi, et al., 2015; Montgomery et al., 2007; Zwartsen et al., 2017). Arylcyclohexylamines: (Shahani, Lingamaneni, & Hemmings, 2002; Nishimura et al., 1998; Hara et al., 1998; Zhao & Sun, 2008; Barann et al., 2015; Hori et al., 1996; Zwartsen et al., 2017). Piperazines: (Nagai et al., 2007; Simmler, Rickli, Schramm, Hoener, & Liechti, 2014; Baumann, Ayestas, Dersch, Partilla, & Rothman, 2000; Samanin et al., 1979; Gobbi et al., 2002).

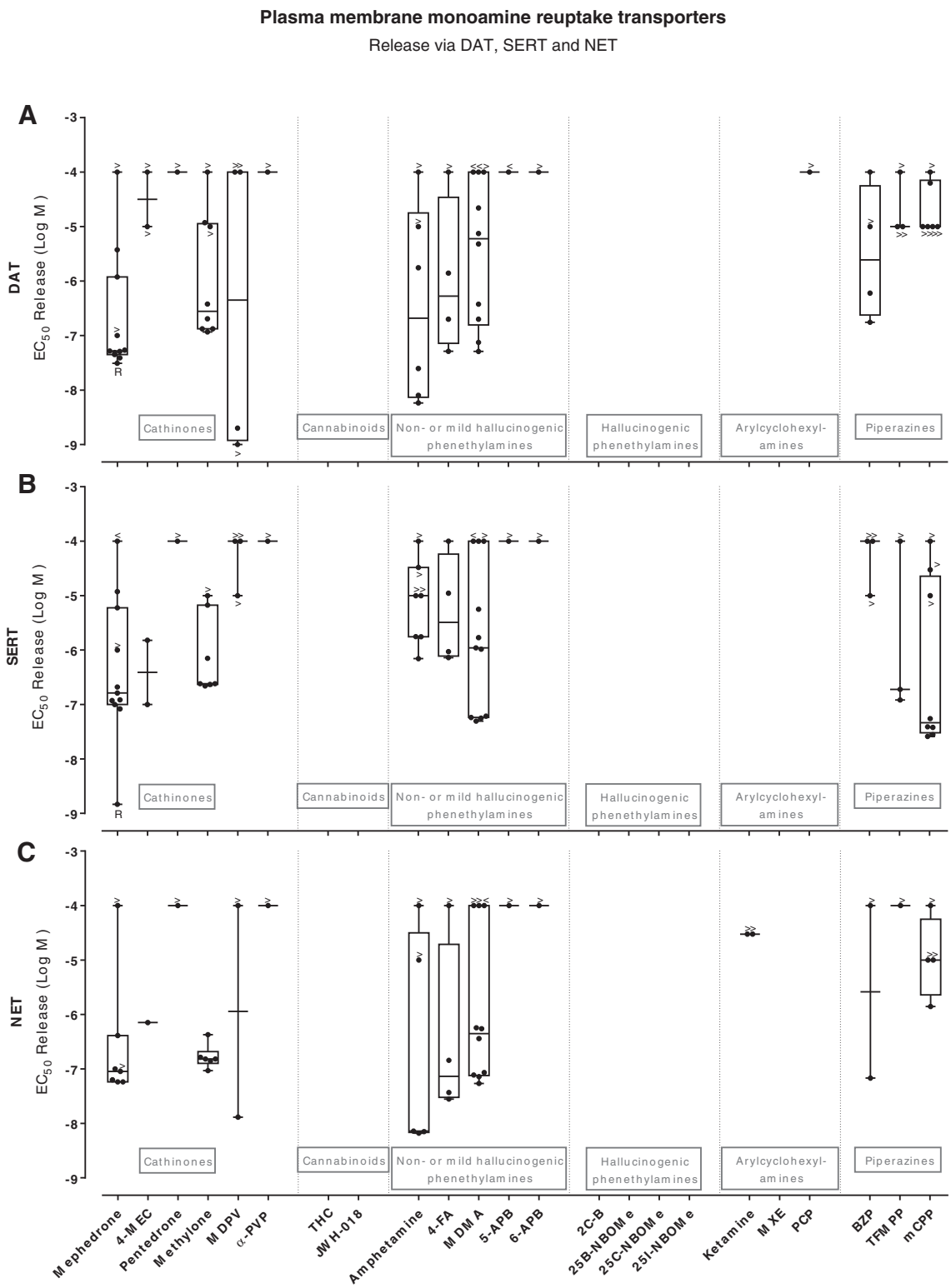


**Fig. 4. Reversal of monoamine reuptake transporters by different classes of drugs.** Graphs depict $EC_{50}$ values for transporter-mediated release, i.e., reversal of monoamine transporters, for DAT (A), SERT (B) and NET (C). > : effect size smaller than 50% at this concentration, < : effect size larger than 50% ($EC_{50}$ not specified) at this concentration, R: R-enantiomer of the drug.

References: Cathinones: (Baumann et al., 2012; Baumann et al., 2013; Eshleman et al., 2013; Gregg et al., 2015; Mayer et al., 2016; Saha et al., 2015; Simmler et al., 2013; McLaughlin et al., 2017; Pifl et al., 2015; Eshleman et al., 2017; Del Bello, Sakloth, Partilla, Baumann, & Glennon, 2015; Nagai et al., 2007; Kolanos et al., 2013; Elmore et al., 2017; Shekar et al., 2017; Luethi et al., in press). Cannabinoids: No data. Non- or mild hallucinogenic phenethylamines: (Samanin et al., 1979; Baumann et al., 2011; Rickli, Hoener, et al., 2015; Baumann et al., 2013; Simmler et al., 2013; Rothman et al., 2001; Eshleman et al., 2017; Nagai et al., 2007; Simmler, Rickli, Hoener, et al., 2014; Rickli, Kopf, et al., 2015; Eshleman et al., 2013; Del Bello et al., 2015; Baumann et al., 2012; Hysek et al., 2012; Heal, Cheetham, Prow, Martin, & Buckett, 1998; Rickli, Luethi, et al., 2015). Hallucinogenic phenethylamines: No data. Arylcylcohexylamines: (Eshleman, Henningsen, Neve, & Janowsky, 1994; Pashkov & Hemmings, 2002; Uryu et al., 2000). Piperazines: (Nagai et al., 2007; Simmler, Rickli, Schramm, et al., 2014; Baumann et al., 2014; Baumann et al., 2004; Rothman & Baumann, 2002; Samanin et al., 1979; Baumann et al., 2000; Rothman et al., 2010; Gobbi et al., 2002).

as potent on reversing both DAT and NET (see Figs. 3-4), clearly arguing for more studies on this particular endpoint.

The effect concentrations of the synthetic cathinones on DAT, NET and SERT are generally well within the range of estimated human brain concentrations (Table 2). However, the reported effects on neurotransmitter receptors are likely less relevant, because these occur only at higher concentrations. Mephedrone, methylone, pentedrone, 4-MEC, α-PVP and MDPV all show limited binding affinity for dopamine D1, D2 and D3 receptors ($K_i$binding > 10 μM). Mephedrone, 4-MEC, methylone and MDPV also have a $K_i$binding > 10 μM for dopamine D4 receptors. Binding to dopamine D5 receptors has been reported only for mephedrone and 4-MEC ($K_i$binding > 10 μM; see Table 1). Similarly, these synthetic cathinones display limited binding affinity for 5-$HT_1$, 5-$HT_2$and α-adrenergic receptors (micromolar range, see Table 1 and Supplemental Figs. 2-7). Effects on other neurotransmitter receptors ($GABA_A$, NMDA, AMPA, kainate, nACh, CB) or ion channels have not been reported, except for limited binding affinity of mephedrone and 4-MEC for mACh receptors ($K_i$binding > 10 μM). Also see Supplemental Figs. 2-7 for a full overview of the targets and effect concentrations of mephedrone, methylone, pentedrone, 4-MEC, α-PVP and MDPV.

### 3.2. Cannabinoids

#### 3.2.1. Introduction

Cannabinoids can be divided in three classes: endocan nabinoids, phytocannabinoids from the *Cannabis* plant, and synthetic cannabinoids. *Cannabis* plants contain over 80 different phytocannabinoids, but $\Delta^9$-tetrahydrocannabinol (THC) is the only psychoactive component (Di Marzo & Piscitelli, 2015). Synthetic cannabinoids appeared on the drug market most recently (EMCDDA, 2009). Nevertheless, they are currently the largest group of NPS monitored by the EMCDDA and, besides cathinones, also one of the fastest growing groups of NPS (EMCDDA, 2016b). Synthetic cannabinoids share limited structural commonality with THC and are chemically manufactured cannabinoids. Initially, synthetic cannabinoids were developed as lead compounds for potential medicines (Pertwee, 2008a, 2008b). Synthetic cannabinoids are smoked similar to cannabis use; they are applied to an inert herbal product after being dissolved in a solvent (Auwärter, Dargan, & Wood, 2013, chap. 13).

In 2008, the first synthetic cannabinoid (JWH-018) was reported through the EU-EWS for NPS (EMCDDA, 2009). In 2015, 24 of the 98 NPS that were reported for the first time to the EU-EWS concerned synthetic cannabinoids (EMCDDA, 2016b). The last year prevalence of use varies between 6-11% in the US, whereas a lower prevalence of use is reported in Europe, between 0.1-1% (World Drug Report, 2016). Synthetic cannabinoids are also known as spice, K2, AM-2201, MDMB-CHMICA, AB-FUBINACA, MAM-2201 and XLR-11, the latter 5 representing the top 5 of seized synthetic cannabinoids in 2014 (EMCDDA, 2016b). New synthetic cannabinoids are constantly appearing on the drug market, although many also disappear quickly and are only reported for a limited time. JWH-018 is a synthetic cannabinoid that has been reported every year by a large number of countries since 2008 (World Drug Report, 2016). Therefore, this review focused on the effects of JWH-018 on the selected targets.

#### 3.2.2. Clinical effects

Although many effects of $\Delta^9$-THC and synthetic cannabinoids overlap during acute intoxication (for review see Fattore, 2016), synthetic cannabinoids are often more toxic than $\Delta^9$-THC, with mass poisonings and even deaths reported (EMCDDA, 2016b). Clinical effects include agitation, anxiety, hallucinations, psychosis, memory and cognitive impairment, acute kidney injury, chest pain, tachyarrhythmia, seizures and unresponsiveness (for review see Fattore, 2016). In the US, emergency department visits due to synthetic cannabinoids exposure have doubled from 2010-2011 to nearly 30.000 (61 visits per 100.000 population), more recent data is unavailable. Also, 65% of the drug-related emergency department visits of younger people (< 20 yrs) were due to synthetic cannabinoids exposure (Bush & Woodwell, 2014).

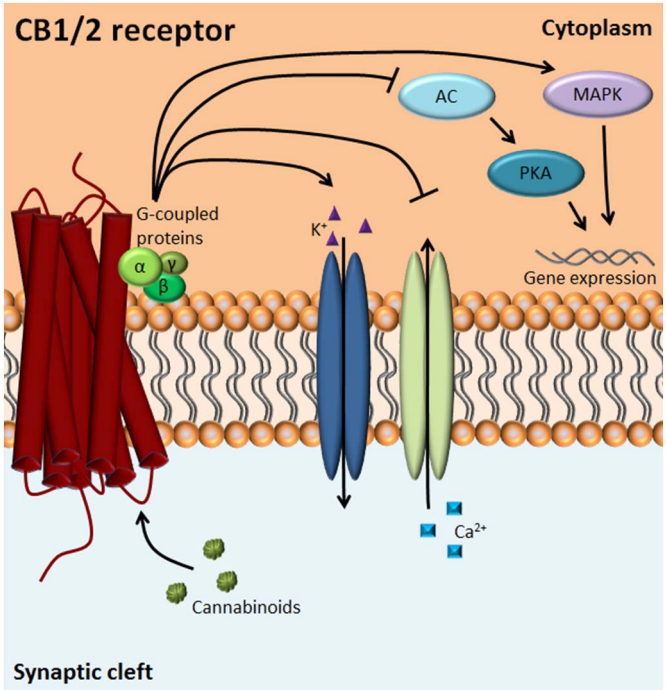


**Fig. 5. Cannabinoid receptors.** Cannabinoid (CB) receptors are G-protein-coupled receptors located in the (presynaptic) cell membrane. Upon activation by cannabinoids, CB receptors inhibit $Ca^{2+}$ channels and activate (inwardly rectifying) $K^+$ channels, resulting in a hyperpolarization and reduction in neurotransmitter release. Additionally, CB receptors can regulate cell functions via controlled gene expression by activation of mitogen-activated protein kinases (MAPK) and inhibition of adenylate cyclase (AC) and cyclic AMP–protein kinase A (PKA) signaling.

#### 3.2.3. Mechanism of action

Synthetic cannabinoids affect the same receptors as $\Delta^9$-THC; the cannabinoid (CB) receptors CB1 and CB2, both G-protein-coupled receptors (GPCRs). CB1 receptors are amongst the most abundant GPCRs in the central nervous system, although they are also present in the peripheral nervous system (Di Marzo, Bifulco, & Petrocellis, 2004). CB2 receptors are mostly present on immune tissues and immune cells, but are also moderately expressed in specific brain areas. Recently CB2 receptors have been implicated in animal drug seeking behavior and were also reported to modulate neuronal network activity (Chen, Gao, Gao, Su, & Wu, 2017). Activation of CB receptors can modulate neurotransmission through many different pathways, resulting in inhibition or stimulation, depending on the location of their expression (Chen et al., 2017; Di Marzo et al., 2004). Activation of CB1 and CB2 receptors results in activation of mitogen-activated protein kinases (MAPK) and inhibition of adenylate cyclase and cyclic AMP–protein kinase A (PKA) signaling (Fig. 5). Activation of CB1 receptors also inhibits L-, N- and P/Q-type VGCCs and stimulates inwardly rectifying $K^+$channels, which reduces neurotransmitter release (for review see Di Marzo, Stella, & Zimmer, 2015).

JWH-018 and $\Delta^9$-THC most potently affect the cannabinoid receptors (Table 1). While $\Delta^9$-THC has a somewhat higher binding affinity for CB1 receptors than JWH-018 (low nanomolar range, Fig. 6A, left),

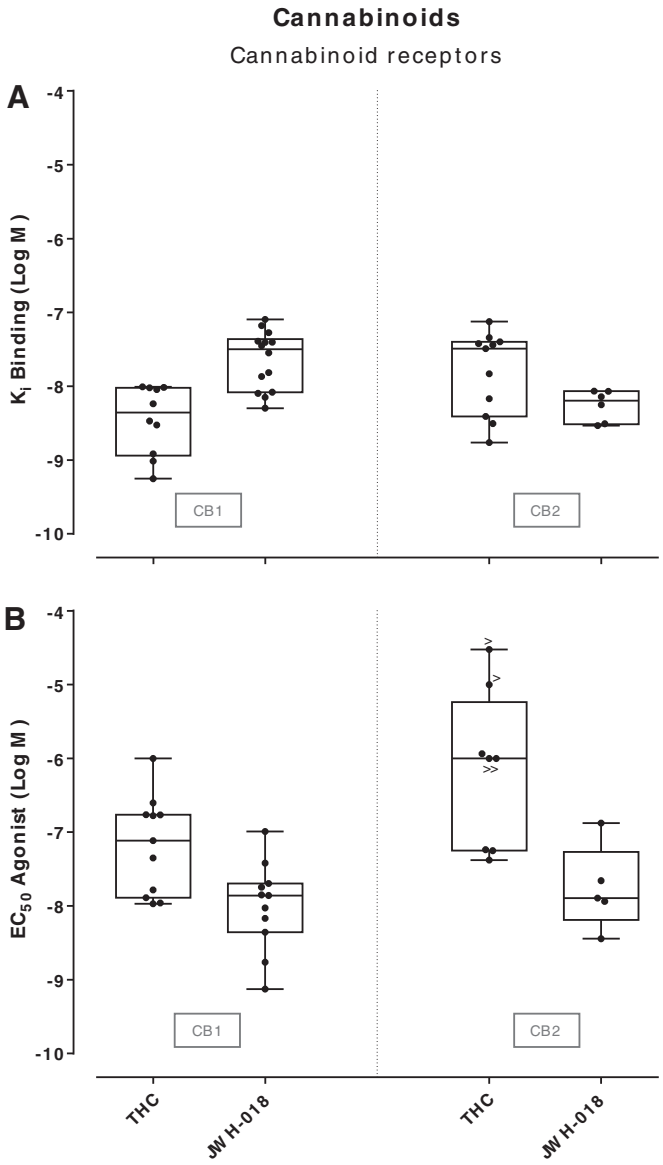


**Fig. 6. Binding to and activation of CB receptors by different cannabinoids.** Graphs depict effects of THC and JWH-018 on binding ($K_i$; A) and activation ($EC_{50}$; B) of CB1 (left) and CB2 (right) receptors. > : effect size smaller than 50% at this concentration. References: $K_i$ binding: (Canazza et al., 2016; Seely et al., 2012; Brents et al., 2011; Bayewitch et al., 1996; Felder et al., 1995; Rhee et al., 1997; Rinaldi-Carmona et al., 1994; Iwamura, Suzuki, Ueda, Kaya, & Inaba, 2001; Brents, Zimmerman, Saffell, Prather, & Fantegrossi, 2013; Brents et al., 2011; De Luca et al., 2016; Vigolo et al., 2015; Aung et al., 2000; Chin, Murphy, Huffman, & Kendall, 1999; Compton et al., 1993; Rajasekaran, Brents, Franks, Moran, & Prather, 2013; Vigolo et al., 2015; Showalter, Compton, Martin, & Abood, 1996; Ford et al., 2017). $EC_{50}$ agonist: (Cannaert, Storme, Franz, Auwärter, & Stove, 2016; Brents et al., 2011; Brents et al., 2012; Banister et al., 2016; Banister, Moir, et al., 2015; Banister, Stuart, et al., 2015; Rinaldi-Carmona et al., 1994; Bayewitch et al., 1996; Felder et al., 1995; Rhee et al., 1997; Canazza et al., 2016; De Luca et al., 2016; Seely et al., 2012; Vigolo et al., 2015; Atwood, Huffman, Straiker, & MacKie, 2010; Rajasekaran et al., 2013; Ford et al., 2017).

both drugs appear to have comparable binding affinities for CB2 receptors (nanomolar range, Fig. 6A, right). Functionally, $\Delta^9$-THC and JWH-018 have agonistic effects on CB receptors, mostly between 10-100 nM, while $\Delta^9$-THC only activated CB2 receptors around and above 100 nM (Fig. 6B). CB receptor activation occurs at concentrations around the estimated human brain concentration during recreational use (Table 2).

Besides cannabinoid receptors, effects of synthetic cannabinoids on several other targets have been investigated. However, at 10 μM, $\Delta^9$-THC and JWH-018 appear unable to bind to monoamine reuptake transporters, dopamine receptors D1-5, serotonin receptors 5-$HT_{1,2A,2C,3,5,6,7}$, α- and β-adrenergic receptors and muscarinic acetylcholine receptors. Binding to the serotonin receptor 5-$HT_{2B}$was observed around 1 μM JWH-018 or $\Delta^9$-THC. Similarly, binding to $GABA_A$receptors was observed at ~1 μM JWH-018 (Supplemental Figs. 8-9).

Functional data is limited for targets other than cannabinoid receptors, although JWH-018 was shown to activate potassium channels ($EC_{50}$~250 μM) and to inhibit $GABA_A$receptors ($IC_{50}$~250 nM). Also, JWH-018 potently inhibited neuronal activity ($IC_{50}$~10 nM).

### 3.3. Phenethylamines

#### 3.3.1. Introduction

Phenethylamines are a class of substances that were on the drug market long before active monitoring was put into place. This class includes older drugs like amphetamine and MDMA, all of which are controlled under the 1971 Convention (EMCDDA, 2012). More recently developed phenethylamines are the third largest group of NPS monitored by the EMCDDA (EMCDDA, 2016b) and were one of the earliest NPS appearing on the market in the late 1980s (EMCDDA, 2009). NPS of the phenethylamine type include 4-fluoroamphetamine (4-FA), benzofurans (5-APB, 6-APB), substances of the 2C series (2C-B, 2C-E etc), and 2C-x-NBOMes (25B-NBOMe, 25C-NBOMe and 25I-NBOMe). Many were developed as psychotropic candidates for psychotherapy, but were never marketed due to adverse effects or lack of desired pharmaceutical effects. The chemist Alexander Shulgin, sometimes called the "godfather of psychedelics", developed many phenethylamines. He described his work and personal experiences with these drugs in his book *Phenethylamines I Have Known And Loved (PIHKAL)*, which was published in 1991 (Shulgin & Shulgin, 1991).

The prevalence of use depends on the specific phenethylamine and the population investigated. For example, the last year prevalence of MDMA use was around 2% among young adults (15-34 yrs, World Drug Report, 2016), whereas this was 46% among Dutch young adults (15-35 years) who went to clubs, parties or festivals in the last year. In that same group, the last year prevalence of 4-FA and 2C-B use was respectively 25% and 10% in 2016, indicating that the use of NPS of the phenethylamine type is closing in on use of older phenethylamines (Monshouwer et al., 2016).

#### 3.3.2. Clinical effects

Exposure to phenethylamines results in stimulatory effects and, depending on the specific phenethylamine, entactogenic and/or psychedelic effects. For example, MDMA is well known for its entactogenic effects, such as intense feelings of euphoria, friendliness, comfort, intimacy, pleasure and empathy (for review see Green, Mechan, Elliott, Shea, & Colado, 2003; Capela et al., 2009). Desirable effects reported following 4-FA exposure overlap those of MDMA and the subjective effects following 4-FA exposure ranged between those of MDMA and amphetamine (Linsen et al., 2015). Exposure to NPS of the 2C series result in a combination of stimulatory and hallucinogenic effects (for review see Dean, Stellpflug, Burnett, & Engebretsen, 2013).

Adverse effects that have been reported following exposure to most phenethylamines include agitation, sympathomimetic toxicity (tachycardia, hypertension), hyperthermia, seizures, rhabdomyolysis and renal failure. Exposure to hallucinogenic phenethylamines (2C series, NBOMEs) can also result in unpleasant hallucinations (for review see Green et al., 2003; Devlin & Henry, 2008; Dean et al., 2013;

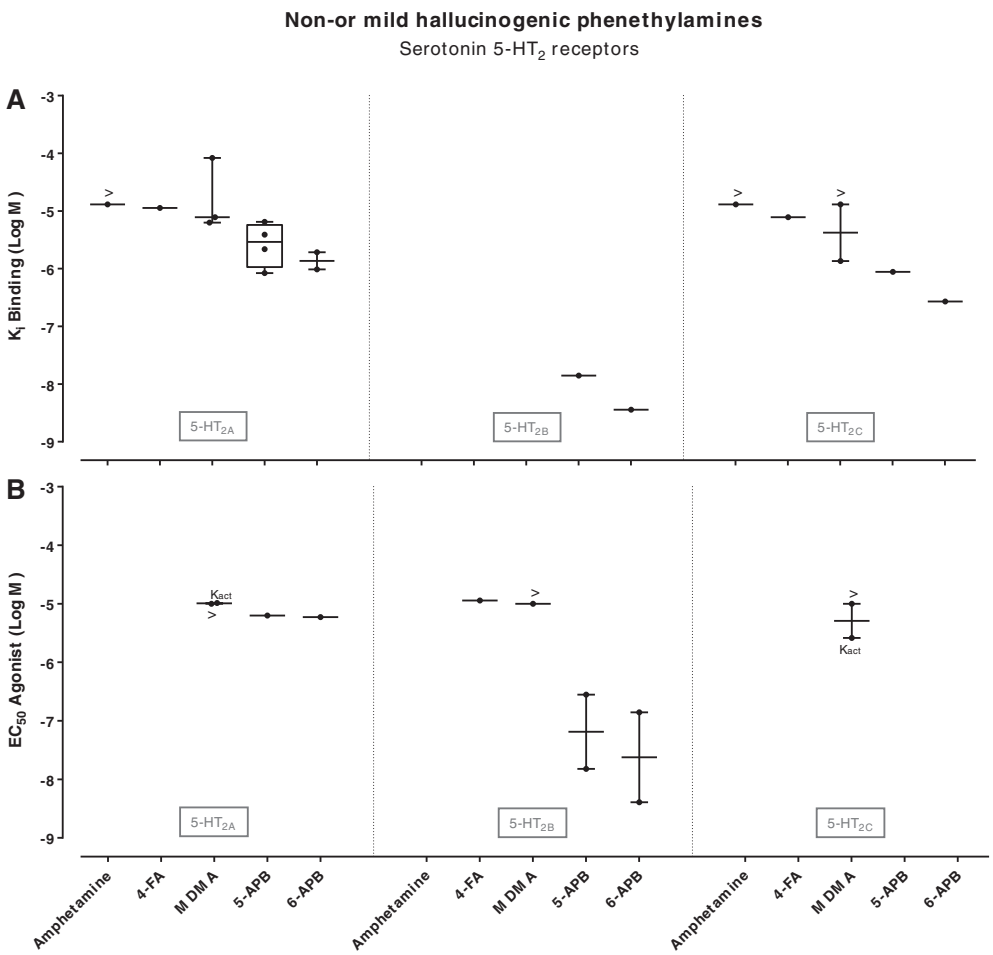


**Fig. 7. Binding to and activation of 5-HT$_2$receptors by different non- or mild hallucinogenic phenethylamines.** Graphs depict effects on binding ($K_i$; A) and activation ($EC_{50}$; B) of 5-HT$_{2A}$ (left), 5-HT$_{2B}$ (middle) and 5-HT$_{2C}$ (right) receptors. > : effect size smaller than 50% at this concentration, $K_{act}$: activation constant.
References: $K_i$ binding: (Iversen et al., 2013; Simmler et al., 2013; Rickli, Hoener, et al., 2015; Eshleman et al., 2013; Dawson et al., 2014; Rickli, Kopf, et al., 2015). $EC_{50}$ agonist: (Shimshoni et al., 2017; Nash, Roth, Brodkin, Nichols, & Gudelsky, 1994; Rickli, Hoener, et al., 2015; Rickli, Kopf, et al., 2015; Iversen et al., 2013).

Halberstadt, 2017). For many phenethylamines that only recently entered the drug market, little scientific data on clinical effects is available. Recently, acute toxicity of 4-FA was reported and effects included agitation, severe headache, anxiety, tachycardia, hypertension, and chest pain. In several users, serious and sometimes life-threatening clinical conditions were reported, including severe cardiotoxicity, convulsions, cerebral hemorrhage and death, even following exposure to just one tablet (Hondebrink, Nugteren-van Lonkhuyzen, et al., 2017; Wijers, van Litsenburg, Hondebrink, Niesink, & Croes, 2017).

### 3.3.3. Mechanism of action

We distinguished two groups of phenethylamines to describe the mechanism of action; no or mild hallucinogenic phenethylamines and hallucinogenic phenethylamines.

*3.3.3.1. Non- or mild hallucinogenic phenethylamines (Amphetamine, 4-FA, MDMA, 5-APB and 6-APB).* The primary mode of action of most non- or mild hallucinogenic phenethylamines is inhibition and/or reversal of plasma membrane monoamine reuptake transporters (DAT, NET, SERT) (Table 1, Figs. 1, 3-4), which occurs at levels relevant for human exposure (Table 2). $IC_{50}$values for uptake overlap for most drugs and transporters, although most studies show more potent inhibition of NET and DAT by amphetamine and 4-FA, compared to MDMA, 5-APB and 6-APB. In contrast, SERT appears to be more potently inhibited by MDMA, 5-APB and 6-APB (Fig. 3).

The data on transporter-mediated release of monoamines shows a large variation. For example, release through DAT following amphetamine exposure is reported at 10 nM ($EC_{50}$), while other studies reported no release at 100 μM (Fig. 4). Looking at the lowest reported values for release, amphetamine, MDMA and 4-FA potently induce release via DAT and NET ($EC_{50}$values 5-50 nM). MDMA also potently induces release via SERT, while amphetamine and MDMA only do so at low micromolar levels. 5-APB and 6-APB do not result in release up to 100 μM, although this was investigated in only one study (Supplemental Figs. 10-14).

The primary mode of action of 5-APB and 6-APB appears to be activation of the serotonin 5-HT$_{2B}$receptors ($EC_{50}$values low nanomolar range), while MDMA does not activate these receptors at 10 μM. 4-FA has also been reported to activate 5-HT$_{2B}$receptors, although at a higher concentration ($EC_{50}$ value low micromolar range; Fig. 7). In addition, 5-APB and 6-APB bind to α2-adrenergic receptors with $K_i$values of respectively 500 nM and 50 nM. At higher concentrations, non- or mild hallucinogenic phenethylamines also bind to other targets, including dopamine D1-3, serotonin 5-HT$_{1A,2A,2C}$, GABA$_A$and glutamatergic receptors (NMDA/Kainate/AMPA; Supplemental Figs. 10-14)).

