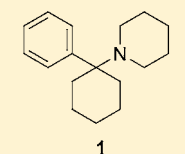


DARK Classics in Chemical Neuroscience: Phencyclidine (PCP)

Jeanette L. Bertron,^{†,§} Mabel Seto,^{†,‡} and Craig W. Lindsley^{*,†,‡,§,||}[†]Vanderbilt Center for Neuroscience Drug Discovery, Vanderbilt University School of Medicine, Nashville, Tennessee 37232, United States[‡]Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232, United States[§]Department of Chemistry, Vanderbilt Institute of Chemical Biology, Vanderbilt University, Nashville, Tennessee 37232, United States^{||}Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, Tennessee 37232, United States

ABSTRACT: Phencyclidine (PCP, “angel dust”, an arylcyclohexylamine) was the first non-natural, man-made illicit drug of abuse, and was coined “the most dangerous drug in America” in the late 1970s (amidst sensational horror stories of the drug’s effects); however, few other illicit drugs have had such a significant and broad impact on society—both good and bad. Originally developed as a new class of anesthetic, PCP-derived psychosis gave way to the PCP hypothesis of schizophrenia (later coined the NMDA receptor hypofunction hypothesis or the glutamate hypothesis of schizophrenia), which continues to drive therapeutic discovery for schizophrenia today. PCP also led to the discovery of ketamine (and a new paradigm for the treatment of major depression), as well as other illicit, designer drugs, such as methoxetamine (MXE) and a new wave of Internet commerce for illicit drugs (sold as research chemicals, or RCs). Furthermore, PCP is a significant contaminant/additive of many illegal drugs sold today, due to its ease of preparation by clandestine chemists. Here, we will review the history, importance, synthesis (both legal and clandestine), pharmacology, drug metabolism, and folklore of PCP, a true DARK classic in chemical neuroscience.

KEYWORDS: Phencyclidine, PCP, schizophrenia, pharmacology, substance abuse, “angel dust”

1
Phencyclidine (PCP)

■ BACKGROUND

In the mid-to-late 1970s, phencyclidine 1 (PCP, “angel dust”) was the most notorious drug in America, garnering unprecedented, negative attention from all media sources and labeled as the “most dangerous drug in America” and “devil drug”.^{1–13} Tales of superhuman strength, users impervious to pain, self-mutilation, and extreme violence, both murders and suicides, led to what some sources referred to as the “dusting of America” (as surveys showed that ~20% of all middle and high school students had tried PCP).^{1–13} *People* (<http://people.com/archive/so-much-for-cocaine-and-ld-angel-dust-is-americas-most-dangerous-new-drug-vol-10-no-10/>) and *Time* (<http://healthland.time.com/2013/08/28/myths-and-facts-about-angel-dust-did-pcp-drive-aaron-hernandez-to-commit-murder/>) magazines, 60 min short films (<http://www.historicfilms.com/tapes/10640>), movies (<https://www.imdb.com/title/tt0083822/reviews>), and songs (<https://www.youtube.com/watch?v=hWitRABYYBk>) all highlighted the dangers of PCP use—and the sensationalism worked. PCP fell in popularity during the 1980s and 1990s, but generational forgetfulness led to a resurgence in the 21st century—both intentional and with many illicit drugs being contaminated with PCP, or with PCP being misrepresented as and/or substituted for other drugs entirely (e.g., LSD, mescaline, psilocybin, THC, cocaine, ecstasy) due to ease of synthesis and lower cost of goods.^{1–15} Importantly, PCP was man-made, which was in sharp contrast to all other drug of abuse (cocaine, LSD, THC, etc. derived from plants) at that time. Furthermore, PCP can be taken by multiple routes of

administration: it can be ingested orally in pill format (PeaCe-Pill), snorted (as a white powder), injected intravenously or subcutaneously (as a liquid solution, Wack), or smoked (by spraying on mint, parsley or cannabis or by dipping cigarettes), which fueled its societal uptake (Figure 1).^{1–15} PCP is sold under a multitude of names on the street including angel dust, PeaCe Pill, hog, lovely, wack, ozone, dust, embalming fluid, rocket fuel, crystal, sherm, shermans, amoeba, amp, animal trunk, and belladonna. When combined with marijuana or tobacco cigarettes, the PCP combinations are often referred to as wet(s), kools, killer joint, fry, super grass, lovelies, and waters. More recently, PCP combined with the club drug MDMA is called elephant flipping or Pikachu.^{1–16}

Phencyclidine 1 (PCP) is considered to be the first arylcyclohexylamine dissociative anesthetic (currently scheduled as a hallucinogen by the United States Drug Enforcement Agency (DEA)), but its creation was by accident (Figure 2).¹⁷ Many publications state that PCP was first synthesized in 1926; however, this is not accurate. The precursor to 1, 1-N-piperidinocyclohexylcarbonitrile (PCC, 2) was synthesized in 1926 by Kotz and Merkel,¹⁸ but it was not further elaborated into 1. That honor fell upon Parke-Davis chemist Victor Maddox (for an ongoing anesthetic program) when, on March 26, 1956, he treated 2 with phenyl magnesium bromide,

Special Issue: DARK Classics in Chemical Neuroscience

Received: May 31, 2018

Accepted: June 21, 2018

Published: June 28, 2018

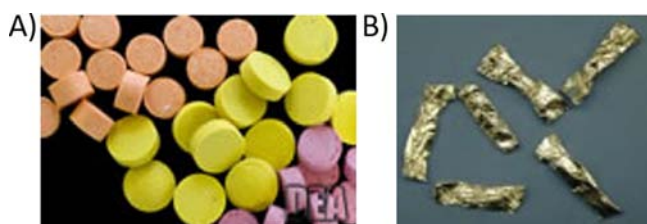


Figure 1. PCP (**1**) is available in many forms. (A) Commonly sold in variously colored tablet form as PeaCe-Pills and (B) as foil-wrapped powder. PCP is also sold as a liquid (PCP dissolved in water, EtOH, or other solvent) or as “dipped” cigarettes/joints. Images courtesy of and with permission of the DEA, www.dea.gov; https://www.dea.gov/pr/multimedia-library/image-gallery/images_other-drugs.shtml.

anticipating addition to the cyano group (and a resulting aryl ketone **3**), but observed instead substitution to provide **1** (PCP or CI-395),¹⁷ via the imine intermediate, known as the Bruylant reaction.¹⁹ Prior to this, other arylcyclohexylamines had been synthesized, including 1-(1-phenylcyclohexyl)amine (PCA, **4**), *N*-ethyl-1-phenylcyclohexylamine (PCE, **5**), and 1-(1-phenylcyclohexyl)morpholine (PCMo, **6**), but biological activity was not explored at that time (later, **4** and **5** emerged as illicit PCP analogues produced by clandestine chemists, *vide infra*).^{20–23}

At Parke-Davis, PCP proved promising as a novel anesthetic, unique for a lack of respiratory depression in rats and unprecedented efficacy in nonhuman primates.^{23–26} These exciting results led to early patent filings as well as disclosures of PCP and its extraordinary profile in 1958 and 1959.^{23,26–32} Studies in humans began in 1957, and the efficacy and lack of respiratory depression was validated in man; however, in the first human trials, agitation, bizarre and aggressive behavior, along with catatonia was observed.^{1–15,23,32–35} Despite these observations, PCP advanced and was marketed under the trade name Sernyl.^{1–15,23,32–36} In parallel, Parke-Davis studied other PCP analogues, such as **5**, in hopes of reducing the adverse events (AEs), but the AEs remained and the company discontinued research in this class.^{23,36} Around this time, efforts in the laboratories of a Parke-Davis consultant, Calvin Stevens, produced analogues in an aryl-amino-cyclohexanone series,²³ that resulted in the discovery of ketamine **7**, also known as CL-369 and CI-581.^{37–40} Human trials began in

1964, and ketamine proved to be effective as an anesthetic with an improved AE profile relative to PCP.^{37–40} Thus, Parke-Davis voluntarily removed Sernyl from the market, patented ketamine, and then launched it as Ketalar in 1969.^{23,37–41} At the same time, PCP was marketed as an animal (namely, nonhuman primates) anesthetic under the trade name Serylan until it was pulled in 1978,²³ due to media attention from illicit manufacture and use (and moved from Schedule III to Schedule II).^{1–15,23} Subsequently, the ease of synthesis for clandestine chemists of PCP and analogues have led to approximately 14 variants available—many as research chemicals (RCs), readily easily obtained via Internet vendors or at Websites (www.chembay.co.uk, www.bluelight.ru, www.RCstandards.com).²³ Other Web sites, run by clandestine chemists, such as the Hive (<https://the-hive.archive.erowid.org/>), show in exhaustive detail how to synthesize PCP and related analogues. Here, PCP inspired the synthesis of the designer drug methoxetamine (**8**, MXE).²³

