Phencyclidine-Based New Psychoactive Substances

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Contents

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Abstract

The serendipitous discovery of phencyclidine (PCP) in 1956 sets the stage for significant research efforts that resulted in a plethora of analogs and derivatives designed to explore the biological effects of this class. PCP soon became the prototypical dissociative agent that eventually sneaked through the doors of clinical laboratories and became an established street drug. Estimations suggest that around 14 PCP analogs were identified as "street drugs" in the period between the 1960s and 1990s. Fast forward to the 2000s, and largely facilitated by advancements in electronic forms of communication made possible through the Internet, a variety of new PCP analogs began to attract the attention of communities interested in the collaborative exploration of these substances. Traditionally, as was the case with the first-generation analogs identified in previous decades, the substances explored represented compounds already known in the scientific literature. As the decade of the noughties unfolded, a number of new PCP-derived substances appeared on the scene, which included some analogs that have not been previously recorded in the published literature. The aim of this chapter is to present a brief introductory overview of substances that have materialized as PCP-derived new psychoactive substances (NPS) in recent years and their known pharmacology. Since *N*-methyl-D-aspartate receptor (NMDAR) antagonism is implicated in mediating the subjective and mind-altering effects of many dissociative drugs, additional data are included from other analogs not presently identified as NPS.

Keywords

Clinical · Designer drugs · Dissociatives · Forensic · NMDA receptor · NPS · Pharmacology · Phencyclidine · Toxicology

Acronyms of the Discussed New Psychoactive Substances (NPS)

2-MeO-PCMo	4-[1-(2-Methoxyphenyl)cyclohexyl]morpholine
3,4-MD-PCE	1-(1,3-Benzodioxol-5-yl)-*N*-ethylcyclohexanamine
3,4-MD-PCMo	4-[1-(1,3-Benzodioxol-5-yl)cyclohexyl]morpholine

3,4-MD-PCPr	1-(1,3-Benzodioxol-5-yl)-*N*-propylcyclohexanamine
3,4-MD-PCPy	1-[1-(1,3-Benzodioxol-5-yl)cyclohexyl]pyrrolidine
3-HO-PCE	3-[1-(Ethylamino)cyclohexyl]phenol
3-HO-PCMe	1-3-Hydroxyphenyl)-*N*-methylcyclohexanamine
3-HO-PCP	3-[1-(Piperidin-1-yl)cyclohexyl]phenol
3-HO-PCPr	1-3-Hydroxyphenyl)-*N*-propylcyclohexanamine
3-Me-4-F-PCP	1-[1-(4-Fluoro-3-methylphenyl)cyclohexyl]piperidine
3-Me-4-MeO-PCP	1-[1-(4-Methoxy-3-methylphenyl)cyclohexyl]piperidine
3-MeO-PCE	*N*-Ethyl-1-(3-methoxyphenyl)cyclohexan-1-amine
3-MeO-PCMe	1-(3-Methoxyphenyl)-*N*-methylcyclohexan-1-amine
3-MeO-PCMMo	4-{[1-(3-Methoxyphenyl)cyclohexyl]methyl}morpholine
3-MeO-PCMo	4-[1-(3-Methoxyphenyl)cyclohexyl]morpholine
3-MeO-PCP	1-[1-(3-Methoxyphenyl)cyclohexyl]piperidine
3-MeO-PCPr	1-(3-Methoxyphenyl)-*N*-propylcyclohexan-1-amine
3-MeO-PCPy	1-[1-(3-Methoxyphenyl)cyclohexyl]pyrrolidine
3-Me-PCMo	4-[1-(3-Methylphenyl)cyclohexyl]morpholine
3-Me-PCPMe	*N*-Methyl-1-(3-methylphenyl)cyclohexanamine
3-Me-PCPy	1-[1-(3-Methylphenyl)cyclohexyl]pyrrolidine
4′-Me-PCP	1-(4-Methyl-1-phenylcyclohexyl)piperidine
4-MeO-PCMo	4-[1-(4-Methoxyphenyl)cyclohexyl]morpholine
4-MeO-PCP	1-[1-(4-Methoxyphenyl)cyclohexyl]piperidine (methoxydine)
4-MeO-PCPy	1-[1-(4-Methoxyphenyl)cyclohexyl]pyrrolidine
4-Me-PCP	1-[1-(4-Methylphenyl)cyclohexyl]piperidine
AB-FUBINACA	*N*-[(2*S*)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-[(4-fluorophenyl)methyl]-1*H*-indazole-3-carboxamide
BnCP	1-(1-Benzylcyclohexyl)piperidine
DXM	Dextromethorphan
MDPV	1-(2*H*-1,3-Benzodioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one
MK-801	(+)-10,11-Dihydro-5*H*-5,10-epiminodibenzo[*a*,*d*][7]annulene (dizocilpine)
MXE	2-(Ethylamino)-2-(3-methoxyphenyl)cyclohexan-1-one (methoxetamine)
PCE	*N*-Ethyl-1-phenylcyclohexan-1-amine (eticyclidine)
PCEEA	*N*-(2-Ethoxyethyl)-1-phenylcyclohexan-1-amine
PCHOEA	2-[(1-Phenylcyclohexyl)amino]ethan-1-ol
PCiP	1-Phenyl-*N*-(propan-2-yl)cyclohexan-1-amine
PCMEA	*N*-(2-Methoxyethyl)-1-phenylcyclohexan-1-amine
PCMo	4-(1-Phenylcyclohexyl)morpholine
PCMPA	*N*-(3-Methoxypropyl)-1-phenylcyclohexan-1-amine
PCP	1-(1-Phenylcyclohexyl)piperidine (phencyclidine)
PCPr	1-Phenyl-*N*-propylcyclohexan-1-amine
PCPy	1-(1-Phenylcyclohexyl)pyrrolidine (rolicyclidine)
TCP	1-[1-(Thiophen-2-yl)cyclohexyl]piperidine (tenocyclidine)
TCPy	1-[1-(Thiophen-2-yl)cyclohexyl]pyrrolidine
U-49900	3,4-Dichloro-*N*-[(1*R*,2*R*)-2-(diethylamino)cyclohexyl]-*N*-methylbenzamide

1 Introduction

Following the serendipitous discovery of phencyclidine (PCP, Fig. 1) in 1956, an avalanche of research efforts emerged over the following decades, which resulted in the exploration of many interesting analogs. These agents were developed in the pursuit of novel therapeutic agents as well as to probe the biological effects in humans and other animals and to understand the function and distribution of PCP binding sites in a variety of in vitro and in vivo test systems (e.g., Petersen and Stillman 1978; Domino 1981; Kamenka and Geneste 1983; Clouet 1986; Domino and Kamenka 1988).

One of the terms used to describe the effects of PCP (and ketamine) is "dissociative anesthetic," which was termed by Toni Domino, the wife of PCP and ketamine researcher Edward F. Domino, in an effort to name this unique class of agents (Domino 2010). The term has since been shortened to "dissociative" to account for the wide variety of clinical uses and effects of these agents. The subjective effects of dissociative drugs are complex and highly dose dependent. For example, low doses typically induce a state of intoxication subjectively comparable to ethanol, which has also been consistent with drug discrimination assays in rodents (Hundt et al. 1998; Krystal et al. 1998; Lodge and Mercier 2015). Psychostimulant

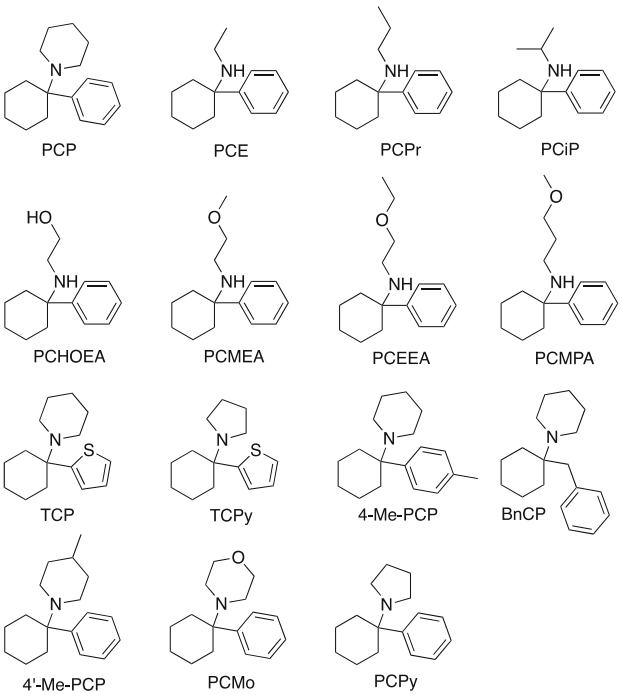

Fig. 1 Phencyclidine (PCP) and examples of first-generation analogs that appeared on the streets between the 1960s and 1990s (Morris and Wallach 2014)

properties are often reported by humans and seen in other animals especially with lower doses (Lodge and Mercier 2015). Other common subjective effects of dissociatives include euphoria, tactile, visual and auditory hallucinations, altered thought patterns, paresthesia, depersonalization, and derealization (Morris and Wallach 2014; Steinpreis 1996). Higher doses in humans and other animals often lead to full dissociation from the sensory environment, anesthesia, catalepsy, and motor impairment. The available data obtained from experiments with human subjects and ethnographic studies showed that subjective effects can vary substantially depending on set and setting in which the drug experience occurs (Pollard et al. 1965; Feldman et al. 1979).

N-Methyl-D-aspartate (NMDA) receptor antagonism is implicated in mediating, at least in part, the subjective and mind-altering effects of many compounds classified as dissociatives (Morris and Wallach 2014; Lodge and Mercier 2015). This is also supported by the fact that structurally diverse antagonists of multiple binding sites on the NMDAR are known to induce such effects. Similarly, this is consistent with the finding that antibodies against NMDAR, as seen in anti-NMDA receptor encephalitis, also induce dissociative effects in humans (Gable et al. 2009). NMDAR is a ligand-(glutamate and glycine as co-agonists) and voltage-gated ion channel, which plays central roles in important biological mechanisms including synaptic signaling and plasticity, cell survival, information processing, memory and learning (Ogden and Traynelis 2011; Hardingham and Bading 2003). NMDAR also has many roles in the periphery including the immune system (Boldyrev et al. 2005). NMDAR has been considered as a potential target of intervention for various disease states including pain, epilepsy, neurodegenerative diseases, tinnitus, and numerous psychiatric disorders (Cull-Candy et al. 2001; Javitt 2007; Paoletti et al. 2013; Traynelis et al. 2010). Currently, it appears that PCP and related arylcyclohexylamines and many related dissociative compounds like MK-801 and diphenidine act as use-dependent (uncompetitive) antagonists of NMDAR by binding inside the channel pore to a site called the PCP binding site. This leads to a blockade of ion conductance through the channel (Kemp and McKernan 2002; Lodge and Mercier 2015). The crystal structure of the heterotetrameric (GluN1/GluN2B) NMDAR was recently solved by two groups, though the PCP binding site within the channel pore was poorly resolved (Lee et al. 2014; Karakas and Furukawa 2014). More recently a cryo-EM structure of a hetereotrimeric NMDAR was published, which has provided information on MK-801 binding inside the channel pore (Lü et al. 2017). Docking studies using homology have been performed and may provide some insight into the PCP binding site (Tikhonova et al. 2004; El M'Barki and Elhallaqui 2017).