*3.3.3.2. Hallucinogenic phenethylamines (2C-B, 25B-NBOMe, 25C-NBOMe, 25I-NBOMe).* The most important mechanism of action of hallucinogenic phenethylamines appears to be activation of serotonin 5-HT$_{2A,B,C}$receptors ($EC_{50}$1-100 nM, Fig. 8, Table 1). Serotonin 5-HT$_2$receptors are G-protein-coupled receptors (GPCRs) that upon activation increase the activity of phospholipase C and/or phospholipase D and phospholipase A2. Ultimately, this can result in

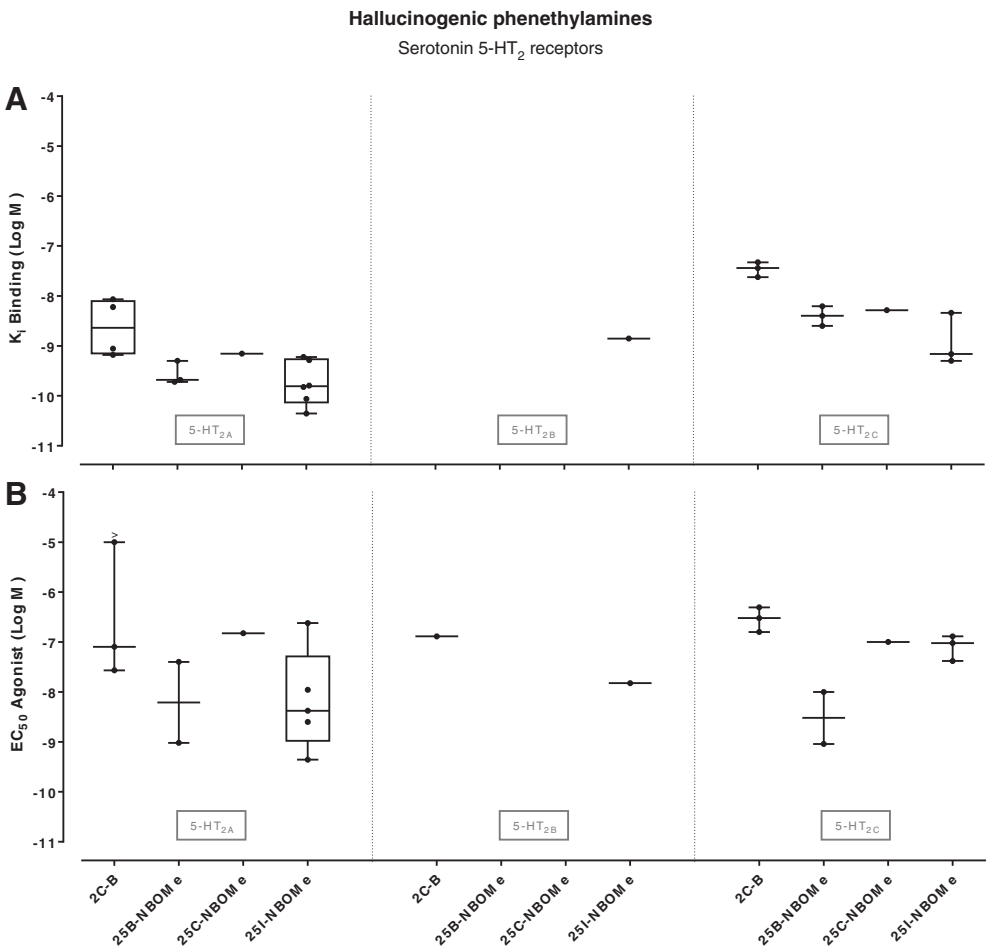


**Fig. 8. Binding to and activation of 5-HT$_2$receptors by different hallucinogenic phenethylamines** Graphs depict effects on binding ($K_i$; A) and activation ($EC_{50}$; B) of 5-HT$_{2A}$ (left), 5-HT$_{2B}$ (middle) and 5-HT$_{2C}$ (right) receptors. > : effect size smaller than 50% at this concentration.
References: $K_i$ binding: (McLean et al., 2006; Rickli, Luethi, et al., 2015; Juncosa et al., 2013; Leth-Petersen et al., 2016; Braden, Parrish, Naylor, & Nichols, 2006; Nichols et al., 2015; Glennon et al., 1994). $EC_{50}$ agonist: (McLean et al., 2006; Rickli, Luethi, et al., 2015; Leth-Petersen et al., 2016; Braden et al., 2006; Nichols et al., 2015; Acuña-Castillo et al., 2002; Moya et al., 2007).

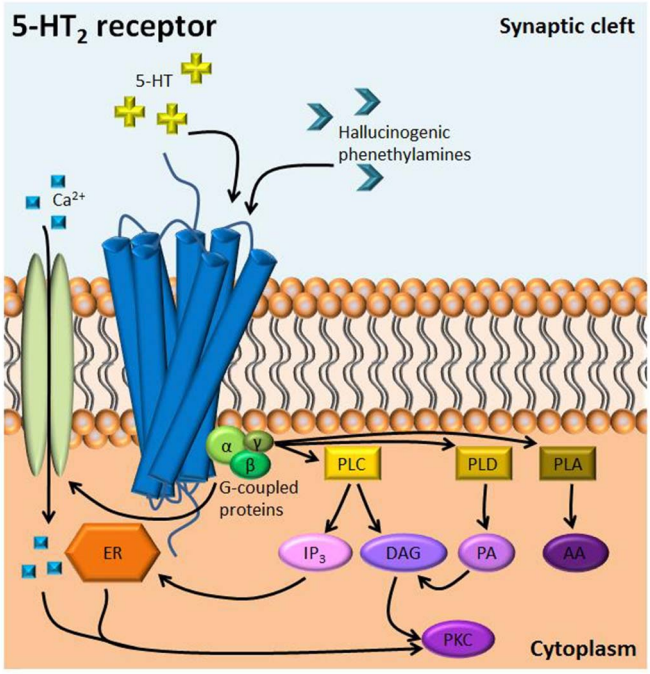


**Fig. 9. Serotonin 5-HT$_2$receptors.** Serotonin 5-HT$_2$ receptors are G-protein-coupled receptors located in the (postsynaptic) cell membrane. Upon activation by endogenous serotonin or hallucinogenic phenethylamines, 5-HT$_2$ receptors increase the influx of $Ca^{2+}$ and the activity of phospholipase C (PLC), phospholipase D (PLD) and/or phospholipase A (PLA). This results in an increase in inositol 1,4,5-triphosphate ($IP_3$), diacylglycerol (DAG), phosphatidic acid (PA) and arachidonic acid (AA) as well as subsequent $Ca^{2+}$ release from intracellular stores such as the endoplasmic reticulum (ER) and activation of protein kinase C (PKC).

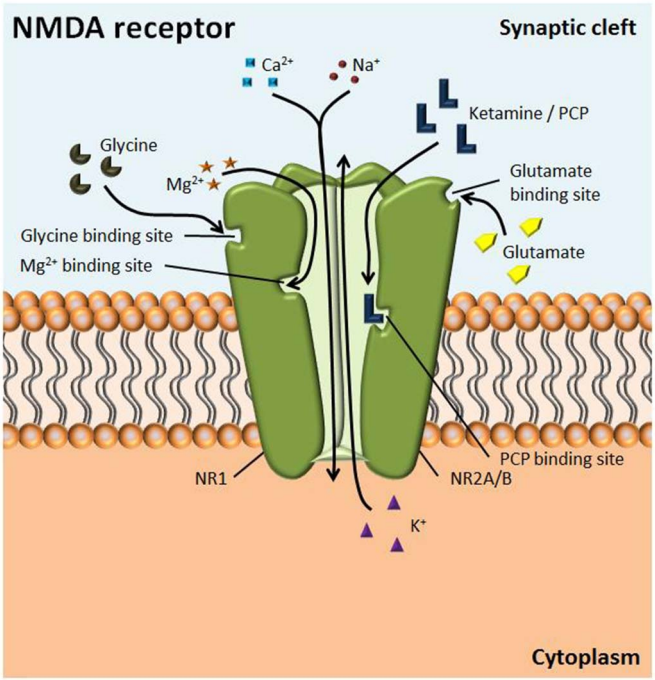


**Fig. 10. NMDA receptors.** NMDA receptors are ligand-gated, voltage-sensitive ionotropic receptors located in the (postsynaptic) cell membrane. Activation of NMDA receptors by endogenous glutamate or glycine results in membrane depolarization via the influx of $Na^+/Ca^{2+}$, efflux of $K^+$, and subsequent activation of intracellular signaling pathways. Arylcyclohexylamines bind to the PCP binding site in the pore of the channel, thereby effectively preventing ion fluxes by physically blocking the pore.

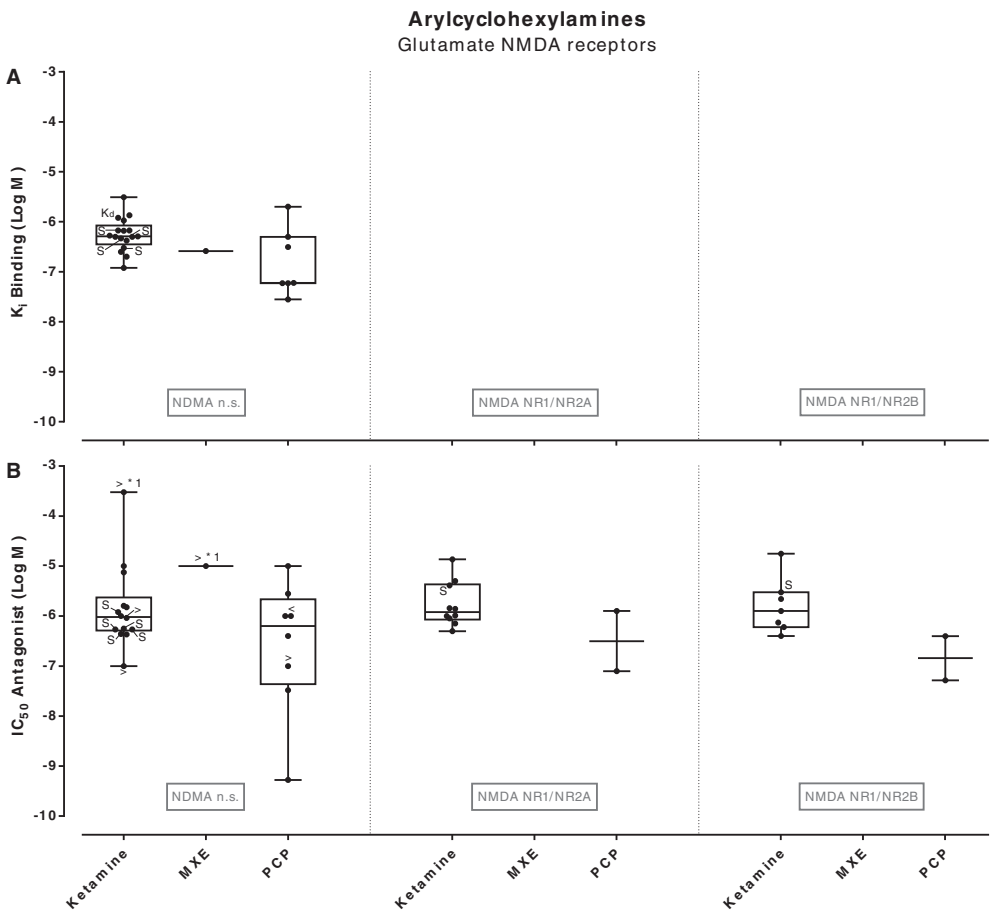


**Fig. 11. Binding to and inhibition of NMDA receptors by different arylcyclohexylamines.** Graphs depict effects on binding ($K_i$; A) and inhibition ($IC_{50}$; B) of NMDA receptors: n.s. non-specified (left), NR1/NR2A (middle) and NR1/NR2B (right). > : effect size smaller than 50% at this concentration, $K_d$: dissociation constant, S: S-enantiomer of the drug. *1: glutamate n.s. References: $K_i$ binding: (Bonifazi et al., 2015; Ebert, Mikkelsen, Thorkildsen, & Borgbjerg, 1997; Sałat et al., 2015; Moaddel et al., 2013; Parsons et al., 1995; Roth et al., 2013; Seeman, Ko, & Tallerico, 2005; Gilling, Jatzke, Hechenberger, & Parsons, 2009; Makhro et al., 2016; Kapur & Seeman, 2002; Köhler, Bergander, Fabian, Schepmann, & Wünsch, 2012; Kang et al., 2017; Rammes, Rupprecht, Ferrari, Zieglgänsberger, & Parsons, 2001; Zanos et al., 2016; Morris et al., 2017). $IC_{50}$ antagonist: (Drejer & Honoré, 1987; Emnett et al., 2013; Parsons et al., 1995; Parsons, 1996; Zanos et al., 2016; Orser, Pennefather, & MacDonald, 1997; Ebert et al., 1997; Pin, Van-Vliet, & Bockaert, 1988; Sekiguchi, Okamoto, & Sakai, 1990; Karasawa et al., 2002; Wang & Takigawa, 2002; Gilling et al., 2009; Heusler, Tourette, & Cussac, 2015; Brosnan & Pham, 2011; Emnett et al., 2015; Liu, Hollmann, Hoenemann, Liu, & Durieux, 2001; Zarantonello et al., 2011; Ogata et al., 2006; Yamakura et al., 2005; Rammes et al., 2001; Yamakura, Sakimura, & Shimoji, 2000; Hondebrink, Kasteel, et al., 2017; Fu et al., 2017; Glasgow, Povysheva, Azofeifa, & Johnson, 2017).

increases in intracellular $Ca^{2+}$ and activation of PKC and intracellular signaling pathways (Millan, Marin, & Mannoury la Cour, 2008; Fig. 9). Serotonin 5-$HT_2$ receptors play important roles in the (central) nervous and cardiovascular system and dysfunction can result in depression, psychosis, addiction and impulsivity as well as hypertension and cardiac failure (Maroteaux et al., 2017). The hallucinogenic effects evoked by phenethylamines are primarily due to activation of the 5-$HT_{2A}$ receptor (Nichols, 2004). For 2C-B, two studies reported activation of the 5-$HT_{2A}$ receptor ($EC_{50}$ 27 and 80 nM), while one study reported inhibition ($IC_{50}$ 5 nM) and another study reported no effect at 10 μM. All NBOMes also potently activate serotonin 5-$HT_{2A}$ receptors (low nanomolar range). Also, 2C-B and the NBOMEs all activate 5-$HT_{2C}$ receptors in the low nanomolar range. 2C-B and 25I-NBOME also potently activate 5-$HT_{2B}$ receptors. In addition to effects on 5-$HT_2$ receptors, hallucinogenic phenethylamines also inhibit uptake of monoamine reuptake transporters, although less potent than the non- or mild hallucinogenic phenethylamines. Of the hallucinogenic phenethylamines, the NBOMEs most potently inhibit SERT and NET ($IC_{50}$ ~ 10 μM; Table 1, Supplemental Figs. 15-18).

For some hallucinogenic phenethylamines binding to other targets is described, including dopamine D1-3 and serotonin 5-$HT_{1,3,5,6,7}$ receptors, although mostly at higher concentrations ($K_i$ values of 250 nM - 10 μM). However, 25I-NBOMe potently binds to serotonin 5-$HT_6$ receptors ($K_i$ value ~30 nM). Hallucinogenic phenethylamines also bind more potently than most non- or mild hallucinogenic phenethylamines to α-adrenergic receptors ($K_i$ < 1 μM; Table 1, Supplemental Figs. 15-18).

### 3.4. Arylcyclohexylamines

#### 3.4.1. Introduction

The first arylcyclohexylamines were synthesized and used in a clinical setting in the 1960's and 1970's. The most well-known arylcyclohexylamine is probably ketamine (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone), also known as 'Special K' or just 'K'. Ketamine is a water soluble phencyclidine (PCP, also known as 'angel dust') derivative that in the past 50 years has been used as a general (and dissociative) anesthetic and in pain management (Chen & Malek, 2015; Sinner & Graf, 2008) as well as in the treatment of several disorders, in particular depression (Sassano-Higgins, Baron, Juarez, Esmaili, & Gold, 2016; Singh et al., 2017; Xu & Lei, 2014). However, by blocking the NMDA receptors, ketamine was reported to produce schizophrenia-like symptoms in healthy adults and to worsen symptoms in schizophrenics (Corazza, Assi, & Schifano, 2013; Javitt, 2004). Just like PCP (Grayson et al., 2016; Mouri, Noda, Enomoto, & Nabeshima, 2007), ketamine has therefore been used for decades to produce rodent models of schizophrenia (Javitt, 2004; Moghaddam & Krystal, 2012). The schizophrenia-like effects of PCP and ketamine not only limit their clinical use, but likely initiated their recreational use. When recreationally used, ketamine is preferably administered by insufflation and to a lesser extent by smoking or injecting (intramuscularly or occasionally intravenously).

PCP is often smoked in combination with tobacco or marijuana and its recreational use has been fluctuating strongly. It was heavily used in the 1960s and '70s (Lodge & Mercier, 2015), after which its use strongly

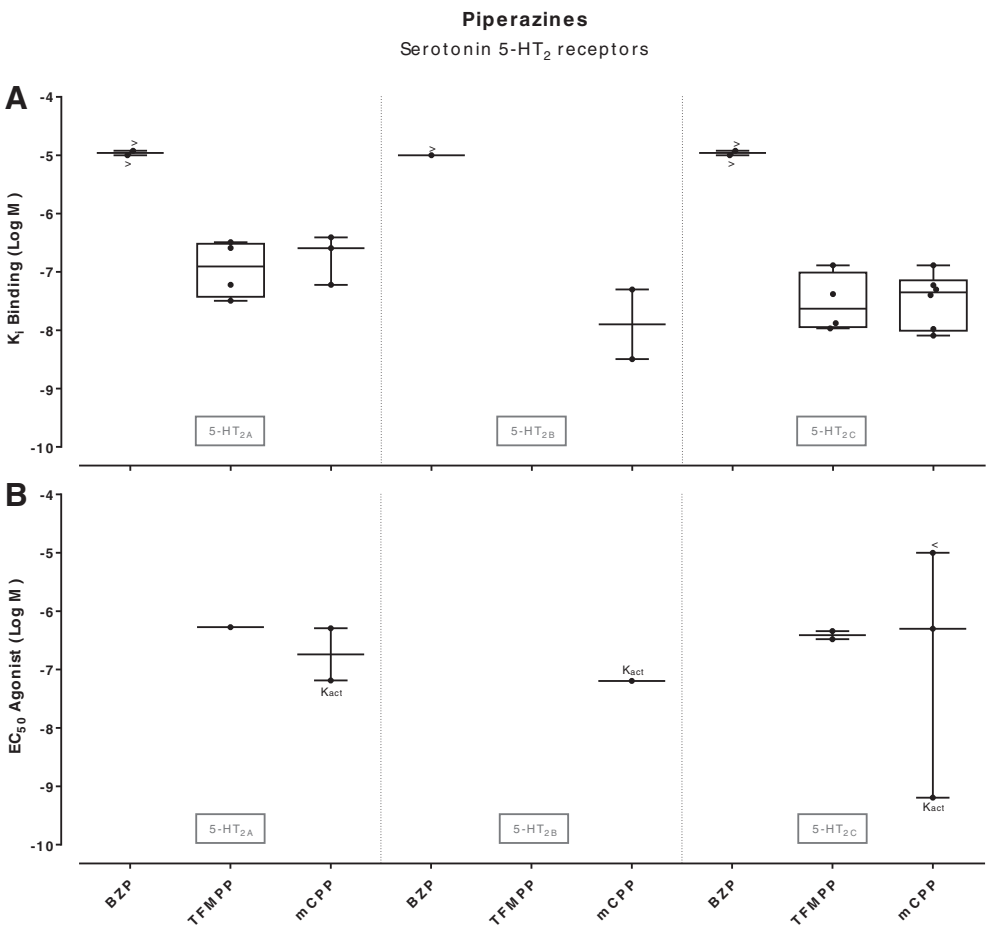


**Fig. 12. Binding to and activation of 5-HT$_2$receptors by different piperazines.** Graphs depict effects on binding ($K_i$; A) and activation ($EC_{50}$; B) for 5-HT$_{2A}$ (left), 5-HT$_{2B}$ (middle) and 5-HT$_{2C}$ (right) receptors. > : effect size smaller than 50% at this concentration, < : effect size larger than 50% at this concentration, $K_{act}$: activation constant.
References: $K_i$ binding: (Simmler, Rickli, Schramm, et al., 2014; Grotewiel, Chu, & Sanders-Bush, 1994; Titeler, Lyon, Davis, & Glennon, 1987; Rothman et al., 2000; Thomas, Gager, Holland, Brown, & Wood, 1996; Quirk et al., 2001; Katz et al., in press). $EC_{50}$ agonist: (Grotewiel et al., 1994; Rothman et al., 2000; Berg et al., 1998; Akiyoshi, Isogawa, Yamada, Nagayama, & Fujii, 1996).

declined. However, it seems that PCP is regaining popularity as the number of PCP-related emergency department visits increased more than 4-fold between 2005-2011 (Bush, 2013). Similarly, ketamine abuse was limited until it became a popular drug on the 'rave' scene in the 1990s. Its popularity increased and a survey among people who went to parties or festivals in the last year in the UK showed that in 2001 25% of the respondents had ever used ketamine, a number that increased up to 68% in 2009. While this percentage is lower in other countries (e.g., 40% in Australia in 2008), ketamine use is widespread in the party scene worldwide, including Asia where it is becoming the drug of choice among young drug users (Kalsi, Wood, & Dargan, 2011; Liu, Lin, Wu, & Zhou, 2016; Morgan & Curran, 2011). Outside the club scene, the prevalence of use is much lower. Last year prevalence among young people (16–24 year) in the UK was around 2%, which is comparable to the US and Canada (Kalsi et al., 2011; Morgan & Curran, 2011).

While ketamine and PCP have an extensive history as a drug of abuse, the ketamine analogue methoxetamine ((RS)-2-(ethylamino)-2-(3-methoxyphenyl)cyclohexanone) entered the drug market as an NPS only in 2010. Methoxetamine, also known as 'MXE', 'Special M', 'M-Ket' and 'MEXXY', was specifically designed to have greater potency at lower doses than ketamine in an attempt to create a 'bladder-friendly' ketamine substitute (Zanda, Fadda, Chiamulera, Fratta, & Fattore, 2016; Zawilska, 2014b). Administration of MXE occurs predominantly by insufflation and oral consumption. It rapidly gained popularity with a life-time prevalence around 5% in the US and the UK. Among ketamine users, lifetime prevalence even amounts to 28% (US: 2012) and 13% (UK: 2012) among ketamine users (Lawn, Borschmann, Cottrel, & Winstock, 2014).

### 3.4.2. Clinical effects

At low recreational doses, ketamine and PCP induce 'giggliness', hallucinations, mild dissociative effects and 'out of body experiences'. At high doses, ketamine induces more severe psychotropic effects (known as the "K-hole") that can range from vivid dreams and hallucinations, to flashbacks, confusion, dissociation, depersonalization and in more severe cases to psychosis and near-death experiences (Corazza et al., 2013; Morgan & Curran, 2011). PCP is additionally known for its tendency to induce aggression and violent behavior as well as psychosis, seizures and coma at higher doses (Bush, 2013).

Due to its wide therapeutic range, death and non-fatal emergencies attributed to ketamine use are relatively rare (Kalsi et al., 2011; Morgan & Curran, 2011). Nevertheless, the number of ketamine-related deaths has increased 10-fold in the UK from 1999 to 2008 (Morgan & Curran, 2011) and severe clinical effects have been reported, including impaired consciousness, tachycardia, chest pain and temporary paralysis (Corazza et al., 2013; Morgan & Curran, 2011; Sassano-Higgins et al., 2016). In addition to these acute symptoms, a range of chronic symptoms has been described, including ulcerative cystitis, intense abdominal pain (known as 'K-cramps'), kidney dysfunction and urinary tract damage, psychosis, and cognitive impairment (Bokor & Anderson, 2014; Corazza et al., 2013; Morgan & Curran, 2011; Sassano-Higgins et al., 2016; Xu & Lei, 2014). However, as ketamine is often used in combination with other drugs such as ethanol, gamma-hydroxybutyrate (GHB), cocaine or MDMA (Kalsi et al., 2011; Morgan & Curran, 2011), it is difficult to ascribe clinical symptoms specifically to a single compound.

As a dissociative anesthetic, MXE produces similar but longer lasting subjective effects as ketamine, including derealization and 'out of body

**Table 1**

**Effect fingerprint of different (classes of) NPS and other drugs.** Drugs are grouped in cathinones, cannabinoids, (non- or mild) hallucinogenic phenethylamines, arylcylcohexylamines, and piperazines. Targets are grouped by effects on monoamine reuptake transporters, receptors and ion channels. The lowest reported drug concentration (log M) that affects the target is listed. For all reported effect concentrations see Figs. 3, 4, 6-8, 11, 12 and Supplemental Figs. 2-24. Colors represent the potency of a drug to affect a specific target; green (> -5.0 M), yellow (-5.1 to -6.0 M), orange (-6.1 to -7.0 M) and red (-7.1 to -10.0 M).

| Drug classification: | | | Cathinones | | | | | | Cannabinoids | | Non- or mild hallucinogenic phenethylamines | | | | | Hallucinogenic phenethylamines | | | | Arylcyclohexylamines | | | Piperazines | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| > 5.0 M; 5.1 – 6.0 M; 6.1 – 7.0 M; 7.1 – 8.0 M; > 8.1 M | | | Mephedrone | 4-MEC | Pentedrone | Methylone | MDPV | α-PVP | THC | JWH-018 | Amphetamine | 4-FA | MDMA | 5-APB | 6-APB | 2C-B | 25B-NBOMe | 25C-NBOMe | 25I-NBOMe | Ketamine | MXE | PCP | BZP | TFMPP | mCPP |
| **Monoamine transporters** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Plasma membrane | $K_i$ Binding | DAT | -5.8[1] | -6.1[2] | -6.5[3] | -5.6[4] | -8.0[4] | -8.2[5] | -5.8[6] | > -5.0[6] | -5.2[4] | -5.0[5] | -5.2[4] | -5.6[7] | -6.2[7] | > -4.5[8] | -5.1[8] | -4.9[8] | -5.3[8] | > -5.0[9] | | | > -5.0[10] | > -4.6[11] | -5.2[11] |
| | | SERT | > -5.0[12] | -5.4[12] | -4.8[3] | > -4.5[4] | -5.9[13] | > -4.5[5] | > -5.0[6] | > -5.0[6] | > -4.6[4] | -4.7[5] | -6.2[14] | -5.5[7] | -4.9[7] | -5.0[8] | -6.1[8] | -5.8[8] | -6.0[8] | > -5.0[9] | -6.3[15] | -5.7[15] | > -5.0[10] | -5.8[11] | -6.2[11] |
| | | NET | > -5.0[12] | -5.2[2] | -5.7[3] | -4.8[13] | -7.1[4] | -7.2[5] | > -5.0[6] | > -5.0[6] | -6.0[4] | -4.9[5] | -4.8[14] | -5.5[7] | -5.7[7] | -4.5[8] | -6.0[8] | -5.8[8] | -5.9[8] | > -5.0[9] | | | -5.1[11] | -4.9[11] | -5.5[11] |
| | $IC_{50}$ Binding | DAT | | | | | | | | | | | > -4.7[16] | > -5.0[16] | | | | | | > -5.0[17] | | | | | -5.4[18] |
| | | SERT | | | | | | | | | | | > -5.0[16] | < -5.0[16] | | | | | | -5.3[19] | | -5.5[20] | | | -6.6[18] |
| | | NET | | | | | | | | | | | > -5.0[16] | > -5.0[16] | | | | | | > -5.0[17] | | | | | > -4.0[18] |
| | $K_i$ Uptake | DAT | | | | | | | | | -7.5[21] | | -5.8[21] | -6.6[22] | -6.8[22] | | | | | S -4.3[23] | | | | | |
| | | SERT | | | | | | | | | -5.8[24] | | -6.6[21] | -6.1[22] | -5.6[22] | | | | | -4.7[19] | | | | | |
| | | NET | | | | | | | | | -7.4[21] | | -6.3[21] | -6.7[22] | -6.9[22] | -4.6[25] | | | | S -4.2[23] | | | | | |
| | $IC_{50}$ Uptake | DAT | -7.0[13] | -6.2[12] | -6.8[3] | -6.5[13] | -8.4[26] | -7.9[27] | | | -7.0[26] | -7.0[3] | -6.7[13] | -5.3[28] | -5.5[7] | -3.7[28] | -4.0[28] | -4.2[8] | -4.3[28] | -4.2[23] | -4.5[28] | | -5.7[29] | > -4.0[11] | -5.1[30] |
| | | SERT | -6.5[1] | -6.3[31] | -5.0[3] | -6.6[32] | -5.9[13] | > -5.0[*1] | | | -5.5[26] | -5.6[33] | -7.0[13] | -6.5[7] | -6.0[7] | -4.7[8] | -5.3[28] | -5.1[8] | -5.4[28] | -3.9[34] | -5.6[28] | -5.6[20] | -4.7[29] | -5.3[11] | -6.8[35] |
| | | NET | -7.3[13] | -5.8[12] | -6.6[3] | -6.6[13] | S -8.0[36] | -7.8[27] | | | -7.2[26] | -7.4[3] | -7.6[13] | -6.8[7] | -6.7[7] | -4.4[8] | -5.2[8] | -5.2[8] | -5.0[8] | -4.1[23] | -4.7[28] | | -6.4[11] | -4.8[11] | -5.8[11] |
| | $EC_{50}$ Release | DAT | R -7.5[37] | > -5.03[1] | > -4.0[3] | -6.9[26] | -9.0[38] | > -4.0[3] | | | -8.2[26] | -7.3[39] | -7.3[40] | < -4.0[7] | > -4.0[7] | | | | | | | > -4.0[41] | -6.8[42] | > -5.0[*2] | > -5.0[*3] |
| | | SERT | R -8.8[37] | -7.03[1] | > -4.0[3] | -6.7[29] | > -5.0[26] | > -4.0[3] | | | -6.2[26] | -6.1[29] | -7.3[40] | > -4.0[7] | > -4.0[7] | | | | | | | | > -5.0[42] | -6.9[42] | -7.6[30] |
| | | NET | -7.2[26] | -6.1[3] | > -4.0[3] | -7.0[29] | -7.9[26] | > -4.0[3] | | | -8.2[26] | -7.6[29] | -7.3[40] | > -4.0[7] | > -4.0[7] | | | | | > -4.5[*4] | | | -7.2[29] | > -4.0[11] | -5.9[29] |
| Vesicular | $K_i$ Binding | VMAT n.s. | | | | | | | | | | | | | | | | | | | | | | | |
| | | VMAT 1 | | | | | | | | | R -4.4[43] | | -4.7[43] | | | | | | | | | | | | |
| | | VMAT 2 | > -3.0[13] | | | > -3.0[13] | -6.0[13] | | | | R -5.9[44] | | -5.4[43] | | | | | | | | | | | | |
| | $IC_{50}$ Binding | VMAT n.s. | | | | | | | | | | | | | | | | | | | | | | | |
| | | VMAT 1 | | | | | | | | | | | | | | | | | | | | | | | |
| | | VMAT 2 | | | | | | | | | -4.4[45] | | > -4.0[*5] | | | | | | | | | | > -4.0[46] | -3.6[46] | -3.7[46] |
| | $K_i$ Uptake | VMAT n.s. | | | | | | | | | | | | | | | | | | | | | | | |
| | | VMAT 1 | | | | | | | | | | | | | | | | | | | | | | | |
| | | VMAT 2 | | | | | | | | | R -5.9[44] | | -5.0[44] | | | | | | | | | | | | |
| | $IC_{50}$ Uptake | VMAT n.s. | | | | | | | | | -5.3[47] | | | | | | | | | | | -4.5[47] | | | |
| | | VMAT 1 | | | | | | | | | | | | | | | | | | | | | | | |
| | | VMAT 2 | -5.5[32] | | | -4.7[32] | > -4.0[13] | | | | R -5.5[46] | | -5.2[13] | | | | | | | | | | > -4.0[46] | -4.9[46] | -3.9[46] |
| | $EC_{50}$ Release | VMAT n.s. | | | | | | | | | -5.7[45] | | | | | | | | | | | | | | |
| | | VMAT 1 | | | | | | | | | | | | | | | | | | | | | | | |
| | | VMAT 2 | -4.2[13] | | | > -4.0[13] | -3.8[13] | | | | R -5.6[46] | | -4.8[46] | | | | | | | | | | > -4.0[46] | -4.7[46] | -4.6[46] |
| **Receptors** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Dopamine | $K_i$ Binding | D1 | > -5.0[*6] | > -5.0[12] | > -4.9[2] | > -5.0[13] | > -5.0[13] | > -4.9[5] | > -5.0[6] | > -5.0[6] | > -4.9[4] | > -4.9[5] | > -5.0[13] | > -4.9[7] | > -4.9[7] | -4.9[8] | -5.0[8] | -4.9[8] | -5.2[8] | | | | > -5.0[10] | > -4.9[11] | > -6.0[48] |
| | | D2 | > -5.0[*6] | > -5.0[*7] | > -5.0[2] | > -5.0[13] | > -5.0[13] | > -5.0[5] | > -5.0[6] | > -5.0[6] | > -4.5[4] | > -4.7[5] | > -5.0[13] | > -5.0[7] | > -5.0[7] | -5.7[8] | -6.1[8] | -5.8[8] | -6.0[8] | -8.1[49] | | -8.6[50] | > -5.0[*8] | -5.9[11] | > -6.0[48] |
| | | D3 | > -5.0[4] | > -5.0[12] | > -4.8[2] | > -5.0[4] | > -5.0[4] | > -4.8[5] | > -5.0[6] | > -5.0[6] | > -4.8[4] | > -4.8[5] | > -5.0[13] | > -5.0[22] | > -5.0[22] | -5.0[8] | -5.6[8] | -5.5[8] | -5.7[8] | | | | > -5.0[10] | -6.3[11] | -5.6[11] |
| | | D4 | > -5.0[*6] | > -5.0[12] | | > -5.0[13] | > -5.0[13] | | > -5.0[6] | > -5.0[6] | | | > -5.0[13] | > -5.4[22] | > -5.0[22] | | | | | | | | > -5.0[10] | | |
| | | D5 | > -5.0[12] | > -5.0[12] | | | | | > -5.0[6] | > -5.0[6] | | | | | | | | | | | | | > -5.0[10] | | |
| | $IC_{50}$ Binding | D1 | | | | | | | | | | | > -5.0[16] | > -5.0[16] | | | | | | > -5.0[17] | | | | | -5.2[51] |
| | | D2 | | | | | | | | | | | > -5.0[16] | > -5.0[16] | | | | | | > -5.0[17] | | | | | -5.0[51] |
| | | D3 | | | | | | | | | | | > -5.0[16] | > -5.0[16] | | | | | | > -5.0[17] | | | | | |
| | | D4 | | | | | | | | | | | > -5.0[16] | > -5.0[16] | | | | | | > -5.0[17] | | | | | |
| | | D5 | | | | | | | | | | | | | | | | | | > -5.0[17] | | | | | |
| | $EC_{50}$ Agonist | D1 | | | | | | | | | | | | | | | | | | | | | | | |
| | | D2 | | | | | | | | | | | | | | | | | | -6.0[52] | | -8.4[53] | | | |
| | | D3 | | | | | | | | | | | | | | | | | | | | | | | |
| | | D4 | | | | | | | | | | | | | | | | | | | | | | | |
| | | D5 | | | | | | | | | | | | | | | | | | | | | | | |