Around 1967, the first nonmedical use of PCP was documented in the Haight-Ashbury district in San Francisco, and the neuroscience and schizophrenia fields were forever changed.^{1–15,23} Patients were being admitted to hospitals displaying all the core symptomology of schizophrenia (positive, negative and cognitive symptom clusters), but the symptoms proved to be caused by recreational PCP use. In fact, in the early reports of PCP-induced psychosis, Luby et al. called PCP “a new schizophrenomimetic drug”.⁴² With repeated high-dose use, the psychosis was more pronounced, and PCP could exacerbate symptoms in stable schizophrenic patients.^{24,42} Soon, these findings were broadly replicated. These findings marked a major paradigm shift from the prevailing dopamine hyperfunction hypothesis of schizophrenia, as PCP recapitulated the disease to a degree previously unknown pharmacologically.^{24,42} The findings by Lodge and co-workers in the 1980s that the pharmacology of PCP (and ketamine) was driven by open channel inhibition of the *N*-methyl-D-aspartate (NMDA) receptor^{43–46} further refined the PCP hypothesis of schizophrenia into the NMDA receptor hypofunction hypothesis or the glutamate hypothesis of schizophrenia, focusing therapeutic development away from dopamine to glutamatergic signaling (*vide infra*).^{47–60}

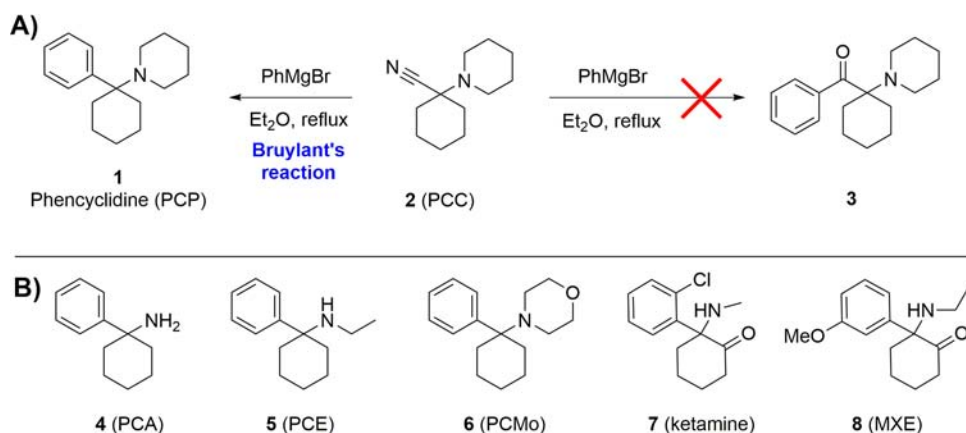


Figure 2. (A) Maddox's original and unintended synthesis of **1** (PCP, CI-395) from **2** (which Parke-Davis had in bulk from a previous analgesia program). Unaware of the Bruylant reaction (**2** to **1**), Maddox anticipated the reaction to produce ketone **3** (or the analogous imine). (B) Structures of PCP analogues **4** (PCs), **5** (PCE), and **6** (PCMo) synthesized prior to PCP, but not assessed pharmacologically. PCP spawned the related ketamine (**7**) and the designer drug methoxetamine, MXE (**8**).²³



Figure 3. PCP drug busts by the DEA. (A–C) Crime scene images of the amount of PCP (in multiple product forms) from the Los Angeles DEA seizure in 2014. (D) DEA image of a mobile PCP lab in the back of a pickup truck. Images courtesy of, and with permission of the DEA, www.dea.gov; https://www.dea.gov/pr/multimedia-library/image-gallery/images_other-drugs.shtml.

Even after the 1970s, PCP still impacts popular culture.^{1–11} In the 1984 film, *The Terminator*, the titular character's invincibility to harm and pain is assumed to be caused by PCP as it is not known that he is a cyborg at that time.⁶¹ Furthermore, PCP usage is portrayed in *Walk Hard: A Dewey Cox Story* where Dewey, the main character, goes on an unclothed, PCP-fueled rampage in which he flips cars.⁶² Recently, real-life instances on PCP-fueled violence have been reported in the news media. Stories involving PCP abuse have highlighted wild acts including cannibalism, murder, kidnapping, and poisoning.^{1–11} Rapper Big Lurch (Antron Singleton) was sentenced to life in prison in 2003 after he was found guilty of murdering his girlfriend (and eating her flesh!) under the influence of PCP.⁶³ In 2013, former NFL player Aaron Hernandez and two co-conspirators were convicted of murder in the first degree. During the trial, Hernandez, an alleged PCP user, claimed that while at the scene of the crime he witnessed his conspirators commit the murder during a violent outburst caused by PCP. The defense even subpoenaed a "PCP expert" to testify to the violent effects of PCP to strengthen their case. It was determined that the fit of psychosis, hypothetically induced by PCP, was impossible to validate and Hernandez was charged with first degree murder.^{64,65} Also in the 2010s, it was reported that the crew of the film, *Titanic*, was exposed to PCP via PCP-spiked clam chowder after a filming bout in 1996.⁶⁶

In recent years, the two largest PCP seizures in DEA history were reported (Figure 3). The first occurred in Houston, TX in

2010, where law enforcement seized 57 gallons of PCP and arrested 11 people for production and intent to distribute.^{67,68} Then, in 2014, the DEA launched an investigation into the production of PCP in Los Angeles, CA, where they encountered a significantly larger operation.^{68,69} During this investigation, the DEA seized around 100 gallons of PCP (approximately 7.7 million doses) along with enough precursors to synthesize thousands of gallons of the drug.^{69,70} Historically, Los Angeles has been considered the central PCP manufacturing and distribution hub in the United States.^{71,72} Coincidentally, there have been no tangible records or statistics of PCP abuse in the United States after these drug busts, which suggests that these large disruptions of the drug supply contributed to a decline in PCP's popularity once again.

PCP is fairly easy to make and therefore relatively inexpensive. Several estimates state that \$30 to \$500 in chemicals can result in over \$30 000 to >\$200 000 worth of PCP, respectively. PCP-laced cigarettes or "joints" cost between \$5 to \$30 depending on whether the PCP is cut with tea leaves, parsley, oregano, mint, tobacco, or cheap marijuana. This low cost has remained consistent since the 1980s, and helped it gain prevalence on the streets. Even today, laced cigarettes (shers) and joints (dusters) are a common vehicle for PCP.^{1–16,23}

One PCP-laced cigarette carries anywhere between 1 and 10 mg of the drug. Here 8–10 mg is considered to be an analgesic dose, whereas 25 mg of PCP or higher is considered to be an overdose (note, the actual dose of PCP in "dippers" varies

greatly).^{1–16,23} Overdose can result in convulsions, respiratory depression, and death via accident or suicide attempt. Patients who have overdosed on PCP are often comatose and unresponsive when they arrive in hospital emergency rooms (ERs). These effects attributed to the labeling of PCP as “America’s most dangerous drug” in 1978, and once again in 2012.^{1,23} PCP was primarily used by teenagers and young adults, and its popularity peaked in the 1960s and 1970s. However, this did not last. Usage of PCP waned in the 1980s and hit an all-time low in 1994. The classification of PCP as a Schedule II drug by the United States Food and Drug Administration (FDA) under the Controlled Substance Act (CSA) in 1978 undoubtedly contributed to its declined use.²³ Furthermore, it is believed that the media played an important role in the downfall of PCP’s popularity. Despite its very realistic danger, some suggest that scare tactics and media sensationalism of horror stories involving PCP abuse made its own contributions to the lessening of PCP use during this time.^{1–16,23} In addition to the scheduling of PCP, the rise in “crack” cocaine usage during this time also diminished the abuse of PCP. Despite the FDA’s best efforts to prevent its abuse, PCP regained popularity decades later. In 2013, a Drug Abuse Warning Network (DAWN) report revealed that PCP-related emergency room visits increased more than 400% from 2005 to 2011, with the largest increases reported from 2009 to 2011, suggesting that PCP usage was on the rise.⁷² The National Institute of Drug Abuse (NIDA) attributed this resurgence to “generational forgetting”—a phenomenon where harmful outcomes experienced by a particular generation is lost on subsequent generations. As of today, the current state of PCP abuse is largely unknown (or not well reported).