The nonmedical use of PCP-derived substances by humans is not a recent phenomenon. It has been estimated that in the period between the 1960s and 1990s, around 14 PCP analogs associated with nonmedical use and availability on the street market have been identified, such as PCE, PCPr, PCiP, PCHOEA, PCMEA, PCEEA, PCMPA, TCP, TCPy, 4-Me-PCP, BnCP, 4′-Me-PCP, PCMo, and PCPy (Fig. 1). Nevertheless, it appeared that only some of these first-generation analogs, such as TCP, PCE, and PCPy, were widely used (Morris and Wallach 2014). Fast forward to the 2000s, and with the advent of the Internet, the exchange of information and the extent of distribution of psychoactive drugs changed

dramatically. Early dissociative drugs sold online included ketamine and DXM. Then around 2008 what appears to be one of the first research chemical dissociatives, 4-MeO-PCP (Fig. 2a), began to appear for sale online. A number of analogs of PCP marketed as research chemicals soon followed which continues to this day. The majority of substances that have so far appeared over the last few decades originated from "legitimate" drug discovery research. However, some other PCP-based analogs represented true inventions made outside the traditional scientific setting. Perhaps one of the most striking aspects related to these particular examples is the ability for dissociative drug *aficionados* to foster information exchange, development of ideas, and collaborations involving online discussion boards that yield novel substances (Morris and Wallach 2014). Some user forums are more sophisticated than others in

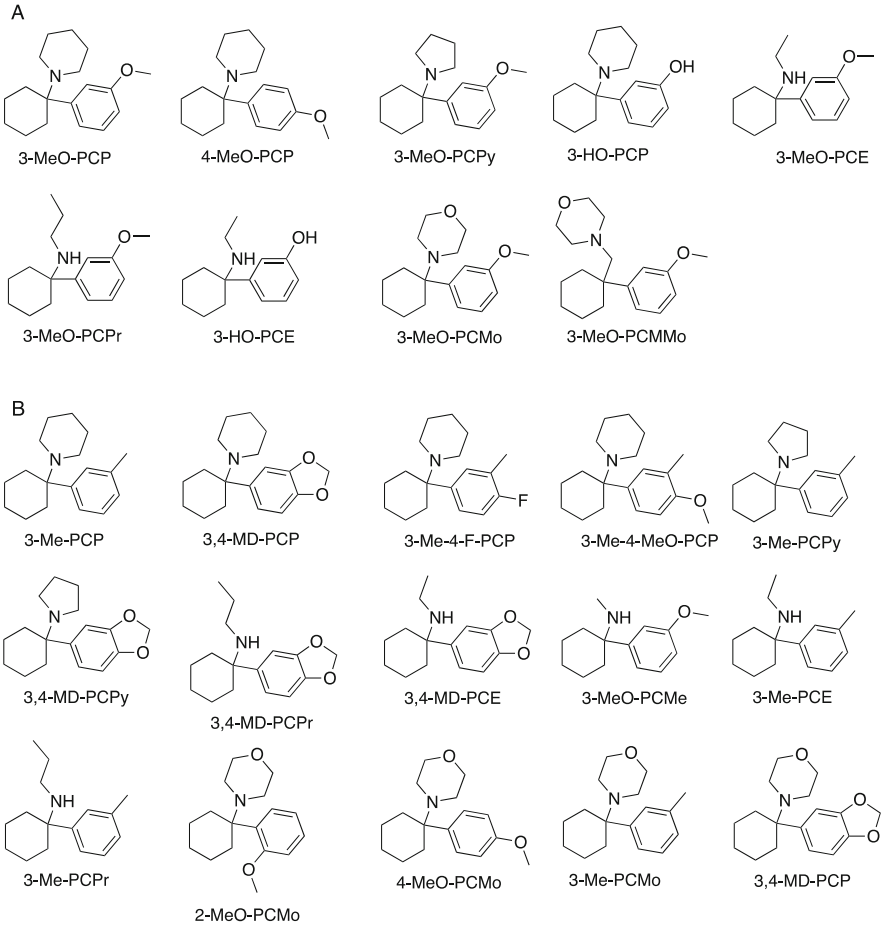

Fig. 2 (**a**) Phencyclidine analogs that appeared as a new psychoactive substance in recent years. (**b**) Representative examples of PCP analogs that have undergone biological testing but which have not yet appeared on the NPS market (Wallach 2014; Colestock et al. 2018)

terms of the extent of exchanging scientific knowledge. Information exchange about the effects and circumstances of drug use can also provide opportunities for exploring harm reduction advice shared between users, at least between those who engage in online technology as recently discussed within the context of dissociative NPS use (Hearne and Van Hout 2016). Examples also exist where users of dissociative substances make clear references to self-medication and treatment (Morris and Wallach 2014), adding to speculations and discussions around the mechanisms of action associated with some of these substances and how these might affect the users' conditions (Coppola and Mondola 2013). Attempting to review the knowledge collected on the large number of PCP-based substances developed over the last 40 years is beyond the scope of this chapter, but it is meant to provide an introduction to some of the dissociative new psychoactive substances (NPS) that have emerged on the market in recent years.

2 PCP

Phencyclidine (PCP) is a potent analgesic and dissociative drug that elicits its effect when administered through oral or parenteral routes. Following its discovery, PCP emerged as a potent anesthetic agent for use in humans under the brand name Serynl®; however, significant untoward effects were soon discovered. These effects included severe cognitive and sensory impairment/deprivation, agitation, and aggressive and bizarre behavior, particularly at higher dosage levels, that led to its discontinuation (Greifenstein et al. 1958; Luby et al. 1959; Meyer et al. 1959; Domino 1964). PCP also was used briefly as a veterinary general anesthetic (Morris and Wallach 2014).

PCP has been investigated extensively in humans and other animals. Doses used in human volunteers depended on the routes of administration and the intent of the study, which impacted on the effects observed. It is also worth acknowledging that early PCP administration studies found that schizophrenic patients were much more sensitive to the drug (Domino 1964). Both PCP and ketamine have been used to evaluate whether these substances elicit certain aspects of psychosis including positive and negative symptoms of schizophrenia in humans and other animals. Based on this research, both PCP and ketamine have been used in research as a model for psychosis (Javitt and Zukin 1991; Murray 2002; Frohlich and Van Horn 2014; Lodge and Mercier 2015; Cadinu et al. 2017). As summarized by Pradhan (1984), minimal intoxicating doses of PCP were reported to be up to 1 mg (intravenously, iv), whereas subanesthetic doses used in several clinical studies were 0.1 mg/kg. Anesthetic doses used in surgical patients were around 0.25 mg/kg iv, and it was noticed that an increase to higher doses (0.50 and 1.0 mg/kg, iv) produced agitation, purposeless movements, and seizures. Oral doses have been administered to up to 30 mg, and inhalation studies carried out in humans suggested that retained doses above 0.225 mg/kg resulted in collapse, prostration, and incapacitation (Pradhan 1984). Even when given at subanesthetic doses (iv, 0.1 mg/kg), significant sensory and cognitive effects were observed, such as alterations in body image, estrangement and isolation, negativism, hostility, drowsiness and apathy, hypnogenic states,

feelings of inebriation, and repetitive motor behavior. Other commonly observed features included rotatory nystagmus, ataxic and slapping gait, and nausea (Luby et al. 1959). More intense reactions were reported by Meyer et al. (1959) who described that 13 out of 80 subjects who received "large" doses (iv) developed a "confusional psychosis" of 12–72 h duration "characterized by feelings of unreality, depression, anxiety, and delusional and illusional experience." The spectrum of effects reported by recreational PCP users has also been reported (Burns and Lerner 1976; Siegel 1978). In addition to the already mentioned literature sources mentioned above, additional historical information on PCP might also be obtained from Lodge and Mercier (2015) and Morris and Wallach (2014). In order to contextualize the emergence of PCP-derived NPS, a brief overview of some of the representative studies and relevant pharmacological data on PCP are presented here.

2.1 Pharmacokinetics

PCP is a weak tertiary amine base with an experimentally derived pKa of 8.5 (Baselt 2011). PCP is lipophilic and Kamenka and Geneste (1981) gave the experimentally derived logP as 5.1. Based on investigations with human volunteers (Cook et al. 1982), plasma binding was determined to be about 65%, and oral bioavailability was estimated at 72%. The apparent terminal phase half-life ($T_{1/2}$) was reported around 21 ± 3 h (harmonic mean 17 h, range 7–46 h) (Cook et al. 1982). In cases of overdose, however, the $T_{1/2}$ has been reported to be up to 4 days (Done et al. 1978; Jackson 1989). Consistent with its high lipophilicity, PCP has been shown to accumulate in adipose and brain tissue (Bey and Patel 2007). Brain concentrations typically exceed blood concentrations (up to twice the amount) as determined in fatal over cases (Cravey et al. 1979). Likewise, PCP has been found to have a fairly large volume of distribution of 6.2 ± 0.3 L/kg (Cook et al. 1982) or 5.3–7.5 L/kg [mean, ~6 L/kg] (Barceloux 2012). A number of studies have investigated the metabolism of PCP (e.g., Wall et al. 1981; Aniline and Pitts 1982; Hallstrom et al. 1983; Cho et al. 1983; Holsztynska and Domino 1983, 1985). Mono-hydroxylations of the cyclohexyl and piperidine ring have been found to be major metabolites detected in urine of humans and animals (Aniline and Pitts 1982; Holsztynska and Domino 1983). PCP is also metabolized through phase II metabolic pathways (including glucuronide and sulfate conjugates) via conjugation of its phase I metabolites (Holsztynska and Domino 1985). Induction of liver enzymes has been found to impact on the metabolism of PCP (Kammerer et al. 1984). Excretion of PCP from human male subjects was found to be largely through urine (72.8 ± 4.0% of dose) with minor amounts found in feces (4.7 ± 0.9%) and perspiration (after iv injection of 1 mg) (Cook et al. 1982).

2.2 Pharmacodynamic Effects In Vitro

PCP has high affinity for the PCP binding site of NMDAR, originally named for the high affinity seen for PCP (Table 1). PCP acts as an uncompetitive use-dependent

inhibitor of NMDAR by blocking the open channel pore (Lodge and Mercier 2015; Wallach 2014). Since NMDAR is a hetereotetrameric receptor, composed of multiple possible subunits, subtype specificity of PCP and related channel blockers for NMDAR types has been reported, and the extent to which this influences the pharmacology of these compounds has been investigated to some extent (reviewed in Lodge and Mercier 2015). In addition, PCP and other high-affinity NMDAR antagonists like MK-801 appear to have long dissociation off-rates and thus become trapped in the channel, leading to longer duration of channel block (Lodge and Mercier 2015). Dissociative effects seen in humans typically correlate well with affinities toward the PCP site of NMDAR and PCP-like discrimination in animal models (Lodge and Mercier 2015). It should be noted that evidence suggests that channel blockers with faster off-rates and modest affinity, like memantine, may be better tolerated therapeutically than compounds with high affinity and slow dissociation off-rates (Wallach 2014; Lipton 2006).

In addition to NMDAR, PCP also has been reported to have affinities at a number of other central nervous system receptor sites with varying potencies. For example, PCP was also found to act as a monoamine reuptake transporter blocker (Aniline and Pitts 1982). Likewise, PCP has been reported to have affinity at the human reuptake transporter of serotonin (SERT) but not dopamine (DAT) or norephinephrine (NET) expressed in HEK293 cells (Table 1) (Roth et al. 2013, 2018). However other studies have shown activities with these transporters. For example, Giros et al. (1992) reported inhibition of [^{3}H]DA reuptake with affinities (K_i = 677 and 430 nM) for rat and human DAT expressed in mouse fibroblast Ltk- cells. Likewise, PCP was found to inhibit monoamine uptake of norepinephrine (NE) (IC_{50} = 520 nM), serotonin (5-HT) (IC_{50} = 800 nM), and dopamine (DA) (IC_{50} = 730 nM) in crude rat brain synaptosomal preparations. PCP had potency similar to d-amphetamine and methylphenidate for catecholamines and was 8 and 34 times more potent than d-amphetamine and methylphenidate in inhibiting [^{3}H]5-HT uptake, respectively (Smith et al. 1977). PCP has shown modest affinity for sigma receptors labeled through several techniques (Largent et al. 1986), and more recently, had high affinity for sigma-2 (K_i = 136 nM) but not sigma-1 (IC_{50} > 10,000 nM) (Roth et al. 2013). PCP has also been found to act as an antagonist at acetylcholine receptors and to inhibit acetylcholinesterase (Aniline and Pitts 1982). [^{3}H]Morphine displacement by PCP was reported using rat brain preparations albeit with a weak K_i value of 11,000 nM. Weak potency was also observed against other opioid radioligands including [^{3}H]leucine-enkephalin (K_i = 73 μM), [^{3}H]ethylketocyclazocine (K_i = 4,100 nM) and [^{3}H]-SKF-10,047 (K_i = 710 nM) (Itzhak et al. 1981a). In comparison, a K_i value of 26,000 nM for PCP against [^{3}H]morphine in rat brain homogenates was reported by Kamenka et al. (1982). Reports of affinity for dopamine D_2 receptors have appeared (Kapur and Seeman 2002; Seeman et al. 2005) although attempts by others to replicate these findings were unsuccessful under the conditions used (Roth et al. 2018; Jordan et al. 2006). PCP was also reported to have modest affinity at 5-HT_2 receptors (K_i = 5,000 nM) by Kapur and Seeman (2002) but not (IC_{50} > 10,000 nM) in another study (Roth et al. 2018).