(*continued on next page*)

**Table 1** (*continued*)

| Drug classification: | | | Cathinones | | | | | | Cannabinoids | | Non- or mild hallucinogenic phenethylamines | | | | | Hallucinogenic phenethylamines | | | | Arylcyclohexylamines | | | Piperazines | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| > 5.0 M; 5.1 – 6.0 M; 6.1 – 7.0 M; 7.1 – 8.0 M; > 8.1 M | | | Mephedrone | 4-MEC | Pentedrone | Methylone | MDPV | α-PVP | THC | JWH-018 | Amphetamine | 4-FA | MDMA | 5-APB | 6-APB | 2C-B | 25B-NBOMe | 25C-NBOMe | 25I-NBOMe | Ketamine | MXE | PCP | BZP | TFMPP | mCPP |
| **Receptors** | | | | | | | | | | | | | | | | | | | | | | | | | |
| 5-HT$_1$ | K$_i$ Binding | n.s. | | | | | | | | | | | -4.6[14] | | | | | | | | | | | -7.2[54] | |
| | | 1a | > -5.0[12] | > -5.0[12] | > -4.7[2] | > -4.7[4] | -5.0[4] | -5.3[5] | > -5.0[6] | > -5.0[6] | -5.2[4] | -5.4[5] | -4.9[4] | -5.5[7] | -5.9[22] | -6.6[8] | -5.4[8] | -5.3[8] | -6.0[55] | | | | > -5.0[10] | -6.8[11] | -7.7[56] |
| | | 1b | -5.8[12] | > -5.0[12] | | | | | > -5.0[6] | > -5.0[6] | | | | > -5.0[22] | > -5.0[22] | | | | -5.2[55] | | | | > -5.0[10] | K$_d$ -6.9[57] | K$_d$ -6.5[57] |
| | | 1d | > -5.0[12] | > -5.0[12] | | | | | > -5.0[6] | > -5.0[6] | | | | -5.3[22] | -5.5[22] | | | | -6.3[55] | | | | > -5.0[10] | K$_d$ -6.6[57] | K$_d$ -5.8[57] |
| | | 1e | | | | | | | > -5.0[6] | > -5.0[6] | | | | | | | | | > -5.0[55] | | | | > -5.0[10] | | |
| | | 1f | | | | | | | | | | | | | | | | | | | | | | | |
| | IC$_{50}$ Binding | n.s. | | | | | | | | | | | | | | | | | | | | -4.1[20] | | | |
| | | 1a | | | | | | | | | | | | | | | | | | > -5.0[17] | | | | | -6.4[51] |
| | | 1b | | | | | | | | | | | | | | | | | | > -5.0[17] | | | | | |
| | | 1d | | | | | | | | | | | | | | | | | | | | | | | -5.9[51] |
| | | 1e | | | | | | | | | | | | | | | | | | | | | | | |
| | | 1f | | | | | | | | | | | | | | | | | | | | | | | |
| | EC$_{50}$ Agonist | n.s. | | | | | | | | | | | | | | | | | | | | | | | |
| | | 1a | -3.9[13] | | | -3.9[13] | -4.2[13] | | | | | | -4.5[13] | | | | | | | | | | | | |
| | | 1b | | | | | | | | | | | | | | | | | | | | | | | |
| | | 1d | | | | | | | | | | | | | | | | | | | | | | | |
| | | 1e | | | | | | | | | | | | | | | | | | | | | | | |
| | | 1f | | | | | | | | | | | | | | | | | | | | | | | |
| 5-HT$_2$ | K$_i$ Binding | n.s. | | | | | | | | | | | -5.3[14] | -6.3[22] | -6.1[22] | | | | | -4.8[52] | | -5.3[52] | | | -7.4[48] |
| | | 2a | -5.4[1] | > -5.0[12] | | -5.0[32] | | | | | | | | | | | | | | | | | | | |
| | | 2b | -5.8[58] | -5.4[2] | > -4.9[2] | > -4.9[4] | > -4.9[4] | > -4.9[5] | > -5.0[6] | > -5.0[6] | > -4.9[4] | -4.9[5] | -5.2[7] | -6.1[7] | -6.0[7] | -9.2[59] | -9.7[60] | -9.2[8] | -10.4[61] | | | | > -5.0[10] | -7.5[62] | -7.2[11] |
| | | 2c | -6.1[12] | > -5.0[12] | | | | | -6.1[6] | -6.5[6] | | | | -7.9[22] | -8.4[22] | | | | -8.9[55] | | | | > -5.0[10] | | -8.5[63] |
| | | | -5.1[58] | -5.3[2] | > -4.9[2] | -5.0[13] | > -4.9[4] | > -4.9[5] | > -5.0[6] | > -5.0[6] | > -4.9[4] | -5.1[5] | -5.9[13] | -6.1[7] | -6.6[7] | -7.6[60] | -8.6[64] | -8.3[8] | -9.3[55] | | | | > -5.0[10] | -8.0[65] | -8.1[65] |
| | IC$_{50}$ Binding | n.s. | | | | | | | | | | | | | | | | | | | | -6.8[20] | | | -6.4[51] |
| | | 2a | | | | | | | | | | | < -5.0[16] | < -5.0[16] | | | | | | > -5.0[17] | | > -4.0[66] | | | |
| | | 2b | | | | | | | | | | | < -5.0[16] | < -5.0[16] | | | | | | > -5.0[17] | | | | | |
| | | 2c | | | | | | | | | | | < -5.0[16] | < -5.0[16] | | | | | | > -5.0[17] | | | | | |
| | EC$_{50}$ Agonist | n.s. | | | | | | | | | | | | | | | | | | | | | | | |
| | | 2a | -6.4[58] | | | | | | | | | | > -5.0[16] | -5.2[7] | -5.2[7] | -7.6[59] | -9.0[64] | -6.8[8] | -9.4[61] | | | | | -6.3[67] | K$_a$ -7.2[63] |
| | | 2b | > -5.0[58] | | | | > -4.7[4] | > -4.7[5] | | | | -4.9[5] | > -5.0[16] | -7.8[22] | -8.4[22] | -6.9[8] | | | -7.8[55] | | | | | | K$_a$ -7.2[63] |
| | | 2c | | | | | | | | | | | K$_d$ -5.6[68] | | | -6.8[69] | -9.0[64] | -7.0[8] | -7.4[55] | | | | | -6.5[70] | K$_a$ -9.2[63] |
| | IC$_{50}$ Antagonist | n.s. | | | | | | | | | | | | | | | | | | | | | | | |
| | | 2a | -4.8[13] | | | -3.8[13] | -3.6[13] | | | | | | -5.2[13] | -5.4[71] | | -8.3[72] | | | | | | | | | |
| | | 2b | | | | | | | | -4.5[6] | | | | | | | | | | | | | | | K$_d$ -7.5[73] |
| | | 2c | > -3.4[13] | | | > -3.0[13] | > -3.0[13] | | | | | | | | | | | | | | | | | | |
| 5-HT$_3$ | K$_i$ Binding | n.s. | | | | | | | > -5.0[6] | > -5.0[6] | | | | | | | | | > -5.0[55] | -4.0[74] | | | > -5.0[10] | | -7.3[75] |
| | IC$_{50}$ Binding | n.s. | | | | | | | | | | | | | | | | | | > -5.0[17] | | | | | |
| | IC$_{50}$ Antagonist | n.s. | | | | | | | | | | | | | | | | | | S -4.0[76] | | | | | |
| 5-HT$_4$ | K$_i$ Binding | n.s. | | | | | | | | | | | | | | | | | | | | | > -5.0[10] | | |
| 5-HT$_5$ | K$_i$ Binding | n.s. | | | | | | | | | | | | | | | | | | | | | | | |
| | | 5a | | | | | | | > -5.0[6] | > -5.0[6] | | | | | | | | | -5.6[55] | | | | | | |
| | IC$_{50}$ Binding | n.s. | | | | | | | | | | | | | | | | | | | | | | | |
| | | 5a | | | | | | | | | | | | | | | | | | > -5.0[17] | | | | | |
| 5-HT$_6$ | K$_i$ Binding | n.s. | > -5.0[12] | > -5.0[12] | | | | | > -5.0[6] | > -5.0[6] | | | | > -5.0[22] | > -5.0[22] | | | | -7.5[55] | | | | | | |
| | IC$_{50}$ Binding | n.s. | | | | | | | | | | | | | | | | | | > -5.0[17] | | | | | |
| 5-HT$_7$ | K$_i$ Binding | n.s. | > -5.0[12] | > -5.0[12] | | | | | > -5.0[6] | > -5.0[6] | | | | -6.0[22] | -6.8[22] | | | | -5.8[55] | | | | | | |
| | IC$_{50}$ Binding | n.s. | | | | | | | | | | | | | | | | | | > -5.0[17] | | | | | |
| | IC$_{50}$ Antagonist | n.s. | | | | | | | | | | | | | | | | | | | | | | -6.1[77] | -6.7[77] |

(*continued on next page*)

**Table 1** (*continued*)

| Drug classification: | | | Cathinones | | | | | | Cannabinoids | | Non- or mild hallucinogenic phenethylamines | | | | | Hallucinogenic phenethylamines | | | | Arylcyclohexylamines | | | Piperazines | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| > 5.0 M; 5.1 – 6.0 M; 6.1 – 7.0 M; 7.1 – 8.0 M; > 8.1 M | | | Mephedrone | 4-MEC | Pentedrone | Methylone | MDPV | α-PVP | THC | JWH-018 | Amphetamine | 4-FA | MDMA | 5-APB | 6-APB | 2C-B | 25B-NBOMe | 25C-NBOMe | 25I-NBOMe | Ketamine | MXE | PCP | BZP | TFMPP | mCPP |
| **Receptors** | | | | | | | | | | | | | | | | | | | | | | | | | |
| α-Adrenergic | $K_i$ Binding | n.s. | | | | | | | | | | | | | | | | | | | | | | | |
| | | α1 | -6.0[58] | > -5.2[2] | > -5.2[2] | > -5.2[4] | > -5.2[4] | > -4.8[5] | > -5.0[6] | > -5.0[6] | > -5.2[4] | > -5.3[5] | > -5.2[4] | -5.5[7] | -5.1[7] | -5.1[8] | -6.4[8] | -6.1[8] | -6.4[8] | $K_d$ -2.5[78] | | | > -5.2[11] | > -5.2[11] | -6.6[48] |
| | | α2 | > -5.3[12] | > -5.0[12] | -4.5[2] | > -4.7[4] | > -4.7[4] | > -4.7[5] | > -5.0[6] | > -5.0[6] | -5.6[4] | -5.4[5] | -5.4[14] | -6.3[22] | -7.3[22] | -6.5[8] | -6.4[8] | -6.3[8] | -6.5[8] | | | | -5.4[10] | -6.1[11] | -6.6[11] |
| | | α3 | | | | | | | | | | | | | | | | | | | | | | | |
| | $IC_{50}$ Binding | n.s. | | | | | | | | | | | | | | | | | | | | | | | |
| | | α1 | | | | | | | | | | | > -5.0[16] | > -5.0[16] | | | | | | > -5.0[17] | | | | | -5.5[51] |
| | | α2 | | | | | | | | | | | > -5.0[16] | < -5.0[16] | | | | | | > -5.0[17] | | | | | -6.2[51] |
| | | α3 | | | | | | | | | | | | | | | | | | | | | | | |
| | $IC_{50}$ Antagonist | n.s. | | | | | | | | | | | | | | | | | | | | | | | |
| | | α1 | | | | | | | | | | | | | | | | | | > -4.4[79] | | | | | |
| | | α2 | | | | | | | | | | | | | | | | | | > -4.4[79] | | | | | |
| | | α3 | | | | | | | | | | | | | | | | | | > -4.4[79] | | | | | |
| β-Adrenergic | $K_i$ Binding | n.s. | | | | | | | | | | | -4.7[14] | | | | | | | | | | | | |
| | | β1 | > -5.0[12] | > -5.0[12] | | | | | > -5.0[6] | > -5.0[6] | | | | > -5.0[22] | -5.4[22] | | | | | | | | > -5.0[10] | | |
| | | β2 | | | | | | | > -5.0[6] | > -5.0[6] | | | | | | | | | | $K_d$ -3.5[78] | | | > -5.0[10] | | |
| | | β3 | | | | | | | > -5.0[6] | > -5.0[6] | | | | | | | | | | | | | > -5.0[10] | | |
| | $IC_{50}$ Binding | n.s. | | | | | | | | | | | | | | | | | | | | | | | -5.6[51] |
| | | β1 | | | | | | | | | | | > -5.0[16] | > -5.0[16] | | | | | | > -5.0[17] | | | | | |
| | | β2 | | | | | | | | | | | > -5.0[16] | > -5.0[16] | | | | | | > -5.0[17] | | | | | |
| | | β3 | | | | | | | | | | | | | | | | | | | | | | | |
| $GABA_A$ | $K_i$ Binding | n.s. | | | | | | | > -5.0[6] | -6.2[6] | | | | | | | | | | | | | | | |
| | | α1 | | | | | | | | | | | | | | | | | | | | | > -5.0[10] | | |
| | | α1β2γ2 | | | | | | | | | | | | | | | | | | | | | | | |
| | | α2 | | | | | | | | | | | | | | | | | | | | | > -5.0[10] | | |
| | | α3 | | | | | | | | | | | | | | | | | | | | | > -5.0[10] | | |
| | | α5 | | | | | | | | | | | | | | | | | | | | | > -5.0[10] | | |
| | | α6 | | | | | | | | | | | | | | | | | | | | | > -5.0[10] | | |
| | | α6β2δ | | | | | | | | | | | | | | | | | | | | | | | |
| | | α6β3δ | | | | | | | | | | | | | | | | | | | | | | | |
| | $IC_{50}$ Binding | n.s. | | | | | | | | | | | > -5.0[16] | > -5.0[16] | | | | | | > -5.0[17] | | | | | > -4.0[51] |
| | | α1 | | | | | | | | | | | | | | | | | | | | | | | |
| | | α1β2γ2 | | | | | | | | | | | | | | | | | | | | | | | |
| | | α2 | | | | | | | | | | | | | | | | | | | | | | | |
| | | α3 | | | | | | | | | | | | | | | | | | | | | | | |
| | | α5 | | | | | | | | | | | | | | | | | | | | | | | |
| | | α6 | | | | | | | | | | | | | | | | | | | | | | | |
| | | α6β2δ | | | | | | | | | | | | | | | | | | | | | | | |
| | | α6β3δ | | | | | | | | | | | | | | | | | | | | | | | |
| | $EC_{50}$ Agonist | n.s. | | | | | | | | | | | | | | | | | | -2.2[80] | > -5.0[79] | | | | |
| | | α1 | | | | | | | | | | | | | | | | | | | | | | | |
| | | α1β2γ2 | | | | | | | | | | | | | | | | | | | | | | | |
| | | α2 | | | | | | | | | | | | | | | | | | | | | | | |
| | | α3 | | | | | | | | | | | | | | | | | | | | | | | |
| | | α5 | | | | | | | | | | | | | | | | | | | | | | | |
| | | α6 | | | | | | | | | | | | | | | | | | | | | | | |
| | | α6β2δ | | | | | | | | | | | | | | | | | | -3.2[81] | | | | | |
| | | α6β3δ | | | | | | | | | | | | | | | | | | -3.6[81] | | | | | |

(*continued on next page*)

**Table 1** (*continued*)

| Drug classification: | | | Cathinones | | | | | | Cannabinoids | | Non- or mild hallucinogenic phenethylamines | | | | | Hallucinogenic phenethylamines | | | | Arylcyclohexylamines | | | Piperazines | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| > 5.0 M | 5.1 – 6.0 M | 6.1 – 7.0 M | 7.1 – 8.0 M | > 8.1 M | Mephedrone | 4-MEC | Pentedrone | Methylone | MDPV | α-PVP | THC | JWH-018 | Amphetamine | 4-FA | MDMA | 5-APB | 6-APB | 2C-B | 25B-NBOMe | 25C-NBOMe | 25I-NBOMe | Ketamine | MXE | PCP | BZP | TFMPP | mCPP |
| **Receptors** | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| $GABA_A$ | $IC_{50}$ Antagonist | n.s. | | | | | | | | | | -6.6[82] | | | | | | | | | | | | | | | |
| | | α1 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | α1β2γ2 | | | | | | | | | | | | | > -3.0[*10] | | | | | | | | | | > -3.0[83] | -3.0[83] | > -4.0[*11] |
| | | α2 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | α3 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | α5 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | α6 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | α6β2δ | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | α6β3δ | | | | | | | | | | | | | | | | | | | | | | | | | |
| $GABA_B$ | $K_i$ Binding | n.s. | | | | | | | | | | | | | | | | | | | | | | | > -5.0[10] | | |
| NMDA | $K_i$ Binding | n.s. | | | | | | | | | | | | | | | | | | | | -6.9[17] | -6.6[15] | -7.6[84] | | | |
| | | NR1/NR2A | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | NR1/NR2B | | | | | | | | | | | | | | | | | | | | | | | | | |
| | $IC_{50}$ Binding | n.s. | | | | | | | | | | | | | > -5.0[16] | > -5.0[16] | | | | | | -6.5[85] | | -4.2[86] | | | |
| | | NR1/NR2A | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | NR1/NR2B | | | | | | | | | | | | | | | | | | | | | | | | | |
| | $IC_{50}$ Antagonist | n.s. | | | | | | | | | | | | | | | | | | | | > -7.0[87] | > -5.0[*12] | -9.3[88] | | | |
| | | NR1/NR2A | | | | | | | | | | | | | | | | | | | | -6.3[89] | | -7.1[90] | | | |
| | | NR1/NR2B | | | | | | | | | | | | | | | | | | | | -6.4[91] | | -7.3[90] | | | |
| AMPA | $IC_{50}$ Binding | n.s. | | | | | | | | | | | | | -5.0[16] | -5.0[16] | | | | | | | | | | | |
| Kainate | $IC_{50}$ Binding | n.s. | | | | | | | | | | | | | -5.0[16] | -5.0[16] | | | | | | | | | | | |
| mACh | $K_i$ Binding | n.s. | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | M1 | > -5.0[12] | > -5.0[12] | | | | | | | -5.8[6] | > -5.0[6] | | | -5.2[14] | > -5.0[22] | > -5.0[22] | | | | | -4.3[92] | | | > -5.0[10] | | |
| | | M2 | > -5.0[12] | > -5.0[12] | | | | | | | > -5.0[6] | > -5.0[6] | | | -4.8[14] | > -5.0[22] | > -5.0[22] | | | | | -3.5[92] | | | > -5.0[10] | | |
| | | M3 | > -5.0[12] | > -5.0[12] | | | | | | | > -5.0[6] | > -5.0[6] | | | | > -5.0[22] | > -5.0[22] | | | | | -3.6[92] | | | > -5.0[10] | | |
| | | M4 | > -5.0[12] | > -5.0[12] | | | | | | | > -5.0[6] | > -5.0[6] | | | | > -5.0[22] | > -5.0[22] | | | | | | | | > -5.0[10] | | |
| | | M5 | > -5.0[12] | > -5.0[12] | | | | | | | > -5.0[6] | > -5.0[6] | | | | > -5.0[22] | > -5.0[22] | | | | | | | | > -5.0[10] | | |
| | $IC_{50}$ Binding | n.s. | | | | | | | | | | | | | > -5.0[16] | > -5.0[16] | | | | | | -4.6[93] | | -4.9[94] | | | -4.6[51] |
| | | M1 | | | | | | | | | | | | | | | | | | | | > -5.0[17] | | | | | |
| | | M2 | | | | | | | | | | | | | | | | | | | | > -5.0[17] | | | | | |
| | | M3 | | | | | | | | | | | | | | | | | | | | > -5.0[17] | | | | | |
| | | M4 | | | | | | | | | | | | | | | | | | | | > -5.0[17] | | | | | |
| | | M5 | | | | | | | | | | | | | | | | | | | | > -5.0[17] | | | | | |
| | $IC_{50}$ Antagonist | n.s. | | | | | | | | | | | | | | | | | | | | > -5.0[95] | | | | | |
| | | M1 | | | | | | | | | | | | | | | | | | | | -5.2[96] | | | | | |
| | | M2 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | M3 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | M4 | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | M5 | | | | | | | | | | | | | | | | | | | | | | | | | |
| nACh | $K_i$ Binding | n.s. | | | | | | | | | | | | | | | | | | | | | | -6.4[97] | | | |
| | | α3β4 | | | | | | | | | | | | | | | | | | | | | | -5.0[97] | > -5.0[10] | | |
| | | α4β2 | | | | | | | | | | | | | | | | | | | | | | | > -5.0[10] | | |
| | | α7 | | | | | | | | | | | | | | | | | | | | | | | > -5.0[10] | | |
| | | α2β2 | | | | | | | | | | | | | | | | | | | | | | | > -5.0[10] | | |
| | | α3β2 | | | | | | | | | | | | | | | | | | | | | | | > -5.0[10] | | |
| | | α2β4 | | | | | | | | | | | | | | | | | | | | | | | > -5.0[10] | | |
| | | α4β4 | | | | | | | | | | | | | | | | | | | | | | | > -5.0[10] | | |
| | | α2βγδ | | | | | | | | | | | | | | | | | | | | | | | | | |

(*continued on next page*)

**Table 1** (*continued*)

| Drug classification: | | | Cathinones | | | | | | Cannabinoids | | Non- or mild hallucinogenic phenethylamines | | | | | Hallucinogenic phenethylamines | | | | Arylcyclohexylamines | | | Piperazines | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| > 5.0 M / 5.1 – 6.0 M / 6.1 – 7.0 M / 7.1 – 8.0 M / > 8.1 M | | | Mephedrone | 4-MEC | Pentedrone | Methylone | MDPV | α-PVP | THC | JWH-018 | Amphetamine | 4-FA | MDMA | 5-APB | 6-APB | 2C-B | 25B-NBOMe | 25C-NBOMe | 25I-NBOMe | Ketamine | MXE | PCP | BZP | TFMPP | mCPP |
| **Receptors** | | | | | | | | | | | | | | | | | | | | | | | | | |
| nACh | IC$_{50}$ Binding | n.s. | | | | | | | | | | | | | | | | | | -5.0$^{98}$ | | | | | |
| | | α3β4 | | | | | | | | | | | | | | | | | | | | | | | |
| | | α4β2 | | | | | | | | | | | < -5.0$^{16}$ | > -5.0$^{16}$ | | | | | | | | | | | |
| | | α7 | | | | | | | | | | | | | | | | | | | | | | | |
| | | α2β2 | | | | | | | | | | | | | | | | | | | | | | | |
| | | α3β2 | | | | | | | | | | | | | | | | | | | | | | | |
| | | α2β4 | | | | | | | | | | | | | | | | | | | | | | | |
| | | α4β4 | | | | | | | | | | | | | | | | | | | | | | | |
| | | α2βγδ | | | | | | | | | | | | | | | | | | | | | | | |
| | IC$_{50}$ Antagonist | n.s. | | | | | | | | | > -4.0$^{99}$ | | > -4.0$^{99}$ | | | | | | | -7.1$^{100}$ | > -5.0$^{*13}$ | | | | > -5.0$^{99}$ |
| | | α3β4 | | | | | | | | | | | | | | | | | | -5.5$^{101}$ | | -5.2$^{102}$ | | | |
| | | α4β2 | | | | | | | | | | | | | | | | | | -4.3$^{103}$ | | > -5.0$^{104}$ | | | |
| | | α7 | | | | | | | | | | | | | | | | | | > -6.0$^{*14}$ | | -5.9$^{102}$ | | | |
| | | α2β2 | | | | | | | | | | | | | | | | | | -4.0$^{105}$ | | > -5.0$^{104}$ | | | |
| | | α3β2 | | | | | | | | | | | | | | | | | | -4.3$^{105}$ | | > -5.0$^{104}$ | | | |
| | | α2β4 | | | | | | | | | | | | | | | | | | -4.5$^{105}$ | | | | | |
| | | α4β4 | | | | | | | | | | | | | | | | | | -6.6$^{106}$ | | | | | |
| | | α2βγδ | | | | | | | | | | | | | | | | | | -4.5$^{107}$ | | | | | |
| Glycine | | No data | | | | | | | | | | | | | | | | | | | | | | | |
| Cannabinoid | K$_i$ Binding | CB1 | | | | | | | -8.3$^{108}$ | -9.3$^{109}$ | | | | | | | | | | | | | | | |
| | | CB2 | | | | | | | -8.8$^{108}$ | -8.5$^{110}$ | | | | | | | | | | | | | | | |
| | IC$_{50}$ Binding | CB1 | | | | | | | | | | | | | | | | | | > -5.0$^{17}$ | | | | | |
| | | CB2 | | | | | | | | | | | | | | | | | | | | | | | |
| | EC$_{50}$ Agonist | CB1 | | | | | | | -8.0$^{111}$ | -9.1$^{112}$ | | | | | | | | | | | | | | | |
| | | CB2 | | | | | | | -7.4$^{113}$ | -8.4$^{114}$ | | | | | | | | | | | | | | | |
| **Ion channels** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Chloride | | No data | | | | | | | | | | | | | | | | | | | | | | | |
| Sodium | IC$_{50}$ Binding | n.s. | | | | | | | | | | | | | | | | | | > -5.0$^{17}$ | | | | | |
| | IC$_{50}$ Antagonist | n.s. | > -4.5$^{115}$ | | | | | | | | | | | | | | | | | > -5.0$^{116}$ | | | | | |
| Potassium | IC$_{50}$ Binding | n.s. | | | | | | | | | | | | | | | | | | > -5.0$^{17}$ | | | | | |
| | EC$_{50}$ Agonist | n.s. | | | | | | | | -3.6$^{6}$ | | | | | | | | | | | | | | | |
| | IC$_{50}$ Antagonist | n.s. | | | | | | | | | | | | | | | | | | -5.4$^{117}$ | | -4.7$^{118}$ | | | |
| Calcium | K$_i$ Binding | n.s. | | | | | | | | | | | | | | | | | | -3.4$^{119}$ | | | | | |
| | IC$_{50}$ Binding | n.s. | | | | | | | | | | | | | | | | | | > -5.0$^{17}$ | | | | | |
| | IC$_{50}$ Antagonist | n.s. | > -4.5$^{115}$ | | | | | | | | > -3.7$^{120}$ | | > -3.0$^{*15}$ | | | | | | | -5.0$^{121}$ | > -5.0$^{122}$ | -5.2$^{123}$ | | -4.3$^{124}$ | > -4.0$^{99}$ |
| **Other endpoints** | | | | | | | | | | | | | | | | | | | | | | | | | |
| [Ca$^{2+}$]$_i$ | EC$_{50}$ Agonist | | | | | | | | | | | | | | | | | | | > -4.0$^{*16}$ | | | | | |
| Exocytosis | IC$_{50}$ Antagonist | | | | | | | | | | > -3.7$^{120}$ | | > -3.0$^{125}$ | | | | | | | -4.6$^{126}$ | | | | | |
| Neuronal act. | IC$_{50}$ | | | | | | | | | -7.9$^{127}$ | -4.0$^{128}$ | -3.9$^{128}$ | -4.0$^{128}$ | | | | | | | -6.2$^{129}$ | -6.3$^{*17}$ | | | | -4.5$^{128}$ |
| ROS | LOEC | | < -1.7$^{130}$ | | | < -2.7$^{131}$ | < -2.9$^{131}$ | | | | | | > -2.8$^{131}$ | | | | | | | < -5.0$^{132}$ | | | > -3.3$^{10}$ | > -4.0$^{133}$ | |
| Cytotoxicity | IC$_{50}$ | | > -4.0$^{134}$ | | | > -4.0$^{134}$ | > -3.5$^{135}$ | | | > -4.5$^{136}$ | > -3.0$^{128}$ | > -3.0$^{128}$ | > -3.0$^{*18}$ | | | | | | | > -5.0$^{137}$ | > -3.0$^{128}$ | > -4.6$^{138}$ | -3.1$^{133}$ | -4.4$^{133}$ | > -3.0$^{128}$ |

*1: 27, 139. *2: 42, 140. *3: 30, 140, 141, 142. *4: 143, 144. *5: 44, 46. *6: 12, 13. *7: 2, 12. *8: 10, 11. *9: 122, **1. *10: 145, 146. *11: 83, 145, 146. *12: 122, **2. *13: 122, **3. *14: 101, 147. *15: 99, 125. *16: 148, 149. *17: 122, 128. *18: 125, 128, 130.