Thus, though arrived at by accident, PCP has shaped drug culture (and pop culture) in the United States, led to novel insights into the pathophysiology of schizophrenia (e.g., the NMDA hypofunction hypothesis of schizophrenia), and led to the discovery of ketamine (now driving new depression drug discovery) as well as new designer drugs (e.g., MXE). In the 60 years since its discovery, there have been many excellent reviews detailing certain aspects of PCP,^{23,24,73,74} but no comprehensive reviews, e.g., the Classics series. In this review, we will discuss the history of phencyclidine and its contributions to neuroscience (past and future), in addition to its synthesis, pharmacology, clinical and street usage, structure–activity relationships, drug metabolism, and folklore. Without question, PCP is a DARK classic in chemical neuroscience.⁷⁵

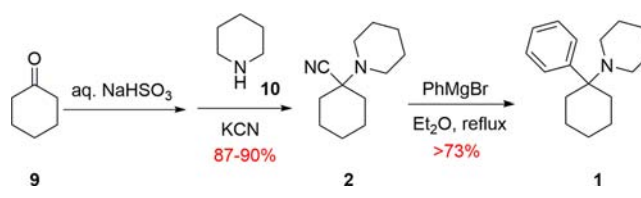
CHEMICAL PROPERTIES AND SYNTHESIS

PCP’s IUPAC name is 1-(1-phenylcyclohexyl)piperidine, which is where the abbreviation PCP originated, though some point to PeaCe Pill as the origin of the abbreviation. PCP is an achiral, lipophilic small molecule with a tertiary amine, and belongs to the arylcyclohexylamine class. PCP has a molecular weight of 243.39 g/mol, a LogP (partition coefficient) of 4.14, and an estimated pK_a of 8.5.²⁴ Upon the original synthesis by Maddox,¹⁷ PCP was obtained from the reaction mixtures as a HBr salt. The free base was found to be a crystalline solid with a sharp melting point between 46.0 and 46.5 °C; however, it is highly insoluble in water and is therefore typically produced as the hydrochloride salt. The HCl salt (the most common form produced by clandestine chemists) is a colorless, crystalline solid with a sharp melting point between 233.0 and 233.5 °C and is readily soluble in

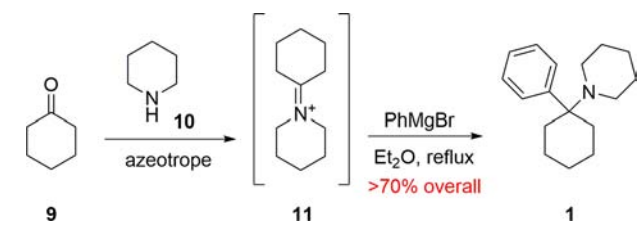
EtOH and water. PCP has no hydrogen bond donors, which along with its lipophilicity are likely why it is able to readily cross the blood-brain barrier (BBB). Interestingly, PCP has a low CNS MPO score (~2.4), suggesting it will show low CNS penetration, but empirical data demonstrates high CNS exposure in preclinical species and humans.⁷⁶ In addition, addicts have commented on the bitter, metallic, and fishy taste of PCP as a both a familiar experience and a sign of product quality.^{1–16}

Numerous syntheses of PCP have appeared over the years, and the vast majority employ the same DEA precursor “watch list” chemicals: cyclohexanone, piperidine, and phenyl organometallic reagents (PhMgX and PhLi).^{23,77,78} Here, we will highlight the major routes employed historically and by clandestine chemists. The original Maddox synthesis of PCP was shown in abbreviated form in Figure 2, from PCC (2), a precursor Maddox had in quantity.¹⁷ PCC, 1-piperidinylcyclohexane carbonitrile, (2) was originally synthesized in 1926 by Kotz and Merkel,¹⁸ and is a major, toxic contaminant in street PCP; however, the degree of contamination varies by lot and the skill of the clandestine chemist.²³ This is key, as PCC (2) is toxic—it liberates cyanide, and there are reports of nausea, fainting, vomiting and hospitalization due to cyanide poisoning; moreover, many street lots of PCP can contain up to 20% PCC, leading to illness—especially if smoked.^{1–11,17,78} There are two major routes to PCP utilizing secondary amine precursors (Schemes 1 and 2), and the most frequent

Scheme 1. Original Maddox (Parke-Davis) Route to PCP (1)

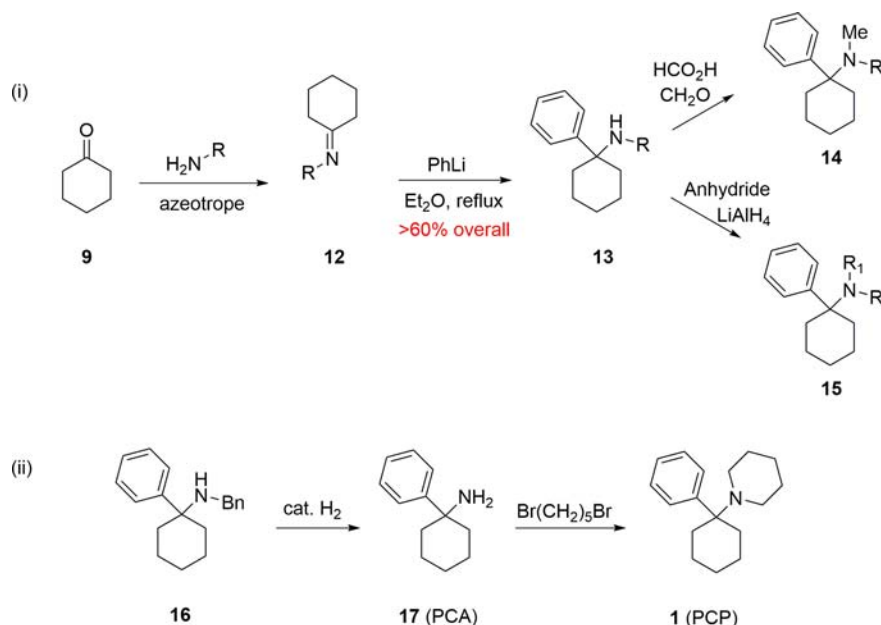


Scheme 2. Kalir Iminium Ion Route to PCP (1)

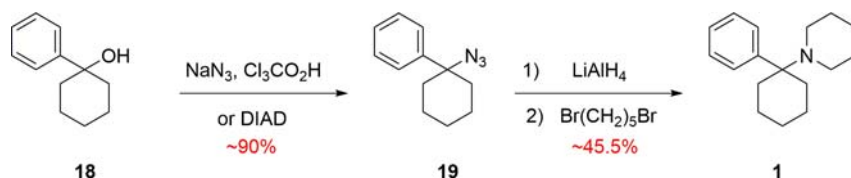


employed by clandestine chemists—directly following the published and patented work by Maddox.^{17,27–32,79} The original Parke-Davis route (Scheme 1) involves suspension of cyclohexanone in aqueous NaHSO₃, followed by the addition of piperidine and KCN to provide PCC (2) in 87–90% yield.^{17,79} Then, a Bruylant reaction¹⁹ with phenylmagnesium bromide delivers PCP (1), with or without quenching and/or conversion to the HCl salt, in yields in excess of 73%. Historical literature exists that suggest the reaction proceeds through direct displacement of the nitrile (with conformationally locked systems), while others argue for an iminium ion intermediate (i.e., the Kalir modification, Scheme 2). Regardless, the route is high yielding, with low difficulty and modest hazards (HCN gas and handling KCN).^{17,78,79} The clandestine chemist’s “bucket method” for

Scheme 3. Primary Amine Precursor Route to PCP (1) and Related Analogues



Scheme 4. Geneste Route to PCP (1) and Related Analogues



PCP production is based on this route.⁷⁸ In a seizure of materials by a DEA forensic chemist, the recipe for PCP by a clandestine chemist was reported. The route was coined the “bucket method” as the clandestine chemist conducted all the reactions in three plastic garbage buckets (denoted buckets A, B, and C) lined with disposable trash bags. Bucket A contained sodium metasilicate and cyclohexanone. Bucket B contained cyanide (likely KCN) and piperidine. Then, the contents of bucket A are added to bucket B (presumably all aqueous) and stirred with a stick, before allowing to stand for 1 day. Upon standing, the product PCC (2) formed as a semicrystalline solid cake on top of the aqueous layer. The solid was collected and allowed to air-dry. The Grignard reagent (spelled by the clandestine chemist as Gernard) was prepared in bucket C by the addition of magnesium turnings, iodine crystals, bromobenzene and 3.5 in. of ether! Notes state that when the “baggie blows” (exothermic production of the PhMgBr), add the PCC (2). Then, the recipe states to stir and pour off cyanide, add more “Coleman” (e.g., petroleum ether), and then pour off liquid. Next, “splash” on muriatic acid and stir—collect the crystals—PCP·HCl. The recipe included details on how to convert to the free base as well. Again, the clandestine chemist used the literature method of Maddox; moreover, this route is compatible with other secondary amines and functionalized aryl/heteroaryl organometallics to prepare PCP analogues.⁷⁸ Recently, the KCN has been replaced with a 1,2,4-triazole with equivalent results (and less toxic reagents) and avoiding the potential for PCC contamination.⁸⁰

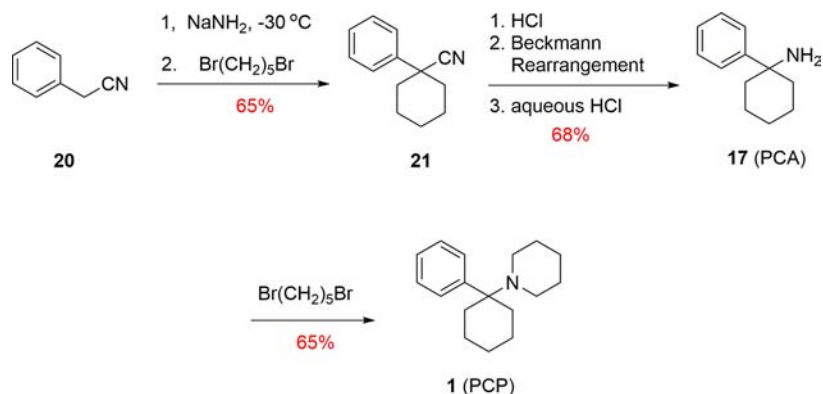
In the Kalir modification (Scheme 2),^{81,82} the same DEA precursor “watch list” chemicals, save for KCN, which lowers

the hazard potential of this variation. Here, cyclohexanone **9** is condensed with piperidine **10** with azeotropic removal of water to *in situ* form the iminium ion **11** with a Dean–Stark trap. Grignard addition into the iminium ion then produces PCP (**1**). Overall yields for this route are upward of 70%. This route has also been reported by clandestine chemists.⁷⁸