Table 1 Representative in vitro binding data of NPS arylcyclohexylamines related to NMDAR, NET, DAT and SERT

Compound	NMDAR	NET	DAT	SERT
PCP	$K_i = 22.1$ nM Colestock et al. (2018) $K_i = 57.9$ nM Wallach (2014) $K_i = 59$ nM Roth et al. (2013) $K_i = 250$ nM Vignon et al. (1982), Chaudieu et al. (1989), and Vignon et al. (1988) $IC_{50} = 27.3$ nM Mendelsohn et al. (1984) $IC_{50} = 90$ nM Quirion et al. (1981) $IC_{50} = 37$ nM Ponchant et al. (1990) $IC_{50} = 250$ nM ([^{3}H]PCP) $IC_{50} = 200$ nM ([^{3}H]TCP) Chaudieu et al. (1987) $IC_{50} = 21$ nM Itzhak (1988)	$IC_{50} > 10{,}000$ nM Roth et al. (2013)	$K_i = 726$ nM Vignon et al. (1988) $IC_{50} = 760$ nM Hamon et al. (1996) $IC_{50} > 10{,}000$ nM Roth et al. (2018) K_i = 430 nM (human) K_i = 677 (rat) Giros et al. (1992)	$K_i = 2{,}234$ nM Roth et al. (2013) IC_{50} = 3000 nM Hori et al. (1996)
PCMo	$K_i = 334.1$ nM Colestock et al. (2018)	$IC_{50} > 10{,}000$ nM Colestock et al. (2018)	$IC_{50} > 10{,}000$ Colestock et al. (2018)	$IC_{50} > 10{,}000$ Colestock et al. (2018)
3-HO-PCE	$IC_{50} = 23$ nM Reel et al. (1988)	–	–	–
3-HO-PCMe	$IC_{50} = 422$ nM Reel et al. (1988)	–	–	–
3-HO-PCP	$K_i = 30$ nM Kamenka et al. (1982), Vignon et al. (1982), Vignon et al. (1988), and Chaudieu et al. (1989) $IC_{50} = 7.4$ nM	$IC_{50} > 10{,}000$ nM Wallach (2014)	$K_i = 1{,}154$ nM Wallach (2014) $IC_{50} = 1{,}360$ nM Vignon et al. (1988)	$IC_{50} > 10{,}000$ Wallach (2014)

	Mendelsohn et al. (1984) $IC_{50} = 6.3$ nM Ponchant et al. (1990) $K_i = 7.4–17.9$ nM Suzuki et al. (1996) $IC_{50} = 30$ nM ([^{3}H]PCP) $IC_{50} = 45$ nM ([^{3}H]TCP) Chaudieu et al. (1987) $IC_{50} = 2$ nM Itzhak (1988)			
3-HO-PCPr	$IC_{50} = 39$ nM Reel et al. (1988)	–	–	–
3-Me-PCE	$K_i = 43.1$ nM Wallach (2014)	$K_i = 598$ nM Wallach (2014)	$IC_{50} > 10{,}000$ nM Wallach (2014)	$K_i = 117$ nM Wallach (2014)
3-Me-PCMe	$K_i = 134.8$ nM Wallach (2014)	$IC_{50} > 10{,}000$ nM Wallach (2014)	$K_i = 1{,}729$ nM Wallach (2014)	$K_i = 1{,}389$ nM Wallach (2014)
3-Me-PCMo	$K_i = 201.8$ nM Colestock et al. (2018)	$IC_{50} > 10{,}000$ nM Colestock et al. (2018)	$K_i = 306$ nM Colestock et al. (2018)	$K_i = 412$ nM Colestock et al. (2018)
3-Me-PCPr	$K_i = 53.5$ nM Wallach (2014)	$K_i = 264$ nM Wallach (2014)	$K_i = 113$ nM Wallach (2014)	$K_i = 853$ nM Wallach (2014)
2-MeO-PCMo	$K_i = 1{,}578$ nM Colestock et al. (2018)	$IC_{50} > 10{,}000$ nM Colestock et al. (2018)	$IC_{50} > 10{,}000$ nM Colestock et al. (2018)	$K_i = 507$ nM Colestock et al. (2018)
3-MeO-PCMo	$K_i = 252.9$ nM Colestock et al. (2018)	$IC_{50} > 10{,}000$ nM Colestock et al. (2018)	$IC_{50} > 10{,}000$ nM Colestock et al. (2018)	$K_i = 697$ nM Colestock et al. (2018)
3-MeO-PCE	$K_i = 30.4$ nM Wallach (2014) $K_i = 61$ nM	$K_i = 1{,}528$ nM Wallach (2014)	$K_i = 906$ nM Wallach (2014)	$K_i = 136$ nM Wallach (2014)

(continued)

Table 1 (continued)

Compound	NMDAR	NET	DAT	SERT
	Roth et al. (2013) 99 nM Reel et al. (1988)	$IC_{50} > 10{,}000$ nM Roth et al. (2013)	$K_i = 743$ nM Roth et al. (2018)	$K_i = 115$ nM Roth et al. (2013)
3-MeO-PCMe	$K_i = 145.1$ nM Wallach (2014) $IC_{50} = 384$ nM Reel et al. (1988)	$K_i = 3{,}238$ nM Wallach (2014)	$IC_{50} > 10{,}000$ nM Wallach (2014)	$K_i = 1{,}368$ nM Wallach (2014)
3-MeO-PCP	$K_i = 38.1$ nM Wallach (2014) $K_i = 20$ nM Roth et al. (2013) $IC_{50} = 90$ nM Vignon et al. (1982), Vignon et al. (1988) and Chaudieu et al. (1989)	$K_i = 1{,}808$ nM Wallach (2014) $IC_{50} > 10{,}000$ nM Roth et al. (2013)	$IC_{50} > 10{,}000$ nM Wallach (2014) $K_i = 743$ nM Roth et al. (2013) $IC_{50} > 10{,}000$ nM Roth et al. (2018) $IC_{50} = 490$ nM Vignon et al. (1988) and Chaudieu et al. (1989)	$K_i = 1{,}571$ nM Wallach (2014) $K_i = 216$ nM Roth et al. (2013)
3-MeO-PCPr	$K_i = 17.9$ nM Wallach (2014) 53% [^{3}H]PCP displacement at 100 nM Reel et al. (1988)	$K_i = 1{,}342$ nM Wallach (2014)	$K_i = 381$ nM Wallach (2014)	$K_i = 700$ nM Wallach (2014)
3-MeO-PCPy	$K_i = 22.3$ nM Wallach (2014)	$K_i = 96$ nM Wallach (2014)	$IC_{50} > 10{,}000$ nM Wallach (2014)	$K_i = 11$ nM Wallach (2014)
3,4-MD-PCE	$K_i = 35.5$ nM Wallach (2014)	$IC_{50} > 10{,}000$ nM Wallach (2014)	$K_i = 2{,}867$ nM Wallach (2014)	$K_i = 637$ nM Wallach (2014)
3,4-MD-PCMo	$K_i = 425.5$ nM Colestock et al. (2018)	$IC_{50} > 10{,}000$ nM Colestock et al. (2018)	$IC_{50} > 10{,}000$ nM Colestock et al. (2018)	$IC_{50} > 10{,}000$ nM Colestock et al. (2018)
3,4-MD-PCPr	$K_i = 24.9$ nM Wallach (2014)	$IC_{50} > 10{,}000$ nM Wallach (2014)	$K_i = 1{,}940$ nM Wallach (2014)	$IC_{50} > 10{,}000$ nM Wallach (2014)

4-MeO-PCP	K_i = 620 nM Wallach (2014) K_i = 404 nM Roth et al. (2013) K_i = 500 nM Vignon et al. (1988) K_i = 1,200 nM Vignon et al. (1982) and Kamenka and Geneste (1983)	K_i = 1,811 nM Wallach (2014) K_i = 713 nM Roth et al. (2013)	IC_{50} > 10,000 nM Roth et al. (2013) K_i = 3,890 nM Vignon et al. (1988)	K_i = 900.7 nM Wallach (2014) K_i = 844 nM Roth et al. (2013)
4-MeO-PCMo	K_i = 2,118 nM Colestock et al. (2018)	IC_{50} > 10,000 nM Colestock et al. (2018)	K_i = 399 nM Colestock et al. (2018)	IC_{50} > 10,000 nM Colestock et al. (2018)
Ketamine	K_i = 323.9 nM Wallach et al. (2016a) K_i = 659 nM Roth et al. (2013) K_i = 800 nM Quirion et al. (1981)	IC_{50} > 10,000 nM Roth et al. (2013) K_i = 66.8 μM Nishimura et al. (1998)	IC_{50} > 10,000 nM Roth et al. (2018) K_i = 62.9 μM Nishimura et al. (1998)	IC_{50} > 10,000 nM Roth et al. (2013) K_i = 161.7 μM Nishimura et al. (1998)

NMDAR N-methyl-D-aspartate receptor, *NET* norepinephrine transporter, *DAT* dopamine transporter, *SERT* serotonin transporter. Radioligands and tissue preparations used for NMDAR binding, [^{3}H]MK-801 (rat brain cortex): Roth et al. (2013), Colestock et al. (2018) (rat forebrain), Wallach et al. (2016a) and Wallach (2014) (rat forebrain). [^{3}H]PCP: Quirion et al. (1981) (rat olfactory bulb slices), Kamenka et al. (1982) (rat brain), Vignon et al. (1982) (rat brain minus cerebellum), Mendelsohn et al. (1984) (rat cortex), Reel et al. (1988) (rat cortex), Vignon et al. (1988) (rat striata), Chaudieu et al. (1987) (rat brain), Chaudieu et al. (1989) (rat brain minus brainstem and cerebellum). [^{3}H]TCP: Chaudieu et al. (1987) (rat brain), Ponchant et al. (1990) (rat brain). [^{3}H]3-HO-PCP: Itzhak (1988) (rat brain). Suzuki et al. (1996) (displacement of [^{3}H]3-HO-PCP in various rat brain regions). Radioligands and tissue preparations used for monoamine reuptake transporters, [^{3}H]nisoxetine (NET), [^{3}H]WIN35,428 (DAT), [^{3}H]citalopram (SERT) (human proteins in transfected HEK293 cells): Wallach (2014), Roth et al. (2013), Roth et al. (2018). [^{3}H]BCTP: Hamon et al. (1996) (rat brain), Vignon et al. 1988 (rat striatal homogenates). [^{3}H]DA, [^{3}H]NE, [^{3}H]5-HT (Human NET and DAT, SERT (rat) in transfected HEK293 cells): Nishimura et al. (1998). [^{3}H]DA (human and rat DAT transfected mouse fibroblast Ltk$^-$ cells): Giros et al. (1992). [^{3}H]paroxetine (rat brain): Hori et al. (1996)

2.3 Effects In Vivo

The behavioral effects of PCP are species and dose dependent. Generally, a biphasic dose response has been observed in which low doses cause excitatory effects and high doses lead to a sedative and cataleptic response (Chen 1981; Balster and Chait 1976; Lodge and Mercier 2015). PCP blocked the tonic hindlimb extension in the maximal electroshock seizure (MES) test in male swiss albino mice (ip, $ED_{50} = 3.1$ mg/kg) (Rogawski et al. 1989). NMDAR antagonism has been implicated in anticonvulsant effects of arylcyclohexylamines in the rodent MES test based on high correlation between potencies and PCP binding site affinities (Leander et al. 1988; Wallach 2014). PCP has been found to cause potent rotarod impairment in mice ($ED_{50} = 4$ mg/kg) (Kamenka et al. 1982) and has also shown motor impairment in the horizontal screen test in male mice ip, $ED_{50} = 1.9$ mg/kg (Rogawski et al. 1989; Leander et al. 1988). For many arylcyclohexylamines, strong correlations have been observed between PCP binding site affinities and rotarod activities in mice and minimal motor impairment in rats (Vignon et al. 1982; Wallach 2014). The LD_{50} of PCP was determined to be 283 μmol/kg in mice (ip) (Vaupel et al. 1984). PCP has been shown to produce pro-convulsant effects at doses ($ED_{50} > 12$ mg/kg) greater than those which block electrically induced convulsions in female Sprague-Dawley rats (Leccese et al. 1986).

PCP has been observed to be self-administered in animal models including rats, beagle dogs, and rhesus monkeys (Aniline and Pitts 1982; Risner 1982; Marquis and Moreton 1987). Interestingly, PCP generalized to ethanol in drug discrimination studies in rats (Hundt et al. 1998; Balster and Chait 1976). Human volunteers with a history of alcohol dependence also describe alcohol-like effects following ketamine administration (Krystal et al. 1998). Furthermore, ethanol acts as an NMDAR antagonist (Krystal et al. 2003). Tolerance to PCP and a withdrawal syndrome have been reported in various animal models (Balster and Chait 1976; Balster and Woolverton 1980). Reports of tolerance in humans also exist although it has not been formally studied (Stillman and Petersen 1979; Pradhan 1984).