**1: GABA n.s., **2: Glutamate n.s., **3: Acetylcholine n.s.

> : effect size smaller than 50% at this concentration, < : effect size larger than 50% at this concentration (IC$_{50}$not specified) at this concentration. K$_d$: dissociation constant, K$_a$: activation constant, S: S-isomer of corresponding compound, R: R-isomer of corresponding compounds, n.s.: non-specified, [Ca$^{2+}$]$_i$: Intracellular calcium concentration, Neuronal act.: Neuronal activity, LOEC: Lowest observed effect concentration.

[1]: (Martínez-Clemente et al., 2012), [2]: (Simmler, Rickli, Hoener, et al., 2014), [3]: (Eshleman et al., 2017), [4]: (Simmler et al., 2013), [5]: (Rickli, Hoener, et al., 2015), [6]: (Wiley et al., 2016), [7]: (Rickli, Kopf, et al., 2015), [8]: (Rickli, Luethi, et al., 2015), [9]: (Can et al., 2016), [10]: (Katz et al., in press) [11]: (Simmler, Rickli, Schramm, et al., 2014), [12]: (Iversen et al., 2014), [13]: (Eshleman et al., 2013), [14]: (Battaglia, Brooks, Kulsakdinun, & De Souza, 1988), [15]: (Roth et al., 2013), [16]: (Shimshoni et al., 2017), [17]: (Sałat et al., 2015), [18]: (Baumann, Mash, & Staley, 1995), [19]: (Martin, Introna, & Aronstam, 1990), [209]: (Hori et al., 1996), [21]: (Rothman et al., 2001), [22]: (Iversen et al., 2013), [23]: (Nishimura et al., 1998), [24]: (Heal et al., 1998), [25]: (Montgomery et al., 2007), [26]: Baumann et al., 2013), [27]: (Marusich et al., 2014), [28]: (Zwartsen et al., 2017), [29]: (Nagai et al., 2007), [30]: (Baumann et al., 2000), [31]: (Saha et al., 2015), [32]: (Lõpez-Arnau et al., 2012), [33]: (Marona-Lewicka et al., 1995), [34]: (Zhao & Sun, 2008), [35]: (Baumann, Ayestas, Dersch, & Rothman, 2001), [36]: (Kolanos, Sakloth, et al., 2015), [37]: (Gregg et al., 2015), [38]: (Shekar et al., 2017), [39]: (Baumann et al., 2011), [40]: (Baumann et al., 2012), [41]: (Eshleman et al., 1994), [442]: (Baumann et al., 2004), [43]: (Erickson, Schäfer, Bonner, Eiden, & Weihe, 1996), [44]: (Schwartz, Weizman, & Rehavi, 2006), [45]: (Teng, Crooks, & Dwoskin, 1998), [46]: (Partilla et al., 2006), [47]: (Ary & Komiskey, 1980), [48]: (Martin et al., 1989), [49]: (Seeman & Guan, 2008), [50]: (Seeman et al., 2005), [51]: (Hamik & Peroutka, 1989), [52]: (Kapur & Seeman, 2002), [53]: (Seeman & Lasaga, 2005), [54]: (Winberg & Nilsson, 1996), [55]: (Nichols et al., 2015), [56]: (Raffa, Shank, & Vaught, 1992), [57]: (Schoeffter & Hoyer, 1989), [58]: (Luethi et al., in press), [59]: (McLean et al., 2006), [60]: (Juncosa et al., 2013), [61]: (Braden et al., 2006), [62]: (Titeler et al., 1987), [63]: (Rothman et al., 2000), [64]: (Leth-Petersen et al., 2016), [65]: (Quirk et al., 2001), [66]: (Rabin, Doat, & Winter, 2000), [67]:

experiences' as well as euphoria, feelings of peacefulness and increased empathy and social interaction. However, the slow onset of the desired effects increases the risk of overdosing (Corazza et al., 2013; Zanda et al., 2016; Zawilska, 2014b). Despite being on the market only since 2010, MXE has already been implicated in a number of fatal and numerous non-fatal intoxications (EMCDDA, 2014; Zanda et al., 2016; Zawilska, 2014b). Clinical symptoms of MXE include reduced ability to focus and concentrate, impaired motor coordination, tremor and in more severe cases anxiety, hypertension, tachycardia and sometimes death (Corazza et al., 2013; Zanda et al., 2016; Zawilska, 2014b).

#### 3.4.3. Mechanism of action

Due to their clinical use, ketamine and to a lesser extent PCP, are among the best studied illicit drugs. Ketamine and PCP are primarily known for their antagonistic effect on NMDA receptors, which is mediated by binding to the PCP binding site (Sinner & Graf, 2008). NMDA receptors are ionotropic glutamate receptors that upon activation allow for the influx of $Na^+$and to a lesser extent $Ca^{2+}$. As a result, NMDA receptors activation causes depolarization and subsequent activation of intracellular signaling pathways (Fig. 10), which are essential in controlling synaptic plasticity, learning and memory (Bouvier, Bidoret, Casado, & Paoletti, 2015; Iacobucci & Popescu, 2017).

Both ketamine and PCP are potent antagonists of both NR2A and NR2B containing NMDA receptors, with $IC_{50}$s in the low and submicromolar range (Table 1, Fig. 11). In addition to this presumed primary mode of action, ketamine and PCP have multiple additional targets. For example, ketamine and PCP bind to and activate dopamine D2 receptors in the nanomolar range, though binding affinity for the other dopamine receptor subtypes seems limited and is hardly investigated. Additionally, ketamine is a modest (micromolar range) inhibitor of nicotinic acetylcholine receptors (nACh), VGCC, voltage-gated sodium channels (VGSC), and the monoamine reuptake transporters (DAT, NET and SERT). On the other hand, ketamine has (very) limited binding affinity for 5-HT receptors, α- and β-adrenergic receptors, $GABA_A$receptors, M1-5 muscarinic acetylcholine receptors and CB1 receptors (Table 1, Supplemental Fig. 19).

Similarly, PCP, although slightly less well-studied, has modest (micromolar range) binding affinity for $5\text{-}HT_2$receptors and the monoamine reuptake transporters DAT, NET and SERT. Moreover, PCP is reported to be a modest (micromolar range) inhibitor of nACh and VGCCs (Table 1, Supplemental Fig. 21).

In strong contrast to ketamine and PCP, MXE effects have hardly been studied. Recent studies indicate that MXE potently inhibits neuronal activity ($IC_{50}$values < 1 μM) and potently binds to NMDA receptors (submicromolar affinity) and SERT (submicromolar affinity). Additionally, MXE inhibits DAT, SERT and NET (micromolar range), but has very limited effects on $GABA_A$- and nACh-receptors and VGCCs (Table 1, Supplemental Fig. 20).

### 3.5. Piperazines

#### 3.5.1. Introduction

Piperazine derivatives are a class of substances that contain a piperazine ring within their chemical structure. Piperazine was originally developed as an antihelminthic and is also included in the chemical structure of many prescription medicines, such as antidepressants and antipsychotics. In addition, piperazine derivatives can be formed during metabolism of prescription medicines, e.g., mCPP is synthesized during metabolism of trazodone and nefazodone (Rotzinger, Fang, Coutts, & Baker, 1998). Misuse of piperazine derivatives as NPS started in New-Zealand and became popular NPS in Europe in 2004 (EMCDDA, 2015b). They were often sold as ecstasy pills, but also under different names, such as "Rapture," "Frenzy," "Bliss," "Charge," "Herbal ecstasy," "A2," "Legal X" and "Legal E". Derivatives most frequently reported include BZP, TFMPP and mCPP (Arbo, Bastos, & Carmo, 2012). Compared to other classes of NPS, the number of new piperazines reported annually

**Table 2**
**Estimated brain concentrations of illicit drugs and NPS.** Estimated brain concentrations were calculated using human blood, serum, or plasma concentrations and brain partitioning factors (BPF) found in literature. All human serum, **blood** (bold reference number) or plasma (underlined) concentrations were obtained from recreational use doses (voluntary intake, driving under the influence or accidental non-fatal intoxications). BPFs were based on human, **rat** (bold) or *mouse* (italic) data from which blood/brain, plasma/brain (underlined) or serum/brain (double underlined) partition coefficients were calculated. When no BPF was found in literature (*; 4-MEC, 5-APB, 6-APB and BZP) a value of 1 was used since most BPFs are > 1.

| Group | Drug | Serum concentration (μM) | Brain partitioning factor (BPF) | Estimated brain concentration (μM) | Estimated relevant test concentration (μM) |
|---|---|---|---|---|---|
| **Cathinones** | Mephedrone | 0.1 – 6 [1, 2, **3**] | 5.6 – 6.2 [4] | 0.6 – 37 | < 100 |
| | 4-MEC | 0.2 – 1.8 [1, 5] | 1 [*] | 0.2 – 1.8 | < 10 |
| | Pentedrone | 0.04 – 1.9 [1, 6] | 1.6 [7] | 0.1 – 3.0 | < 10 |
| | Methylone | 0.01 – 18 [1, **8**, **9**] | 1.4 – 2.0 [8, 10] | 0.01 – 36 | < 100 |
| | MDPV | 0.02 – 6.9 [1, 11, **12**, 13] | 0.8 – 4.4 [12, 14] | 0.02 – 30 | < 100 |
| | α-PVP | 0.01 – 2.6 [15, **16**] | 0.1 – 0.8 [7, 17] | 0.001 – 2.1 | < 10 |
| **Cannabinoids** | THC | 0.001 – 0.1 [18, **19**] | 2.7 – 3.5 [20] | 0.003 – 0.4 | < 1 |
| | JWH-018 | 0.001 – 0.03 [21, **22**, 23] | 1.4 – 16 [*24*, 25] | 0.001 – 0.5 | < 1 |
| **Non- or mild hallucinogenic phenethylamines** | Amphetamine | 0.04 – 28 [26, **27**, **28**] | 8.6 – 12 [29, 30, 31] | 0.3 – 336 | < 1000 |
| | 4-FA | 0.03 – 3.8 [32, **33**] | 3.2 [*34*] | 0.1 – 12 | < 100 |
| | MDMA | 0.1 – 14 [**28**, 35, **36**] | 2.3 – 32 [37, 38, 39] | 0.2 – 448 | < 1000 |
| | 5-APB | 0.01 – 0.2 [40] | 1 [*] | 0.1 – 0.2 | < 1 |
| | 6-APB | 1.1 [41] | 1 [*] | 1.1 | < 10 |
| **Hallucinogenic phenethylamines** | 2C-B | 0.01 – 0.1 [**42**] | 6.6 – 15 [43] | 0.1 – 1.5 | < 10 |
| | 25B-NBOMe | 0.0004 – 0.03 [44, 45] | 10 [**46**] | 0.004 – 0.3 | < 1 |
| | 25C-NBOMe | 0.001 – 0.002 [47, **48**] | 4.7 – 9.8 [48, *49*] | 0.005 – 0.02 | < 0.1 |
| | 25I-NBOMe | 0.001 – 0.1 [50, 51] | 7.2 [52] | 0.01 – 0.7 | < 1 |
| **Arylcyclohexyl-amines** | Ketamine | 0.04 – 7.6 [53, **54**] | 2.5 – 4.0 [55, 56] | 0.1 – 30 | < 100 |
| | MXE | 0.04 – 2.1 [57, **58**, **59**] | 2.1 – 2.9 [60] | 0.1 – 6.1 | < 10 |
| | PCP | 0.02 – 0.8 [61, **62**] | 9.0 [63] | 0.2 – 7.2 | < 10 |
| **Piperazines** | BZP | 0.2 – 36 [64, 65, 66] | 1 [*] | 0.2 – 36 | < 100 |
| | TFMPP | 0.3 – 1.2 [64, 67] | 74 [68] | 22 – 89 | < 100 |
| | mCPP | 0.1 – 1.6 [**42**, 69] | 17 – 53 [68, 70, 71, 72, 73, *73*] | 1.7 – 85 | < 100 |

[1]: (Elliott & Evans, 2014),[2]: (Wood et al., 2010),[3]: (Cosbey, Peters, Quinn, & Bentley, 2013),[4]: (Hadlock et al., 2011),[5]: (Férec et al., 2013),[6]: (Expert committee on drug dependence, 2016),[7]: (Sykutera, Cychowska, & Bloch-Boguslawska, 2015),[8]: (DeRoux & Dunn, 2017),[9]: (Cawrse et al., 2012),[10]: (Lõpez-Arnau et al., 2012),[11]: (Thornton, Gerona, & Tomaszewski, 2012),[12]: (Marinetti & Antonides, 2013),[13]: (Kriikku, Wilhelm, Schwarz, & Rintatalo, 2011),[14]: (Wyman et al., 2013),[15]: (Beck, Franzén, Bäckberg, Signell, & Helander, 2016),[16]: (Adamowicz et al., 2016b),[17]: (Hasegawa et al., 2014),[18]: (Daldrup & Mußhoff, 1993),[19]: (Khiabani, Bramness, Bjorneboe, & Morland, 2006),[20]: (Hartung, Kauferstein, Ritz-Timme, & Daldrup, 2014),[21]: (Mußhoff et al., 2014),[22]: (Yeakel & Logan, 2013),[23]: (Kneisel & Auwärter, 2012),[24]: (Poklis et al., 2012),[25]: (Wiebelhaus et al., 2012),[26]: (Lee, Song, Hwang, & Chou, 2000),[27]: (Gustavsen, Morland, & Bramness, 2006),[28]: (Senna et al., 2010),[29]: (Rivière, Gentry, & Owens, 2000),[30]: (White et al., 2014),[31]: (Hendrickson, Laurenzana, & Owens, 2006),[32]: (Röhrich, Becker, Kaufmann, Zörntlein, & Urban, 2012),[33]: (Karinen & Hoiseth, 2017),[34]: (Shiue et al., 1993),[35]: (Morefield, Keane, Felgate, White, & Irvine, 2011),[36]: (Augsburger et al., 2005),[37]: (Mueller, Yuan, & Felim, 2009),[38]: (García-Repetto et al., 2003),[39]: (De Letter, Bouche, Van Bocxlaer, Lambert, & Piette, 2004),[40]: (Welter, Kavanagh, Meyer, & Maurer, 2015),[41]: (Férec et al., 2014),[42]: (Adamowicz et al., 2016a),[43]: (Rohanová, Páleníček, & Balíková, 2008),[44]: (Poklis, Nanco, Troendle, Wolf, & Poklis, 2014),[45]: (Gee, Schep, Jensen, Moore, & Barrington, 2016),[46]:Shintani-Ishida, Saka, Nakamura, Yoshida, & Ikegaya, in press),[47]: (Rose, Poklis, & Poklis, 2013),[48]: (Kristofic et al., 2016),[49]: (Wardwell et al., 2015),[50]: (Poklis, Charles, Wolf, & Poklis, 2013),[51]: (Hermanns-Clausen, Angerer, Kithinji, Grunmann, & Auwärter, 2017),[52]: (Poklis, Devers, et al., 2014),[53]: (Abbara et al., 2017),[54]: (Cheng & Dao, 2017),[55]: (Moore et al., 1997),[56]: (Hartvig et al., 1995),[57]: (Wood, Davies, Puchnarewicz, Johnston, & Dargan, 2012),[58]: (Wikström, Thelander, Dahlgren, & Kronstrand, 2013),[59]: (Elian & Hackett, 2014),[60]: (Horsley et al., 2016),[61]: (Walberg, McCarron, & Schulze, 1983),[62]: (Kunsman, Levine, Costantino, & Smith, 1997),[63]: (Jackson, 1989),[64]: (Wood et al., 2008),[65]: (Gee et al., 2008),[66]: (Button et al., 2006),[67]: (Elliott, 2011),[68]: (Caccia, Fong, Garattini, & Notarnicola, 1985),[69]: (Kovaleva, Devuyst, De Paepe, & Verstraete, 2008),[70]: (Ulrichsen, Partilla, & Dax, 1992),[71]: (DeVane, Boulton, Miller, & Miller, 1999),[72]: (Caccia, Ballabio, Fanelli, Guiso, & Zanini, 1981),[73]: (Nacca, Guiso, Fracasso, Cervo, & Caccia, 1998).

to monitoring agencies is very low; in 2015 only 3 piperazines were reported for the first time (EMCDDA, 2016b). Prevalence data on the use of piperazines is very limited, outdated and scattered. In Spain, the last year prevalence of use was below 1% from 2010-2013, while BZP was used in the last year by 13% of the New Zealand youth (16-17 yrs) in 2008 (World Drug Report, 2016). In the UK, a last year prevalence use of BZP use among people regularly going to (dance) clubs was reported to be 12% and 5% in 2010 and 2011 respectively (EMCDDA, 2015b).

### 3.5.2. Clinical effects

Desirable effects reported following BZP exposure include stimulatory effects, euphoria and increased sociability (Lin, Bangs, Lee, Kydd, & Russell, 2009). The stimulant effects of BZP are milder than those of methamphetamine, and when combined with TFMPP, the euphoria and entactogenic effects perceived are similar to that induced by MDMA. TFMPP alone produces mild stimulant and hallucinogenic effects, as does mCPP. At higher doses of BZP, hallucinogenic effects are also reported. Adverse effects following BZP exposure include anxiety, agitation, confusion, headache, palpitations, tachycardia, hypertension, chest pain, hyperthermia, seizures and collapse (for review see Elliott, 2011; Schep, Slaughter, Vale, Beasley, & Gee, 2011).

### 3.5.3. Mechanism of action

Several targets have been investigated for piperazines, although the results for most targets only consist of a single data point (see Supplemental Figs. 22-24). TFMPP and mCPP most potently bind to serotonin receptors 5-$HT_{1A\text{-}D,\ 2A\text{-}C}$($K_i$values 3-300 nM), while BZP only binds to these receptors at micromolar levels. In correspondence, mCPP potently activates 5-$HT_{2A\text{-}C}$($K_{act}$in nanomolar range, Fig. 12). However, while TFMPP has a nanomolar binding affinity for 5-$HT_{2A,C}$, activation only occurs at higher concentrations (300-500 nM). Functional data for activation of inhibition of 5-$HT_1$receptors is absent. Compared to the other drugs and drug groups, mCPP binds to α-adrenergic receptors relatively potently ($K_i$250 nM). Piperazines also inhibit uptake by monoamine reuptake transporters, but mostly at a higher concentration ($IC_{50}$values in low micromolar range). However, mCPP potently inhibits uptake via SERT ($IC_{50}$~150 nM) and BZP via NET ($IC_{50}$~400 nM). In addition, at a low concentration, BZP induces release of monoamines via DAT and NET ($IC_{50}$~150 and 50 nM, respectively), while TFMPP and mCPP induce release via SERT ($IC_{50}$~125 nM and 25 nM, respectively; Supplemental Figs. 22-24).

**Table 3**

**Effect fingerprint of different (classes of) illicit drugs and NPS related to estimated human brain concentrations.** Drugs are grouped in cathinones, cannabinoids, (non- or mild) hallucinogenic phenethylamines, arylcylcohexylamines, and piperazines. Targets are grouped by effects on monoamine reuptake transporters, receptors and ion channels. The lowest reported drug concentration (log M) that affects the target is listed. Targets without data are not listed (see Table 1). For all reported effect concentrations see Figs. 3, 4, 6-8, 11, 12 and Supplemental Figs. 2-24. Relevant test concentrations are listed per drug in the second row (calculated in Table 2). Reported effect concentrations are color-labeled if above (green) or within (red) the relevant test concentration. Reported effect concentrations in grey indicate a larger than (>) value that is within the relevant test concentration (target was examined, but no or < 50% effect was detected). For references see Table 1.

| Drug classification: | | | Cathinones | | | | | | Cannabinoids | | Non- or mild hallucinogenic phenethylamines | | | | | Hallucinogenic phenethylamines | | | | Arylcyclohexylamines | | | Piperazines | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| <Estimated relevant test concentration / > Estimated relevant test concentration | | | Mephedrone | 4-MEC | Pentedrone | Methylone | MDPV | α-PVP | THC | JWH-018 | Amphetamine | 4-FA | MDMA | 5-APB | 6-APB | 2C-B | 25B-NBOMe | 25C-NBOMe | 25I-NBOMe | Ketamine | MXE | PCP | BZP | TFMPP | mCPP |
| Estimated relevant test concentration (Log M) : | | | < -4.0 | < -5.0 | < -5.0 | < -4.0 | < -4.0 | < -5.0 | < -6.0 | < -6.0 | < -3.0 | < -4.0 | < -3.0 | < -6.0 | < -5.0 | < -5.0 | < -6.0 | < -7.0 | < -6.0 | < -4.0 | < -5.0 | < -5.0 | < -4.0 | < -4.0 | < -4.0 |
| **Monoamine transporters** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Plasma membrane | $K_i$ Binding | DAT | -5.8 | -6.1 | -6.5 | -5.6 | -8.0 | -8.2 | -5.8 | > -5.0 | -5.2 | -5.0 | -5.2 | -5.6 | -6.2 | > -4.5 | -5.1 | -4.9 | -5.3 | > -5.0 | | | > -5.0 | > -4.6 | -5.2 |
| | | SERT | > -5.0 | -5.4 | -4.8 | > -4.5 | -5.9 | > -4.5 | > -5.0 | > -5.0 | > -4.6 | -4.7 | -6.2 | -5.5 | -4.9 | -5.0 | -6.1 | -5.8 | -6.0 | > -5.0 | -6.3 | -5.7 | > -5.0 | -5.8 | -6.2 |
| | | NET | > -5.0 | -5.2 | -5.7 | -4.8 | -7.1 | -7.2 | > -5.0 | > -5.0 | -6.0 | -4.9 | -4.8 | -5.5 | -5.7 | -4.5 | -6.0 | -5.8 | -5.9 | > -5.0 | | | -5.1 | -4.9 | -5.5 |
| | $IC_{50}$ Binding | DAT | | | | | | | | | | | > -4.7 | > -5.0 | | | | | | > -5.0 | | | | | -5.4 |
| | | SERT | | | | | | | | | | | > -5.0 | < -5.0 | | | | | | -5.3 | | -5.5 | | | -6.6 |
| | | NET | | | | | | | | | | | > -5.0 | > -5.0 | | | | | | > -5.0 | | | | | > -4.0 |
| | $K_i$ Uptake | DAT | | | | | | | | | -7.5 | | -5.8 | -6.6 | -6.8 | | | | | S -4.3 | | | | | |
| | | SERT | | | | | | | | | -5.8 | | -6.6 | -6.1 | -5.6 | | | | | -4.7 | | | | | |
| | | NET | | | | | | | | | -7.4 | | -6.3 | -6.7 | -6.9 | -4.6 | | | | S -4.2 | | | | | |
| | $IC_{50}$ Uptake | DAT | -7.0 | -6.2 | -6.8 | -6.5 | -8.4 | -7.9 | | | -7.0 | -7.0 | -6.7 | -5.3 | -5.5 | -3.7 | -4.0 | -4.2 | -4.3 | -4.2 | -4.5 | | -5.7 | > -4.0 | -5.1 |
| | | SERT | -6.5 | -6.3 | -5.0 | -6.6 | -5.9 | > -5.0 | | | -5.5 | -5.6 | -7.0 | -6.5 | -6.0 | -4.7 | -5.3 | -5.1 | -5.4 | -3.9 | -5.6 | -5.6 | -4.7 | -5.3 | -6.8 |
| | | NET | -7.3 | -5.8 | -6.6 | -6.6 | S -8.0 | -7.8 | | | -7.2 | -7.4 | -7.6 | -6.8 | -6.7 | -4.4 | -5.2 | -5.2 | -5.0 | -4.1 | -4.7 | | -6.4 | -4.8 | -5.8 |
| | $EC_{50}$ Release | DAT | R -7.5 | > -5.0 | > -4.0 | -6.9 | -9.0 | > -4.0 | | | -8.2 | -7.3 | -7.3 | < -4.0 | > -4.0 | | | | | | | > -4.0 | -6.8 | > -5.0 | > -5.0 |
| | | SERT | R -8.8 | -7.0 | > -4.0 | -6.7 | > -5.0 | > -4.0 | | | -6.2 | -6.1 | -7.3 | > -4.0 | > -4.0 | | | | | | | | > -5.0 | -6.9 | -7.6 |
| | | NET | -7.2 | -6.1 | > -4.0 | -7.0 | -7.9 | > -4.0 | | | -8.2 | -7.6 | -7.3 | > -4.0 | > -4.0 | | | | | > -4.5 | | | -7.2 | > -4.0 | -5.9 |
| Vesicular membrane | $K_i$ Binding | VMAT 1 | | | | | | | | | R -4.4 | | -4.7 | | | | | | | | | | | | |
| | | VMAT 2 | > -3.0 | | | > -3.0 | -6.0 | | | | R -5.9 | | -5.4 | | | | | | | | | | | | |
| | $IC_{50}$ Binding | VMAT 2 | | | | | | | | | -4.4 | | > -4.0 | | | | | | | | | | > -4.0 | -3.6 | -3.7 |
| | $K_i$ Uptake | VMAT 2 | | | | | | | | | R -5.9 | | -5.0 | | | | | | | | | | | | |
| | $IC_{50}$ Uptake | VMAT n.s. | | | | | | | | | -5.3 | | | | | | | | | | | -4.5 | | | |
| | | VMAT 2 | -5.5 | | | -4.7 | > -4.0 | | | | R -5.5 | | -5.2 | | | | | | | | | | > -4.0 | -4.9 | -3.9 |
| | $EC_{50}$ Release | VMAT n.s. | | | | | | | | | -5.7 | | | | | | | | | | | | | | |
| | | VMAT 2 | -4.2 | | | > -4.0 | -3.8 | | | | R -5.6 | | -4.8 | | | | | | | | | | > -4.0 | -4.7 | -4.6 |
| **Receptors** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Dopamine | $K_i$ Binding | D1 | > -5.0 | > -5.0 | > -4.9 | > -5.0 | > -5.0 | > -4.9 | > -5.0 | > -5.0 | > -4.9 | > -4.9 | > -5.0 | > -4.9 | > -4.9 | -4.9 | -5.0 | -4.9 | -5.2 | | | | > -5.0 | > -4.9 | > -6.0 |
| | | D2 | > -5.0 | > -5.0 | > -5.0 | > -5.0 | > -5.0 | > -5.0 | > -5.0 | > -5.0 | > -4.5 | > -4.7 | > -5.0 | > -5.0 | > -5.0 | -5.7 | -6.1 | -5.8 | -6.0 | -8.1 | | -8.6 | > -5.0 | -5.9 | > -6.0 |
| | | D3 | > -5.0 | > -5.0 | > -4.8 | > -5.0 | > -5.0 | > -4.8 | > -5.0 | > -5.0 | > -4.8 | > -4.8 | > -5.0 | > -5.0 | > -5.0 | -5.0 | -5.6 | -5.5 | -5.7 | | | | > -5.0 | -6.3 | -5.6 |
| | | D4 | > -5.0 | > -5.0 | | > -5.0 | > -5.0 | | > -5.0 | > -5.0 | | | > -5.0 | > -5.4 | > -5.0 | | | | | | | | > -5.0 | | |
| | | D5 | > -5.0 | > -5.0 | | | | | > -5.0 | > -5.0 | | | | | | | | | | | | | > -5.0 | | |
| | $IC_{50}$ Binding | D1 | | | | | | | | | | | > -5.0 | > -5.0 | | | | | | > -5.0 | | | | | -5.2 |
| | | D2 | | | | | | | | | | | > -5.0 | > -5.0 | | | | | | > -5.0 | | | | | -5.0 |
| | | D3 | | | | | | | | | | | > -5.0 | > -5.0 | | | | | | > -5.0 | | | | | |
| | | D4 | | | | | | | | | | | > -5.0 | > -5.0 | | | | | | > -5.0 | | | | | |
| | | D5 | | | | | | | | | | | | | | | | | | > -5.0 | | | | | |
| | $EC_{50}$ Agonist | D2 | | | | | | | | | | | | | | | | | | -6.0 | | -8.4 | | | |
| 5-$HT_1$ | $K_i$ Binding | n.s. | | | | | | | | | | | -4.6 | | | | | | | | | | | -7.2 | |
| | | 1a | > -5.0 | > -5.0 | > -4.7 | > -4.7 | -5.0 | -5.3 | > -5.0 | > -5.0 | -5.2 | -5.4 | -4.9 | -5.5 | -5.2 | -6.6 | -5.4 | -5.3 | -6.0 | | | | > -5.0 | -6.8 | -7.7 |
| | | 1b | -5.8 | > -5.0 | | | | | > -5.0 | > -5.0 | | | | > -5.0 | > -5.0 | | | | -5.2 | | | | > -5.0 | $K_d$ -6.9 | $K_d$ -6.5 |
| | | 1d | > -5.0 | > -5.0 | | | | | > -5.0 | > -5.0 | | | | -5.3 | -5.5 | | | | -6.3 | | | | > -5.0 | $K_d$ -6.6 | $K_d$ -5.8 |
| | | 1e | | | | | | | > -5.0 | > -5.0 | | | | | | | | | > -5.0 | | | | > -5.0 | | |
| | $IC_{50}$ Binding | n.s. | | | | | | | | | | | | | | | | | | | | -4.1 | | | |
| | | 1a | | | | | | | | | | | | | | | | | | > -5.0 | | | | | -6.4 |
| | | 1b | | | | | | | | | | | | | | | | | | > -5.0 | | | | | |
| | | 1d | | | | | | | | | | | | | | | | | | | | | | | -5.9 |
| | $EC_{50}$ Agonist | 1a | -3.9 | | | -3.9 | -4.2 | | | | | | -4.5 | | | | | | | | | | | | |

(*continued on next page*)