The third route to PCP (**1**) and analogues such as PCE (**5**) is actually the second most popular choice of clandestine chemists,^{78,81,82} and one again follows published routes described by Maddox^{17,77,78} employing primary amine precursors (Scheme 3). Here, cyclohexanone is condensed with various primary amines to form a Schiff’s base intermediate **12**, which is then treated with PhLi to form **13**. From **13**, one can access PCP (**1**), PCE (**5**), and any number of analogues of PCP.⁸³ Also from **13**, an Eschweiler–Clark methylation can lead to novel tertiary amine congeners **14**, while treatment of **13** with an anhydride, followed by reduction with LiAlH₄ affords more complex tertiary amine analogues **15**. Initial condensation with benzyl amine (and PhLi addition gives **16**), followed by hydrogenation provides primary amine **17** (PCA), which can undergo a double alkylation to provide PCP (**1**). This route offers tremendous diversity, overall yields of ~60%, and with minimal hazards—it is clear why this is a top choice of clandestine chemists.⁷⁸

An expedient three step route (or four step if starting from **9**) to PCP was developed by Geneste (Scheme 4),^{84,85} but has yet to be adopted by clandestine chemists (likely due to the higher hazards associated with this route, e.g., NaN₃ and LiAlH₄).⁷⁸ Starting from commercial 1-phenyl-1-cyclohexanol **18**, conversion to the tertiary azide **19** with either NaN₃ or

Scheme 5. Alternative Route to PCP (1) and Related Analogues

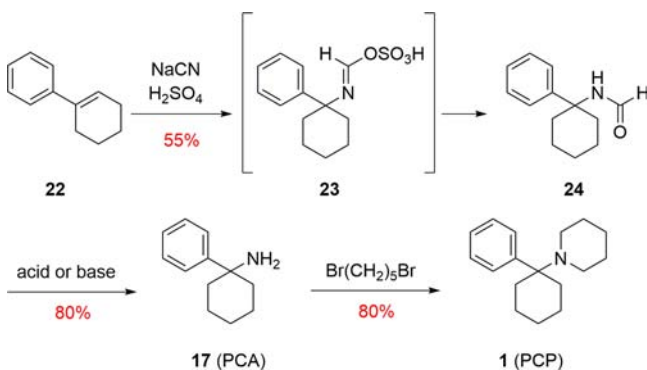


DIAD, followed by reduction affords 17 (PCA). A double alkylation with 1,5-dibromopentane delivers PCP (1) in ~40% overall yield, but with significant more chemical complexity than the other routes previously described.

Another alternative synthesis of PCP (1) represents a departure once again from the previous routes (Scheme 5).^{78,79} This route employs non-DEA “watch list” reagents, but is also significantly more difficult and hazardous than earlier routes (thus, has not been adopted by clandestine chemists). Here, generation of sodium amide at low temperature serves as a base to deprotonate the benzylic site on 2-phenylacetone (20) and subsequent double alkylation to provide 21 in 65% yield. Hydrolysis of the nitrile to the primary carboxamide, followed by Beckmann rearrangement to the *N*-formyl amine and hydrolysis leads to PCA (17) in 68% yield. Repetition of the known standard double alkylation sequence provides PCP (1) in 65% yield and ~30% overall yield.^{78,79}

Another alternative route to PCP (1) has been reported that employs fundamentally different starting materials (“non-DEA watch list”) and is anchored by a Ritter reaction sequence (Scheme 6). Here, 2,3,4,5-tetrahydro-1,1'-biphenyl 22 is

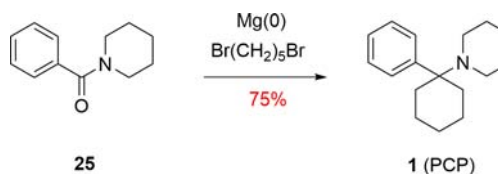
Scheme 6. Alternative Route to PCP (1) and Related Analogues Employing a Ritter Reaction Sequence



treated with NaCN in sulfuric acid to facilitate a Ritter reaction to provide the *N*-formyl amide 24 in 55% yield. Hydrolysis under either acidic or alkaline conditions then affords PCA (17) in ~80% yield. Lastly, the standard double alkylation sequence with 1,5-dibromopentane produces PCP (1) in 80% yield, for an overall yield of ~30% with minimal hazards and a low level of synthetic difficulty. Despite these positive attributes, no clandestine chemists have been reported to use this approach.

Finally, a one-step approach to PCP (1) has also been described in the patent literature (though no reports of application by clandestine chemists).^{26–32,78} Here (Scheme 7),

Scheme 7. Another Alternative, One-Step Route to PCP (1) and Related Analogues



another non-DEA “watch list” starting material, *N*-benzoylpiperidine (25), is employed; however, it is made from benzoyl chloride and DEA “watched” piperidine. In this case, an organometallic species is generated from Mg (0) and 1,5-dibromopentane under anhydrous conditions to deliver PCP (1) in 75% yield.^{26–32,78}

■ DRUG METABOLISM AND PHARMACOKINETICS

Once PCP moved from Schedule III to Schedule II of the Controlled Substance Act (CSA) in 1978, legitimate research was greatly limited and restricted;²³ however, a significant body of work does exist in the primary literature regarding the metabolism and pharmacokinetics of PCP (1).^{86–89} In the early human studies, PCP was administered I.V., but illicit use follows multiple routes of administration (I.V., P.O., and nasal) indicating good oral bioavailability and good CNS exposure (though there are no sources for quantifiable data).^{24,35} Typical dosage: average tablet is 1–6 mg, a laced cigarette of joint might contain between 1 and 10 mg of 1, I.V. is typically 0.1–0.25 mg/kg and ~10 mg for inhalation. The onset of PCP effects is dependent upon the route of administration with intravenous injection and inhalation having the most rapid onset of action (0.5–5 min) and ingestion having the slowest (15–60 min). The duration of a PCP “high” typically lasts between 4 and 6 h, but in some cases it has been reported to last up to 48 h or even weeks. The human elimination $t_{1/2}$ varies in humans from 7 to 57 h (average $t_{1/2}$ ~ 17 h), with a bimodal distribution.^{1–16,23,24,35,78} With a high $\log P$ (>4, some sources quote values of 5.2 and 6.1),^{2–16} and a large volume of distribution (V_d = 6.2 L/kg), PCP is highly brain penetrant and readily absorbed by adipose tissue, where it has been detected out to 4 weeks (after no drug was detected in plasma). Moreover, due to the depot effect in brain and fat, the

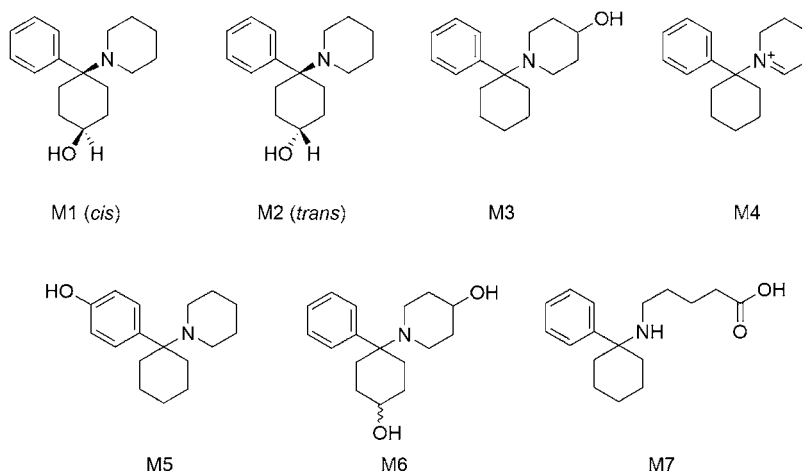


Figure 4. Reported major metabolites M1–M7 of PCP in human liver microsomes and/or hepatocytes.

pharmacodynamic effects of PCP are experienced long after plasma/serum levels of the drug are cleared. Based on the lipophilicity coupled with a protonatable nitrogen, PCP also is known to undergo enterohepatic recirculation, wherein the drug recirculates through the gut and is reabsorbed. Coupled with accumulation in lipid stores and slow release, chronic PCP users can experience highs for weeks or months, and in some cases leading to “PCP intoxication”.^{1–16,23,24,35,78,86–89}

This prolonged exposure, even in acute use, can lead to “PCP flashback”, where drug levels may once again reach pharmacodynamic exposure levels long after an acute dose has been taken.