It is unknown how metabolites might contribute to the pharmacological activity of PCP however several have shown activity in various animal models. The *para*-hydroxylated metabolite of PCP (piperidine ring) produced PCP-like stimulus in rats trained to differentiate PCP from saline although the potency dropped to about 37%. 4-Hydroxylation at the cyclohexane ring reduced potency to 3% (Shannon 1981b). Both metabolites may possess reinforcing properties based on intravenous self-administration studies in beagle dogs although the potency relative to PCP was low (3% and 6%) (Risner 1982).

2.4 Clinical Toxicology

A large body of literature exists describing intoxications and fatalities involving PCP and a particularly relevant contribution to harmful effects and death include behavioral abnormalities that might lead to significantly impaired judgment and high-risk behavior (Cravey et al. 1979; Aniline and Pitts 1982; Showalter and Thornton 1977).

In a prospective study of 1,000 episodes of acute PCP intoxication (predominant route of administration was smoking), and with 60% of cases being attributed to PCP alone, a variety of clinical features were recorded, including nystagmus and hypertension. Severe alterations in vital signs were uncommon in patients who smoked only PCP. Forty-six percent of patients were alert and oriented, but cases of coma and excitement were also observed. Violent behavior (35%), agitation (34%), and bizarre behavior were encountered in 29% of cases (McCarron et al. 1981). Common findings from intoxication with PCP include a "drunken state," disorientation, catatonic effects, delusions, and hallucinations (Aniline and Pitts 1982; Showalter and Thornton 1977). High doses have been reported to lead to respiratory depression, coma, seizure activity, and fatality. Prolonged psychosis has been reported in some chronic users (Aniline and Pitts 1982; Bey and Patel 2007). The concentrations detected in various biofluids have been reported to vary substantially (Aniline and Pitts 1982; Walberg et al. 1983; Barceloux 2012), which makes the ability to identify direct correlations between concentration and drug effect challenging.

3 4-MeO-PCP

The publication of 4-MeO-PCP (Fig. 2a) synthesis dates back to at least the early 1960s as part of a systematic search for PCP analogs with potential clinical use (e.g., Anonymous 1960; Maddox et al. 1965). The first signs of underground 4-MeO-PCP experimentation began to surface in 1999, but it was not until about 2008 that 4-MeO-PCP arrived in online shops as one of the first research chemical dissociative drugs (Morris and Wallach 2014). The first notification of its detection within the European early warning system (EU-EWS) was reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in early 2011 (EMCDDA–Europol 2012).

4-MeO-PCP is active via the oral and parenteral route and is reported to induce dissociative effects but with substantially reduced potency relative to PCP and the positional isomer 3-MeO-PCP. Users generally describe active doses in the 50–100 mg range, which appears to be at least an order of magnitude below that of PCP and 3-MeO-PCP (Anonymous 2008). Analytical characterizations of various PCP and PCPy analogs and positional isomers including 4-MeO-PCP have been described (e.g., Costa and Speaker 1983; Brine et al. 1984; Ohta et al. 1987; Gole et al. 1988c; Casale 2011; Wallach et al. 2014).

3.1 Pharmacokinetics

Detailed pharmacokinetic investigations involving 4-MeO-PCP could not be identified at the time of writing, but the case report literature suggests that 4-MeO-PCP, similar to closely related analogs, can be identified in several biological matrices in the form of the parent species without having to rely solely on the detection of metabolites. Since 3-MeO-PCP biotransformation was revealed

to result, among others, in the formation of the *O*-demethylated product (3-HO-PCP) (Michely et al. 2017), further studies are warranted to confirm whether this metabolic conversion is also observed to any significant extent with 4-MeO-PCP. Although previously considered unclear (e.g., Gole et al. 1988a, b; Holsztynska and Domino 1985), the formation of the phenolic 4-HO-PCP metabolite derived from PCP has been identified in an in vitro study using human and rat liver microsomes and recombinant P450 2B incubations (Driscoll et al. 2007), and the extent to which this metabolite might occur with both PCP and 4-MeO-PCP in vitro deserves further study. Notably, 4-HO-PCP was reported to be a reactive material which underwent rapid decomposition under experimental conditions to yield a reactive quinone methide intermediate capable of reacting with nucleophiles including water and glutathione (GSH) (Driscoll et al. 2007).

3.2 Pharmacodynamic Effects In Vitro

4-MeO-PCP has shown modest binding affinity (Table 1) at the PCP binding site of NMDAR (Wallach 2014; Roth et al. 2013; Vignon et al. 1982; Kamenka and Geneste 1983). Its NMDAR affinity is lower than that obtained for PCP but more comparable (although still reduced slightly) to that determined for ketamine (Table 1). This reduced NMDAR affinity is also consistent with reports of its lower potency in humans compared to PCP and 3-MeO-PCP (Morris and Wallach 2014). Other recent investigations using human recombinant GluN1/N2A and GluN1/N2B preparations and the FLIPR/Ca^{2+} assay confirmed that 4-MeO-PCP was able to demonstrate antagonist properties at both NMDAR subtypes ($pIC_{50} = 4.8$ and 5.4) at reduced potency compared to PCP ($pIC_{50} = 5.9$ and 6.4) and ketamine ($pIC_{50} = 5.3$ and 5.9, respectively) (Zarantonello et al. 2011).

The structure activity relationship of arylcyclohexylamines has been fairly well characterized. Changes in the aromatic region can have dramatic impact on NMDAR affinity. For example, electron-donating substituents in the 2-, and 4-position generally lower NMDAR affinity, whereas electron-donating groups located at the 3-position of the phenyl ring either increase or do not reduce affinity relative to PCP. Electron-withdrawing substituents (e.g., fluorine) reduce potency relative to PCP in all positions although are generally better tolerated in the 3-position (Wallach 2014). However, a variety of 3,4-disubstituted analogs were found to retain affinity compared to PCP ($K_i = 57.9$ nM), such as 3,4-MD-PCP ($K_i = 62.8$ nM) or 3-Me-4-F-PCP ($K_i = 44.2$ nM). On the other hand, 3-Me-4-MeO-PCP displayed a reduction in affinity ($K_i = 185.3$ nM) (Fig. 2b), whereas it was still around three times higher compared to 4-MeO-PCP (Wallach 2014) (Table 1). Replacement of the phenyl ring for thiophene as in TCP and tiletamine increases NMDAR affinity and in vivo potency whereas many other aryl substitutions such as naphthyl, benzyl-, or aliphatic replacements led to loss of potency (Wallach 2014). Notably, Kalir reported 4-MeO-PCP (40% PCP) to be more potent than 2-MeO-PCP (30% PCP), though specific experimental details about how "central potency" was determined were not reported (Kalir 1981). 2-MeO-PCP did not induce dissociative effects at a dose of

12 mg (oral as HCl salt). A subsequent 18 mg dose induced only subtle effects although which appeared dissociative in nature (personal communication).

In addition to NMDAR affinity, 4-MeO-PCP has shown affinity at the human monoamine transporters SERT and NET but not DAT expressed in HEK293 cells ($IC_{50} > 10{,}000$ nM) (Table 1) and the sigma-1 ($K_i = 296$ nM and 517 nM) and sigma-2 receptors ($K_i = 143$ nM and 326 nM) (Roth et al. 2013; Wallach 2014). PCP ($IC_{50} = 500$ nM) and a range of other PCP analogs including 4-MeO-PCP ($IC_{50} = 3890$ nM) were shown to inhibit [^{3}H]DA uptake into rat brain synaptosomes (Vignon et al. 1988). 4-MeO-PCP also had weak affinity toward the alpha-2C adrenergic receptor subtype ($K_i = 5{,}214$ nM) (Wallach 2014).

Similar to PCP, 4-MeO-PCP displayed competitive butyrylcholinesterase and acetylcholinesterase inhibition, and potentiation of smooth muscle contractions in guinea-pig ileum preparations (Maayani et al. 1974). Binding experiments carried out with membrane preparations high in acetylcholine receptor density obtained from the electric organ of *Torpedo ocellata* demonstrated that a number of analogs modified at the phenyl ring (including 4-MeO-PCP, $K_i = 1{,}930$ nM) had comparable affinities (Haring et al. 1983). Electrophysiological studies to probe the impact of a number of PCP analogs including 4-MeO-PCP on nerve-evoked end-plate current (EPCs) recorded from the frog sartorius muscle revealed time- and voltage-dependent decreases in EPC amplitude (Aguayo and Albuquerque 1986). In an ex vivo model of protection, 4-MeO-PCP blocked *N*-methyl-D-aspartate (NMDA) (10 μM), and kainic acid (KA) (20 μM) mediated cell death in rat pup hippocampal slices with IC_{50} values of 4.65 and 42.95 μM, respectively (Wallach 2014). This protection against KA is intriguing as a comparably potent action was not seen with most other arylcyclohexylamines evaluated in this system including 3-MeO-PCP (Wallach 2014).

3.3 Effects In Vivo

Maddox and co-workers reported that 4-MeO-PCP was among the most active derivatives with cataleptic activity following intramuscular injections in pigeons. Although details were not reported, maximum activity for PCP, 4-MeO-PCP, and other derivatives were found at the 6–25 mg/kg level. On the other hand, 4-MeO-PCP was not among the most active drugs for antagonizing the tonic hindlimb extension in the MES test at least not in the range of 3–12.5 mg/kg (Maddox et al. 1965). Data published by Kalir et al. (1969) suggested that 4-MeO-PCP (at 10 mg/kg) did neither impact rotarod performance nor a conditioned avoidance response in albino mice and albino rats respectively. Digging behavior displayed by gerbils with 4-MeO-PCP (5 mg/kg) was not affected, and behavioral changes in cats (200 μg intraventricular injection) were also not observed. TCP, however, emerged as the most active compound during these studies (Kalir et al. 1969). Data published later, however, indicated that 4-MeO-PCP did impair rotarod performance in mice at a potency of about 25% relative to PCP (ED_{50} 11.8 mg/kg vs. 3.00 mg/kg, respectively) (Kalir et al. 1978). In contrast to PCP, 4-MeO-PCP did not induce mydriasis in mice and guinea pigs (Maayani et al. 1974). 4-MeO-PCP

was confirmed to cause impairment in the rotarod assay (subcutaneous administration) where the ED_{50} was reported to be 20 mg/kg in mice (male and female albino ICR), which was 5- and 4.17-fold less potent than PCP and 3-MeO-PCP, respectively (Vignon et al. 1982; Kamenka and Geneste 1983). 4-MeO-PCP was found to have activity in vivo at 30 mg/kg (but not 1, 3, or 10 mg/kg) in the MES test, consistent with its potency as an NMDAR antagonist (Wallach 2014). 4-MeO-PCP induced rotarod impairment in male CF-1 mice (intraperitoneal, ip) at 30, 100, and 300 mg/kg (Wallach 2014). Potency of 4-MeO-PCP in the MES and rotarod tests was reduced compared to 3-MeO-PCP and that generally reported for PCP (Wallach 2014). Notably, deaths were observed in male CF-1 mice at 100 and 300 mg/kg doses (ip), and 4-MeO-PCP was inactive (ip) against subcutaneous metrazole-induced seizure at doses from 1 to 30 mg/kg in mice. In contrast 3-MeO-PCP did show activity in this experimental model (Wallach 2014). The related compound and potential metabolite, 4-HO-PCP showed a significant loss in activity compared to PCP ([^{3}H]PCP $K_i = 20{,}000$ nM, $ED_{50} = 28$ mg/kg in rotarod test in mice), which represented a ~667- and ~13-fold reduction compared to 3-HO-PCP for affinity and rotarod potency, respectively (Vignon et al. 1982).

3.4 Clinical Toxicology

What appears to be the first published report of suspected 4-MeO-PCP intoxication involved a 45-year-old male with psychiatric history and emerged in 2012 with clinical features including disorientation, hypersalivation, tremors and occasional myoclonic jerks, scanning speech with dysarthria, and nystagmus in all directions of lateral gaze. The patient was reported to slowly respond to commands. Notably however the patient also ingested ethanol. The analytical confirmation of 4-MeO-PCP could not be obtained and was based on the self-report of the user (Misselbrook and Hamilton 2012).