**Table 3** (*continued*)

| Drug classification: | | | Cathinones | | | | | | Cannabinoids | | Non- or mild hallucinogenic phenethylamines | | | | | Hallucinogenic phenethylamines | | | | Arylcyclohexylamines | | | Piperazines | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| <Estimated relevant test concentration / > Estimated relevant test concentration | | | Mephedrone | 4-MEC | Pentedrone | Methylone | MDPV | α-PVP | THC | JWH-018 | Amphetamine | 4-FA | MDMA | 5-APB | 6-APB | 2C-B | 25B-NBOMe | 25C-NBOMe | 25I-NBOMe | Ketamine | MXE | PCP | BZP | TFMPP | mCPP |
| Estimated relevant test concentration (Log M) : | | | < -4.0 | < -5.0 | < -5.0 | < -4.0 | < -4.0 | < -5.0 | < -6.0 | < -6.0 | < -3.0 | < -4.0 | < -3.0 | < -6.0 | < -5.0 | < -5.0 | < -6.0 | < -7.0 | < -6.0 | < -4.0 | < -5.0 | < -5.0 | < -4.0 | < -4.0 | < -4.0 |
| Receptors | | | | | | | | | | | | | | | | | | | | | | | | | |
| 5-HT$_2$ | $K_i$ Binding | n.s. | -5.4 | > -5.0 | | -5.0 | | | | | | | -5.3 | -6.3 | -6.1 | | | | | -4.8 | | -5.3 | | | -7.4 |
| | | 2a | -5.8 | -5.4 | > -4.9 | > -4.9 | > -4.9 | > -4.9 | > -5.0 | > -5.0 | > -4.9 | -4.9 | -5.2 | -6.1 | -6.0 | -9.2 | -9.7 | -9.2 | -10.4 | | | | > -5.0 | -7.5 | -7.2 |
| | | 2b | -6.1 | > -5.0 | | | | | -6.1 | -6.5 | | | | -7.9 | -8.4 | | | | -8.9 | | | | > -5.0 | | -8.5 |
| | | 2c | -5.1 | -5.3 | > -4.9 | -5.0 | > -4.9 | > -4.9 | > -5.0 | > -5.0 | > -4.9 | -5.1 | -5.9 | -6.1 | -6.6 | -7.6 | -8.6 | -8.3 | -9.3 | | | | > -5.0 | -8.0 | -8.1 |
| | $IC_{50}$ Binding | n.s. | | | | | | | | | | | | | | | | | | | | -6.8 | | | -6.4 |
| | | 2a | | | | | | | | | | | < -5.0 | < -5.0 | | | | | | > -5.0 | | > -4.0 | | | |
| | | 2b | | | | | | | | | | | < -5.0 | < -5.0 | | | | | | > -5.0 | | | | | |
| | | 2c | | | | | | | | | | | < -5.0 | < -5.0 | | | | | | > -5.0 | | | | | |
| | $EC_{50}$ Agonist | 2a | -6.4 | | | | | | | | | | > -5.0 | -5.2 | -5.2 | -7.6 | -9.0 | -6.8 | -9.4 | | | | | -6.3 | $K_a$ -7.2 |
| | | 2b | > -5.0 | | | | > -4.7 | > -4.7 | | | | -4.9 | > -5.0 | -7.8 | -8.4 | -6.9 | | | -7.8 | | | | | | $K_a$ -7.2 |
| | | 2c | | | | | | | | | | | $K_d$ -5.6 | | | -6.8 | -9.0 | -7.0 | -7.4 | | | | | -6.5 | $K_a$ -9.2 |
| | $IC_{50}$ Antagonist | 2a | -4.8 | | | -3.8 | -3.6 | | | | | | -5.2 | -5.4 | | -8.3 | | | | | | | | | |
| | | 2b | | | | | | | | -4.5 | | | | | | | | | | | | | | | $K_d$ -7.5 |
| | | 2c | > -3.4 | | | > -3.0 | > -3.0 | | | | | | | | | | | | | | | | | | |
| 5-HT$_3$ | $K_i$ Binding | n.s. | | | | | | | > -5.0 | > -5.0 | | | | | | | | | > -5.0 | -4.0 | | | > -5.0 | | -7.3 |
| | $IC_{50}$ Binding | n.s. | | | | | | | | | | | | | | | | | | > -5.0 | | | | | |
| | $IC_{50}$ Antagonist | n.s. | | | | | | | | | | | | | | | | | | S -4.0 | | | | | |
| 5-HT$_4$ | $K_i$ Binding | n.s. | | | | | | | | | | | | | | | | | | | | | > -5.0 | | |
| 5-HT$_5$ | $K_i$ Binding | 5a | | | | | | | > -5.0 | > -5.0 | | | | | | | | | -5.6 | | | | | | |
| | $IC_{50}$ Binding | 5a | | | | | | | | | | | | | | | | | | > -5.0 | | | | | |
| 5-HT$_6$ | $K_i$ Binding | n.s. | > -5.0 | > -5.0 | | | | | > -5.0 | > -5.0 | | | | > -5.0 | > -5.0 | | | | -7.5 | | | | | | |
| | $IC_{50}$ Binding | n.s. | | | | | | | | | | | | | | | | | | > -5.0 | | | | | |
| 5-HT$_7$ | $K_i$ Binding | n.s. | > -5.0 | > -5.0 | | | | | > -5.0 | > -5.0 | | | | -6.0 | -6.8 | | | | -5.8 | | | | | | |
| | $IC_{50}$ Binding | n.s. | | | | | | | | | | | | | | | | | | > -5.0 | | | | | |
| | $IC_{50}$ Antagonist | n.s. | | | | | | | | | | | | | | | | | | | | | | -6.1 | -6.7 |
| α-Adrenergic | $K_i$ Binding | α1 | -6.0 | > -5.2 | > -5.2 | > -5.2 | > -5.2 | > -4.8 | > -5.0 | > -5.0 | > -5.2 | > -5.3 | > -5.2 | -5.5 | -5.1 | -5.1 | -6.4 | -6.1 | -6.4 | $K_d$ -2.5 | | | > -5.2 | > -5.2 | -6.6 |
| | | α2 | > -5.3 | > -5.0 | -4.5 | > -4.7 | > -4.7 | > -4.7 | > -5.0 | > -5.0 | -5.6 | -5.4 | -5.4 | -6.3 | -7.3 | -6.5 | -6.4 | -6.3 | -6.5 | | | | -5.4 | -6.1 | -6.6 |
| | | α3 | | | | | | | | | | | | | | | | | | | | | | | |
| | $IC_{50}$ Binding | α1 | | | | | | | | | | | > -5.0 | > -5.0 | | | | | | > -5.0 | | | | | -5.5 |
| | | α2 | | | | | | | | | | | > -5.0 | < -5.0 | | | | | | > -5.0 | | | | | -6.2 |
| | $IC_{50}$ Antagonist | α1 | | | | | | | | | | | | | | | | | | > -4.4 | | | | | |
| | | α2 | | | | | | | | | | | | | | | | | | > -4.4 | | | | | |
| | | α3 | | | | | | | | | | | | | | | | | | > -4.4 | | | | | |
| β-Adrenergic | $K_i$ Binding | n.s. | | | | | | | | | | | -4.7 | | | | | | | | | | | | |
| | | β1 | > -5.0 | > -5.0 | | | | | > -5.0 | > -5.0 | | | | > -5.0 | -5.4 | | | | | | | | > -5.0 | | |
| | | β2 | | | | | | | > -5.0 | > -5.0 | | | | | | | | | | $K_d$ -3.5 | | | > -5.0 | | |
| | | β3 | | | | | | | > -5.0 | > -5.0 | | | | | | | | | | | | | > -5.0 | | |
| | $IC_{50}$ Binding | n.s. | | | | | | | | | | | | | | | | | | | | | | | -5.6 |
| | | β1 | | | | | | | | | | | > -5.0 | > -5.0 | | | | | | > -5.0 | | | | | |
| | | β2 | | | | | | | | | | | > -5.0 | > -5.0 | | | | | | > -5.0 | | | | | |

(*continued on next page*)

**Table 3** (*continued*)

| Drug classification: | | | Cathinones | | | | | | Cannabinoids | | Non- or mild hallucinogenic phenethylamines | | | | | Hallucinogenic phenethylamines | | | | Arylcyclohexylamines | | | Piperazines | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| <Estimated relevant test concentration / > Estimated relevant test concentration | | | Mephedrone | 4-MEC | Pentedrone | Methylone | MDPV | α-PVP | THC | JWH-018 | Amphetamine | 4-FA | MDMA | 5-APB | 6-APB | 2C-B | 25B-NBOMe | 25C-NBOMe | 25I-NBOMe | Ketamine | MXE | PCP | BZP | TFMPP | mCPP |
| Estimated relevant test concentration (Log M) : | | | < -4.0 | < -5.0 | < -5.0 | < -4.0 | < -4.0 | < -5.0 | < -6.0 | < -6.0 | < -3.0 | < -4.0 | < -3.0 | < -6.0 | < -5.0 | < -5.0 | < -6.0 | < -7.0 | < -6.0 | < -4.0 | < -5.0 | < -5.0 | < -4.0 | < -4.0 | < -4.0 |
| Receptors | | | | | | | | | | | | | | | | | | | | | | | | | |
| $GABA_A$ | $K_i$ Binding | n.s. | | | | | | | > -5.0 | -6.2 | | | | | | | | | | | | | | | |
| | | α1 | | | | | | | | | | | | | | | | | | | | | > -5.0 | | |
| | | α2 | | | | | | | | | | | | | | | | | | | | | > -5.0 | | |
| | | α3 | | | | | | | | | | | | | | | | | | | | | > -5.0 | | |
| | | α5 | | | | | | | | | | | | | | | | | | | | | > -5.0 | | |
| | | α6 | | | | | | | | | | | | | | | | | | | | | > -5.0 | | |
| | $IC_{50}$ Binding | n.s. | | | | | | | | | | | > -5.0 | > -5.0 | | | | | | > -5.0 | | | | | > -4.0 |
| | $EC_{50}$ Agonist | n.s. | | | | | | | | | | | | | | | | | | -2.2 | > -5.0*1 | | | | |
| | | α6β2δ | | | | | | | | | | | | | | | | | | -3.2 | | | | | |
| | | α6β3δ | | | | | | | | | | | | | | | | | | -3.6 | | | | | |
| | $IC_{50}$ Antagonist | n.s. | . | | | | | | | -6.6 | | | | | | | | | | | | | | | |
| | | α1β2γ2 | | | | | | | | | | | > -3.0 | | | | | | | | | | > -3.0 | -3.0 | > -4.0 |
| $GABA_B$ | $K_i$ Binding | n.s. | | | | | | | | | | | | | | | | | | | | | > -5.0 | | |
| NMDA | $K_i$ Binding | n.s. | | | | | | | | | | | | | | | | | | -6.9 | -6.6 | -7.6 | | | |
| | $IC_{50}$ Binding | n.s. | | | | | | | | | | | > -5.0 | > -5.0 | | | | | | -6.5 | | -4.2 | | | |
| | $IC_{50}$ Antagonist | n.s. | | | | | | | | | | | | | | | | | | > -7.0 | > -5.0*2 | -9.3 | | | |
| | | NR1/NR2A | | | | | | | | | | | | | | | | | | -6.3 | | -7.1 | | | |
| | | NR1/NR2B | | | | | | | | | | | | | | | | | | -6.4 | | -7.3 | | | |
| AMPA | $IC_{50}$ Binding | n.s. | | | | | | | | | | | -5.0 | -5.0 | | | | | | | | | | | |
| Kainate | $IC_{50}$ Binding | n.s. | | | | | | | | | | | -5.0 | -5.0 | | | | | | | | | | | |
| mACh | Ki Binding | M1 | > -5.0 | > -5.0 | | | | | -5.8 | > -5.0 | | | -5.2 | > -5.0 | > -5.0 | | | | | -4.3 | | | > -5.0 | | |
| | | M2 | > -5.0 | > -5.0 | | | | | > -5.0 | > -5.0 | | | -4.8 | > -5.0 | > -5.0 | | | | | -3.5 | | | > -5.0 | | |
| | | M3 | > -5.0 | > -5.0 | | | | | > -5.0 | > -5.0 | | | | > -5.0 | > -5.0 | | | | | -3.6 | | | > -5.0 | | |
| | | M4 | > -5.0 | > -5.0 | | | | | > -5.0 | > -5.0 | | | | > -5.0 | > -5.0 | | | | | | | | > -5.0 | | |
| | | M5 | > -5.0 | > -5.0 | | | | | > -5.0 | > -5.0 | | | | > -5.0 | > -5.0 | | | | | | | | > -5.0 | | |
| | IC50 Binding | n.s. | | | | | | | | | | | > -5.0 | > -5.0 | | | | | | -4.6 | | -4.9 | | | -4.6 |
| | | M1 | | | | | | | | | | | | | | | | | | > -5.0 | | | | | |
| | | M2 | | | | | | | | | | | | | | | | | | > -5.0 | | | | | |
| | | M3 | | | | | | | | | | | | | | | | | | > -5.0 | | | | | |
| | | M4 | | | | | | | | | | | | | | | | | | > -5.0 | | | | | |
| | | M5 | | | | | | | | | | | | | | | | | | > -5.0 | | | | | |
| | IC50 Antagonist | n.s. | | | | | | | | | | | | | | | | | | > -5.0 | | | | | |
| | | M1 | | | | | | | | | | | | | | | | | | -5.2 | | | | | |
| nACh | $K_i$ Binding | n.s. | | | | | | | | | | | | | | | | | | | | -6.4 | | | |
| | | α3β4 | | | | | | | | | | | | | | | | | | | | -5.0 | | | |
| | $IC_{50}$ Binding | n.s. | | | | | | | | | | | | | | | | | | -5.0 | | | | | |
| | | α4β2 | | | | | | | | | | | < -5.0 | > -5.0 | | | | | | | | | | | |
| | $IC_{50}$ Antagonist | n.s. | | | | | | | | | > -4.0 | | > -4.0 | | | | | | | -7.1 | > -5.0*3 | | | | > -5.0 |
| | | α3β4 | | | | | | | | | | | | | | | | | | -5.5 | | -5.2 | > -5.0 | | |
| | | α4β2 | | | | | | | | | | | | | | | | | | -4.3 | | > -5.0 | > -5.0 | | |
| | | α7 | | | | | | | | | | | | | | | | | | > -6.0 | | -5.9 | > -5.0 | | |
| | | α2β2 | | | | | | | | | | | | | | | | | | -4.0 | | > -5.0 | > -5.0 | | |
| | | α3β2 | | | | | | | | | | | | | | | | | | -4.3 | | > -5.0 | > -5.0 | | |
| | | α2β4 | | | | | | | | | | | | | | | | | | -4.5 | | | > -5.0 | | |
| | | α4β4 | | | | | | | | | | | | | | | | | | -6.6 | | | > -5.0 | | |
| | | α2βγδ | | | | | | | | | | | | | | | | | | -4.5 | | | | | |

(*continued on next page*)

**Table 3** (*continued*)

| Drug classification: | | | Cathinones | | | | | | Cannabinoids | | Non- or mild hallucinogenic phenethylamines | | | | | Hallucinogenic phenethylamines | | | | Arylcyclohexylamines | | | Piperazines | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| <Estimated relevant test concentration / > Estimated relevant test concentration | | | Mephedrone | 4-MEC | Pentedrone | Methylone | MDPV | α-PVP | THC | JWH-018 | Amphetamine | 4-FA | MDMA | 5-APB | 6-APB | 2C-B | 25B-NBOMe | 25C-NBOMe | 25I-NBOMe | Ketamine | MXE | PCP | BZP | TFMPP | mCPP |
| Estimated relevant test concentration (Log M) : | | | < -4.0 | < -5.0 | < -5.0 | < -4.0 | < -4.0 | < -5.0 | < -6.0 | < -6.0 | < -3.0 | < -4.0 | < -3.0 | < -6.0 | < -5.0 | < -5.0 | < -6.0 | < -7.0 | < -6.0 | < -4.0 | < -5.0 | < -5.0 | < -4.0 | < -4.0 | < -4.0 |
| **Receptors** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Cannabinoid | $K_i$ Binding | CB1 | | | | | | | -8.3 | -9.3 | | | | | | | | | | | | | | | |
| | | CB2 | | | | | | | -8.8 | -8.5 | | | | | | | | | | | | | | | |
| | $IC_{50}$ Binding | CB1 | | | | | | | | | | | | | | | | | | > -5.0 | | | | | |
| | $EC_{50}$ Agonist | CB1 | | | | | | | -8.0 | -9.1 | | | | | | | | | | | | | | | |
| | | CB2 | | | | | | | -7.4 | -8.4 | | | | | | | | | | | | | | | |
| **Ion channels** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Sodium | $IC_{50}$ Binding | n.s. | | | | | | | | | | | | | | | | | | > -5.0 | | | | | |
| | $IC_{50}$ Antagonist | n.s. | > -4.5 | | | | | | | | | | | | | | | | | > -5.0 | | | | | |
| Potassium | $IC_{50}$ Binding | n.s. | | | | | | | | | | | | | | | | | | > -5.0 | | | | | |
| | $EC_{50}$ Agonist | n.s. | | | | | | | | -3.6 | | | | | | | | | | | | | | | |
| | $IC_{50}$ Antagonist | n.s. | | | | | | | | | | | | | | | | | | -5.4 | | -4.7 | | | |
| Calcium | $K_i$ Binding | n.s. | | | | | | | | | | | | | | | | | | -3.4 | | | | | |
| | $IC_{50}$ Binding | n.s. | | | | | | | | | | | | | | | | | | > -5.0 | | | | | |
| | $IC_{50}$ Antagonist | n.s. | > -4.5 | | | | | | | | > -3.7 | | > -3.0 | | | | | | | -5.0 | > -5.0 | -5.2 | | -4.3 | > -4.0 |
| **Other endpoints** | | | | | | | | | | | | | | | | | | | | | | | | | |
| $[Ca^{2+}]_i$ | $EC_{50}$ Agonist | | | | | | | | | | | | | | | | | | | > -4.0 | | | | | |
| Exocytosis | $IC_{50}$ Antagonist | | | | | | | | | | > -3.7 | | > -3.0 | | | | | | | -4.6 | | | | | |
| Neuronal act. | $IC_{50}$ | | | | | | | | | -7.9 | -4.0 | -3.9 | -4.0 | | | | | | | -6.2 | -6.3 | | | | -4.5 |
| ROS | LOEC | | < -1.7 | | | < -2.7 | < -2.9 | | | | | | > -2.8 | | | | | | | < -5.0 | | | > -3.3 | > -4.0 | |
| Cytotoxicity | $IC_{50}$ | | > -4.0 | | | > -4.0 | > -3.5 | | | > -4.5 | > -3.0 | > -3.0 | > -3.0 | | | | | | | > -5.0 | > -3.0 | > -4.6 | -3.1 | -4.4 | > -3.0 |

> : effect size smaller than 50% at this concentration, < : effect size larger than 50% at this concentration ($IC_{50}$not specified) at this concentration. $K_d$: dissociation constant, $K_a$: activation constant, S: S-isomer of corresponding compound, R: R-isomer of corresponding compounds, n.s.: non-specified.*1: GABA n.s.,*2: Glutamate n.s.,*3: Acetylcholine n.s., $[Ca^{2+}]_i$: Intracellular calcium concentration, Neuronal act.: Neuronal activity, LOEC: Lowest observed effect concentration.
*1: GABA n.s.,*2: Glutamate n.s.,*3: Acetylcholine n.s.

## 4. Discussion

We reviewed the available data on effects and effect concentrations of a large number of specific NPS on distinct molecular targets to obtain *effect fingerprints*. The full overview is provided in Table 1and clearly illustrates that many data gaps exist. Not surprisingly, effects on plasma membrane monoamine reuptake transporters are well studied for most illicit drugs and NPS. Receptor binding profiles for dopamine and serotonin receptors are also well studied. However, binding profiles for other receptors or ion channels are largely absent, with the exception of CB receptors for (synthetic) cannabinoids. Similarly, functional data regarding effects on receptors, ion channels and integrated endpoints such as neuronal activity are largely missing. Notably, it is difficult to establish if the gaps in the profiles are simply due to a lack of data (i.e. not studied) or result from publication bias, which likely hampers publication of negative/low potency results. Until these gaps are filled, complete effect fingerprints are hard to derive, even for the well-studied drugs and NPS.

Nevertheless, these data clearly highlight the main mechanisms of action for the different NPS studied. Inhibition and/or reversal of monoamine reuptake transporters is the main mechanism of action for cathinones and several phenethylamines, whereas hallucinogenic phenethylamines and piperazines primarily activate 5-$HT_2$receptors. For cannabinoids the main mechanism of action is the activation of cannabinoids receptors. Arylcyclohexylamines primarily inhibit NDMA receptors, but also seem potent dopamine D2 receptor agonists. Besides effects on the main mechanism(s) of action, it is clear that most of these drugs and NPS affect additional targets (Table 1, Supplemental Figs. 1-24). However, to determine the human relevance of the primary and additional targets, effect concentrations should be correlated to the estimated human brain concentrations during recreational use of these NPS.

For most drugs, estimated brain concentrations exceed blood concentrations (brain partitioning factor (BPF) > 1, Table 2). Notably, the estimated brain concentrations can differ several orders of magnitude for the different NPS. For example, estimated brain concentrations are in the low nanomolar range for most hallucinogenic phenethylamines, with the exception of 2C-B that can reach micromolar levels. The relative contribution of a particular target to the clinical effects is thus largely determined by whether the effect concentration of a particular target is within the estimated brain concentration (Table 3, concentrations in red indicate targets that are likely to be affected during recreational use).

When effect concentrations are related to concentrations relevant for human exposure during recreational use, additional relevant targets become apparent for most NPS. As shown in Table 3, the clinical symptoms of cathinones may also be due to binding to 5-$HT_{1\text{-}2}$receptors and α1 adrenergic receptors, as well as inhibition and/or reversal of vesicular monoamine transporters. Also for non- or mild hallucinogenic phenethylamines many more targets may contribute to the clinical symptoms, including vesicular monoamine transporters, 5-HT receptors, α- and β-adrenergic receptors, AMPA- and kainate receptors, and mACh receptors. Similarly, the clinical symptoms of cannabinoids may be due to activation of cannabinoids receptors as well as to effects on other targets (DAT, 5-$HT_2$receptors, $GABA_A$receptors and mACh receptors). At estimated brain concentrations during recreational use, arylcyclohexylamines also affect a number of additional targets, including DAT, SERT, NET, serotonin receptors, muscarinic and nicotinic ACh receptors and VGCCs. In particular piperazines show a broad range of targets at estimated brain concentrations including not only 5-$HT_2$receptors, but also DAT, SERT, NET, vesicular monoamine transporters, α- and β-adrenergic receptors, mACh receptors and VGCCs. On the other hand, most hallucinogenic phenethylamines seem to only affect 5-$HT_2$receptors at estimated brain concentrations. 2C-B is a clear exception in this group as it seems that effects on SERT, NET, dopamine receptors, 5-HT receptors and α-adrenergic receptors may also contribute to the clinical symptoms.

While the effect fingerprints of NPS are still incomplete, relating them to human relevant concentrations highlights that many targets can contribute to the clinical symptoms. It is therefore essential to complement the current effect fingerprints with additional data to fill the gaps as this will aid in risk assessment and possibly in predicting which NPS may likely result in severe clinical effects.

Importantly, the current data clearly argue for additional measurements as the data show a large variation in reported effects and effect sizes, often spanning up to 4-5 orders of magnitude (see Figs. 3, 4, 6-8, 11, 12 and Supplemental Figs. 2-24). For example, release of monoamines via NET following BZP exposure resulted in $EC_{50}$values ranging from 63 nM to > 100 μM (Supplemental Fig. 22) and activation of CB2 receptors by THC resulted in $EC_{50}$values ranging from 42 nM to > 30 μM (Supplemental Fig. 8). In addition, for many NPS-target combinations only a single data point is currently available. Furthermore, for many targets, only binding data is available and functional data is lacking. Binding studies provide limited pharmacological insight, since it remains unknown whether NPS binding activates or inhibits a specific target, or does not affect the target at all. For example, mephedrone did not bind to NET at 10 μM (Supplemental Figs. 1-2), while functional studies reported inhibition of uptake at 50 nM (Fig. 3and Supplemental Fig. 2) and release of monoamines via NET at 63 nM (Fig. 4 and Supplemental Fig. 2). Similarly, not all studies report the maximum effect, although $EC_{50}$values are reported. Even for extremely low efficacies (maximum responses as little as 4%), $EC_{50}$values have been calculated (e.g., Acuña-Castillo et al., 2002; note that when such a low efficacy was reported, we did not include this data as agonistic activity as we used a threshold of > 5% minimal effect size). Overall, there is thus a clear need to extend existing data and until that time, interpretation of reported data can be challenging.

Additionally, there is a clear need to derive new data as many targets have not been studied yet, while the number of NPS is enormous and continues to grow. To obtain useful neuropharmacological effect fingerprints, a battery of *in vitro* assays should be applied that preferably focusses on functional effects rather than on binding. Based on our review of affected targets, such a battery should include at least: inhibition and reversal of both plasma membrane and vesicular monoamine transporter as well as activation or inhibition of dopamine, serotonin, ACh, GABA, glutamate, cannabinoid, and adrenergic receptors.

Notably, investigating the effect of a specific NPS on an integrated endpoint, such as neuronal activity, could replace (and thus speedup) several single targets in the future. Although neuronal activity is potently inhibited by drugs that potently activate cannabinoid receptors (JWH-018; Table 1, Supplemental Fig. 9) and drugs that inhibit NMDA receptors (ketamine, MXE, Table 1 Supplemental Figs. 19-20), more data is necessary to investigate the predictive value of such integrated endpoints. Preferably, such novel assays have metabolic capacity or include testing of metabolites to better mimic the human *in vivo* situation.

While this review focused on neuropharmacological and neurotoxicological effects of NPS, other target organs are also of relevance. For example, looking at the clinical effects, the potency of NPS to induce cardiovascular- and hepatotoxicity should be investigated. Also, to realistically mimic the human exposure situation, it may be needed to include pyrolysis products as some NPS are heated before use, which can alter their chemical structure and result in different pharmacological activity (Thomas et al., 2017).

To reduce variation in reported effect concentrations, experimental guidelines may be formulated regarding which cell lines and assays are appropriate to measure activation or inhibition of specific targets. Due to the large variation observed in effect concentrations, these should preferably be obtained by at least two separate laboratories. Human models are preferred over cell lines derived from animal models and human induced pluripotent stem cell (iPSC)-derived models are

preferred over human (immortalized/cancer) cell lines. However, application of iPSC-derived models for pharmacology and toxicity testing (Tukker et al., 2016) and future technologies like 3D-cultures, microfluidics and organ-on-a-chip are still in their infancy.

The increasing use of NPS and the large gap in neuropharmacological data for most NPS poses a risk for public health, which is clear from the reported intoxications and fatalities following NPS use. Although a large overlap in clinical effects is observed between different NPS, some classes are more associated with severe effects or mortality than others. Predicting which NPS is likely to result in severe effects, prior to the actual occurrence of severe effects, could improve public health. Although guidelines and innovative (combinations of) assays may need to be developed, *in vitro* screening batteries are best suited to provide neuropharmacological data in a high-throughput and cost-effective manner. These batteries will yield specific effect fingerprints of NPS that aid risk assessment and could possibly shorten the time between market entering and regulation.

## Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pharmthera.2017.10.022.

## References

Abbara, C., Ferec, S., Leroux, G., Bretaudeau-Deguigne, M., Lelievre, B., Boels, D., et al. (2017). 2,5-dimethoxy-4- chloroamphetamine, a LSD-like designer drug: Clinical and analytical documentation of non-fatal exposure in five patients. *Toxicologie Analytique et Clinique, 29*, 82–89.

Abdrakhmanova, G. R., Blough, B. E., Nesloney, C., Navarro, H. A., Damaj, M. I., & Carroll, F. I. (2010). In vitro and in vivo characterization of a novel negative allosteric modulator of neuronal nAChRs. *Neuropharmacology, 59*, 511–517.

Acuña-Castillo, C., Villalobos, C., Moya, P. R., Saez, P., Cassels, B. K., & Huidobro-Toro, J. P. (2002). Differences in potency and efficacy of a series of phenylisopropylamine/phenylethylamine pairs at 5-HT2A and 5-HT2C receptors. *British Journal of Pharmacology, 136*, 510–519.

Adachi, N., Numakawa, T., Kumamaru, E., Itami, C., Chiba, S., Iijima, Y., et al. (2013). Phencyclidine-induced decrease of synaptic connectivity via inhibition of BDNF secretion in cultured cortical neurons. *Cerebral Cortex, 23*, 847–858.

Adamowicz, P., Gieron, J., Gil, D., Lechowicz, W., Skulska, A., & Tokarczyk, B. (2016a). The prevalence of new psychoactive substances in biological material – a three-year review of casework in Poland. *Drug Testing and Analysis, 8*, 63–70.

Adamowicz, P., Gieron, J., Gil, D., Lechowicz, W., Skulska, A., Tokarczyk, B., et al. (2016b). Blood concentrations of α-pyrrolidinovalerophenone (α-PVP) determined in 66 forensic samples. *Forensic Toxicology, 34*, 227–234.

Akiyoshi, J., Isogawa, K., Yamada, K., Nagayama, H., & Fujii, I. (1996). Effects of antidepressants on intracellular Ca2 + mobilization in CHO cells transfected with the human 5-HT2C receptors. *Biological Psychiatry, 39*, 1000–1008.

Antkowiak, B. (1999). Differnt actions of general anesthetics on the firing patterns of neocortical neurons mediated by the GABA A receptor. *Anesthesiology, 91*, 500–511.

Appadu, B., & Lambert, D. (1996). Interaction of iv anaesthetic agents with 5-HT3 receptors. *British Journal of Anaesthesia, 76*, 271–273.

Arbo, M. D., Bastos, M. L., & Carmo, H. F. (2012). Piperazine compounds as drugs of abuse. *Drug and Alcohol Dependence, 122*, 174–185.

Arbo, M. D., Silva, R., Barbosa, D. J., Da Silva, D. D., Silva, S. P., Teixeira, J. P., et al. (2016). In vitro neurotoxicity evaluation of piperazine designer drugs in differentiated human neuroblastoma SH-SY5Y cells. *Journal of Applied Toxicology, 36*, 121–130.

Arias, H. R., Feuerbach, D., Targowska-Duda, K. M., & Jozwiak, K. (2010). Catharanthine alkaloids are noncompetitive antagonists of muscle-type nicotinic acetylcholine receptors. *Neurochemistry International, 57*, 153–161.

Aronstam, R. S., Narayanan, L., & Wenger, D. A. (1982). Ketamine inhibition of ligand binding to cholinergic receptors and ion channels. *European Journal of Pharmacology, 78*, 367–370.

Ary, T. E., & Komiskey, H. L. (1980). Phencyclidine: Effect on the accumulation of 3H-Dopamine in synaptic vesicles. *Life Sciences, 26*, 575–578.

Atwood, B. K., Huffman, J., Straiker, A., & MacKie, K. (2010). JWH018, a common constituent of "Spice" herbal blends, is a potent and efficacious cannabinoid CB1 receptor agonist. *British Journal of Pharmacology, 160*, 585–593.

Augsburger, M., Donzé, N., Ménétrey, A., Brossard, C., Sporkert, F., Giroud, C., et al. (2005). Concentration of drugs in blood of suspected impaired drivers. *Forensic Science International, 153*, 11–15.