The primary site of PCP (**1**) metabolism is in the liver (by multiple cytochrome P₄₅₀'s, CYPs), with only 10% excreted unchanged in the urine (as determined by radiolabeled PCP).^{86–88} Studies in human liver microsomes and hepatocytes have identified up to seven phase I oxidative metabolites (Figure 4) and a number of phase II conjugates (both glutathione (GSH) and *N*-acetyl cysteine (NAC)). Major human metabolites result from hydroxylation of the cyclohexane ring to produce *cis*-M1 and *trans*-M2, along with hydroxylation of the piperidine ring in the 4-position (M3), and data suggests the 3-position as well. A reactive iminium ion metabolite M4 has been described, potentially leading to C-linked GSH conjugates. Early reports indicate hydroxylation of the phenyl ring (M5), but later reports do not describe this metabolite. Finally, M6 results from hydroxylation of both the cyclohexane and piperidine rings, as well as the open chain acid, M7, which can also be further conjugated. Multiple P₄₅₀'s contribute to the oxidative metabolism of PCP, with CYP3A, CYP2B, and CYP2C families predominant (Figure 5). In addition, the metabolism of PCP by CYP2B6 leads to mechanism-based inactivation of the enzyme—a major metabolizing enzyme of multiple drugs. Many laboratories focused on understanding this phenomenon.^{86–88} In 2007, Hollenberg and Shebley identified a single residue, K262R, in CYP2B6 that ablated the mechanism-based inactivation of the enzyme by PCP.⁸⁹

■ PHARMACOLOGY

The discovery of PCP's efficacy as an anesthetic and early SAR around analogues employed classical pharmacology of the 1950s–1970s; study the pharmacology in animals first, blind to the molecular pharmacology giving rise to the *in vivo*

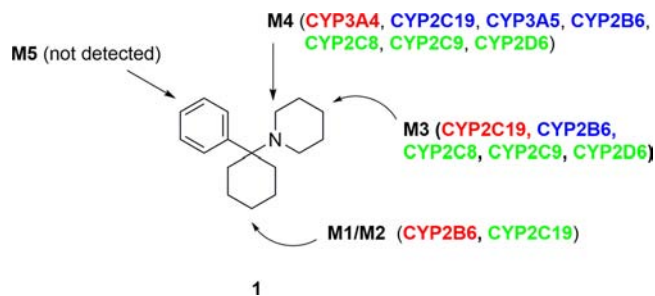


Figure 5. CYP mapping of each P₄₅₀ that contributes to the formation of M1–M5. Red indicates major contributor, blue indicates minor contributor, and green indicates very minor contribution. Adapted from Wienkers et al.⁸⁷

efficacy.^{24–26,33,43–46,50,52,54,59} Later, upon recognition of activity as an *N*-methyl-D-aspartate (NMDA) receptor antagonist, optimization was driven by displacement of [³H]-PCP and more recently, assessing NMDA receptor inhibition in functional or electrophysiological assays.^{24–26,33,43–46,50,52,54,59,90} The molecular pharmacology of phencyclidine (**1**) is extremely complex, and its effects on humans are believed to be a direct result of its many interactions.^{90–93} Table 1 represents a compilation from various sources for binding (*K*_i's) and mode of pharmacology of **1** that have been reported.^{90–93} PCP binds at two high affinity sites in guinea pig brain membranes that are differentiated by their sensitivity to MK-801. PCP binds at both the MK-801 sensitive site (PCP₁ *K*_i = 92 nM) associated with NMDA receptors and the MK-801 insensitive site (PCP₂ *K*_i = 154 nM) that is associated with biogenic amine transporters.^{90–93} Overall, MK-801 possesses a much cleaner pharmacological profile than PCP, and in combination with the DEA scheduling of PCP, MK-801 is utilized more often in preclinical models of NMDA hypofunction.

In addition to the discrete receptor pharmacology highlighted in Table 1, PCP (**1**) also inhibits dopamine uptake ([³H]-DA uptake IC₅₀ = 347 nM) and serotonin uptake ([³H]-HT uptake IC₅₀ = 1,424 nM), in contrast to MK-801. PCP also binds with high affinity to D₂ and elicits functional (EC₅₀ = 144 nM). On a systems level, we know that PCP has multiple effects on glutamate transmission, including NMDA receptor inhibition and increasing glutamatergic transmission at non-NMDA receptors (G-protein mediated response). In addition,

Table 1. Overview of Combined Molecular Pharmacology of PCP (1)^{90–93}

receptor	K_i (nM)	mode of pharmacology ^a	species
NMDA	44–59	antagonist	human
PCP ₁	92	ND	human
PCP ₂	154	ND	human
sigma 1 (σ_1)	>10 000	ND	human
sigma 2 (σ_2)	136	agonist	rat
D ₂ ^{high}	2.6–4.3	agonist	rat/ human
D ₂	>10 000	ND	human
5-HT _{2A}	≥5000	weak agonist	rat
SERT	2234	inhibitor	human
NET	>10 000	inhibitor	human
DAT	>10 000	inhibitor	human
opiate receptors (DOR, NOR, KOR, MOR)	>10 000	ND	human

^aND = not determined.

PCP inhibits GABAergic output while decreasing dopamine (DA) and norepinephrine (NE) uptake.^{24–26,33,43–46,50,52,54,59,90–93}

Studies have shown that PCP is able to directly interact with a multitude of receptors such as the NMDA receptor, sigma (σ_2) receptor, D₂ dopamine receptor, 5-HT_{2A} serotonin receptor, nicotinic acetylcholine receptor (nAChR), and serotonin transporter (SERT).^{24–26,33,43–46,50,52,54,59,93} Interestingly, these direct interactions can also mediate downstream changes in neurotransmission. One particularly well-studied example is the effects of NMDA receptor antagonism on dopaminergic, GABAergic, and glutamatergic signaling in the brain. In 2013, the molecular pharmacology profile of PCP (1) and several analogues were assessed across a panel of 56 molecular targets including GPCRs, ion channel, transporters and the NMDA receptor.⁹¹ PCP (1) was found to have affinity for only three of the 56 targets: NMDA ($pK_i = 7.23 \pm 0.007$, $K_i = 59$ nM), SERT ($pK_i = 5.65 \pm 0.005$, $K_i = 2,234$ nM), and sigma (σ_2 , $pK_i = 6.82 \pm 0.009$, $K_i = 136$ nM). In contrast, other PCP analogues in this study showed significant affinity for the norepinephrine transporter (NET) and sigma (σ_1) as well.⁹³ In this section, we will focus on the effects of PCP's actions on its “primary” target, the NMDA receptor.

In the 1980s, Lodge and Anis demonstrated that dissociative anesthetics such as PCP and ketamine, an analogue of PCP within the arylcyclohexylamine class, were both able to inhibit an NMDA receptor-mediated excitatory response in cat neurons.^{43–46} This NMDA receptor antagonism is thought to explain the dissociative anesthesia, catalepsy, catatonia, and analgesia caused by arylcyclohexylamine drugs.²⁴ Many other anesthetic actions are primarily mediated by enhancing inhibitory current through the GABA_A receptor (ionotropic γ -aminobutyric acid receptor A), which can cause global nervous system depression, as opposed to the region-specific modulation caused by PCP. These differences in mechanism between PCP and other anesthetics may explain the differences in their actions on both animals and human patients.^{24,43–46}

Today, PCP is mainly described as a noncompetitive antagonist of the NMDA receptor ($K_i = 59$ nM),⁹³ which is primarily expressed throughout the brain on postsynaptic membranes. The NMDA receptor is an ionotropic glutamate receptor that consists of four subunits: two obligate GluN1 (NR1) subunits with two GluN2 (NR2) or GluN3 subunits.

The tetramer composition is dependent on brain region and developmental stage.^{94–97} There are four possible GluN2 subunits, GluN2A–D, and two possible GluN3 subunits, GluN3A–B. NMDA receptor activation requires the binding of glutamate, the major excitatory neurotransmitter in the brain, and glycine. Upon activation, cations such as Na⁺, K⁺, and Ca²⁺ are allowed to flow through the NMDA receptor and, subsequently, the cell membrane. This positive current flow results in cellular depolarization and the initiation of downstream biological effects. NMDA receptor function is important for mediating excitatory neurotransmission throughout the brain and has roles in synaptic plasticity, learning and memory, and cognition.^{94–97}

PCP binds inside of the pore of the NMDA receptor near the Q/R/N site, which is important for calcium ion permeability, and also distinct from the glutamate and glycine binding sites. There, an asparagine residue, N598, is important for voltage-dependent Mg²⁺ channel blockade and for noncompetitive antagonist activity.^{94–97} Furthermore, PCP is a use-dependent antagonist; the ion channel must be open for the molecule to bind. PCP's activation-dependent mechanism of action may explain why PCP may only have effects on some brain regions, but not others.^{24,78,94–97}

Finally, administration of PCP (1) produces sustained and robust positive relative cerebral blood volume (rCBV) changes in discrete cortico-limbo-thalamic regions (e.g., medial prefrontal, cingulate, orbit-frontal and retrosplenial cortices) of the brain as measured by pharmacologic magnetic resonance imaging (phMRI).⁹⁸ These rCBV changes further extended in to the motor and visual cortices, with similar time-course activation across thalamus, hippocampus, and medial prefrontal cortex. The effects of PCP on qEEG in the prefrontal cortex of conscious rats were also studied. Low doses induced a dose-dependent increase in EEG power in the frontal cortex (1–3 Hz) with decreases in power at higher frequencies (9–30 Hz). At higher doses, the entire spectrum shifted to positive values, suggesting an increase in cortical synchronization.⁹⁹ These studies further highlight the dysfunctional glutamatergic neurotransmission as a response to PCP administration.