A fatality associated with 4-MeO-PCP and the serotonergic hallucinogen 4-hydroxy-*N*-methyl-*N*-ethyltryptamine (4-HO-MET) was presented in 2015 where a 54-year-old man with a history of mental health issues, drug abuse, and hypertension was found dead as a consequence of mixed drug intoxication. The peripheral blood concentration of 4-MeO-PCP was determined at 8,200 ng/mL (central blood concentration was 14,000 ng/mL). Liver and urine concentrations were determined to be 120 mg/kg and 140 mg/L. An amount of 280 mg 4-MeO-PCP was also detected in the gastric contents suggesting oral ingestion of a high dose. Prescription drugs including venlafaxine, olanzapine, lorazepam, and hydroxyzine were also detected at therapeutic concentrations (McIntyre et al. 2015).

A number of intoxications involving 3-MeO-PCP and 4-MeO-PCP were reported from Sweden as part of the STRIDA project beginning in early-mid-2013. Intoxications were reported to resemble those of other dissociative drugs, but co-exposure to other NPS and/or classical "drugs of abuse" was frequently observed. Serum concentrations of 4-MeO-PCP in these cases were generally below 200 ng/mL, although in one case, a higher concentration (705 ng/mL) was detected (17–705 ng/mL, mean: 178, median: 131 ng/mL). Urine concentrations of 4-MeO-

PCP ranged from 61 to 71,673 ng/mL (mean: 14,979, median: 6506 ng/mL). Clinical features included hypertension, tachycardia, altered mental status (confusion, disorientation, dissociation, and/or hallucinations), agitation, and nystagmus among others. Cases involving only 4-MeO-PCP, however, were not described independently and most cases involved 3-MeO-PCP (Backberg et al. 2015).

The analysis of postmortem peripheral blood and urine specimens was reported from a case involving an accidental multiple drug-induced fatality in a 31-year-old male. The results revealed the detection of the synthetic opioids tetrahydrofuranylfentanyl (blood, 339 ng/mL; urine, >5,000 ng/mL) and U-49900 (blood, 1.5 ng/mL; urine, 2.2 ng/mL) but also an unspecified isomer of "MeO-PCP" (blood, 1.0 ng/mL; urine, 31.8 ng/mL). Alprazolam (10 ng/mL), paroxetine (10 ng/mL), topiramate (6,500 ng/mL), zolpidem (8.6 ng/mL), trazodone (360 ng/mL), aripiprazole (170 ng/mL), chlorpheniramine (63 ng/mL), dextro/levomethorphan (46 ng/mL), and promethazine (27 ng/mL) were also detected in blood, reflecting the individual's history of being treated for psychiatric disorders (Krotulski et al. 2017).

4 3-MeO-PCP

The synthesis and/or analytical characterizations of 3-MeO-PCP have been described on several occasions (e.g. Geneste et al. 1979; Brine et al. 1984; Ohta et al. 1987; Carroll et al. 1988; Haradahira et al. 1998; Zarantonello et al. 2011; De Paoli et al. 2013; Wallach et al. 2014), and the preparation of the ^{11}C-labeled counterpart via ^{11}C-methylation of 3-HO-PCP was published by Haradahira et al. (1998). Initial descriptions on the psychoactive effects of 3-MeO-PCP featured on the Internet appeared slightly later following those of 4-MeO-PCP. This was then followed by enthusiastic endorsement of the former compound by research chemical *aficionados*, which then culminated in a concerted research effort coordinated and executed by members of online communities to design, characterize, and explore a variety of arylcyclohexylamines including 3-MeO-PCP, 3-MeO-PCE, 3-MeO-PCPr, and 2-oxo-PCE, but also several new compounds such as 3-MeO-PCPy and MXE. Consistent with scientific research studies on a range of phenyl ring substituted PCP derivatives, the presence of the electron-donating methoxy group in the *meta*-position (3-position) increased potency compared to the *para*-position (4-position). 3-MeO-PCP is active via oral and parenteral routes and induces dissociative effects starting at around 5 mg although much higher doses are often reported (Morris and Wallach 2014). It appears that at present 3-MeO-PCP might be among the more popular representatives of the simple arylcyclohexylamine NPS based on availability, online discussion board postings, and the extent of reported intoxications in the literature. Notification of the first detection of 3-MeO-PCP by members of the EU-EWS was received by the EMCDDA in 2012 (EMCDDA–Europol 2013).

4.1 Pharmacokinetics

A systematic study regarding the biotransformation of 3-MeO-PCP was presented by Michely et al. (2017), who employed rat and pooled human liver microsomes but also included the identification of the cytochrome P450 (CYP) isoenzymes involved using human recombinant isozymes. Furthermore, the metabolic fate in male Wistar rats using urinalysis was investigated. 3-MeO-PCP was found to undergo extensive metabolism including multiple aliphatic hydroxylations at the cyclohexyl ring and piperidine ring, single aromatic hydroxylation, carboxylation after ring opening, *O*-demethylation, and glucuronidation. Hydroxylation reactions at the cyclohexyl ring were catalyzed by CYP2B6, whereas piperidine hydroxylations were catalyzed by CYP2B6 and CYP2C19. *O*-Demethylation was catalyzed by CYP2C19, CYP2B6, and CYP2D6 (Michely et al. 2017). One of the metabolites of particular interest is 3-HO-PCP, which is also a research chemical available for sale at this time (Sect. 6 below). A tentative identification of the *O*-demethyl species 3-HO-PCP together with confirmed identification of 3-MeO-PCP in postmortem femoral blood has been presented by Bakota et al. (2016) although it is unknown whether this could have also arisen from 3-HO-PCP consumption as well. The detection of three 3-MeO-PCP metabolites in human urine samples tentatively suggesting hydroxylations at the piperidine and cyclohexyl rings have also been reported (Zidkova et al. 2017). Although controlled clinical studies have not investigated the pharmacokinetics of 3-MeO-PCP in humans, an elimination $T_{1/2}$ was estimated to be ~11 h based on the analysis of four blood samples taken during the course of a hospitalization case (Johansson et al. 2017). Similarly, Backberg et al. (2015) estimated an elimination $T_{1/2}$ of ~10 h based on the analysis of two blood samples taken from an intoxication case.

4.2 Pharmacodynamic Effects In Vitro

Available data suggest that 3-MeO-PCP shows slightly higher affinity toward the PCP site of NMDAR than PCP. Correspondingly, NMDAR affinity was reported to be an order of magnitude higher than 4-MeO-PCP (Table 1). 3-MeO-PCP has also been reported to have affinities for DAT, SERT, and NET (Table 1), but some discrepancies exist between the studies (Roth et al. 2013; Wallach 2014; Vignon et al. 1988). The affinity values determined for the sigma-1 receptor under identical screening conditions were $K_i = 42$ nM (Roth et al. 2013) and $K_i = 436$ nM (Wallach 2014), respectively, and whereas an $IC_{50} > 10{,}000$ nM was reported by Roth et al. (2013) for sigma-2 receptor affinity, a K_i value of 154.4 nM was reported by Wallach (2014). In the study reported by Vignon et al. (1982) and Kamenka and Geneste (1983) ([^{3}H]PCP as radioligand), the affinity of 3-MeO-PCP increased ~2.8-fold relative to PCP (Table 1), whereas 2-MeO-PCP and 4-MeO-PCP had reduced affinity by a factor of 2 and 4.8, respectively. A recent investigation obtained a K_i value of 147.5 nM for 2-MeO-PCP ([^{3}H]MK-801 in rat forebrain) (Wallach and Colestock unpublished), which was 3.87-times lower than 3-MeO-PCP but 4.2-

times higher than 4-MeO-PCP under identical conditions (Wallach 2014). 3-MeO-PCP (IC_{50} = 490 nM) and PCP (IC_{50} = 500 nM) had comparable potency on inhibition of [^{3}H]DA uptake into rat brain synaptosomes although 3-MeO-PCP was ~eightfold more potent than 4-MeO-PCP (Table 1) (Vignon et al. 1988). In an ex vivo model of neuroprotection, 3-MeO-PCP blocked NMDA (10 μM), and kainic acid (20 μM) mediated cell death in rat pup hippocampal slices with IC_{50} values of 0.381 and 208.1 μM, respectively. In comparison, the IC_{50} values measured for 4-MeO-PCP were 4.65 and 42.95 μM, respectively (Wallach 2014). In one study, 3-MeO-PCP had fairly high affinity at the kappa opioid receptor (KOR, K_i = 168.8 nM) (Wallach 2014) but lower affinity at MOR (K_i = 9,418 nM) (Wallach 2014). However this was not seen in Roth et al. (2013) using equivalent assays.

The related compounds 3,4-MD-PCP (NMDAR K_i = 62.8 nM) and 3-Me-PCP (NMDAR K_i = 34.8 nM) (Fig. 2) also have high affinities for NMDAR with modest to low affinities at monoamine transporters (Table 1), and all show affinities at sigma-1 and sigma-2 (Wallach 2014). These compounds illustrate that electron-donating substituents in the 3-position led to an increase or did not alter affinity for NMDAR relative to PCP. 3,4-MD-PCP is active in humans inducing dissociative effects via parenteral and oral routes at doses from 5–20 mg (HCl salt). Likewise, 3-Me-PCP is an active dissociative (parenteral and oral routes) at 5–10 mg (HCl salt) (personal communication). The high potency of these compounds is consistent with their high affinities for the PCP binding site of NMDAR.

4.3 Effects In Vivo

3-MeO-PCP was found to potently inhibit the tonic hindlimb extension in the MES test (male CF-1 mice MES ip ED_{50} = 3.2 mg/kg and oral (po) ED_{50} = 6.6 mg/kg and male Sprague-Dawley rat ip ED_{50} = 4.05 mg/kg and po ED_{50} = 3.2 mg/kg). Affinities for the PCP binding site of NMDAR and NMDAR antagonism potency correlated well with potency in the MES test for a series of arylcycloalkylamines (Wallach 2014; Wallach unpublished). Likewise, 3-MeO-PCP caused rotarod impairment in male CF-1 mice (ip, ED_{50} = 5.2 mg/kg and po, ED_{50} = 11.29 mg/kg) and minimal motor impairment in male Sprague-Dawley rats (ip, ED_{50} = 5.94 mg/kg, po, ED_{50} = 15.3 mg/kg). This motor impairment was typically seen at doses slightly higher compared to those found to exert anticonvulsant effects (Wallach 2014). Notably, the protective index (MES ED_{50}/rotarod ED_{50}) of 3-MeO-PCP was slightly higher in these models than that reported for PCP but not as high as some other derivatives (e.g., 3-MeO-PCPy) (Wallach 2014). Similar to observations made with the MES test, rotarod potencies showed high correlation with PCP binding site affinities (Wallach 2014). Comparable rotarod potency in mice was reported in another study with an ED_{50} of 4.8 mg/kg, which was only slightly less potent than PCP (4 mg/kg) and 4.17-fold more potent than 4-MeO-PCP (Vignon et al. 1982; Chaudieu et al. 1989). 3-MeO-PCP also showed protection against metrazole-induced seizures in male CF-1 mice (partial protection at 20 mg/kg, po) and rats (po, ED_{50} = 9.4 mg/kg). During evaluation of anticonvulsant and rotarod testing at

the 100 mg/kg (ip), mice were described as sedated, and some test subjects died at 100 and 300 mg/kg doses (Wallach 2014).

4.4 Clinical Toxicology

Three deaths associated with 3-MeO-PCP that occurred in Sweden were reported to the EMCDDA in October 2014 (EMCDDA–Europol 2015). An attempted murder case was reported in which a male drug user with a history of drug use and drug-induced psychosis was reported to have snorted "large quantities" of 3-MeO-PCP and MDPV (a psychostimulant NPS), in addition to inhaling butane gas. Clinical features of the intoxication included vivid visual, auditory, and tactile hallucinations and bizarre ideas. Notably, the hallucinations were reported to take 6 weeks to fully resolve. It was unclear whether this might have been related to the history of drug-induced psychosis, which had been treated with risperidone, which he stopped taking prior to this event due to side effects. Analytical confirmation from the analysis of biofluids, however, was not presented (Stevenson and Tuddenham 2014).