Aung, M. M., Griffin, G., Huffman, J. W., Wu, M. J., Keel, C., Yang, B., et al. (2000). Influence of the N-1 alkyl chain length of cannabimimetic indoles upon CB1 and CB2 receptor binding. *Drug and Alcohol Dependence, 60*, 133–140.

Auwärter, V., Dargan, P. I., & Wood, D. M. (2013). Synthetic cannabinoid receptor agonists. *Novel Psychoactive Substances*. Elsevier Inc..

Banister, S. D., Longworth, M., Kevin, R., Sachdev, S., Santiago, M., Stuart, J., et al. (2016). Pharmacology of valinate and tert-leucinate synthetic cannabinoids 5F-AMBICA, 5F-AMB, 5F-ADB, AMB-FUBINACA, MDMB- FUBINACA, MDMB-CHMICA, and their analogues. *ACS Chemical Neuroscience, 7*, 1241–1254.

Banister, S. D., Moir, M., Stuart, J., Kevin, R. C., Wood, K. E., Longworth, M., et al. (2015). Pharmacology of indole and indazole synthetic cannabinoid designer drugs AB-FUBINACA, ADB-FUBINACA, AB-PINACA, ADB- PINACA, 5F-AB-PINACA, 5F-ADB-PINACA, ADBICA, and 5F-ADBICA. *ACS Chemical Neuroscience, 6*, 1546–1559.

Banister, S. D., Stuart, J., Kevin, R. C., Edington, A., Longworth, M., Wilkinson, S. M., et al. (2015). Effects of bioisosteric fluorine in synthetic cannabinoid designer drugs JWH-018, AM-2201, UR-144, XLR-11, PB-22, 5F-PB-22, APICA, and STS-135. *ACS Chemical Neuroscience, 6*, 1445–1458.

Barann, M., Stamer, U. M., Lyutenska, M., Stüber, F., Bönisch, H., & Urban, B. (2015). Effects of opioids on human serotonin transporters. Naunyn-Schmiedeberg's. *Archives of Pharmacology, 388*, 43–49.

Battaglia, G., Brooks, B. P., Kulsakdinun, C., & De Souza, E. B. (1988). Pharmacologic profile of MDMA (3,4- methylenedioxymethamphetamine) at various brain recognition sites. *European Journal of Pharmacology, 149*, 159–163.

Baumann, M. H., Ayestas, M. A., Dersch, C. M., Partilla, J. S., & Rothman, R. B. (2000). Serotonin transporters, serotonin release, and the mechanism of fenfluramine neurotoxicity. *Annals of the New York Academy of Sciences, 914*, 172–186.

Baumann, M. H., Ayestas, M. A., Dersch, C. M., & Rothman, R. B. (2001). 1-(m-Chlorophenyl)piperazine (mCPP) dissociates in vitro serotonin release from long-term serotonin depletion in rat brain. *Neuropsychopharmacology, 24*, 492–501.

Baumann, M. H., Ayestas, M. A., Partilla, J. S., Sink, J. R., Shulgin, A. T., Daley, P. F., et al. (2012). The designer methcathinone analogs, mephedrone and methylone, are substrates for monoamine transporters in brain tissue. *Neuropsychopharmacology, 37*, 1192–1203.

Baumann, M. H., Bukhari, M. O., Lehner, K. R., Anizan, S., Rice, K. C., Concheiro, M., & Huestis, M. A. (2017). Neurophamracology of 3,4-methylenedioxypyrovalerone (MDPV), its metabolites, and related analogs. *Neurophamacology of New Psychoactive Substances (NPS). Vol. 32. Neurophamacology of New Psychoactive Substances (NPS)* (pp. 93–117).

Baumann, M. H., Bulling, S., Benaderet, T. S., Saha, K., Ayestas, M. A., Partilla, J. S., et al. (2014). Evidence for a role of transporter-mediated currents in the depletion of brain serotonin induced by serotonin transporter substrates. *Neuropsychopharmacology, 39*, 1355–1365.

Baumann, M. H., Clark, R. D., Budzynski, A. G., Partilla, J. S., Blough, B. E., & Rothman, R. B. (2004). Effects of "legal X" piperazine analogs on dopamine and serotonin release in rat brain. *Annals of the New York Academy of Sciences, 1025*, 189–197.

Baumann, M. H., Clark, R. D., Woolverton, W. L., Wee, S., Blough, B. E., & Rothman, R. B. (2011). In vivo effects of amphetamine analogs reveal evidence for serotonergic inhibition of mesolimbic dopamine transmission in the rat. *Journal of Pharmacology and Experimental Therapeutics, 337*, 218–225.

Baumann, M. H., Mash, D. C., & Staley, J. K. (1995). The serotonin agonist m-chlorophenylpiperazine (mCPP) binds to serotonin transporter sites in human brain. *NeuroReport, 6*, 2150–2152.

Baumann, M. H., Partilla, J. S., Lehner, K. R., Thorndike, E. B., Hoffman, A. F., Holy, M., et al. (2013). Powerful cocaine- like actions of 3,4-methylenedioxypyrovalerone (MDPV), a principal constituent of psychoactive "bath salts" products. *Neuropsychopharmacology, 38*, 552–562.

Bayewitch, M., Rhee, M., Avidor-reiss, T., Breuer, A., Mechoulam, R., & Vogel, Z. (1996). (-)-Delta9- tetrahydrocannabinol antagonizes the peripheral cannabinoid receptor-mediated inhibition of adenylyl cyclase. *Journal of Biological Chemistry, 271*, 9902–9905.

Beck, O., Franzén, L., Bäckberg, M., Signell, P., & Helander, A. (2016). Toxicity evaluation of α-pyrrolidinovalerophenone (α-PVP): results from intoxication cases within the STRIDA project. *Clinical Toxicology, 54*, 568–575.

Berg, K. A., Maayani, S., Goldfarb, J., Scaramellini, C., Leff, P., & Clarke, W. P. (1998). Effector pathway-dependent relative efficacy at serotonin type 2A and 2C receptors: evidence for agonist-directed trafficking of receptor stimulus. *Molecular Pharmacology, 54*, 94–104.

Bevan, R., Rose, M., & Duggan, K. (1997). Evidence for direct interaction of ketamine with alpha and beta2 adrenoreceptors. *Clinical and Experimental Pharmacology and Physiology, 24*, 923–926.

Bokor, G., & Anderson, P. D. (2014). Ketamine: An update on its abuse. *Journal of Pharmacy Practice, 27*, 582–586.

Bonifazi, A., Del Bello, F., Mammoli, V., Piergentili, A., Petrelli, R., Cimarelli, C., et al. (2015). Novel potent N-methyl-D-aspartate (NMDA) receptor antagonists or delta1 receptor ligands based on properly substituted 1,4- dioxane ring. *Journal of Medicinal Chemistry, 58*, 8601–8615.

Bouvier, G., Bidoret, C., Casado, M., & Paoletti, P. (2015). Presynaptic NMDA receptors: Roles and rules. *Neuroscience, 311*, 322–340.
Braden, M., Parrish, J., Naylor, J., & Nichols, D. (2006). Molecular interaction of serotonin 5-HT2A receptor residues Phe339 (6.51) and Phe340 (6.52) with superpotent N-benzyl phenethylamine agonists. *Molecular Pharmacology, 70*, 1956–1964.
Brents, L. K., Gallus-Zawada, A., Radominska-Pandya, A., Vasiljevik, T., Prisinzano, T. E., Fantegrossi, W. E., et al. (2012). Monohydroxylated metabolites of the K2 synthetic cannabinoid JWH-073 retain intermediate to high cannabinoid 1 receptor (CB1R) affinity and exhibit neutral antagonist to partial agonist activity. *Biochemical Pharmacology, 83*, 952–961.
Brents, L. K., Reichard, E. E., Zimmerman, S. M., Moran, J. H., Fantegrossi, W. E., & Prather, P. L. (2011). Phase 1 hydroxylated metabolites of the k2 synthetic cannabinoid JWH-018 retain in vitro and in vivo cannabinoid 1 receptor affinity and activity. *PLoS ONE, 6*, 1–9.
Brents, L. K., Zimmerman, S. M., Saffell, A. R., Prather, P. L., & Fantegrossi, W. E. (2013). Differential drug-drug interactions of the synthetic Cannabinoids JWH-018 and JWH-073: implications for drug abuse liability and pain therapy. *Journal of Pharmacology and Experimental Therapeutics, 346*, 350–361.
Bretteville-Jensen, A. L., Tuv, S. S., Bilgrei, O. R., Fjeld, B., & Bachs, L. (2013). Synthetic cannabinoids and cathinones; Prevalence and markets. *Forensic Science Review, 25*, 7.
Brog, J. S., & Beinfeld, M. C. (1990). Inhibition of carbachol-induced inositol phosphate accumulation by phencyclidine, phencyclidine-like ligands and sigma agonists involves blockade of the muscarinic cholinergic receptor: a novel dioxadrol-preferring interaction. *Journal of Pharmacology and Experimental Therapeutics, 254*, 952–956.
Brosnan, R. J., & Pham, T. L. (2011). Does anesthetic additivity imply a similar molecular mechanism of anesthetic action at N-Methyl-D-aspartate receptors? *Anesthesia and Analgesia, 112*, 568–573.
Brunt, T. M., Poortman, A., Niesink, R. J. M., & van den Brink, W. (2011). Instability of the ecstasy market and a new kid on the block: mephedrone. *Journal of Psychopharmacology, 25*, 1543–1547.
Bush, D. M. (2013). Drug Abuse Warning Network. (2013). *The CBHSQ Report: Emergency department visits involving phencyclidine (PCP)*. Rockville, MD: Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality.
Bush, D. M., & Woodwell, D. (2014). *The CBHSQ report: Update: Drug-related emergency department visits involving synthetic cannabinoids.* Rockville, MD: Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, Drug Abuse Warning Network.
Button, J., Wood, D. M., Dargan, P. I., Ovaska, H., Jones, A. L., Ramsey, J., et al. (2006). A gas chromatography massspectrometric method for the quantitative analysis of the recreational drug N-benzylpiperazine in serum. *Therapeutic Drug Monitoring, 29*, 496.
Caccia, S., Ballabio, M., Fanelli, R., Guiso, G., & Zanini, G. (1981). Determination of plasma and brain concentrations of trazodone and its metabolite, 1-m-chlorophenylpiperazine, by gas-liquid chromatography. *Journal of Chromatography, 210*, 311–318.
Caccia, S., Fong, M. H., Garattini, S., & Notarnicola, A. (1985). 1-aryl-piperazine as active metabolites of drugs with an aryl-piperazine side-chain. *Biochemical Pharmacology, 34*, 393–394.
Cameron, K. N., Kolanos, R., Solis, E., Glennon, R. A., & De Felice, L. J. (2013). Bath salts components mephedrone and methylenedioxypyrovalerone (MDPV) act synergistically at the human dopamine transporter. *British Journal of Pharmacology, 168*, 1750–1757.
Can, A., Zanos, P., Moaddel, R., Kang, H. J., Dossou, K. S. S., Wainer, I. W., et al. (2016). Effects of ketamine and ketamine metabolites on evoked striatal dopamine release, dopamine receptors, and monoamine transporters. *Journal of Pharmacology and Experimental Therapeutics, 359*, 159–170.
Canazza, I., Ossato, A., Trapella, C., Fantinati, A., De Luca, M. A., Margiani, G., et al. (2016). Effect of the novel synthetic cannabinoids AKB48 and 5F-AKB48 on "tetrad", sensorimotor, neurological and neurochemical responses in mice. In vitro and in vivo pharmacological studies. *Psychopharmacology, 233*, 3685–3709.
Cannaert, A., Storme, J., Franz, F., Auwärter, V., & Stove, C. P. (2016). Detection and activity profiling of synthetic cannabinoids and their metabolites with a newly developed bioassay. *Analytical Chemistry, 88*, 11476–11485.
Capela, J. P., Carmo, H., Remião, F., Bastos, M. L., Meisel, A., & Carvalho, F. (2009). Molecular and cellular mechanisms of ecstasy-induced neurotoxicity: An overview. *Molecular Neurobiology, 39*, 210–271.
Cawrse, B. M., Levine, B., Jufer, R. A., Fowler, D. R., Vorce, S. P., Dickson, A. J., et al. (2012). Distribution of methylone in four postmortem cases. *Journal of Analytical Toxicology, 36*, 434–439.
Chen, D. J., Gao, M., Gao, F. F., Su, Q. X., & Wu, J. (2017). Brain cannabinoid receptor 2: expression, function and modulation. *Acta Pharmacologica Sinica, 38*, 312–316.
Chen, L., & Malek, T. (2015). Follow me down the K-hole: Ketamine and its modern applications. *Critical Care Nursing Quarterly, 38*, 211–216.
Cheng, W. C., & Dao, K. L. (2017). The occurrence of alcohol/drugs by toxicological examination of selected drivers in Hong Kong. *Forensic Science International, 275*, 242–253.
Chin, C. N., Murphy, J. W., Huffman, J. W., & Kendall, D. A. (1999). The third transmembrane helix of the cannabinoid receptor plays a role in the selectivity of aminoalkylindoles for CB2, peripheral cannabinoid receptor. *Journal of Pharmacology and Experimental Therapeutics, 291*, 837–844.
Coates, K. M., & Flood, P. (2001). Ketamine and its preservative, benzethonium chloride, both inhibit human recombinant alpha7 and alpha4beta2 neuronal nicotinic acetylcholine receptors in Xenopus oocytes. *British Journal of Pharmacology, 134*, 871–879.
Compton, D. R., Rice, K. C., De Costa, B. R., Razdan, R. K., Melvin, L. S., Johnson, M. R., et al. (1993). Cannabinoid structure-activity relationships: correlation of receptor binding and in vivo activities. *The Journal of Pharmacology and Experimental Therapeutics, 265*, 218–226.
Connolly, J., Boulter, J., & Heinemann, S. F. (1992). Alpha4-2beta2 and other nicotinic acetylcholine receptor subtypes as targets of psychoactive and addictive drugs. *British Journal of Pharmacology, 105*, 657–666.
Corazza, O., Assi, S., & Schifano, F. (2013). From "Special K" to "Special M": The evolution of the recreational use of ketamine and methoxetamine. *CNS Neuroscience & Therapeutics, 19*, 454–460.
Cosbey, S. H., Peters, K. L., Quinn, A., & Bentley, A. (2013). Mephedrone (methylmethcathinone) in toxicology casework: A northern ireland perspective. *Journal of Analytical Toxicology, 37*, 74–82.
Cozzi, N. V., Sievert, M. K., Shulgin, A. T., Jacob, P., & Ruoho, A. E. (1999). Inhibition of plasma membrane monoamine transporters by β- ketoamphetamines. *European Journal of Pharmacology, 381*, 63–69.
Crespi, D., Mennini, T., & Gobbi, M. (1997). Carrier-dependent and Ca2 +-dependent 5-HT and dopamine release induced by (+)-amphetamine, 3,4-methylendioxy-methamphetamine, p-chloroamphetamine and (+)- fenfluramine. *British Journal of Pharmacology, 121*, 1735–1743.
Daldrup, T., & Mußhoff, F. (1993). Detection of cannabinoids in serum of vehicle drivers after smoking cannabis in coffee shops. *Alcohol, Drugs and Traffic Safety,* 497–504.
Dawson, P., Opacka-Juffry, J., Moffatt, J. D., Daniju, Y., Dutta, N., Ramsey, J., et al. (2014). The effects of benzofury (5-APB) on the dopamine transporter and 5-HT2-dependent vasoconstriction in the rat. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 48*, 57–63.
De Letter, E. A., Bouche, M. P. L. A., Van Bocxlaer, J. F., Lambert, W. E., & Piette, M. H. A. (2004). Interpretation of a 3,4-methylenedioxymethamphetamine (MDMA) blood level: discussion by means of a distribution study in two fatalities. *Forensic Science International, 141*, 85–90.
De Luca, M. A., Bimpisidis, Z., Melis, M., Marti, M., Caboni, P., Valentini, V., et al. (2015). Stimulation of in vivo dopamine transmission and intravenous self-administration in rats and mice by JWH-018, a Spice cannabinoid. *Neuropharmacology, 99*, 705–714.
De Luca, M. A., Castelli, M. P., Loi, B., Porcu, A., Martorelli, M., Miliano, C., et al. (2016). Native CB1 receptor affinity, intrinsic activity and accumbens shell dopamine stimulant properties of third generation SPICE/K2 cannabinoids: BB-22, 5F-PB-22, 5F-AKB-48 and STS-135. *Neuropharmacology, 105*, 630–638.
Dean, B. V., Stellpflug, S. J., Burnett, A. M., & Engebretsen, K. M. (2013). 2C or not 2C: Phenethylamine designer drug review. *Journal of Medical Toxicology, 9*, 172–178.
Del Bello, F., Sakloth, F., Partilla, J. S., Baumann, M. H., & Glennon, R. A. (2015). Ethylenedioxy homologs of N- methyl-(3,4-methylenedioxyphenyl)-2-aminopropane (MDMA) and its corresponding cathinone analog methylenedioxymethcathinone: Interactions with transporters for serotonin, dopamine, and norepinephrine. *Bioorganic and Medicinal Chemistry, 23*, 5574–5579.
Den Hollander, B., Sundström, M., Pelander, A., Ojanperä, I., Mervaala, E., Korpi, E. R., et al. (2014). Keto amphetamine toxicity-focus on the redox reactivity of the cathinone designer drug mephedrone. *Toxicological Sciences, 141*, 120–131.
Den Hollander, B., Sundström, M., Pelander, A., Siltanen, A., Ojanperä, I., Mervaala, E., et al. (2015). Mitochondrial respiratory dysfunction due to the conversion of substituted cathinones to methylbenzamides in SH-SY5Y cells. *Scientific Reports, 5*, 14924.
DeRoux, S. J., & Dunn, W. A. (2017). "Bath Salts" the New York city medical examiner experience: A 3-year retrospective review. *Journal of Forensic Sciences, 62*, 695–699.
DeVane, C. L., Boulton, D. W., Miller, L. F., & Miller, R. L. (1999). Pharmacokinetics of trazodone and its major metabolite m-chlorophenylpiperazine in plasma and brain of rats. *The International Journal of Neuropsychopharmacology, 2*, 17–23.
Devlin, R. J., & Henry, J. A. (2008). Review clinical review: Major consequences of illicit drug consumption. *Critical Care, 12*, 1–7.
Di Marzo, V., Bifulco, M., & Petrocellis, L. D. (2004). The endocannabinoid system and its therapeutic exploitation. *Nature Reviews, 3*, 771–784.
Di Marzo, V., & Piscitelli, F. (2015). The Endocannabinoid System and its Modulation by Phytocannabinoids. *Neurotherapeutics, 12*, 692–698.
Di Marzo, V., Stella, N., & Zimmer, A. (2015). Endocannabinoid signalling and the deteriorating brain. *Nature Reviews, 16*, 30–42.
Drejer, J., & Honoré, T. (1987). Phencyclidine analogues inhibit NMDA-stimulated [3H]GABA release from cultured cortex neurons. *European Journal of Pharmacology, 143*, 287–290.
Drug Enforcement Administration (2014). National Forensic Laboratory Information System. Special Report: synthetic cannabinoids and synthetic cathinones reported in NFLIS, 2010–2013. US Drug Enforcement Administration, Springfield. Accessed 28 June 2017 via: https://www.deadiversion.usdoj.gov/nflis/spec_rpt_CathCan_2013.pdf.
Durieux, M. E. (1995). Inhibition by Ketamine of Muscarinic Acetylcholine Receptor Function. *Anesthesia and Analgesia, 81*, 57–62.
Eaton, M. J., Labarca, C., & Eterovíc, V. A. (2000). M2 mutations of the nicotinic acetylcholine receptor increase the potency of the non-competitive inhibitor phencyclidine. *Journal of Neuroscience Research, 61*, 44–51.
Ebert, B., Mikkelsen, S., Thorkildsen, C., & Borgbjerg, F. M. (1997). Norketamine, the main metabolite of ketamine, is a non-competitive NMDA receptor antagonist in the rat cortex and spinal cord. *European Journal of Pharmacology, 333*, 99–104.
Elian, A. A., & Hackett, J. (2014). A polydrug intoxication involving methoxetamine in a drugs and driving case. *Journal of Forensic Sciences, 59*, 854–858.
Elliott, S. (2011). Current awareness of piperazines: Pharmacology and toxicology. *Drug Testing and Analysis, 3*, 430–438.
Elliott, S., & Evans, J. (2014). A 3-year review of new psychoactive substances in casework. *Forensic Science International, 243*, 55–60.
Elmore, J. S., Dillon-Carter, O., Partilla, J. S., Ellefsen, K. N., Concheiro, M., Suzuki, M., et al. (2017). Pharmacokinetic profiles and pharmacodynamic effects for methylone

and its metabolites in rats. *Neuropsychopharmacology, 42*, 649–660.
EMCDDA, European Monitoring Centre for Drugs and Drug Addiction (2009). Annual Report: The state of the drugs problem in Europe. ISBN 978-92-9168-384-0 Publications Office of the European Union, Luxembourg. Accessed 02-02-2017 via: http://www.emcdda.europa.eu/system/files/publications/970/EMCDDA_AR2009_EN.pdf.
EMCDDA, European Monitoring Centre for Drugs and Drug Addiction (2012). Classification of controlled drugs. via: http://www.emcdda.europa.eu/html.cfm/index146601EN.html, Accessed date: 13 June 2017.
EMCDDA, European Monitoring Centre for Drugs and Drug Addiction (2014). Europol joint report on a new psychoactive substance: methoxetamine (2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone). via: http://www.emcdda.europa.eu/publications/joint-report/methoxetamine, Accessed date: 1 July 2017.
EMCDDA, European Monitoring Centre for Drugs and Drug Addiction (European Monitoring Centre for Drugs and Drug Addiction, 2015a). New psychoactive substances in Europe. An update from the EU Early Warning System. via: http://www.emcdda.europa.eu/publications/2015/new-psychoactive-substances, Accessed date: 10 October 2016.
EMCDDA, European Monitoring Centre for Drugs and Drug Addiction (European Monitoring Centre for Drugs and Drug Addiction, 2015b). Drug profiles: BZP and other piperazines drug profiles. via: http://www.emcdda.europa.eu/publications/drug-profiles/bzp, Accessed date: 14 April 2017.
EMCDDA, European Monitoring Centre for Drugs and Drug Addiction (European Monitoring Centre for Drugs and Drug Addiction, 2016a). Action on new drugs. via: http://www.emcdda.europa.eu/activities/action-on-new-drugs, Accessed date: 6 December 2017.
EMCDDA, European Monitoring Centre for Drugs and Drug Addiction (European Monitoring Centre for Drugs and Drug Addiction, 2016b). European Drug Report: Trends and Developments. via: http://www.emcdda.europa.eu/edr2016, Accessed date: 1 July 2017.
Emnett, C. M., Eisenman, L. N., Mohan, J., Taylor, A. A., Doherty, J. J., Paul, S. M., et al. (2015). Interaction between positive allosteric modulators and trapping blockers of the NMDA receptor channel. *British Journal of Pharmacology, 172*, 1333–1347.
Emnett, C. M., Eisenman, L. N., Taylor, A. M., Izumi, Y., Zorumski, C. F., & Mennerick, S. (2013). Indistinguishable synaptic pharmacodynamics of the N-methyl-D-aspartate receptor channel blockers memantine and ketamine. *Molecular Pharmacology, 84*, 935–947.
Erickson, J. D., Schäfer, M. K. H., Bonner, T. I., Eiden, L. E., & Weihe, E. (1996). Distinct pharmacological properties and distribution in neurons and endocrine cells of two isoforms of the human vesicular monoamine transporter. *Proceedings of the National Academy of Sciences of the United States of America, 93*, 5166–5171.
Eshleman, A. J., Henningsen, R. A., Neve, K. A., & Janowsky, A. (1994). Release of dopamine via the human transporter. *Molecular Pharmacology, 45*, 312–316.
Eshleman, A. J., Wolfrum, K. M., Hatfield, M. G., Johnson, R. A., Murphy, K. V., & Janowsky, A. (2013). Substituted methcathinones differ in transporter and receptor interactions. *Biochemical Pharmacology, 85*, 1803–1815.
Eshleman, A. J., Wolfrum, K. M., Reed, J. F., Kim, S. O., Swanson, T., Johnson, R. A., et al. (2017). Structure-activity relationships of substituted cathinones, with transporter binding, uptake and release. *Journal of Pharmacology and Experimental Therapeutics, 360*, 33–47.
Expert Committee on Drug Dependence (2016). Pentedrone; Critical review report. World Health Organization. Fattore, L. Review supporting the relationship between cannabinoids and psychosis. *Biological Psychiatry, 79*, 539–548.
Fattore, L. (2016). Synthetic cannabinoids - Further evidence supporting the relationship between cannabinoids and psychosis. *Biological Psychiatry, 79*, 539–548.
Felder, C. C., Joyce, K. E., Briley, E. M., Mansouri, J., Mackie, K., Blond, O., et al. (1995). Comparison of the pharmacology and signal transduction of the human cannabinoid CB1 and CB2 receptors. *Molecular Pharmacology, 48*, 443–450.
Férec, S., Boels, D., Bretaudeau, M., Lelièvre, B., Leborgne, I., & Harry, P. (2013). Exposition aiguë à la 4-méthyl- éthylcathinone (4MEC), autre nouvelle drogue de synthèse accessible via Internet. *Annales de Toxicologie Analytique, 25*, 146–147.
Férec, S., Gandemer, L., Peters, M., Boels, D., Bretaudeau-Deguigne, M., & Gegu, C. (2014). Psychostimulants de synthèse en accès sur Internet: à propos de 4 nouveaux cas (2C-T-4, 6-APB, 6-APDB, 5-MeO-DALT). *Toxicologie Analytique et Clinique, 26*, S30.
Ffrench-Mullen, J. M. H., & Rogawski, M. A. (1989). Interaction of phencyclidine with voltage-dependent potassium channels in cultured rat hippocampal neurons: comparison with block of the NMDA receptor-ionophore complex. *Journal of Neuroscience, 9*, 4051–4061.
Ffrench-Mullen, J. M. H., & Rogawski, M. A. (1992). Phencyclidine block of calcium current in isolated guinea-pig hippocampal neurones. *Journal of Physiology, 456*, 85–105.
Fleckenstein, A. E., Volz, T. J., Riddle, E. L., Gibb, J. W., & Hanson, G. R. (2007). New insights into the mechanism of action of amphetamines. *Annual Review of Pharmacology and Toxicology, 47*, 681–698.
Flood, P., & Krasowski, M. D. (2000). Intravenous anesthetics differentially modulate ligand-gated ion channels. *Anesthesiology, 92*, 1418–1425.
Ford, B. M., Franks, L. N., Tai, S., Fantegrossi, W. E., Stahl, E. L., Berquist, M. D., Cabanlong, C. V., et al. (2017). Characterization of structurally novel G protein biased $CB_1$ agonists: Implications for drug development. *Pharmacological Research, 125*, 161–177.
Fu, B., Liu, C., Zhang, Y., Fu, X., Zhang, L., & Yu, T. (2017). Ketamine attenuates the glutamatergic neurotransmission in the ventral posteromedial nucleus slices of rats. *BMC Anesthesiology, 17*, 111.
García-Repetto, R., Moreno, E., Soriano, T., Jurado, C., Giménez, M. P., & Menéndez, M. (2003). Tissue concentrations of MDMA and its metabolite MDA in three fatal cases of overdose. *Forensic Science International, 135*, 110–114.
Gee, P., Gilbert, M., Richardson, S., Moore, G., Paterson, S., & Graham, P. (2008). Toxicity from the recreational use of 1-benzylpiperazine. *Clinical Toxicology, 46*, 802–807.
Gee, P., Schep, L. J., Jensen, B. P., Moore, G., & Barrington, S. (2016). Case series: toxicity from 25B-NBOMe – a cluster of N-bomb cases. *Clinical Toxicology, 54*, 141–146.
Gilling, K. E., Jatzke, C., Hechenberger, M., & Parsons, C. G. (2009). Potency, voltage-dependency, agonist concentration-dependency, blocking kinetics and partial untrapping of the uncompetitive N-methyl-d- aspartate (NMDA) channel blocker memantine at human NMDA (GluN1/GluN2A) receptors. *Neuropharmacology, 56*, 866–875.
Glasgow, N. G., Povysheva, N. V., Azofeifa, A. M., & Johnson, J. W. (2017). Mementine and ketamine differentially alter NMDA receptor desensitization. *The Journal of Neuroscience, 37*, 9686–9704.
Glennon, R. A. (2014). Bath salts, mephedrone, and methylenedioxypyrovalerone as emerging illicit drugs that will need targeted therapeutic intervention. *Advances in Pharmacology, 69*, 581–620.
Glennon, R. A., Dukat, M., El-Bermawy, M., Law, H., De Los Angeles, J., Teitler, M., et al. (1994). Influence of amine substituents on 5-HT2A versus 5-HT2C binding of phenylalkyl- and indolylalkylamines. *Journal of Medicinal Chemistry, 37*, 1929–1935.
Global Drug Survey (2015). The global drug survey 2015 findings: Other novel psychoactive drugs (NPS). via: https://www.globaldrugsurvey.com/the-global-drug-survey-2015-findings/, Accessed date: 26 June 2017.
Gobbi, M., Moia, M., Pirona, L., Ceglia, I., Reyes-Parada, M., Scorza, C., et al. (2002). p-Methylthioamphetamine and 1-(m-chlorophenyl)piperazine, two non-neurotoxic 5-HT releasers in vivo, differ from neurotoxic amphetamine derivatives in their mode of action at 5-HT nerve endings in vitro. *Journal of Neurochemistry, 82*, 1435–1443.
Gowrishankar, R., Hahn, M. K., & Blakely, R. D. (2014). Good riddance to dopamine: Roles for the dopamine transporter in synaptic function and dopamine-associated brain disorders. *Neurochemistry International, 73*, 42–48.
Grayson, B., Barnes, S. A., Markou, A., Piercy, C., Podda, G., & Neill, J. C. (2016). Postnatal phencyclidine (PCP) as a neurodevelopmental animal model of schizophrenia pathophysiology and symptomatology: A review social behaviour. *Current Topics in Behavioral Neurosciences, 29*, 403–428.
Green, A. R., King, M. V., Shortall, S. E., & Fone, K. C. F. (2014). The preclinical pharmacology of mephedrone; Not just MDMA by another name. *British Journal of Pharmacology, 171*, 2251–2268.
Green, A. R., Mechan, A. O., Elliott, J. M., Shea, E. O., & Colado, M. I. (2003). The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"). *Pharmacological Reviews, 55*, 463–508.
Greene, S. L., Kerr, F., & Braitberg, G. (2008). Review article: Amphetamines and related drugs of abuse. *Emergency Medicine Australasia, 20*, 391–402.
Gregg, R. A., Baumann, M. H., Partilla, J. S., Bonano, J. S., Vouga, A., Tallarida, C. S., et al. (2015). Stereochemistry of mephedrone neuropharmacology: Enantiomer-specific behavioural and neurochemical effects in rats. *British Journal of Pharmacology, 172*, 883–894.
Grotewiel, M. S., Chu, S., & Sanders-Bush, E. (1994). m-Chlorophenylpiperazine and m-trifluoromethylphenylpiperazine are partial agonists at cloned 5-HT2A receptors expressed in fibroblasts. *Journal of Pharmacology and Experimental Therapeutics, 271*, 1122–1126.
Gustavsen, I., Morland, J., & Bramness, J. G. (2006). Impairment related to blood amphetamine and/or methamphetamine concentration in suspected drugged drivers. *Accident Analysis and Prevention, 38*, 490–495.
Hadlock, G. C., Webb, K. M., McFadden, L. M., Chu, P. W., Ellis, J. D., Allen, S. C., et al. (2011). 4- Methylmethcathinone (mephedrone): neuropharmacological effects of a designer stimulant of abuse. *Journal of Pharmacology and Experimental Therapeutics, 339*, 530–536.
Halberstadt, A. L. (2017). Pharmacology and toxicology of N-benzylphenethylamine ("NBOMe") hallucinogens. *Neurophamacology of New Psychoactive Substances (NPS)* (pp. 283–311). .
Hamik, A., & Peroutka, S. J. (1989). 1-(m-Chlorophenyl)piperazine (mCPP) interactions with neurotransmitter receptors in the human brain. *Biological Psychiatry, 25*, 569–575.
Hara, K., Yamakura, T., Sata, T., & Harris, R. A. (2005). The effects of anesthetics and ethanol on alpha2 adrenoceptor subtypes expressed with G protein-coupled inwardly rectifying potassium channels in Xenopus oocytes. *Anesthesia and Analgesia, 101*, 1381–1388.
Hara, K., Yanagihara, N., Minami, K., Ueno, S., Toyohira, Y., Sata, T., et al. (1998). Ketamine interacts with the noradrenaline transporter at a site partly overlapping the desipramine binding site. Naunyn-Schmiedeberg's. *Archives of Pharmacology, 358*, 328–333.
Harel-Dupas, C., Cloëz, I., & Fillion, G. (1991). Antagonism by antidepressant drugs of the inhibitory effect of trifluoromethylphenylpiperazine (TFMPP) on [3H]acetylcholine release in rat or guinea-pig hippocampal synaptosomes. *European Neuropsychopharmacology, 1*, 157–164.
Hartung, B., Kauferstein, S., Ritz-Timme, S., & Daldrup, T. (2014). Sudden unexpected death under acute influence of cannabis. *Forensic Science International, 237*, e11–e13.
Hartvig, P., Valtysson, J., Lindner, K. J., Kristensen, J., Karlsten, R., Gustafsson, L. L., et al. (1995). Central nervous system effects of subdissociative doses of (S)-ketamine are related to plasma and brain concentrations measured with positron emission tomography in healthy volunteers. *Clinical Pharmacology and Therapeutics, 58*, 165–173.
Hasegawa, K., Suzuki, O., Wurita, A., Minakata, K., Yamagishi, I., Nozawa, H., et al. (2014). Postmortem distribution of a-pyrrolidinovalerophenone and its metabolite in body fluids and solid tissues in a fatal poisoning case measured by LC-MS-MS with the standard addition method. *Forensic Toxicology, 32*, 225–234.
Hatakeyama, N., Yamazaki, M., Shibuya, N., Yamamura, S., & Momose, Y. (2001). Effects of ketamine on voltage- dependent calcium currents and membrane potentials in