■ BEHAVIORAL PHARMACOLOGY

PCP is unique among the psychostimulant drugs in that it is able to not only to induce the positive symptoms of schizophrenia (e.g., paranoia, hallucinations, violent behavior, delusions and impulsivity), but it also the negative symptoms (e.g., social withdrawal, blunted affect and emotional lability) and induce significant cognitive deficits (e.g., impaired performance on vigilance tasks, the Wisconsin card sorting task, delayed and free recall as well as verbal fluency and recognition memory).^{51,56,59} Thus, PCP can mirror the broad symptom clusters of schizophrenia unlike any other drug-induced psychopathology, and hence the characterization of PCP by Luby as “a new schizophrenomimetic drug”.⁴² These original finding were established in small, well-controlled clinical settings with acute (single-dose) PCP, but recreational, chronic/repeated dosing of PCP in humans leads to a persistent schizophrenia phenotype embodying the positive, negative and cognitive symptom clusters (Table 2).^{59,100–105}

These human observations then led to preclinical modeling of the effects of acute and chronic PCP in rats and nonhuman primates (Table 3),^{106–127} which showed remarkable translation and laid the groundwork for preclinical models to drive next generation antipsychotic drug development based on the

Table 2. Neuropsychiatric Symptoms Induced by Acute versus Chronic PCP (1) Use in Humans^{a42,59,100–105}

symptom/ biological effect	acute PCP	chronic PCP
psychosis	intense (lasts hours)	intense (lasts days to weeks)
hallucinations	visual illusions (lasts hours)	auditory and paranoid (lasts days to weeks)
delusions	yes (last hours)	religion-based (lasts days to weeks)
thought disorders	yes (last hours)	yes (lasts days to weeks)
affect	catatonic to euphoric (last hours)	labile, anxious, paranoid (lasts days to weeks)
cognition	impaired (transient)	impaired (persistently)
cerebral blood flow	increased (transient)	decreased (persistently)

^aAdapted from Jentsch and Roth.⁵⁹**Table 3. Effects of Acute versus Chronic PCP (1) Use in Rodents and Nonhuman Primate**^{a42,59,106–117}

species	behavior	acute	chronic
rodent	frontal cortical function	impaired	impaired
rodent	temporal cortex function	impaired	preserved
rodent	sensorimotor gating	impaired	unknown
rodent	motor function	impaired	preserved
rodent	motivation	impaired	preserved
rodent	associative processes	impaired	preserved
rodent	social behavior	reduced	reduced
rodent	locomotion	increased	augmented response to amphetamine
nonhuman primate	frontal cortical function	impaired	impaired
nonhuman primate	temporal cortex function	impaired	unknown
nonhuman primate	motor function	impaired	preserved
nonhuman primate	motivation	impaired	preserved
nonhuman primate	social behavior	reduced	unknown
nonhuman primate	locomotion	reduced	Increased (accompanied by stereotypy)

^aAdapted from Jentsch and Roth.⁵⁹

NMDA receptor hypofunction hypothesis.^{46–60} Another key finding was that PCP suppresses dendritic glutamate-induced bursting in prefrontal cortical (PFC) pyramidal cells, and since bursting is required for activation of GABA interneurons, the suppression may lead to weakening of connections, thereby contributing to the psychotomimetic effects of PCP.¹¹⁸

■ STRUCTURE–ACTIVITY RELATIONSHIPS

In the beginning, Maddox, upon confirming that PCP (1) was a novel compound, submitted it for general pharmacological screening to the Chen lab at Parke-Davis (Figure 6).¹⁷ Here, Chen and co-workers found that PCP had unique CNS properties (from ataxia, excitation, and catalepsy to surgical anesthesia) across species and dose groups.^{24–26,36} Especially in the rhesus monkey, PCP (1) showed a taming/quieting effect at low doses and permitted major surgery at higher doses of 5–10 mg/kg (inducing anesthesia and catalepsy), distinct from other agents available at the time. Based on the exciting results, Maddox prepared over 60 analogues that were then tested by Chen in a screening paradigm based on the righting reflex of the pigeon.^{24–26,36} As elaborated by Maddox, PCP (1) was unique in that it was the first compound synthesized in the arylcyclohexylamine class, and remained the most potent and efficacious compound—initial SAR could not improve upon 1.¹⁷

Over time, all SAR around 1 focused on exploring the same three regions, and despite the method of evaluation (*in vivo* PD, [³H]-PCP displacement, NMDA affinity/function), SAR trends were remarkably consistent. The cyclohexyl moiety was essential for activity.¹¹⁹ Contraction to 3-, 4- and 5-membered rings lost significant activity in the [³H]-PCP displacement assay and were inactive to weak *in vivo* (rat discriminative stimulus (DS) test). Further expansion to 7- and 8-membered ring congeners lost activity as well, but the 8-membered ring was ~72% of 1 in terms of [³H]-PCP displacement, but inactive in the rat DS test.¹²⁰ Also, limited methyl substitution on the cyclohexyl ring and/or incorporation of amines (e.g., piperidine analogues) similarly lost activity. Furthermore, constrained congeners lost all activity at displacing [³H]-PCP but gained potency at the sigma (σ_2) receptor.¹²¹ Thus, the cyclohexyl moiety proved an essential pharmacophore, and a pharmacophore model was developed (Figure 7).^{122,123} Areas tolerant of changes proved to be substitutions on the phenyl ring and heterocyclic ring replacements, as well as alternate amines (Figure 7). In the 2013 study that evaluated PCP (1)

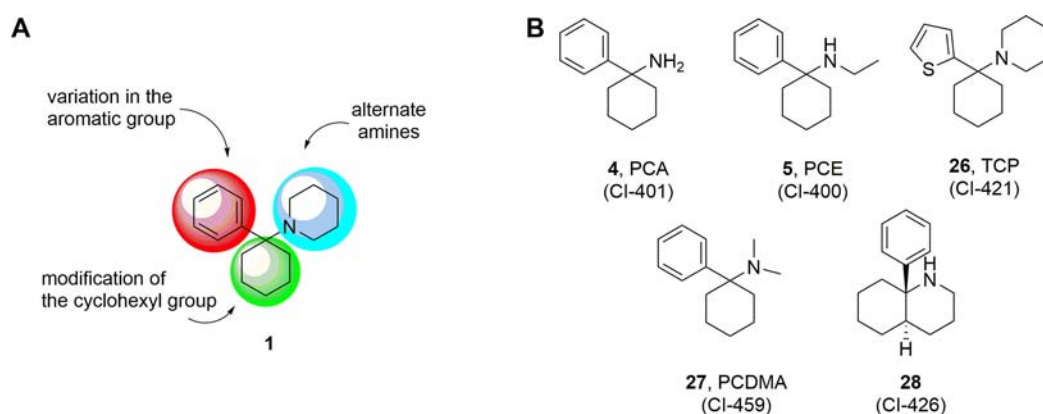


Figure 6. (A) Initial SAR by Maddox to optimize PCP (1) and (B) PCP analogues that advanced as back-ups to PCP 4, 5, 26–28, but failed to afford superior efficacy or lack of AEs (coined “emergence phenomenon”) in preclinical species/man.

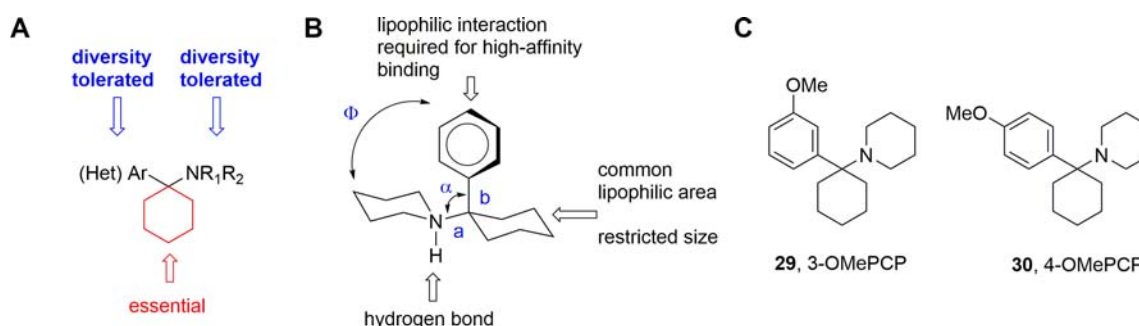


Figure 7. (A) SAR overview, (B) pharmacophore model of PCP (**1**), wherein $a = 1.650 \text{ \AA}$, $b = 1.543 \text{ \AA}$, $\alpha = 2.518 \text{ \AA}$, and $\Phi = 109^\circ$, and (C) potent methoxyphenyl analogues **29** and **30**.

against 56 targets, both 3-OMe-PCP (**29**) and 4-OMe-PCP (**30**) were included, though these are newer, and designer PCP analogues that emerged after 2004. Here, **29** was about 3-times more potent than **1** (NMDA ($pK_i = 7.69 \pm 0.008$, $K_i = 20 \text{ nM}$) while **30** was moderately less potent (NMDA ($pK_i = 6.39 \pm 0.006$, $K_i = 404 \text{ nM}$)).⁹³ As will be discussed in more detail later, PCE (**5**) and 3-OMe-PCP (**29**) are the most potent analogues of PCP produced by clandestine chemists and used recreationally, and **29** is available online as a research chemical (RC).⁷⁸