In an evaluation of data collected as part of the Swedish STRIDA project, 56 patients tested positive for 3-MeO-PCP and 11 for 4-MeO-PCP in the period between July 2013 and March 2015, and eight of these cases involved both substances (Backberg et al. 2015). The detection of 3-MeO-PCP alone (not involving other drugs) was encountered in only seven cases, and the clinical features noted in these instances included hypertension, tachycardia, confusion, disorientation, dissociation, and hallucinations. Two intoxications were considered severe (poisoning severity score (PSS) = 3), four as moderate (PSS = 2), and one as mild (PSS = 1). The concentrations of 3-MeO-PCP in serum were found to be generally below 110 ng/mL, albeit one case revealed a concentration of 242 ng/mL (Backberg et al. 2015).

A postmortem analysis of blood samples obtained from a fatal intoxication case of a 29-year-old male revealed a 3-MeO-PCP concentration of 139 ng/mL together with 4.1 mg/L diphenhydramine, a marijuana metabolite (presumptively positive), and amphetamine below 100 ng/mL. Congested lungs and distended bladder indicating urinary retention and moderate atherosclerosis were also noted during autopsy (Bakota et al. 2016).

Two nonfatal intoxications involving young males (19 and 21 years), exhibiting a comatose state (Glasgow coma score = 3), respiratory acidosis, right anisocoria, mydriatic pupils and hypothermia, required hospitalization. A delirious and agitated state, including euphoria was still noted in one case 24 h after hospitalization. Blood-alcohol concentrations were 2.0 and 1.7 g/L. Measured blood and urine concentrations were 350.0 and 6,109.2 ng/mL and 180.1 and 3,003.6 ng/mL, respectively (Bertol et al. 2017).

Fifteen minutes after consuming 3-MeO-PCP (routes of administration not reported), two males (37 and 40 years) were reported to have experienced "disorientation, hallucinations, spastic leg postures, and facial grimacing." In the first case (~2 h after drug ingestion), hypertension, tachycardia, and signs of psychotic behavior and altered mental status (Glasgow coma scale = 10–12) but

also increased muscle tone with spastic leg postures were noted. Serum concentration of 3-MeO-PCP, 2 h after drug ingestion, was 49 ng/mL. In addition to methamphetamine (121 ng/mL) and amphetamine at 10 ng/mL were detected. The patient was discharged 24 h after hospital admission and reported complete amnesia during the period of intoxication. In the second case, the patient was described with a deteriorating state of consciousness (Glasgow coma scale = 12), hypertension, and tachycardia. The medical history included diabetes mellitus with chronic renal failure and a renal transplant 2 years previously. Current medication included prednisone, tacrolimus, and mycophenolate mofetil. Serum concentration of 3-MeO-PCP measured, approximately 2 h after drug ingestion, was 66 ng/mL. Complete amnesia was reported during the time of intoxication, and the patient was discharged 8 h after hospital admission. Both subjects were administered naloxone and flumazenil during transport to the hospital with no noticed effect. Three hydroxylated metabolites of 3-MeO-PCP tentatively identified as piperidine and cyclohexane ring transformation products were identified in urine of both patients (Zidkova et al. 2017).

A nonfatal intoxication and seven deaths (March 2014–June 2016) involving 3-MeO-PCP were reported in Sweden (Johansson et al. 2017). The nonfatal intoxication (19-year-old male) involved a drug user found in a catatonic state at home (Glasgow coma scale = 11) whose clinical features were described as tachycardia, hypertension, and tachypnea. The patient also developed pyrexia and lactic acidosis, became agitated and began to hallucinate, which triggered treatment with diazepam and haloperidol followed by propofol and intubation after the patient began to snore and exhibited reduced oxygen saturation. The concentrations of 3-MeO-PCP in whole blood obtained from various sampling intervals were 0.14 μg/g at admission to the emergency department, 0.08 μg/g 2.5 h after admission, 0.06 μg/g 5 h after admission, and 0.04 μg/g 17 h after admission. The fatal cases involved six males and one female (age range 20–32, mean 26, median 27), all found dead at home. The causes of death were deemed accidental in five cases and suicide in two of the cases. The femoral blood concentrations of 3-MeO-PCP ranged between 0.05 and 0.38 μg/g (postmortem interval 48–244 h). Other drugs were identified in six out of seven cases (Johansson et al. 2017).

A 26-year-old male with a history of substance use disorder presented with generalized hypertonia, ocular revulsion, and contact rupture following the ingestion of multiple drugs on the same day. In addition to his daily therapy which included, oxazepam 50–150 mg/day, venlafaxine 37.5 mg and 80 mg methadone orally (regular therapy) he claimed to have taken 1 g MDMA by several injections of 100 mg and 20–30 "reefers" (joints) of AB-FUBINACA (synthetic cannabinoid receptor agonist) and 200 mg 3-MeO-PCP. Intensive care treatment involved midazolam and propofol administration. The patient fell into coma and required mechanical ventilation for 4 days. Analysis of blood and urine samples and drug paraphernalia confirmed the detection of AB-FUBINACA, 3-MeO-PCP, methadone, MDMA, venlafaxine, and benzodiazepine (details not reported) (Lomenech et al. 2017). In a related publication, it was stated that the same individual believed that he had consumed 4-MeO-PCP, which, following analysis of powdered sample

and biofluids, transpired to be the 3-MeO-PCP isomer (concentration not reported). Quantitative blood results for the following substances were identified: methadone = 278 ng/mL, venlafaxine = 190 ng/mL, oxazepam = 33 ng/mL, and MDMA = 72 ng/mL (Allard et al. 2017).

A case involving an intoxication with the dissociative MXE and 3-MeO-PCP was described in a 27-year-old male with a history of attention deficit hyperactivity disorder, bipolar disorder, and hypertension. He reported taking prescribed lithium, methylphenidate, and trazadone. The patient was hypertensive and tachycardic and showed signs of dissociated affect, a delayed verbal response to questions, ataxia, and vertical nystagmus. Several blood samples were obtained, and detected concentrations were 279 ng/mL, 205 ng/mL, and 180 ng/mL for MXE and 167 ng/mL, 131 ng/mL, and 90 ng/mL for 3-MeO-PCP at 0, 2, and 3 h, respectively (Thornton et al. 2017).

Two deaths involving males (21 and 58 years) have been reported that revealed postmortem (peripheral/central) blood concentrations of 3,200 ng/mL and 630 ng/mL 3-MeO-PCP, respectively. In addition, methamphetamine (110 ng/mL) was detected in the 58-year-old. In addition, this patient was prescribed a number of medications that were not tested for. In the other case ethanol (0.047 g/100 mL), bupropion (1,800 ng/mL), delorazepam, paroxetine, and mitragynine (levels not determined) were also detected in blood (Mitchell-Mata et al. 2017).

The analysis of postmortem peripheral blood and urine specimens was reported that originated from an accidental multiple drug-induced fatality involving a 31-year-old male. The results revealed the detection of the synthetic opioids tetrahydrofuranylfentanyl (blood, 339 ng/mL; urine, >5,000 ng/mL) and U-49900 (blood, 1.5 ng/mL; urine, 2.2 ng/mL) but also an unspecified isomer of "MeO-PCP" (blood, 1.0 ng/mL; urine, 31.8 ng/mL). Alprazolam (10 ng/mL), paroxetine (10 ng/mL), topiramate (6,500 ng/mL), zolpidem (8.6 ng/mL), trazodone (360 ng/mL), aripiprazole (170 ng/mL), chlorpheniramine (63 ng/mL), dextro/levomethorphan (46 ng/mL), and promethazine (27 ng/mL) were also detected in blood, reflecting the individual's history of being treated for psychiatric disorders (Krotulski et al. 2017).

A 27-year-old male with a history of schizophrenia was hospitalized for 3-MeO-PCP intoxication (qualitatively confirmed with detection in urine sample). He had amnesia and reported feeling sedated and "loopy." He expressed delusions, for example, stating he "was an alien with green blood." Vital signs were normal except for borderline tachycardia, mild hypokalemia, hypophosphatemia, slightly increased aspartate aminotransferase, and indirect bilirubemia (Chang and Smith 2017).

5 3-MeO-PCPy

In contrast to PCPy, which had a history in scientific research and illicit street drug presence, 3-MeO-PCPy does not appear to have been described in the scientific literature prior to its inception and development by members of an online discussion

forum (Morris and Wallach 2014), and as such the available information is more limited. The synthesis and analytical characterizations has been described (Wallach et al. 2014). 3-MeO-PCPy does not appear to have ever reached the popularity of 3-MeO-PCP or other dissociative NPS such as MXE although it is an active dissociative in humans at 5–10 mg (HCl salt) and is active after parenteral and oral routes of administration and was described as "stimulating" (personal communication).

5.1 Pharmacokinetics

Together with 3-MeO-PCP, an extensive metabolism study was undertaken with 3-MeO-PCPy that included incubations with rat and pooled human liver microsomes, administration in male Wistar rats for urinalysis, and exposure to human recombinant cytochrome P450 isoforms (Michely et al. 2017). As with 3-MeO-PCP, 3-MeO-PCPy also underwent extensive biotransformation including multiple aliphatic hydroxylations at the heterocyclic and cyclohexyl rings, carboxylation after ring opening, single aromatic hydroxylation, *O*-demethylation, and glucuronidation. In contrast to 3-MeO-PCP, the metabolite resulting from a single hydroxylation at the cyclohexyl ring was not detected. Lactam formation was another feature observed for 3-MeO-PCPy that was not observed with 3-MeO-PCP. Experiments with recombinant isozymes revealed that *O*-demethylation was catalyzed by CYP2D6, CYP2C9, and CYP2B6, whereas pyrrolidine ring hydroxylation was catalyzed by CYP2B6 (Michely et al. 2017).

5.2 Pharmacodynamic Effects In Vitro

3-MeO-PCPy was found to have high affinity at the PCP site of NMDAR in rat forebrain (K_i = 22.3 nM), as well as at human monoamine reuptake transporters NET (K_i = 96 nM), and SERT (K_i = 11 nM) expressed in HEK293 cells. However, 3-MeO-PCPy lacked significant affinity (IC_{50} > 10,000 nM) at DAT under the experimental conditions used (Table 1). In addition, receptor screening results also revealed a K_i value of 2,398 nM at the alpha-2A adrenergic receptor subtype. High affinity for monoamine sites appears common with a number of pyrrolidine containing arylcyclohexylamines (Wallach 2014). For example, the related compounds 3-Me-PCPy and 3,4-MD-PCPy (Fig. 2b) have also been synthesized and investigated, although so far they have not appeared as research chemicals offered for sale. Both showed high affinity for the PCP binding site of NMDAR (Table 1) consistent with electron-donating substituents located at the *meta*-position (K_i = 52.3 and 46.9 nM for 3-Me- and 3,4-MD-PCPy, respectively). Both compounds are reported to be active in humans with dissociative effects starting at doses around 5 mg (as HCl salts) through nasal insufflation with a several hour duration (personal communication).

Notably, 3-Me-PCPy showed high affinities for DAT, NET, and SERT comparable to or higher than its NMDAR affinity (39, 45, 5.6, and 52.3 nM, respectively), which was not shared by its PCP counterpart 3-Me-PCP. Furthermore, 3-Me-PCPy was also shown to act as a reuptake inhibitor at these transporters (Wallach 2014). 3,4-MD-PCPy lacked significant affinity at DAT ($IC_{50} > 10{,}000$ nM) but showed modest affinity at NET and SERT ($K_i = 420$ and 115 nM). This is a similar trend to that seen with 3-MeO-PCPy. The substituted PCPy series generally were found to have higher affinities at monoamine reuptake transporters than their PCP counterparts (Wallach 2014). Interestingly, some users have reported 3-Me-PCPy to show a notable psychostimulant activity in addition to dissociative effects, which suggests that this might be an unusual feature compared to structurally related compounds. Interestingly, PCPy has been said to have sedative effects similar to barbiturates (Shulgin and MacLean 1976). Four and eight mg doses (nasal insufflation of HCl salt) were reported to induce a relaxing ethanol-like state where sleep was possible (a state uncommon with most other arylcyclohexylamines which tend to be slightly stimulating especially at lower to medium doses) although it was reported to clearly represent a dissociative effect and distinct in nature from the effects induced by classic GABAergics including benzodiazepines and barbiturates (personal communication). Efforts should be made to further investigate the potential pharmacological reasons for these apparently unique effects. For comparison purposes, the IC_{50} values obtained from NMDAR binding studies of PCPy were 290 nM ([^{3}H]-MK-801, rat cortex homogenate) (Stefek et al. 1990), 140 nM ([^{3}H]PCP, rat brain homogenate) (Kozlowski et al. 1986), and 200 nM ([^{3}H]PCP, rat brain homogenate) (Zukin and Zukin 1979). Displacement studies of [^{3}H]PCP-specific binding in rat olfactory bulb slices revealed PCPy ($IC_{50} = 65$ nM) to be more potent than PCP ($IC_{50} = 90$ nM) and almost equipotent to TCP ($IC_{50} = 54$ nM). PCE was shown to be more potent ($IC_{50} = 15$ nM), whereas ketamine was much less potent ($IC_{50} = 800$ nM) (Quirion et al. 1981). When employing [^{3}H]PCP-specific binding to guinea-pig ileum preparations, the rank order of potency among a number of PCP analogs showed (IC_{50}): TCP (300 nM) > PCE (400 nM) > PCPy (450 nM) > PCP (500 nM) > PCMo (1,000 nM) > ketamine (5,500 nM) (Gintzler et al. 1982). However, it is unclear which receptor(s) were being labeled in this experiment, which makes interpretation of these particular results challenging.