single bullfrog atrial cells. *Journal of Anesthesia, 15*, 149–153.
Heal, D. J., Cheetham, S. C., Prow, M. R., Martin, K. F., & Buckett, W. R. (1998). A comparison of the effects on central 5-HT function of sibutramine hydrochloride and other weight-modifying agents. *British Journal of Pharmacology, 125*, 301–308.
Hendrickson, H., Laurenzana, E., & Owens, S. M. (2006). Quantitative determination of total methamphetamine and active metabolites in rat tissue by liquid chromatography with tandem mass spectrometric detection. *The AAPS Journal, 8*, E709–17.
Hermanns-Clausen, M., Angerer, V., Kithinji, J., Grunmann, C., & Auwärter, V. (2017). Bad trip due to 25I-NBOMe: a case report from the EU project SPICE II plus. *Clinical Toxicology, 55*, 922–924.
Heusler, P., Tourette, A., & Cussac, D. (2015). Potencies and unblocking kinetic properties of antagonists at recombinant human NMDA receptors in a Xenopus oocytes model. Naunyn-Schmiedeberg's. *Archives of Pharmacology, 388*, 509–516.
Hevers, W., Hadley, S. H., Lu, H., & Amin, J. (2008). *Ketamine, but not phencyclidine, selectively modulates cerebellar GABA A receptors containing alpha6 and beta subunits. 28*, 5383–5393.
Hirota, K., Hashimoto, Y., & Lambert, D. G. (2002). Interaction of intravenous anesthetics with recombinant human M1-M3 muscarinic receptors expressed in Chinese hamster ovary cells. *Anesthetic Pharmacology, 95*, 1607–1610.
Hirota, K., & Lambert, D. G. (1996). I.v. anaesthetic agents do not interact with the verapamil binding site on L- type voltage-sensitive Ca2 + channels. *British Journal of Anaesthesia, 77*, 385–386.
Hoffman, A. F., Lycas, M. D., Kaczmarzyk, J. R., Spivak, C. E., Baumann, M. H., & Lupica, C. R. (2017). Disruption of hippocampal synaptic transmission and long-term potentiation by psychoactive synthetic cannabinoid "Spice" compounds: Comparison with Δ9-tetrahydrocannabinol. *Addiction Biology, 22*, 1–10.
Holmes, J. C., & Rutledge, C. O. (1976). Effects of the d- and l-isomers of amphetamine on uptake, release and catabolism of norepinephrine, dopamine and 5-hydroxytryptamine in several regions of rat brain. *Biochemical Pharmacology, 25*, 447–451.
Hondebrink, L., Hermans, E. J. P., Schmeink, S., van Kleef, R. G. D. M., Meulenbelt, J., & Westerink, R. H. S. (2015). Structure-dependent inhibition of the human α1β2γ2 GABAA receptor by piperazine derivatives: A novel mode of action. *NeuroToxicology, 51*, 1–9.
Hondebrink, L., Kasteel, E. E. J., Tukker, A. M., Wijnolts, F. M. J., Verboven, A. H. A., & Westerink, R. H. S. (2017). Neuropharmacological characterization of the new psychoactive substance methoxetamine. *Neuropharmacology, 123*, 1–9.
Hondebrink, L., Meulenbelt, J., Meijer, M., Van Den Berg, M., & Westerink, R. H. S. (2011). High concentrations of MDMA ('ecstasy') and its metabolite MDA inhibit calcium influx and depolarization-evoked vesicular dopamine release in PC12 cells. *Neuropharmacology, 61*, 202–208.
Hondebrink, L., Meulenbelt, J., Rietjens, S. J., Meijer, M., & Westerink, R. H. S. (2012). Methamphetamine, amphetamine, MDMA ('ecstasy'), MDA and mCPP modulate electrical and cholinergic input in PC12 cells. *NeuroToxicology, 33*, 255–260.
Hondebrink, L., Meulenbelt, J., Timmerman, J. G., Van Den Berg, M., & Westerink, R. H. S. (2009). Amphetamine reduces vesicular dopamine content in dexamethasone-differentiated PC12 cells only following l-DOPA exposure. *Journal of Neurochemistry, 111*, 624–633.
Hondebrink, L., Meulenbelt, J., van Kleef, R. G. D. M., van den Berg, M., & Westerink, R. H. S. (2011). Modulation of human GABAA receptor function: A novel mode of action of drugs of abuse. *NeuroToxicology, 32*, 823–827.
Hondebrink, L., Nugteren-van Lonkhuyzen, J. J., Rietjens, S. J., Brunt, T. M., Venhuis, B., Soerdjbalie-Maikoe, V., et al. (2017). Fatalities, cerebral hemorrhage and severe cardiovascular toxicity following exposure to the new psychoactive substance 4-fluoroamphetamine (4-FA): a prospective cohort study. *Annals of Emergency Medicine*. http://dx.doi.org/10.1016/j.annemergmed.2017.07.482.
Hondebrink, L., Tan, S., Hermans, E., van Kleef, R. G. D. M., Meulenbelt, J., & Westerink, R. H. S. (2013). Additive inhibition of human α1β2γ2 GABAA receptors by mixtures of commonly used drugs of abuse. *NeuroToxicology, 35*, 23–29.
Hondebrink, L., Verboven, A. H. A., Drega, W. S., Schmeink, S., de Groot, M. W. G. D. M., van Kleef, R. G. D. M., et al. (2016). Neurotoxicity screening of (illicit) drugs using novel methods for analysis of microelectrode array (MEA) recordings. *NeuroToxicology, 55*, 1–9.
Hori, T., Suzuki, T., Baba, A., Abe, S., Yamamoto, T., Moroji, T., et al. (1996). Effects of phencyclidine metabolites on serotonin uptake in rat brain. *Neuroscience Letters, 209*, 153–156.
Horsley, R. R., Lhotkova, E., Hajkova, K., Jurasek, B., Kuchar, M., & Palenicek, T. (2016). Detailed pharmacological evaluation of methoxetamine (MXE), a novel psychoactive ketamine analogue - Behavioural, pharmacokinetic and metabolic studies in the Wistar rat. *Brain Research Bulletin, 126*, 102–110.
Howell, L. L., & Kimmel, H. L. (2008). Monoamine transporters and psychostimulant addiction. *Biochemical Pharmacology, 75*, 196–217.
Hysek, C. M., Simmler, L. D., Nicola, V. G., Vischer, N., Donzelli, M., Krähenbühl, S., et al. (2012). Duloxetine inhibits effects of MDMA ("ecstasy") in vitro and in humans in a randomized placebo-controlled laboratory study. *PLoS ONE, 7*, 1–15.
Iacobucci, G. J., & Popescu, G. K. (2017). NMDA receptors: linking physiological output to biophysical operation. *Nature Reviews, 18*, 236–249.
Irnaten, M., Wang, J., Chang, K. S. K., & Andresen, M. C. (2002). Ketamine inhibits sodium currents in identified cardiac parasympathetic neurons in nucleus ambiguus. *Anesthesiology, 96*, 59–66.
Irnaten, M., Wang, J., Venkatesan, P., Evans, C., K Chang, K. S., Andresen, M. C., et al. (2002). Ketamine inhibits presynaptic and postsynaptic nicotinic excitation of identified cardiac parasympathetic neurons in nucleus ambiguus. *Anesthesiology, 96*, 667–674.
Iversen, L., Gibbons, S., Treble, R., Setola, V., Huang, X. P., & Roth, B. L. (2013). Neurochemical profiles of some novel psychoactive substances. *European Journal of Pharmacology, 700*, 147–151.
Iversen, L., White, M., & Treble, R. (2014). Designer psychostimulants: Pharmacology and differences. *Neuropharmacology, 87*, 59–65.
Iwamura, H., Suzuki, H., Ueda, Y., Kaya, T., & Inaba, T. (2001). In vitro and in vivo pharmacological characterization of JTE- 907, a novel selective ligand for cannabinoid CB2 receptor. *Pharmacology, 296*, 420–425.
Jackson, J. E. (1989). Phencyclidine pharmacokinetics after a massive overdose. *Annals of Internal Medicine, 111*, 613–615.
Javitt, D. C. (2004). Glutamate as a therapeutic target in psychiatric disorders. *Molecular Psychiatry, 9*, 984–997.
Juncosa, J. I., Hansen, M., Bonner, L. A., Cueva, J. P., Maglathlin, R., McCorvy, J. D., et al. (2013). Extensive rigid analogue design maps the binding conformation of potent N-benzylphenethylamine 5-HT2A serotonin receptor agonist ligands. *ACS Chemical Neuroscience, 4*, 96–109.
Kalsi, S. S., Wood, D. M., & Dargan, P. I. (2011). The epidemiology and patterns of acute and chronic toxicity associated with recreational ketamine use. *Emerging Health Threats Journal, 4*, 1–10.
Kang, H., Park, P., Bortolotto, Z., Brandt, S. D., Colestock, T., Wallach, J., et al. (2017). Ephenidine: A new psychoactive agent with ketamine-like NMDA receptor antagonist properties. *Neuropharmacology, 112*, 144–149.
Kapur, S., & Seeman, P. (2002). NMDA receptor antagonists ketamine and PCP have direct effects on the dopamine D(2) and serotonin 5-HT(2)receptors-implications for models of schizophrenia. *Molecular Psychiatry, 7*, 837–844.
Karasawa, J. I., Yamamoto, H., Yamamoto, T., Sagi, N., Horikomi, K., & Sora, I. (2002). MS-377, a selective sigma receptor ligand, indirectly blocks the action of PCP in the N-methyl-D-aspartate receptor ion-channel complex in primary cultured rat neuronal cells. *Life Sciences, 70*, 1631–1642.
Karinen, R., & Hoiseth, G. (2017). A literature review of blood concentrations of new psychoactive substances classified as phenethylamines, aminoindanes, arylalkylamines, arylcyclohexylamines, an d indoalkylamines. *Forensic Science International, 276*, 120–125.
Katz, D. P., Majrashi, M., Ramesh, S., Govindarajulu, M., Bhattacharya, D., Bhattacharya, S., et al. (2017). Comparing the dopaminergic neurotoxic effects of benzylpiperazine and benzoylpiperazine. *Toxicology Mechanisms and Methods*. http://dx.doi.org/10.1080/15376516.2017.1376024 (in press).
Kelly, J. P. (2011). Cathinone derivatives: A review of their chemistry, pharmacology and toxicology. *Drug Testing and Analysis, 3*, 439–453.
Khiabani, H. Z., Bramness, J. G., Bjorneboe, A., & Morland, J. (2006). Relationship between THC concentration in blood and impairment in apprehended drivers. *Traffic Injury Prevention, 7*, 11–116.
Kilpatrick, G. J., Jones, B. J., & Tyers, M. B. (1987). Identification and distribution of 5-HT3 receptors in rat brain using radioligand binding. *Nature, 330*, 746–748.
Kimmel, H. L., Carroll, F. I., & Kuhar, M. J. (2001). Locomotor stimulant effects of novel phenyltropanes in the mouse. *Drug and Alcohol Dependence, 65*, 25–36.
Kneisel, S., & Auwärter, V. (2012). Analysis of 30 synthetic cannabinoids in serum by liquid chromatography- electrospray ionization tandem mass spectrometry after liquid-liquid extraction. *Journal of Mass Spectrometry, 47*, 825–835.
Köhler, J., Bergander, K., Fabian, J., Schepmann, D., & Wünsch, B. (2012). Enantiomerically pure 1,3-dioxanes as highly selective NMDA and $\sigma_1$ receptor ligands. *Journal of Medicinal Chemistry, 55*, 8953–8957.
Kolanos, R., Partilla, J. S., Baumann, M. H., Hutsell, B. A., Banks, M. L., Negus, S. S., et al. (2015). Stereoselective actions of methylenedioxypyrovalerone (MDPV) to inhibit dopamine and norepinephrine transporters and facilitate intracranial self-stimulation in rats. *ACS Chemical Neuroscience, 6*, 771–777.
Kolanos, R., Sakloth, F., Jain, A. D., Partilla, J. S., Baumann, M. H., & Glennon, R. A. (2015). Structural modification of the designer stimulant α-pyrrolidinovalerophenone (α-PVP) influences potency at dopamine transporters. *ACS Chemical Neuroscience, 6*, 1726–1731.
Kolanos, R., Solis, E., Sakloth, F., Defelice, L. J., & Glennon, R. A. (2013). "Deconstruction" of the abused synthetic cathinone methylenedioxypyrovalerone (MDPV) and an examination of effects at the human dopamine transporter. *ACS Chemical Neuroscience, 4*, 1524–1529.
Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology, 35*, 217–238.
Korpi, E. R., Den Hollander, B., Farooq, U., Vashchinkina, E., Rajkumar, R., Nutt, D. J., et al. (2015). Mechanisms of action and persistent neuroplasticity by drugs of abuse. *Pharmacological Reviews, 67*, 872–1004.
Kovaleva, J., Devuyst, E., De Paepe, P., & Verstraete, A. (2008). Acute chlorophenylpiperazine overdose: a case Elian, A. A., & Hackett, J. (2014). A polydrug intoxication involving methoxetamine in a drugs and driving case. *Journal of Forensic Sciences, 59*, 854–858.
Kriikku, P., Wilhelm, L., Schwarz, O., & Rintatalo, J. (2011). New designer drug of abuse: 3,4- Methylenedioxypyrovalerone (MDPV). Findings from apprehended drivers in Finland. *Forensic Science International, 210*, 195–200.
Kristofic, J. J., Chmiel, J. D., Jackson, G. F., Vorce, S. P., Holler, J. M., Robinson, S. L., et al. (2016). Detection of 25C- NBOMe in three related cases. *Journal of Analytical Toxicology, 40*, 466–472.
Kunsman, G. W., Levine, B., Costantino, A., & Smith, M. L. (1997). Phencyclidine blood concentrations in DRE cases. *Journal of Analytical Toxicology, 21*, 498–502.
Lawn, W., Borschmann, R., Cottrel, A., & Winstock, A. (2014). Methoxetamine: Prevalence of use in the USA and UK and associated urinary problems. *Journal of Substance Use, 21*, 115–120.
Lee, M. R., Song, Y. S., Hwang, B. H., & Chou, C. C. (2000). Determination of amphetamine and methamphetamine in serum via headspace derivatization solid-phase microextraction-gas chromatography-mass spectrometry. *Journal of Chromatography A, 896*, 265–273.
Leth-Petersen, S., Petersen, I. N., Jensen, A. A., Bundgaard, C., Beak, M., Kehler, J., et al.

(2016). 5-HT2A /5-HT2C receptor pharmacology and intrinsic clearance of N-benzylphenethylamines modified at the primary site of metabolism. *Journal of Biochemical and Molecular Toxicology, 7*, 1614–1619.
Lin, J. C., Bangs, N., Lee, H., Kydd, R. R., & Russell, B. R. (2009). Determining the subjective and physiological effects of BZP on human females. *Psychopharmacology, 207*, 439–446.
Linsen, F., Koning, R. P. J., Van Laar, M., Niesink, R. J. M., Koeter, M. W., & Brunt, T. M. (2015). 4-Fluoroamphetamine in the Netherlands: more than a one-night stand. *Addiction, 110*, 1138–1143.
Liu, H. T., Hollmann, M. W., Hoenemann, C. W., Liu, W. H., & Durieux, M. E. (2001). Modulation of NMDA receptor function by ketamine and magnesium: Part I. *Anesthesia and Analgesia, 92*, 1173–1183.
Liu, Y., Lin, D., Wu, B., & Zhou, W. (2016). Ketamine abuse potential and use disorder. *Brain Research Bulletin, 126*, 68–73.
Liu, F., Patterson, T. A., Sadovova, N., Zhang, X., Liu, S., Zou, X., et al. (2013). Ketamine-induced neuronal damage and altered N-methyl-d-aspartate receptor function in rat primary forebrain culture. *Toxicological Sciences, 131*, 548–557.
Lodge, D., & Mercier, M. S. (2015). Ketamine and phencyclidine: The good, the bad and the unexpected. *British Journal of Pharmacology, 172*, 4254–4276.
Lõpez-Arnau, R., Martínez-Clemente, J., Pubill, D., Escubedo, E., & Camarasa, J. (2012). Comparative neuropharmacology of three psychostimulant cathinone derivatives: Butylone, mephedrone and methylone. *British Journal of Pharmacology, 167*, 407–420.
Luethi, D., Kolaczynska, K. E., Docci, L., Krähenbühl, S., Hoener, M. C., & Liechti, M. E. (2017). Pharmacological profile of mephedrone analogs and related new psychoactive substances. *Neuropharmacology*. http://dx.doi.org/10.1016/j.neuropharm.2017.07.026 (in press).
Makhro, A., Tian, Q., Kaestner, L., Kosenkov, D., Faggian, G., Gassmann, M., et al. (2016). Cardiac N-methyl D- aspartate receptors as a pharmacological target. *Journal of Cardiovascular Pharmacology, 68*, 356–373.
Mantz, J., Delumeau, J. C., Cordier, J., & Petitet, F. (1994). Differential effects of propofol and ketamine on cytosolic calcium concentrations of astrocytes in primary culture. *British Journal of Anaesthesia, 72*, 351–352.
Marinetti, L. J., & Antonides, H. M. (2013). Analysis of synthetic cathinones commonly found in bath salts in human performance and postmortem toxicology: Method development, drug distribution and interpretation of results. *Journal of Analytical Toxicology, 37*, 135–146.
Marona-Lewicka, D., Rhee, G.-S., Sprague, J. E., & Nichols, D. E. (1995). Psychostimulant-like effects of p- fluoroamphetamine in the rat. *European Journal of Pharmacology, 287*, 105–113.
Maroteaux, L., Ayme-dietrich, E., Aubertin-kirch, G., Banas, S., Quentin, E., Lawson, R., et al. (2017). New therapeutic opportunities for 5-HT 2 receptor ligands. *Pharmacology and Therapeutics, 170*, 14–36.
Martin, G. E., Elgin, R. J. J., Mathiasen, J. R., Davis, C. B., Kesslick, J. M., Baldy, W. J., et al. (1989). Activity of aromatic substituted phenylpiperazines lacking affinity for dopamine binding sites in a preclinical test of antipsychotic efficacy. *Journal of Medicinal Chemistry, 32*, 1052–1056.
Martin, D. C., Introna, R. P., & Aronstam, R. S. (1990). Inhibition of neuronal 5-HT uptake by ketamine, but not halothane, involves disruption of substrate recognition by the transporter. *Neuroscience Letters, 112*, 99–103.
Martínez-Clemente, J., Escubedo, E., Pubill, D., & Camarasa, J. (2012). Interaction of mephedrone with dopamine and serotonin targets in rats. *European Neuropsychopharmacology, 22*, 231–236.
Marusich, J. A., Antonazzo, K. R., Wiley, J. L., Blough, B. E., Partilla, J. S., & Baumann, M. H. (2014). Pharmacology of novel synthetic stimulants structurally related to the "bath salts" constituent 3,4- methylenedioxypyrovalerone (MDPV). *Neuropharmacology, 87*, 206–213.
Mayer, F. P., Wimmer, L., Dillon-Carter, O., Partilla, J. S., Burchardt, N. V., Mihovilovic, M. D., et al. (2016). Phase I metabolites of mephedrone display biological activity as substrates at monoamine transporters. *British Journal of Pharmacology,* 2657–2668.
McLaughlin, G., Morris, N., Kavanagh, P. V., Power, J. D., Dowling, G., Twamley, B., et al. (2017). Synthesis, characterization and monoamine transporter activity of the new psychoactive substance mexedrone and its N-methoxy positional isomer, N-methoxymephedrone. *Drug Testing and Analysis, 9*, 358–368.
McLean, T. H., Parrish, J. C., Braden, M. R., Marona-Lewicka, D., Gallardo-Godoy, A., & Nichols, D. E. (2006). 1- Aminomethylbenzocycloalkanes: Conformationally restricted hallucinogenic phenethylamine analogues as functionally selective 5-HT2A receptor agonists. *Journal of Medicinal Chemistry, 49*, 5794–5803.
Meng, H., Cao, J., Kang, J., Ying, X., Ji, J., Reynolds, W., et al. (2012). Mephedrone, a new designer drug of abuse, produces acute hemodynamic effects in the rat. *Toxicology Letters, 208*, 62–68.
Millan, M. J., Marin, P., & Mannoury la Cour, C. (2008). Signaling at G-protein-coupled serotonin receptors: recent advances and future research directions. *Trends in Pharmacological Sciences, 29*, 454–464.
Moaddel, R., Abdrakhmanova, G., Kozak, J., Jozwiak, K., Toll, L., Jimenez, L., et al. (2013). Sub-anesthetic concentrations of (R,S)-ketamine metabolites inhibit acetylcholine-evoked currents in α7 nicotinic acetylcholine receptors. *European Journal of Pharmacology, 698*, 228–234.
Moghaddam, B., & Krystal, J. H. (2012). Capturing the angel in "angel dust": Twenty years of translational neuroscience studies of NMDA receptor antagonists in animals and humans. *Schizophrenia Bulletin, 38*, 942–949.
Monshouwer, K., van der Pol P., Drost Y. C., van Laar, M. W. (2016). Het Grote Uitgaansonderzoek 2016: uitgaanspatronen, middelengebruik en preventieve maatregelen onder uitgaande jongeren en jongvolwassenen. Trimbos-instituut, Utrecht. Accessed on 23-06-2016 via: https://assets.trimbos.nl/docs/da0f3e40-3ad6-498d-852c-9d59105a85c2.pdf.
Monteggia, L. M., & Zarate, C. J. (2015). Antidepressant actions of ketamine: from molecular mechanisms to clinical practice. *Current Opinion in Neurobiology, 30*, 139–143.
Montgomery, T., Buon, C., Eibauer, S., Guiry, P. J., Keenan, A. K., & McBean, G. J. (2007). Comparative potencies of 3,4-methylenedioxymethamphetamine (MDMA) analogues as inhibitors of [3H]noradrenaline and [3H]5-HT transport in mammalian cell lines. *British Journal of Pharmacology, 152*, 1121–1130.
Moore, K. A., Kilbane, E. M., Jones, R., Kunsman, G., Levine, B., & Smith, M. (1997). Tissue distribution of ketamine in a mixed rug fatality. *Journal of Forensic Sciences, 46*, 1183–1185.
Morefield, K. M., Keane, M., Felgate, P., White, J. M., & Irvine, R. J. (2011). Pill content, dose and resulting plasma concentrations of 3,4-methylendioxymethamphetamine (MDMA) in recreational 'ecstasy' users. *Addiction, 106*, 1293–1300.
Morgan, C. J. A., & Curran, H. V. (2011). Ketamine use: a review. *Addiction, 107*, 27–38.
Morris, P. J., Moaddel, R., Zanos, P., Moore, C., Gould, T., Zarate, C. A., & Thomas, C. J. (2017). Synthesis and N-methyl-D-aspartate (NMDA) receptor activity of ketamine metabolites. *Organic Letters, 19*, 4572–4575.
Mouri, A., Noda, Y., Enomoto, T., & Nabeshima, T. (2007). Phencyclidine animal models of schizophrenia: Approaches from abnormality of glutamatergic neurotransmission and neurodevelopment. *Neurochemistry International, 51*, 173–184.
Moya, P. R., Berg, K. A., Gutierrez-Hernandez, M. A., Saez-Briones, P., Reyes-Parada, M., Cassels, B. K., et al. (2007). Functional selectivity of hallucinogenic phenethylamine and phenylisopropylamine derivatives at human 5-hydroxytryptamine (5-HT) 2A and 5-HT 2C receptors. *Pharmacology, 321*, 1054–1061.
Mueller, M., Yuan, J., & Felim, A. (2009). Further studies on the role of metabolites in ( ± )-3, 4-methylenedioxymethamphetamine-induced serotonergic neurotoxicity. *Drug Metabolism and Disposition, 37*, 2079–2086.
Mugele, J., Nañagas, K. A., & Tormoehlen, L. M. (2012). Serotonin syndrome associated with MDPV use: a case report. *Annals of Emergency Medicine, 60*, 100–102.
Mußhoff, F., Madea, B., Kernbach-Wighton, G., Bicker, W., Kneisel, S., Hutter, M., et al. (2014). Driving under the influence of synthetic cannabinoids ("Spice"): A case series. *International Journal of Legal Medicine, 128*, 59–64.
Nacca, A., Guiso, G., Fracasso, C., Cervo, L., & Caccia, S. (1998). Brain-to-blood partition and in vivo inhibition of 5- hydroxytryptamine reuptake and quipazine-mediated behaviour of nefazodone and its main active metabolites in rodents. *British Journal of Pharmacology, 125*, 1617–1623.
Nagai, F., Nonaka, R., & Kamimura, K. S. H. (2007). The effects of non-medically used psychoactive drugs on monoamine neurotransmission in rat brain. *European Journal of Pharmacology, 559*, 132–137.
Nakanishi, M., Mori, T., Nishikawa, K., Sawada, M., Kuno, M., & Asada, A. (2007). The effects of general anesthetics on P2X7 and P2Y receptors in a rat microglial cell line. *Anesthesia and Analgesia, 104*, 1136–1144.
Napolitano, A., Cesura, A. M., & Da Prada, M. (1995). The role of monoamine oxidase and catechol O-methyltransferase in dopaminergic neurotransmission. *Journal of Neuronal Transmission Supplementum, 45*, 35–45.
Nash, J. F., Roth, B. L., Brodkin, J. D., Nichols, D. E., & Gudelsky, G. A. (1994). Effects of the R(-) and S(+) isomers of MDA and MDMA on phosphitidyl inositol turnover in cultured cells expressing 5-HT2A or 5-HT2C receptors. *Neuroscience Letters, 177*, 111–115.
Nichols, D. E. (2004). Hallucinogens. *Pharmacology and Therapeutics, 101*, 131–181.
Nichols, D. E., Sassano, M. F., Halberstadt, A. L., Klein, L. M., Brandt, S. D., Elliott, S. P., et al. (2015). N-Benzyl-5- methoxytryptamines as potent serotonin 5-HT2 receptor family agonists and comparison with a series of phenethylamine analogues. *ACS Chemical Neuroscience, 6*, 1165–1175.
Nishimura, M., Sato, K., Okada, T., Yoshiya, I., Schloss, P., Shimada, S., et al. (1998). Ketamine inhibits monoamine transporters expressed in human embryonic kidney 293 cells. *Anesthesiology, 88*, 768–774.
Ogata, J., Shiraishi, M., Namba, T., Smothers, C. T., Woodward, J. J., & Harris, R. A. (2006). Effects of anesthetics on mutant N-methyl-D-aspartate receptors expressed in Xenopus oocytes. *Pharmacology, 318*, 434–443.
Orser, B. A., Pennefather, P. S., & MacDonald, J. F. (1997). Multiple mechanisms of ketamine blockade of N-methyl- D-aspartate receptors. *Anesthesiology, 86*, 903–917.
Parsons, C. G. (1996). Comparative patch-clamp studies with freshly dissociated rat hippocampal and striatal neurons on the NMDA receptor antagonistic effects of amantadine and memantine. *European Journal of Neuroscience, 8*, 446–454.
Parsons, C. G., Quack, G., Bresink, I., Baran, L., Przegalinski, E., Kostowski, W., et al. (1995). Comparison of the potency, kinetics and voltage-dependency of a series of uncompetitive NMDA receptor antagonists in vitro with anticonvulsive and motor impairment activity in vivo. *Neuropharmacology, 34*, 1239–1258.
Partilla, J. S., Dempsey, A. G., Nagpal, A. S., Blough, B. E., Baumann, M. H., & Rothman, R. B. (2006). Interaction of amphetamines and related compounds at the vesicular monoamine transporter. *The Journal of Pharmacology and Experimental Therapeutics, 319*, 237–246.
Pashkov, V. N., & Hemmings, H. C. (2002). The Effects of general anesthetics on norepinephrine release from isolated rat cortical nerve terminals. *Anesthesia and Analgesia, 95*, 1274–1281.
Pertwee, R. G. (2008a). Ligands that target cannabinoid receptors in the brain: From THC to anandamide and beyond. *Addiction Biology, 13*, 147–159.
Pertwee, R. G. (2008b). The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: D9- tetrahydrocannabinol, cannabidiol and D9-tetrahydrocannabivarin. *British Journal of Pharmacology, 153*, 199–215.
Pifl, C., Reither, H., & Hornykiewicz, O. (2015). The profile of mephedrone on human monoamine transporters differs from 3,4-methylenedioxymethamphetamine primarily by lower potency at the vesicular monoamine transporter. *European Journal of Pharmacology, 755*, 119–126.
Pin, J. P., Van-Vliet, B. J., & Bockaert, J. (1988). NMDA- and kainate-evoked GABA release from striatal neurones differentiated in primary culture: Differential blocking by