ADVERSE EFFECTS AND DOSAGE

In addition to the psychotomimetic effects elicited by PCP (which recapitulate the positive, negative, and cognitive symptom clusters of schizophrenia),^{46–60} PCP also can produce a spectrum of adverse physiological events: tachycardia, blood pressure elevation, nystagmus (involuntary eye movement), acute rhabdomyolysis (death of skeletal muscle fibers and release into blood stream), myoglobinuria (myoglobin in urine due to rhabdomyolysis), seizure, memory loss, coma, elevated body temperature (up to 108°F), and death (violent/suicide).^{24,78,124–127} PCP can also lead to neurotoxicity in the brain (in rats, Olney's lesions),¹²⁷ which can lead to other long-term effects after secession from usage. Spieglewsky and Markou demonstrated that withdrawal of chronic PCP usage can cause depression(s) in brain reward function, akin to anhedonia.¹²⁸ From numerous controlled patient and/or volunteer studies with PCP, the effects of different doses and routes of administration are known.³⁵ From inhalation studies with volunteers, a retained dose of $0.1\text{--}0.15 \text{ mg/kg}$ led to reported feelings of unreality, dissociation from reality, visual disturbances, and affective changes within 1–3 min. At inhaled doses between 0.15 and 0.225 mg/kg , the above-mentioned symptoms were intensified and subjects were incapacitated. At doses up to 1 mg/kg , subjects collapsed, and retained doses between 1 and 10 mg/kg led to convulsions with the LD_{50} found to be 15 mg/kg . When given orally, doses 5 to 30 mg (up to 0.48 mg/kg) produced anesthesia and catalepsy. I.V. administration of 0.1 mg/kg induced robust mental and physical effects 3–4 min post dose, with peak intensity recorded at 10 min. At low doses, normal subjects reported a variety of psychological effects including sensory changes (increased sensitivity to outside stimuli, perceived changes in body image, dizziness, sensory illusions, and distortions), cognitive changes (difficulty thinking, e.g. “mind speeding up”, overestimation of elapsed time, connections between words lost), affective changes (depersonalization, mood changes, irritability, disinhibition), unpredictable behav-

ioral changes (“out of control”, bursts of aggression, hyperactivity, repetitive movements), and changes in level of consciousness (“spacy”, “drunk”, “relaxed”, dissociated from reality).³⁵ Smith classified PCP-adverse events into four types: type I (acute PCP toxicity), type II (PCP-induced prolonged toxic psychosis), type III (PCP-precipitated psychotic episodes), and type IV (PCP-induced depression).¹⁰⁷ There are also three stages of PCP intoxication: Stage I (delirious, approximately $2\text{--}5 \text{ mg}$ ingested), Stage II (comatose, unresponsive to pain, $5\text{--}20 \text{ mg}$ ingested), and Stage III (unresponsive, comatose, $25+$ mg ingested).¹²⁷ Another major concern with PCP use is prolonged psychosis, long after drug use has stopped, with accounts of psychosis lasting 4–6 weeks after use (and EEG is abnormal for several weeks as well). Importantly, after bouts of prolonged psychosis, PCP-induced depression can result, with a high comorbid rate of suicide. Furthermore, PCP has long been tied to extreme violence, lack of pain sensation, superhuman strength, cannibalism, self-mutilation, and self-enucleation (e.g., eyes, teeth).^{1–16,35} While there have been comparative risk assessment studies of drugs of abuse, none have included PCP. From the literature that exists,¹³⁰ PCP shares similar toxicological thresholds with heroin and amphetamine (in rodents), but is far more toxic than alcohol, tetrahydrocannabinol (THC), methamphetamine and MDMA. For comparison, the daily dose range for PCP is $1\text{--}20 \text{ mg}$ (depending on route of administration, and with doses $>25 \text{ mg}$ leading to death), while that of heroin is $5\text{--}300 \text{ mg}$, cocaine is $20\text{--}100 \text{ mg}$, THC is $10\text{--}60 \text{ mg}$, amphetamine is $5\text{--}50 \text{ mg}$, methamphetamine is $5\text{--}150 \text{ mg}$, and MDMA is $50\text{--}700 \text{ mg}$.¹²⁹ One study did examine the lethal effects of amphetamine and PCP head-to-head in mice. Interestingly, the LD_{50} of amphetamine decreased 30-fold between isolated ($LD_{50} = 87.9 \text{ mg/kg}$) and aggregated ($LD_{50} = 2.8 \text{ mg/kg}$) housing conditions; in contrast, PCP showed little variance based on housing conditions: isolated ($LD_{50} = 64.5 \text{ mg/kg}$) and aggregated ($LD_{50} = 48.4 \text{ mg/kg}$), a 1.3-fold difference.¹³⁰

HISTORY AND IMPORTANCE IN NEUROSCIENCE

From a serendipitous discovery in the laboratory,¹⁷ to adverse events as a “new schizophrenomimetic drug”,⁴² to further optimization providing ketamine (and later a new role for the rapid treatment of major depressive disorder (MDD)),⁴⁶ to the most “dangerous drug in America”,¹ to new insights into NMDA receptor hypofunction^{47–60} (and new animal models to drive schizophrenia drug development), and finally new designer drugs sold as RCs on the Internet,²³ PCP holds a special place in neuroscience and has left an indelible mark on American society. Truly, PCP, one of the first man-made, all

synthetic illicit drugs of abuse, is a leading contender for the most important and impactful Dark Classic in chemical neuroscience. From the earliest trials in humans, PCP (**1**) was a safe and effective anesthetic and analgesic (relative to other agents available at the time in terms of effects on respiration and heart rate), but produced unprecedented and frightening signs of psychosis and delirium (initially referred to as emergence phenomenon) during recovery.²⁴ In Luby's initial account, PCP was referred to as a "new schizophrenomimetic drug" in the title of his now classic 1959 manuscript.⁴² Not only did PCP induce schizophrenia-like symptoms in healthy volunteers, it exacerbated symptoms in stable schizophrenic patients that lasted weeks.^{24,35,42} Over the next 60 years, the negative, positive, cognitive, and electrophysiological signs of schizophrenia mimicked by PCP (**1**) were recapitulated and reported by dozens of clinicians.^{47–60} In the 1960s, there were more psychiatric admissions due to PCP overdose (mistaken for schizophrenia) than actual schizophrenia, and the symptoms could last for weeks after the drug was taken.^{1–16}

These human findings led to the PCP hypothesis of schizophrenia, later coined the glutamate hypothesis and/or the NMDA receptor hypofunction hypothesis.^{47–60} The importance and impact of the paradigm shift from drug discovery efforts targeting dopamine and dopamine hyperfunction (with D₂ antagonists) to a focus on restoring a balance in glutamatergic signaling and attention to the NMDA receptor pharmacology cannot be more strongly stated. The human data with PCP led to new rodent models with PCP, ketamine, or MK-801 challenge models to evaluate potential new antipsychotics as well as genetic models,^{47–60} such as the NR-1 knockdown mice.¹³¹ Moreover, this new focus led to novel antipsychotic targets and drug candidates including mGlu₅ PAMs, M₁ PAMs, M₄ PAMs, GlyT1 inhibitors, DAAO inhibitors, mGlu_{2/3} agonists, mGlu₂ PAMs, AMPA PAMs, and numerous ion channel modulators that could potentiate NMDA receptor function.^{132–140} Without PCP, much of what we know about schizophrenia and its etiology would likely not exist, and the field would not have so many promising, nondopaminergic targets/drugs in the pipeline.

PCP has also contributed to the development of ketamine (**7**).^{23,38,40,41,43,46,80,93} Ketamine resulted from second-generation structure–activity relationship studies of PCP. It has its own stories of illicit usage (Special K) as well as utility in the clinic and in the laboratory.⁴¹ Today, ketamine is still used as a surgical anesthetic for both human and veterinary use, an analgesic, and a treatment for status epilepticus among other diseases and disorders. In the early 2000s, ketamine was found to have rapid and potent antidepressant activity and to reduce suicidal ideology.^{41,141} Ketamine displayed robust antidepressant activity across multiple preclinical models of depression (e.g., forced swim, tail suspension) in mice and rats.¹⁴¹ In 2006, a single intravenous infusion of ketamine was found to reduce depressive symptoms in patients with treatment-resistant major depression, and the efficacy was retained for over a week in a significant percentage of the patients in that trial.¹⁴² These findings led to a revolution in drug discovery efforts directed toward novel antidepressants, and ketamine quickly found itself as the gold standard comparator preclinically for novel mechanisms.⁴¹ Interestingly, not all NMDA antagonists share the antidepressant activity of ketamine. Unlike the antidepressant activity of ketamine in a differential-reinforcement-of-low-rate (DRL) 72 s schedule of reinforcement

paradigm, MK-801 actually afforded a stimulant-like profile in the DRL 72 s, as well as stimulant-like facilitation of intracranial self-stimulation (ICSS).¹²⁴ From these studies, it was concluded that ketamine possessed stringer antidepressant effects, but lower abuse-related potential than MK-801. In the same paradigm, PCP (10 mg/kg) showed weak antidepressant efficacy, but more pronounced abuse-related effects. In another study, PCP (15 mg/kg) showed no efficacy in a rat forced swim assay, where ketamine is efficacious at 5 mg/kg.^{142,143} These findings led Negus and co-workers to postulate that the antidepressant effects of NMDA antagonists is tied to their affinity for the NMDA receptor.¹²⁴ To this point, low affinity ($K_i = 1190$ nM) and highly cleared ($t_{1/2} = 2–3$ h) ketamine displays robust antidepressant efficacy in the DRL 72 s model with little liability for abuse potential (e.g., the ICSS paradigm). In contrast, high affinity ($K_i = 2.5$ nM) and similarly highly cleared ($t_{1/2} = 2–3$ h) MK-801 fails to demonstrate antidepressant activity, yet engenders abuse-related facilitation of ICSS. PCP falls in-between these two extremes, with moderate affinity ($K_i = 42–59$ nM) and extended $t_{1/2}$ that produces a mixed profile of partial antidepressant efficacy and abuse-related facilitation of ICSS.¹⁴³ Thus, ketamine is unique among the NMDA antagonist ligands.^{143,144} Outside of the clinic, ketamine is still used to investigate schizophrenia, depression, post-traumatic stress disorder, and more.⁴¹ Together, PCP and ketamine have contributed immensely to the field of neuroscience and medicine.^{23,38,40,41,43,46,80,93}