5.3 Effects In Vivo

3-MeO-PCPy (po) prevented the tonic hindlimb extension in the MES test and caused rotarod impairment in male CF-1 mice ($ED_{50} = 8.03$ and 19.21 mg/kg, respectively). In male Sprague-Dawley rats (po), the MES ED_{50} and rotarod ED_{50} values were 11.04 and 17.39 mg/kg, respectively. Deaths were reported in mice at 100 and 300 mg/kg (ip). Furthermore, it was found that 3-MeO-PCPy showed protection against metrazole-induced seizures at doses from 10 to 30 mg/kg and protected (po) against 6 Hz seizure in male CF-1 mice (Wallach 2014).

The ring-unsubstituted analog PCPy was also active in the rotarod test (mice) and completely abolished (at 8 mg/kg) the conditioned avoidance response in rats, and

although less potent, this compared qualitatively with TCP. Both drugs disrupted digging ability in gerbils (Kalir et al. 1969). PCPy was also observed to produce PCP-like discriminative stimulus effects in rats (two-choice, shock escape-avoidance task) comparable to those produced by 3.0 mg/kg PCP (ip). In comparison, TCP was 1.31-fold more potent, whereas its pyrrolidine counterpart (TCPy) dropped to 87% of the PCP potency. PCMo and ketamine only displayed 10% potency relative to PCP whereas PCE was determined to be almost six times more potent than PCP in this assay (Shannon 1981b). In another study assessing PCP-like discriminative stimuli effects in rats, PCPy was found to show a 0.91-fold potency of PCP. Overall it was confirmed that substitutions on the nitrogen atom of PCP either increased or decreased potency but without affecting efficacy (Cone et al. 1984; Shannon 1981a). In a PCP discriminative stimulus test in pigeons, the potency of PCPy was slightly higher than that observed with PCP (McMillan et al. 1988).

PCPy was also found to be equipotent to PCP in producing increases in avoidance response rates in rats (electric shock avoidance), thus, confirming pharmacological similarities to PCP and other closely related analogs (Shannon and DeGregorio 1981). Studies in beagle dogs revealed that PCPy showed reinforcing properties with a potency of 27% of that of PCP (Risner 1982). In the squirrel monkey PCP, appropriate responding was produced in the following rank order (ED_{50}) for drug lever responding: TCP (0.036 mg/kg) > PCP (0.055 mg/kg) = PCE (0.058 mg/kg) > PCPy (0.07 mg/kg) > PCMo (0.37 mg/kg) > ketamine (0.48 mg/kg) (Brady and Balster 1981). In the rotarod test in mice, the PCPy (ip) ED_{50} value determined was 16.4 μmol/kg (PCP 17.6 μmol/kg), whereas the LD_{50} value was 206 μmol/kg (PCP LD_{50} = 283 μmol/kg) (Vaupel et al. 1984). PCPy, similar to PCP and other analogs, showed both pro- and anticonvulsive effects in female Sprague-Dawley rats (Leccese et al. 1986). In male Sprague-Dawley derived rats, PCPy induced behaviorial effects consistent with PCP including ataxia, headweaving, turning, backpedalling, sniffling and turning with more or less comparable potency to PCP in most of these responses (Cho et al. 1991). PCPy showed reduced potency relative to PCP in inducing a number of effects in dogs including tachycardia, mydriasis, analgesia, hypersecretion, hypernea, and flexor reflex depression, and PCPy was about half as potent as PCP in general PCP behavioral effects (Vaupel 1983).

5.4 Clinical Toxicology

Reports of acute toxicity associated with 3-MeO-PCPy could not be identified. Interestingly, an acute intoxication in a 31-year-old male induced by PCPy was reportedly successfully treated with three intramuscular injections of 2 mg physostigmine salicylate administered in 20 min intervals, which led to reversal of clinical features. In this case report, a 31-year-old male presented with horizontal nystagmus, resting tremor of the upper limbs, agitation, hostility, suspiciousness, panic, and thoughts of impending doom approximately 3–4 h following ingestion (Giannini and Castellani 1982). The application of 5 mg haloperidol (im) has also been reported to

resolve PCPy psychosis in 20 hospitalized male subjects when compared to placebo (Giannini et al. 1985).

6 3-HO-PCP

3-HO-PCP has been the subject of pharmacological research when it was discovered that it showed high affinity toward NMDAR and opioid receptor subtypes, with the potential contributions of the latter to the psychopharmacological profile warranting further studies. The syntheses and analytical characterizations have been described (e.g., Kalir et al. 1978; Kamenka et al. 1982; Brine et al. 1984; Gole et al. 1988c; Wallach 2014). 3-HO-PCP has been the topic of continuous discussion over the years in Internet discussion forums dedicated to the topic of arylcyclohexylamines, and it appears that its emergence as a research chemical was noticed around 2009. In addition to dissociative effects, some users report opioid-like effects with this compound, consistent with its pharmacology described below (Morris and Wallach 2014). 3-HO-PCP is reported to be active at doses from 1 to 10 mg in humans (Anonymous 2012a). A report involving analytically confirmed material found it fully active at 6 mg with nasal insufflation inducing classic dissociative effects with "opioid" activity (personal communication). Notably, unpleasant dissociative effects and muscle tension have been reported although not shared by others (Anonymous 2012b).

6.1 Pharmacokinetics

Detailed pharmacokinetic investigations employing 3-HO-PCP specifically could not be identified. However, as described above, 3-HO-PCP has been detected in rat urine and in incubations with rat and human liver microsomes as a metabolite of 3-MeO-PCP. Furthermore, CYP activity screening with human recombinant isozymes revealed that *O*-demethylation of 3-MeO-PCP was catalyzed by CYP2C19, CYP2B6, and CYP2D6 (Michely et al. 2017). Likewise, 3-HO-PCP was tentatively identified without confirmation with reference material in postmortem blood samples obtained from a fatal intoxication case associated with 3-MeO-PCP (Bakota et al. 2016). The extent to which 3-HO-PCP might arise from PCP metabolism in humans in significant quantities warrants further investigations (e.g., Gole et al. 1988a, b; Holsztynska and Domino 1985; Ohta et al. 1987).

6.2 Pharmacodynamic Effects In Vitro

3-HO-PCP was shown to be a potent NMDAR antagonist with typically higher affinity than that observed for PCP and 3-MeO-PCP (Table 1). In addition, 3-HO-PCP (IC_{50} = 1,360 nM) was reported to show an almost threefold reduced

ability to inhibit [^{3}H]DA uptake into rat brain synaptosomes when compared to PCP (IC_{50} = 500 nM) and 3-MeO-PCP (IC_{50} = 490 nM) (Chaudieu et al. 1989). In terms of binding to monoamine reuptake transporters, 3-HO-PCP lacked affinities for human NET and SERT (IC_{50} > 10,000 nM) and had only weak affinity for DAT (K_i = 1,154 nM) expressed in HEK293 cells. Affinities measured for additional targets included alpha-2A (K_i = 581 nM), alpha-2C (K_i = 3,311 nM), sigma-1 (K_i = 239 nM), and sigma-2 receptors (K_i = 395 nM) (Wallach 2014). Autoradiographic studies in rat brain tissue slices showed that the [^{3}H]3-HO-PCP binding site was identical to the PCP binding site also labeled by [^{3}H]TCP and [^{3}H]MK 801 (Suzuki et al. 1996). However, the high affinity seen at MOR suggests that this may not be the case.

In addition, 3-HO-PCP has been found to have potent affinity at MOR. For example, the IC_{50} values against [^{3}H]morphine binding in rat brain (minus cerebellum) was found to be 39 nM by comparison PCP, IC_{50} = 11,000 nM and morphine, IC_{50} = 2.8 nM. Functional activity experiments with 3-HO-PCP showed opioid-like inhibition in guinea pig ileum preparations which were naloxone-reversible. However, 3-HO-PCP also antagonized the inhibitory effects of morphine in guinea pig ileum, and morphine induced evoked contractions in mouse vas deferens suggesting mixed agonist-antagonist action, possibly suggesting a partial agonist profile (Itzhak et al. 1981a). The same group obtained a K_i value of 55 nM for 3-HO-PCP obtained from displacement of [^{3}H]morphine in rat brain (minus cerebellum) (For comparison PCP, IC_{50} = 13,000 nM; morphine, IC_{50} = 4.2 nM) (Itzhak et al. 1981b). Appreciable affinities have been determined for 3-HO-PCP using a number of radiolabeled ligands to label different opioid sites (and sigma receptors) in rat brain homogenates (minus cerebellum): K_i = 2,300 nM ([^{3}H]leucin enkephalin), K_i = 140 nM [^{3}H] ethylketocycloazocine, and K_i = 42 nM ([^{3}H]SKF-10047) (Itzhak et al. 1981a). Similar results have been reported by others (Kamenka et al. 1982; Johnson et al. 1984) and more recently by Wallach (2014) (MOR, K_i = 86 nM; KOR K_i = 1,096 nM).

6.3 Effects In Vivo

3-HO-PCP (ED_{50} = 1.24 mg/kg) was found to be more potent than PCP (ED_{50} = 3.00 mg/kg) and equipotent to PCE (ED_{50} = 1.25 mg/kg) in the rotarod test in male and female albino ICR mice (Kalir et al. 1978), which has been confirmed subsequently with ED_{50} values of 2.2 mg/kg for 3-HO-PCP and 4 mg/kg for PCP (sc) (Vignon et al. 1982; Kamenka et al. 1982; Kamenka and Geneste 1983). 3-HO-PCP caused motor impairment in the mouse platform test (ED_{50} = 9.40 μmol/kg, ip) with a relative potency to PCP of 1.1 (Domino et al. 1983). Regarding the interactions with potential MOR-related opioid activity, 3-HO-PCP was shown to have potent analgesic effects in vivo in a writhing test using acetic acid in male ICR mice with an ED_{50} of 1.3 mg/kg (sc). In comparison, morphine and PCP administration (sc) gave ED_{50} values of 0.42 and 2.8 mg/kg. The effect of 3-HO-PCP in the writhing test was reduced to 32% with naloxone (0.5 mg/

kg), again suggesting contributions via MOR to the analgesic effects (Itzhak et al. 1981b).

6.4 Clinical Toxicology

Reports of acute toxicity associated with 3-HO-PCP could not be identified. Should 3-HO-PCP be formed in humans, for example, from metabolic hydroxylation of PCP or metabolic demethylation of 3-MeO-PCP (Michely et al. 2017; Bakota et al. 2016), then pharmacological contributions from such a metabolite warrant further investigation.

7 3-MeO-PCE, 3-MeO-PCPr, and 3-HO-PCE

User discussions about the emergence of 3-HO-PCE started to appear in 2012 although the limited information available creates uncertainties about its psychopharmacological profile in users. Both 3-MeO-PCE and 3-MeO-PCPr arose from collaborative research efforts between individuals linked via an online discussion forum and appeared as research chemicals in 2010 and 2011, respectively (Morris and Wallach 2014). Both are fairly potent dissociatives in humans and are active via parenteral and oral routes with dissociative effects starting below 10 mg although higher doses are also commonly reported (Anonymous 2017, 2018b, personal communication). A notification about the detection of 3-MeO-PCE was received by the EMCDDA in November 2010 (EMCDDA–Europol 2011). The syntheses of 3-MeO-PCE, 3-MeO-PCPr, and 3-HO-PCE and some analytical and pharmacological characterizations including use in bioanalytical method development and investigations of positional isomers have been described (Reel et al. 1988; De Paoli et al. 2013; Dresen et al. 2014; Wallach et al. 2016b; Lehmann et al. 2017). A notification about the detection of 3-HO-PCE was received by the EMCDDA in November 2017 (EMCDDA, personal communication).