phencyclidine. *Neuroscience Letters, 87*, 87–92.
Poklis, J. L., Amira, D., Wise, L. E., Wiebelhaus, J. M., Haggerty, B. J., & Poklis, A. (2012). Detection and disposition of JWH-018 and JWH-037 in mice after exposure to "Magic Gold" smoke. *Forensic Science International, 220*, 91–96.
Poklis, J. L., Charles, J., Wolf, C. E., & Poklis, A. (2013). High-performance liquid chromatography tandem mass spectrometry method for the determination of 2CC-NBOMe and 25I-NBOMe in human serum. *Biomedical Chromatography, 27*, 1794–1800.
Poklis, J. L., Devers, K. G., Arbefeville, E. F., Pearson, J. M., Houston, E., & Poklis, A. (2014). Postmortem detection of 25I-NBOMe [2-(4-iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine] in fluids and tissues determined by high performance liquid chromatography with tandem mass spectrometry from a traumatic death. *Forensic Science International, 234*, 1–15.
Poklis, J. L., Nanco, C. R., Troendle, M. M., Wolf, C. E., & Poklis, A. (2014). Determination of 4-bromo-2,5- dimethoxy-N-[(2-methoxyphenyl)methyl]-benzeneethanamine (25B-NBOMe) in serum and urine by high performance liquid chromatography with tandem mass spectrometry in a case of severe intoxication. *Drug Testing and Analysis, 6*, 764–769.
Prosser, J. M., & Nelson, L. S. (2012). The toxicology of bath salts: A review of synthetic cathinones. *Journal of Medical Toxicology, 8*, 33–42.
Quirk, K., Lawrence, A., Jones, J., Misra, A., Harvey, V., Lamb, H., et al. (2001). Characterisation of agonist binding on human 5-HT2C receptor isoforms. *European Journal of Pharmacology, 419*, 107–112.
Rabin, R. A., Doat, M., & Winter, J. C. (2000). Role of serotonergic 5-HT2A receptors in the psychotomimetic actions of phencyclidine. *International Journal of Neuropsychopharmacology, 3*, 333–338.
Raffa, R. B., Shank, R. P., & Vaught, J. L. (1992). Etoperidone, trazodone and MCPP: in vitro and in vivo identification of serotonin 5-HT1A (antagonistic) activity. *Psychopharmacology, 108*, 320–326.
Rajasekaran, M., Brents, L. K., Franks, L. N., Moran, J. H., & Prather, P. L. (2013). Human metabolites of synthetic cannabinoids JWH-018 and JWH-073 bind with high affinity and act as potent agonists at cannabinoid type- 2 receptors. *Toxicology and Applied Pharmacology, 269*, 100–108.
Rammes, G., Rupprecht, R., Ferrari, U., Zieglgänsberger, W., & Parsons, C. G. (2001). The N-methyl-D-aspartate receptor channel blockers memantine, MRZ 2/579 and other amino-alkyl-cyclohexanes antagonise 5-HT3 receptor currents in cultured HEK-293 and N1E-115 cell systems in a non-competitive manner. *Neuroscience Letters, 306*, 81–84.
Rhee, M. H., Vogel, Z., Barg, J., Bayewitch, M., Levy, R., Hanuš, L., et al. (1997). Cannabinol derivatives: Binding to cannabinoid receptors and inhibition of adenylylcyclase. *Journal of Medicinal Chemistry, 40*, 3228–3233.
Rickli, A., Hoener, M. C., & Liechti, M. E. (2015). Monoamine transporter and receptor interaction profiles of novel psychoactive substances: Para-halogenated amphetamines and pyrovalerone cathinones. *European Neuropsychopharmacology, 25*, 365–376.
Rickli, A., Kopf, S., Hoener, M. C., & Liechti, M. E. (2015). Pharmacological profile of novel psychoactive benzofurans. *British Journal of Pharmacology, 172*, 3412–3425.
Rickli, A., Luethi, D., Reinisch, J., Buchy, D., Hoener, M. C., & Liechti, M. E. (2015). Receptor interaction profiles of novel N-2-methoxybenzyl (NBOMe) derivatives of 2,5-dimethoxy-substituted phenethylamines (2C drugs). *Neuropharmacology, 99*, 546–553.
Rietjens, S. J., Hondebrink, L., Westerink, R. H. S., & Meulenbelt, J. (2012). Pharmacokinetics and pharmacodynamics of 3,4-methylenedioxymethamphetamine (MDMA): interindividual differences due to polymorphisms and drug–drug interactions. *Critical Reviews in Toxicology, 42*, 854–876.
Rinaldi-Carmona, M., Barth, F., Héaulme, M., Shire, D., Calandra, B., Congy, C., et al. (1994). SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. *FEBS Letters, 350*, 240–244.
Rivière, G. J., Gentry, W. B., & Owens, S. M. (2000). Disposition of methamphetamine and its metabolite amphetamine in brain and other tissues in rats after intravenous administration. *The Journal of Pharmacology and Experimental Therapeutics, 292*, 1042–1047.
Rogawski, M. A., Pieniek, M., Suzuki, S., & Ffrench-Mullen, J. M. H. (1988). Phencyclidine selectively blocks the sustained voltage-dependent potassium conductance in PC12 cells. *Brain Research, 456*, 38–48.
Rohanová, M., Páleníček, T., & Balíková, M. (2008). Disposition of 4-bromo-2,5-dimethoxyphenethylamine (2C-B) and its metabolite 4-bromo-2-hydroxy-5-methoxyphenethylamine in rats after subcutaneous administration. *Toxicology Letters, 178*, 29–36.
Röhrich, J., Becker, J., Kaufmann, T., Zörntlein, S., & Urban, R. (2012). Detection of the synthetic drug 4- fluoroamphetamine (4-FA) in serum and urine. *Forensic Science International, 215*, 3–7.
Rose, S. R., Poklis, J. L., & Poklis, A. (2013). A case of 25I-NBOMe (25-I) intoxication: a new potent 5-HT2A agonist designer drug. *Clinical Toxicology, 51*, 174–177.
Roth, B. L., Gibbons, S., Arunotayanun, W., Huang, X. P., Setola, V., Treble, R., et al. (2013). The ketamine analogue methoxetamine and 3- and 4-methoxy analogues of phencyclidine are high affinity and selective ligands for the glutamate NMDA receptor. *PLoS ONE, 8*, 2–6.
Rothman, R. B., & Baumann, M. H. (2002). Serotonin releasing agents: neurochemical, therapeutic and adverse effects. *Pharmacology, Biochemistry and Behavior, 71*, 825–836.
Rothman, R. B., Baumann, M. H., Blough, B. E., Jacobson, A. E., Rice, K. C., & Partilla, J. S. (2010). Evidence for non- competitive modulation of substrate-induced serotonin release. *Synapse, 64*, 862–869.
Rothman, R. B., Baumann, M. H., Dersch, C. M., Romero, D. V., Rice, K. C., Carroll, F. I. V. Y., et al. (2001). Amphetamine-type central nervous norepinephrine more potently than they release dopamine and serotonin. *Synapse, 39*, 32–41.
Rothman, R. B., Baumann, M. H., Savage, J. E., Rauser, L., McBride, A., Hufeisen, S. J., et al. (2000). Evidence for possible involvement of 5-HT(2B) receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. *Circulation, 102*, 2836–2841.
Rotzinger, S., Fang, J., Coutts, R. T., & Baker, G. B. (1998). Human CYP2D6 and metabolism of m- chlorophenylpiperazine. *Biological Psychiatry, 44*, 1185–1191.
Saha, K., Partilla, J. S., Lehner, K. R., Seddik, A., Stockner, T., Holy, M., et al. (2015). "Second-generation" mephedrone analogs, 4-MEC and 4-MePPP, differentially affect monoamine transporter function. *Neuropsychopharmacology, 40*, 1321–1331.
Sałat, K., Siwek, A., Starowicz, G., Librowski, T., Nowak, G., Drabik, U., et al. (2015). Antidepressant-like effects of ketamine, norketamine and dehydronorketamine in forced swim test: Role of activity at NMDA receptor. *Neuropharmacology, 99*, 301–307.
Salgado, V. L. (2016). Antagonist pharmacology of desensitizing and non-desensitizing nicotinic acetylcholine receptors in cockroach neurons. *NeuroToxicology, 56*, 188–195.
Samanin, R., Mennini, T., Ferraris, A., Bendotti, C., Borsini, F., & Garattini, S. (1979). m-Chlorophenylpiperazine: a central serotonin agonist causing powerful anorexia in rats. *Naunyn-Schmiedeberg's Archives of Pharmacology, 308*, 159–163.
Sassano-Higgins, S., Baron, D., Juarez, G., Esmaili, N., & Gold, M. (2016). A review of ketamine abuse and diversion. *Depression and Anxiety, 33*, 718–727.
Schep, L. J., Slaughter, R. J., Vale, J. A., Beasley, D. M. G., & Gee, P. (2011). The clinical toxicology of the designer "party pills" benzylpiperazine and trifluoromethylphenylpiperazine. *Clinical Toxicology, 49*, 131–141.
Schoeffter, P., & Hoyer, D. (1989). Interaction of arylpiperazines with 5-HT1A, 5-HT1B, 5-HT1C and 5-HT1D receptors: do discriminatory 5-HT1B receptor ligands exist? *Naunyn-Schmiedeberg's Archives of Pharmacology, 339*, 675–683.
Schwartz, K., Weizman, A., & Rehavi, M. (2006). The effect of psychostimulants on [3H] dopamine uptake and release in rat brain synaptic vesicles. *Journal of Neural Transmission, 113*, 1347–1352.
Seely, K. A., Brents, L. K., Radominska-Pandya, A., Endres, G. W., Keyes, G. S., Moran, J. H., et al. (2012). A major glucuronidated metabolit of JWH-018 is a neutral antagonist at CB1 receptors. *Chemical Research in Toxicology, 25*, 825–827.
Seeman, P., & Guan, H. C. (2008). Phencyclidine and glutamate agonist LY379268 stimulate dopamine D2 high receptors: D2 basis for schizophrenia. *Synapse, 62*, 819–828.
Seeman, P., Ko, F., & Tallerico, T. (2005). Dopamine receptor contribution to the action of PCP, LSD and ketamine psychotomimetics. *Molecular Psychiatry, 10*, 877–883.
Seeman, P., & Lasaga, M. (2005). Dopamine agonist action of phencyclidine. *Synapse, 58*, 275–277.
Sekiguchi, M., Okamoto, K., & Sakai, Y. (1990). Glycine-insensitive NMDA-sensitive receptor expressed in Xenopus oocytes by guinea pig cereellar mRNA. *Journal of Neuroscience, 10*, 2148–2155.
Senna, M. C., Augsburger, M., Aebi, B., Briellmann, T. A., Donzé, N., Dubugnon, J. L., et al. (2010). First nationwide study on driving under the influence of drugs in Switzerland. *Forensic Science International, 198*, 11–16.
Shahani, S. K., Lingamaneni, R., & Hemmings, H. C. J. (2002). General anesthetic actions on norepinephrine, dopamine, and γ-aminobutyric acid transporters in stably transfected cells. *Anesthesia and Analgesia, 95*, 893–899.
Shekar, A., Aguilar, J. I., Galli, G., Cozzi, N. V., Brandt, S. D., Ruoho, A. E., et al. (2017). Atypical dopamine efflux caused by 3,4-methylenedioxypyrovalerone (MDPV) via the human dopamine transporter. *Journal of Chemical Neuroanatomy, 84*, 69–74.
Shimshoni, J. A., Winkler, I., Golan, E., & Nutt, D. (2017). Neurochemical binding profiles of novel indole and benzofuran MDMA analogues. *Naunyn-Schmiedeberg's Archives of Pharmacology, 390*, 15–24.
Shintani-Ishida, K., Saka, K., Nakamura, M., Yoshida, K. I., & Ikegaya, H. (2017). Experimental study on the postmortem redistribution of the substituted phenethylamine, 25B-NBOME. *Journal of Forensic Sciences*. http://dx.doi.org/10.1111/1556-4029.13583 (in press).
Shiue, C. Y., Shiue, G. G., Rysavy, J. A., Pleus, R. C., Huang, H., Bai, L. Q., et al. (1993). Fluorine-18 and carbon-11 labeled amphetamine analogs – Synthesis, distribution, binding characteristics in mice and rats and a PET study in monkey. *Nuclear Medicine and Biology, 20*, 973–981.
Showalter, V. M., Compton, D. R., Martin, B. R., & Abood, M. E. (1996). Evaluation of binding in a transfected cell line expressing a peripheral cannabinoid receptor (CB2): Identification of cannabinoid receptor subtype selective ligands. *Journal of Pharmacology and Experimental Therapeutics, 278*, 989–999.
Shulgin, A., & Shulgin, A. (1991). *PIHKAL: Phenethylamines I have known and loved: A chemical love story*.
Simmler, L. D., Buser, T. A., Donzelli, M., Schramm, Y., Dieu, L. H., Huwyler, J., et al. (2013). Pharmacological characterization of designer cathinones in vitro. *British Journal of Pharmacology, 168*, 458–470.
Simmler, L. D., Rickli, A., Hoener, M. C., & Liechti, M. E. (2014). Monoamine transporter and receptor interaction profiles of a new series of designer cathinones. *Neuropharmacology, 79*, 152–160.
Simmler, L. D., Rickli, A., Schramm, Y., Hoener, M. C., & Liechti, M. E. (2014). Pharmacological profiles of aminoindanes, piperazines, and pipradrol derivatives. *Biochemical Pharmacology, 88*, 237–244.
Singh, I., Morgan, C., Curran, V., Nutt, D., Schlag, A., & McShane, R. (2017). Ketamine treatment for depression: opportunities for clinical innovation and ethical foresight. *The Lancet Psychiatry, 4*, 419–426.
Sinner, B., Friedrich, O., Zink, W., Zausig, Y., & Graf, B. M. (2011). The toxic effects of s (+)-ketamine on differentiating neurons in vitro as a consequence of suppressed neuronal Ca2+ oscillations. *Anesthesia and Analgesia, 113*, 1161–1169.
Sinner, B., & Graf, B. M. (2008). Ketamine. *Handbook of Experimental Pharmacology* (pp. 313–333). .

Sogawa, C., Sogawa, N., Ohyama, K., Kikura-Hanajiri, R., Goda, Y., Sora, I., et al. (2011). Methylone and monoamine transporters: correlation with toxicity. *Current Neuropharmacology, 9*, 58–62.
Spiller, H. A., Ryan, M. L., Weston, R. G., & Jansen, J. (2011). Clinical experience with and analytical confirmation of "bath salts" and "legal highs" (synthetic cathinones) in the United States. *Clinical Toxicology, 49*, 499–505.
Stenovec, M., Lasic, E., Bozic, M., Bobnar, S. T., Stout, R. S., Jr., Grubisic, V., et al. (2016). Ketamine inhibits ATP- evoked exocytotic release of brain-derived neurotrophic factor from vesicles in cultured rat astrocytes. *Molecular Neurobiology, 53*, 6882–6896.
Stogner, J. M., & Miller, B. L. (2013). Investigating the "bath salt" panic: The rarity of synthetic cathinone use among students in the United States. *Drug and Alcohol Review, 32*, 545–549.
Sykutera, M., Cychowska, M., & Bloch-Boguslawska, E. (2015). A fatal case of pentedrone and a- pyrrolidinovalerophenone poisoning. *Journal of Analytical Toxicology, 39*, 324–329.
Teng, L., Crooks, P. A., & Dwoskin, L. P. (1998). Lobeline displaces [3H]dihydrotetrabenazine binding and releases [3H]dopamine from rat striatal synaptic vesicles: Comparison with d-amphetamine. *Journal of Neurochemistry, 71*, 258–265.
Thomas, D. R., Gager, T. L., Holland, V., Brown, A. M., & Wood, M. D. (1996). m-Chlorophenylpiperazine (mCPP) in an antagonist at the cloned human 5-HT2B receptor. *NeuroReport, 7*, 1457–1460.
Thomas, B. F., Lefever, T. W., Cortes, R. A., Grabenauer, M., Kovach, A. L., Cox, A. O., et al. (2017). Thermolytic degradation of synthetic cannabinoids: chemical exposures and pharmacological consequences. *Journal of Pharmacology and Experimental Therapeutics, 361*, 162–171.
Thornton, S. L., Gerona, R. R., & Tomaszewski, C. A. (2012). Psychosis from a bath salt product containing Flephedrone and MDPV with serum, urine and, and product quantification. *Journal of Medical Toxicology, 8*, 310–313.
Titeler, M., Lyon, R. A., Davis, K. H., & Glennon, R. A. (1987). Selectivity of serotonergic drugs for multiple brain serotonin receptors. Role of [3H]-4-bromo-2,5-dimethoxyphenylisopropylamine ([3H]DOB), a 5-HT2 agonist radioligand. *Biochemical Pharmacology, 36*, 3265–3271.
Tomiyama, K.-I., & Funada, M. (2014). Cytotoxicity of synthetic cannabinoids on primary neuronal cells of the forebrain: The involvement of cannabinoid CB1 receptors and apoptotic cell death. *Toxicology and Applied Pharmacology, 274*, 17–23.
Torres, G. E., Gainetdinov, R. R., & Caron, M. G. (2003). Plasma membrane monoamine transporters: structure, regulation and function. *Neuroscience, 4*, 13–25.
Tukker, A. M., de Groot, M. W. G. D. M., Wijnolts, F. M. J., Kasteel, E. J., Hondebrink, L., & Westerink, R. H. S. (2016). Is the time right for in vitro neurotoxicity testing using human iPSC-derived neurons? *ALTEX, 33*, 261–271.
Ulrichsen, J., Partilla, J. S., & Dax, E. M. (1992). Long-term administration of meta-chlorophenylpiperazine (meta- CPP) to rats induces changes in serotonin receptor-binding, dopamine levels and locomotor-activity without altering prolactin and corticosterone secretion. *Psychopharmacology, 107*, 229–235.
UNODC, United Nations Office on Drugs and Crime (2013). World drug campaign leaflet: NPS, New psychoactive substances. via: http://www.unodc.org/documents/drugs/printmaterials2013/NPS_leaflet/WDC13_NPS_leaflet_EN_LORES.pdf, Accessed date: 6 December 2017.
UNODC, United Nations Office on Drugs and Crime Early warning advisory on new psychoactive substances: Legal responses. via: https://www.unodc.org/LSS/Page/NPS, Accessed date: 10 October 2016.
Uryu, K., Minami, K., Yanagihara, N., Hara, K., Toyohira, Y., Izumi, F., et al. (2000). Inhibition by neuromuscular blocking drugs of norepinephrine transporter in cultured bovine adrenal medullary cells. *Anesthesia and Analgesia, 91*, 546–551.
Valente, M. J., Bastos, M. L., Fernandes, E., Carvalho, F., Guedes de Pinho, P., & Carvalho, M. (2017). Neurotoxicity of β-keto amphetamines: deathly mechanisms elicited by methylone and MDPV in human dopaminergic SH- SY5Y cells. *ACS Chemical Neuroscience, 8*, 850–859.
Verrico, C. D., Miller, G. M., & Madras, B. K. (2007). MDMA (Ecstasy) and human dopamine, norepinephrine, and serotonin transporters: Implications for MDMA-induced neurotoxicity and treatment. *Psychopharmacology, 189*, 489–503.
Vigolo, A., Ossato, A., Trapella, C., Vincenzi, F., Rimondo, C., Seri, C., et al. (2015). Novel halogenated derivates of JWH-018: Behavioral and binding studies in mice. *Neuropharmacology, 95*, 68–82.
Villalobos, C. A., Bull, P., Sáez, P., Cassels, B. K., & Huidobro-Toro, J. P. (2004). 4-Bromo-2,5-dimethoxyphenethylamine (2C-B) and structurally related phenylethylamines are potent 5-$HT_{2A}$ receptor antagonists in Xenopus laevis oocytes. *British Journal of Pharmacology, 141*, 1167–1174.
Volkow, N. D., Fowler, J. S., Wang, G. J., Baler, R., & Telang, F. (2009). Neuropharmacology imaging dopamine's role in drug abuse and addiction. *Neuropharmacology, 56*, 3–8.
Walberg, C. B., McCarron, M. M., & Schulze, B. W. (1983). Quantitation of phencyclidine in serum by enzyme immunoassay: results in 405 patients. *Journal of Analytical Toxicology, 7*, 106–110.
Wang, D. S., Penna, A., & Orser, B. A. (2017). Ketamine increases the function of γ-aminobutyric acid type A receptors in hippocampal and cortical neurons. *Anesthesiology, 126*, 666–677.
Wang, H., & Takigawa, M. (2002). The selective sigma ligand MS-377 attenuates the blockade by phencyclidine of NMDA-induced intracellular calcium. *International Journal of Neuropsychopharmacology, 5*, 239–242.
Wardwell, C. M., Poklis, J. L., Wiebelhaus, J. M., Mason, B. L., Wise, L. E., & Poklis, A. (2015). Disposition of the 5-$HT_{2A}$ agonist designer hallucinogen, 2-(4-chloro-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine (25C-NBOMe), in the mouse. Abstract (P16) at SOFT 2015. http://www.soft-tox.org/files/meeting_abstracts/SOFT_2015_meeting_abstracts.pdf.
Weber, M., Motin, L., Gaul, S., Beker, F., Fink, R. H. A., & Adams, D. J. (2005). Intravenous anesthetics inhibit nicotinic acetylcholine receptor-mediated currents and Ca2 + transients in rat intracardiac ganglion neurons. *British Journal of Pharmacology, 144*, 98–107.
Welter, J., Kavanagh, P., Meyer, M. R., & Maurer, H. H. (2015). Benzofuran analogues of amphetamine and methamphetamine: studies on the metabolism and toxicological analysis of 5- APB and 5-MAPB in urine and plasma using GC-MS and LC-(HR)-$MS^n$ techniques. *Analytical and Bioanalytical Chemistry, 407*, 1371–1388.
White, S. J., Hendrickson, H. P., Atchley, W. T., Laurenzana, E. M., Gentry, W. B., Williams, D. K., et al. (2014). Treatment with a monoclonal antibody against methamphetamine and amphetamine reduces maternal and fetal rat brain concentrations in late pregnancy. *Drug Metabolism and Disposition, 42*, 1285–1291.
Wiebelhaus, J. M., Poklis, J. L., Poklis, A., Vann, R. E., Lichtman, A. H., & Wise, L. E. (2012). Inhalation exposure to smoke from synthetic "marijuana" produces potent cannabimimetic effects in mice. *Drug and Alcohol Dependence, 126*, 316–323.
Wijers, C. H. W., van Litsenburg, R. T. H., Hondebrink, L., Niesink, R. J. M., & Croes, E. A. (2017). Acute toxic effects related to 4-fluoroamphetamine. *The Lancet, 389*, 600.
Wikström, M., Thelander, G., Dahlgren, M., & Kronstrand, R. (2013). An accidental fatal intoxication with methoxetamine. *Journal of Analytical Toxicology, 37*, 43–46.
Wiley, J. L., Lefever, T. W., Marusich, J. A., Grabenauer, M., Moore, K. N., Huffman, J. W., et al. (2016). Evaluation of first generation synthetic cannabinoids on binding at non-cannabinoid receptors and in a battery of in vivo assays in mice. *Neuropharmacology, 110*, 143–153.
Williams, J. M., & Galli, A. (2006). The dopamine transporter: A vigilant border control for psychostimulant action. In H. H. Sitte, & M. Freissmuth (Eds.). *Handbook of Experimental Pharmacology* (pp. 215–232). (175th ed.). Berlin, Heidelberg: Springer Berlin Heidelberg.
Winberg, S., & Nilsson, G. (1996). Multiple high-affinity binding sites for [3H]serotonin in the brain of a teleost fish, the Arctic charr (Salvelinus alpinus). *Journal of Experimental Biology, 199*, 2429–2435.
Winstock, A. (2011, March). The 2011 Mixmag drugs survey. *Mixmag* (pp. 49–59). .
Wojcieszak, J., Andrzejczak, D., Woldan-Tambor, A., & Zawilska, J. B. (2016). Cytotoxic Activity of pyrovalerone derivatives, an emerging group of psychostimulant designer cathinones. *Neurotoxicity Research, 30*, 239–250.
Wood, D. M., Button, J., Lidder, S., Ramsey, J., Holt, D. W., & Dargan, P. I. (2008). Dissociative and sympathomimetic toxicity associated with recreational use of 1-(3-trifluoromethylphenyl) piperazine (TFMPP) and 1- benzylpiperzine (BZP). *Journal of Medical Toxicology, 4*, 254–257.
Wood, M., Chaubey, M., Atkinson, P., & Thomas, D. R. (2000). Antagonist activity of meta-chlorophenylpiperazine and partial agonist activity of 8-OH-DPAT at the 5-HT7 receptor. *European Journal of Pharmacology, 396*, 1–8.
Wood, D. M., Davies, S., Puchnarewicz, M., Button, J., Archer, R., Ovaska, H., et al. (2010). Recreational use of Mephedrone (4-methylmethcathinone, 4-MMC) with associated sympathomimetic toxicity. *Journal of Medical Toxicology, 6*, 327–330.
Wood, D. M., Davies, S., Puchnarewicz, M., Johnston, A., & Dargan, P. I. (2012). Acute toxicity associated with the recreational use of the ketamine derivative methoxetamine. *European Journal of Clinical Pharmacology, 68*, 853–856.
Wood, D. M., Greene, S. L., & Dargan, P. I. (2013). Five-year trends in self-reported recreational drugs associated with presentation to a UK emergency department with suspected drug-related toxicity. *European Journal of Emergency Medicine, 20*, 263–267.
World Drug Report (2015). United Nations Office on Drugs and Crime, United Nations publication, Sales No. E.15.XI.6. via: https://www.unodc.org/documents/wdr2015/World_Drug_Report_2015.pdf, Accessed date: 14 September 2016.
World Drug Report (2016). United Nations Office on Drugs and Crime, United Nations publication, Sales No. E.16.XI.7. via: https://www.unodc.org/wdr2016/, Accessed date: 14 September 2017.
World Drug Report (2017). United Nations Office on Drugs and Crime, United Nations publication, Sales No. E.17.XI.7. via: https://www.unodc.org/wdr2017/index.html, Accessed date: 28 September 2017.
Wyman, J. F., Lavins, E. S., Engelhart, D., Armstrong, E. J., Snell, K. D., Boggs, P. D., et al. (2013). Postmortem tissue distribution of MDPV following lethal intoxication by "bath salts". *Journal of Analytical Toxicology, 37*, 182–185.
Xu, J., & Lei, H. (2014). Ketamine- An update on its clinical uses and abuses. *CNS Neuroscience & Therapeutics, 20*, 1015–1020.
Yamakura, T., Askalany, A. R., Petrenko, A. B., Kohno, T., Baba, H., & Sakimura, K. (2005). The NR3B subunit does not alter the anesthetic sensitivities of recombinant N-methyl-D-aspartate receptors. *Anesthesia and Analgesia, 100*, 1687–1692.
Yamakura, T., Chavez-Noriega, L. E., & Harris, R. A. (2000). Subunit-dependent inhibition of human neuronal nicotinic acetylcholine receptors and other ligand-gated ion channels by dissociative anesthetics ketamine and dizocilpine. *Anesthesiology, 92*, 1144–1153.
Yamakura, T., Sakimura, K., & Shimoji, K. (2000). The stereoselective effects of ketamine isomers on heteromeric N-methyl-D-aspartate receptor channels. *Anesthesia and Analgesia, 91*, 225–229.
Yeakel, J. K., & Logan, B. K. (2013). Blood synthetic cannabinoid concentrations in cases of suspected impaired driving. *Journal of Analytical Toxicology, 37*, 547–551.
Zanda, M. T., Fadda, P., Chiamulera, C., Fratta, W., & Fattore, L. (2016). Methoxetamine, a novel psychoactive substance with serious adverse pharmacological effects: A review of case reports and preclinical findings. *Behavioral Pharmacology, 27*, 489–496.
Zanos, P., Moaddel, R., Morris, P. J., Georgiou, P., Fischell, J., Elmer, G. I., et al. (2016). NMDAR inhibition- independent antidepressant actions of ketamine metabolites. *Nature, 533*, 1–18.
Zarantonello, P., Bettini, E., Paio, A., Simoncelli, C., Terreni, S., & Cardullo, F. (2011). Novel analogues of ketamine and phencyclidine as NMDA receptor antagonists. *Bioorganic and Medicinal Chemistry Letters, 21*, 2059–2063.
Zawilska, J. B. (2014a). Mephedrone and other cathinones. *Current Opinion in Psychiatry,*

*27*, 256–262.
Zawilska, J. B. (2014b). Methoxetamine – a novel recreational drug with potent hallucinogenic properties. *Toxicology Letters, 230*, 402–407.
Zhao, Y., & Sun, L. (2008). Antidepressants modulate the in vitro inhibitory effects of propofol and ketamine on norepinephrine and serotonin transporter function. *Journal of Clinical Neuroscience, 15*, 1264–1269.
Zwartsen, A., Verboven, A. H. A., van Kleef, R. G. D. M., Wijnolts, F. M. J., Westerink, R. H. S., & Hondebrink, L. (2017). Measuring inhibition of monoamine reuptake transporters by new psychoactive substances (NPS) in real-time using a high-throughput, fluorescence-based assay. *Toxicology in Vitro, 45*, 60–71.