7.1 Pharmacokinetics

At the time of writing, information on pharmacokinetic parameters on 3-MeO-PCE, 3-MeO-PCPr, and 3-HO-PCE could not be identified. Further studies are warranted, in particular to confirm whether the analytical detection of 3-HO-PCE and 3-HO-PCPr would arise from biotransformations of the *O*-methylated parent drugs as is the case with some structurally related compounds.

7.2 Pharmacodynamic Effects In Vitro

Limited information is available about the pharmacology of 3-HO-PCE. One study published by researchers from Eli Lilly found high affinity for the PCP binding site (IC_{50} = 23 nM, [^{3}H]PCP, rat cortex). Data collected from the same experiments

revealed an IC_{50} value of 99 nM for 3-MeO-PCE, whereas 3-MeO-PCPr was not quantified but showed 53% displacement of [^{3}H]-PCP at a 100 nM concentration (93.6% at 1,000 nM). Similarly, 3-HO-PCPr, which might be revealed as a potentially active metabolite of 3-MeO-PCPr, was also found to have high PCP site binding affinity (IC_{50} = 39 nM) (Reel et al. 1988). More recently, 3-MeO-PCE was reported to have high affinity at the PCP binding site of NMDAR ([^{3}H]-MK-801, rat brain) in two studies, which uncovered K_i values of 61 nM (Roth et al. 2013) and 30.4 nM (Wallach 2014) (Table 1). 3-MeO-PCE also showed affinity for human SERT (K_i = 115 and 136 nM), DAT (K_i = 743 and 906 nM), and NET (IC_{50} > 10,000 nM and K_i = 1,528 nM) expressed in HEK293 cells. Also under identical screening conditions, the determined affinities for sigma receptor subtypes were K_i = 4,519 and 1,725 nM (sigma-1) and K_i = 525 and 636 nM (sigma-2), respectively (Roth et al. 2013; Wallach 2014; Roth et al. 2018). 3-MeO-PCPr was also confirmed to show an appreciable affinity (K_i = 17.9 nM) for the PCP site of NMDAR using [^{3}H]-MK-801 in rat forebrain (Table 1). In addition, 3-MeO-PCPr showed modest affinities for DAT (K_i = 381 nM), NET (K_i = 1,342 nM), SERT (K_i = 700 nM) (Table 1), sigma-1 (K_i = 1,579 nM), sigma-2 (K_i = 467.5), and KOR (K_i = 1,318 nM) (Wallach 2014).

Although apparently not available as research chemicals at the present, a number of other *N*-alkylated arylcyclohexylamines, such as 3-Me-PCMe, 3-Me-PCE, 3-MeO-PCMe, 3-Me-PCPr, 3,4-MD-PCE, and 3,4-MD-PCPr (Fig. 2b), have been investigated for their interaction with a number of biological targets. All have shown affinities toward the PCP binding site of NMDAR in rat forebrain and some monoamine reuptake transporters comparable to other analogs (Table 1). The only examples found to have some affinity for KOR were 3-MeO-PCPr (K_i = 1,318 nM), 3-Me-PCPr (K_i = 832 nM), and 3,4-MD-PCPr (K_i = 998 nM). These compounds did not show significant affinities for MOR (IC_{50} > 10,000 nM). Apart from 3,4-MD-PCPr that did not show > 50% displacement of radioligand at a concentration of 10,000 nM at sigma-1 receptor, all others showed affinities at the sigma-1 (K_i = 227–2,817 nM) and all showed sigma-2 binding site (K_i = 104–1,235 nM). Notably, 3,4-MD-PCPr was the most selective for the PCP binding site of NMDAR of a large series of arylcycloalkylamines evaluated (Wallach 2014) making it potentially valuable for further research requiring selective NMDAR antagonists and for investigations into structure activity relationship features that improve selectivity (Wallach 2014). Consistent with the observed NMDAR binding affinities some of these compounds have been found to be potent dissociative agents in humans. For example, 3-MeO-PCMe (Fig. 2b) was reported to be active at 11 mg (nasal insufflation of the HCl salt) with mild dissociative effects at this dose. Likewise, 3-Me-PCE, 3,4-MD-PCE, and 3,4-MD-PCPr (Fig. 2b) are potent dissociatives with activity beginning between 5 and 10 mg (nasal insufflation of HCl salts). 3,4-MD-PCPr was also reported to have about a 3.5 h duration with a 5 mg dose (personal communication).

7.3 Effects In Vivo

A number of *N*-alkylated arylcyclohexylamines were evaluated in a pigeon catalepsy test where catalepsy was considered present if the test animal was unable to right

itself when laid on their back (right reflex) and when the "head drop" was not observed. The minimum effective dose (MED) was defined as the lowest dose at which two-thirds of animals displayed catalepsy following intramuscular injection of test drugs. The results included MED values for 3-MeO-PCMe (>40 mg/kg), 3-MeO-PCE (10 mg/kg), 3-MeO-PCPr (20 mg/kg), 3-HO-PCMe (40 mg/kg), 3-HO-PCE (2.5 mg/kg), and 3-HO-PCPr (40 mg/kg). The MED determined for PCP was 2.5 mg/kg, which suggested that 3-HO-PCE was equipotent whereas 3-MeO-PCE dropped in potency by a factor of four (Reel et al. 1988). PCE, PCPr, and PCPy showed reduced potency relative to PCP in inducing a number of effects in dogs including tachycardia, mydriasis, analgesia, hypersecretion, hypernea, and flexor reflex depression. PCE and PCPr were about half and a third as potent as PCP in general PCP behavioral effects, respectively (Vaupel 1983). However, potencies maybe species and/or model specific as in Fischer-derived CDF male rats PCE and PCPr were 5.79 and 0.97 times as potent as PCP in a PCP discrimination paradigm (Shannon et al. 1981b).

7.4 Clinical Toxicology

Reports of acute toxicity associated with 3-MeO-PCE, 3-MeO-PCPr, and 3-HO-PCE could not be identified.

8 3-MeO-PCMo

3-MeO-PCMo was first offered as a research chemical in 2015 and appears to have been a novel compound at the time. Its origin as a research chemical was presumably meant to circumvent legislation in the UK. The aryl-unsubstituted parent compound PCMo was reported to be a "street analog" of PCP (Morris and Wallach 2014). Users have reported dissociative effects with 3-MeO-PCMo following parenteral and oral routes of administration. 3-MeO-PCMo is reported to have a rather low potency with active doses requiring 100–500 mg or greater to induce desired effects (Anonymous 2015a, b, c, 2018a). This makes it one of the least potent of the research chemical dissociatives. 3-MeO-PCMo was first notified to the EMCDDA in August 2015 (EMCDDA–Europol 2016). The syntheses and analytical characterizations of 3-MeO-PCMO and closely related analogs and positional isomers have been described (Ahmadi et al. 2011a, b; Colestock et al. 2018). The detection of a methylene linker analog called 3-MeO-PCMMo (Fig. 2) has been recently reported to the EMCDDA (EMCDDA–Europol 2017). Although information about this particular compound is currently unavailable, it has been shown that the *N*-methyl-1-(1-phenylcyclohexyl)methanamine structural template might open the door to a variety of interesting triple monoamine transporter blockers (e.g., Shao et al. 2011). The unsubstituted primary amine counterpart (1-phenylcyclohexyl)methanamine (PCMA) has been investigated and was described as having weak affinity for the PCP binding site ($K_i = 5{,}100$ nM, [^{3}H]-TCP in rat brain) along with anticonvulsant

effects (Thurkauf et al. 1990). The related isomer BnCP (Fig. 1) was a first generation illicit street analog of PCP.

8.1 Pharmacokinetics

Information about the pharmacokinetic properties of 3-MeO-PCMo could not be identified.

8.2 Pharmacodynamic Effects In Vitro

3-MeO-PCMo was found to have modest affinity for the PCP site of NMDAR with a K_i value of 252.9 nM ([^{3}H]MK-801, rat brain). This was slightly higher than ketamine (K_i = 323.9 nM) in this study but over tenfold lower than PCP (K_i = 22.1 nM) (Table 1). This modest NMDAR affinity is consistent with reports of its low potency in humans although it seems less potent than ketamine suggesting additional factors may be relevant. In addition to affinity for NMDAR, 3-MeO-PCMo showed modest affinity at SERT (K_i = 697 nM), sigma-2 (K_i = 299 nM), and alpha-2A (K_i = 1,446 nM), but lacked affinity (IC_{50} > 10,000 nM) for DAT, NET, MOR, sigma-1, and many other CNS receptor sites (Colestock et al. 2018). A number of related morpholine-containing arylcyclohexylamines were also evaluated in this study, which included 2-MeO-PCMo, 4-MeO-PCMo, 3-Me-PCMo, 3,4-PCMo, and PCMo (Table 1). 3-MeO-PCMo had a slightly higher NMDAR affinity than PCMo. Of the three methoxy-substituted PCMo positional isomers, the rank order of affinity for the PCP site of NMDAR was 3-, 2-, and 4-MeO-PCMo (Table 1) (Colestock et al. 2018), again consistent with other arylcyclohexylamines (Wallach 2014). Of the series of PCMo compounds investigated, only 3-Me-PCMo had higher NMDAR affinity than 3-MeO-PCMo. The high affinity seen with 3-Me-PCMo and 3-MeO-PCMo, compared to PCMo, is again in agreement with known SAR where electron-donating groups located at the 3-position increase or do not affect NMDAR affinity. All investigated PCMo analogs showed affinity for sigma-2 but not sigma-1 with K_i values for sigma-2 ranging between 167 nM (PCMo) and 808 nM (4-MeO-PCMo). PCMo was the only compound in the series that showed weak affinity at the serotonin 5-HT_{2A} receptor (K_i = 3,639 nM), and 3-Me-PCMo was the only compound with affinity toward the alpha-2C adrenergic receptor subtype (K_i = 1,448 nM) (Colestock et al. 2018).

8.3 Effects In Vivo

PCMo and several aryl-substituted derivatives have shown analgesic effects in rats using tail immersion and formalin tests (Ahmadi et al. 2011a, b), but specific information about 3-MeO-PCMo could not be identified. PCMo showed

significantly reduced potency relative to PCP in inducing a number of effects in dogs including tachycardia, mydriasis, analgesia, hypersecretion, hypernea, and flexor reflex depression. Similar to 3-MeO-PCMo, PCMo has been reported to have low potency in humans (Morris and Wallach 2014). This is confirmed in animal studies; for example, PCMo was about 1/40th as potent as PCP in inducing general PCP-like behavioral effects in dogs (Vaupel 1983), and PCMo was 1/10th the potency of PCP in a PCP discrimination paradigm in rats which was comparable to ketamine (Shannon et al. 1981b).

8.4 Clinical Toxicology

Reports of acute toxicity associated with 3-MeO-PCMo could not be identified.

9 Conclusions

Scientific and psychonautic curiosity and the motivation to search for drugs perceived to be potentially useful for self-medication appeared to have played a role in establishing collaborations between members of online drug forums. These collaborations provided ideas for compounds that subsequently appeared on the research chemical market. The available pharmacological data suggest that the phencyclidine-based NPS showed high to moderate affinities for the NMDAR, which seemed to correlate with the dissociative activity in humans. The comparison between available information on 3-MeO-PCP and 4-MeO-PCP has consistency with results from early studies where *meta*-substitution on the phenyl ring with an electron-donating group often leads to increased or equipotent NMDAR affinity whereas *para*- substitution decrease affinity. Correspondingly, 3-MeO-PCP is reported to be at least an order of magnitude more potent than 4-MeO-PCP in humans. Likewise, switching the piperidine ring of PCP to a morpholine as in PCMo leads to a loss of NMDAR affinity and potency in humans. Some non-NMDAR receptor interactions have been noted with the arylcyclohexylamines described including affinity to monoamine transporters, sigma receptors, and occasionally also opioid receptor and alpha-adrenergic subtypes. Clinical features reported from acute intoxication cases have included confusion, hallucination, dissociation, catatonia, euphoria, comatose states, nystagmus, as well as hypertension and tachycardia. The research chemical market is constantly evolving in response to numerous factors including legislative and market demand. One may thus anticipate a variety of new dissociative substances to emerge. The employment of chemical manufacturers overseas makes it a relatively straightforward proposition for entrepreneurs in the NPS field to manifest ideas for new compounds. The potential for some of these compounds to have therapeutic uses is captivating. More research is warranted to further explore the properties of these dissociative drugs, particularly their potential medical value, and this field is not anticipated to get boring any time soon.

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