The legacy of PCP also includes a darker side. The first nonmedical use of PCP (**1**) was documented in the United States between 1967 and 1968 in San Francisco, California, and shortly thereafter in Miami, Seattle, Chicago, and Philadelphia.^{1–16,23} PCP had a rapid launch and was available in pill, liquid, and solid form—and clandestine chemists found it inexpensive and easy to prepare following extensive primary and patent literature. Decades later, clandestine chemists would benefit from the Internet and sites like the HIVE that provided extensive detail on how to synthesize PCP and related analogues.²³ America, and the media, was captivated by PCP-fueled horror stories involving wild acts including cannibalism, murder, kidnapping, and poisoning (Figure 8).^{1–16,23} In the late 1970s, *People* and *Time* magazine declared PCP "America's most dangerous drug" and 60 min and other short films ratcheted up the terror to scare PCP-users straight.^{1–16} In a particularly compelling piece by Morgan and Kagan entitled "The Dusting of America: The Image of Phencyclidine (PCP) in the Popular Media," they found a record high of articles on PCP (247) in 1978 and another 42 in 1979.¹ The stories focused on PCP-users gouging out their eyes, nude users dying after hails of bullets fired, users drowning in inches of water in the shower, murders, cannibalism, catching self on fire, tales of superhuman strength, and so forth. The before untold level of negative, sensational press at this time led to PCP being moved to a Schedule II drug, and popularity dropped.^{1–16,23,145} However, it resurged in the early-to-mid 2000s. Moreover, PCP is the ultimate drug of deception. Many drugs of abuse are either laced with PCP or substituted entirely for PCP due to the ease and cost of production by clandestine chemists.^{1–16,23}

No sooner had nonmedical PCP documented in the United States, than PCP analogues appeared on the street. However, these early PCP analogues were all known in the primary/patent literature, and many prepared originally by Maddox.^{17,28–32}

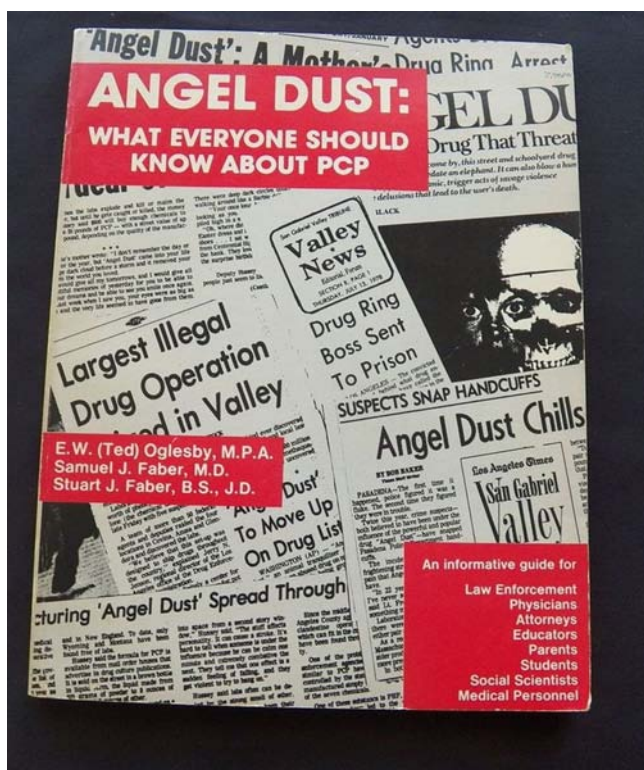


Figure 8. Example of one of many books on PCP published during this era. Photo courtesy Lega-Books and Stuart J. Faber.⁴

PCE (5) was the first documented PCP analogue detected and prepared by clandestine chemists in Los Angeles in 1969.^{23,73} Doses of 5 were smaller than those of PCP, suggesting greater potency. In 1972, TCP (26) was detected on the street, and users also reported greater potency and a longer duration of action. TCP was the first arylcyclohexylamine to be placed on Schedule I (August 11, 1975), followed by TCE (October 25, 1978).²³ Numerous other amine analogues were reported, synthesized by clandestine chemists between 1968 and 1990, the so-called first-generation PCP analogues (Figure 9).²³ Importantly, none of these are “designer drugs”—they were all previously known compounds.^{17,27–32} Moreover, many sources state that over 60 PCP analogues appeared on the street, yet the actual number is closer to 14, as shown in Figure 9.²³

Recently, other arylcyclohexylamine derivatives such as 3-OH-PCP, 3-MeO-PCE (29), and methoxetamine (8, MXE, street names: roflocopt, mket, mexxy) among others are sold as true “designer” drugs (or Research Chemicals, RCs, on the Internet), designed by clandestine chemists, that are still abused today.^{23,93} Similar to PCP and ketamine, these drugs have hallucinatory elements and cause feelings of euphoria. These drugs arose to popularity in the early 2000s due to their effects and also because they were not scheduled for much of their existence. As one example, MXE has been detailed in popular news and on Internet forums where stories about its use include its effects, its popularity, and even overdose and death caused by the drug. Due to these effects, MXE was recently classified as a Schedule II drug by the United Nations in November 2016.²³

With humble, serendipitous beginnings as a “failed” anesthetic, the existence of PCP has had a profound impact and shaped the culture of the United States, as well as multiple fields of neuroscience today. PCP never had quite the

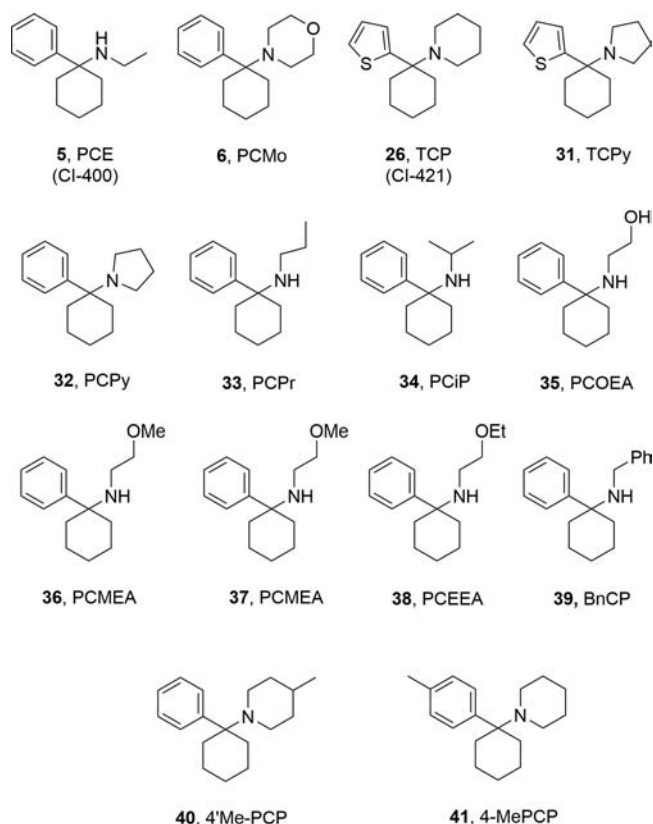


Figure 9. Structures of first generation street analogues of PCP detected between 1967 and 1990.²³

popularity of other drugs of abuse such as cocaine and heroin, or even newer drugs like MDMA or ecstasy, and its history is relatively short in comparison to that of other drugs. Despite these traits, PCP has had a substantial impact on neuroscience and American culture. From outrageous stories detailing psychosis, feats of invincibility, and even cannibalism, to incredible scientific discoveries, PCP has left a significant mark on history, placing it among one the greatest DARK Classics in Chemical Neuroscience.

AUTHOR INFORMATION

Corresponding Author

*E-mail: craig.lindsley@vanderbilt.edu.

ORCID

Craig W. Lindsley: 0000-0003-0168-1445

Author Contributions

J.L.B. and M.S. contributed equally. J.L.B., M.S., and C.W.L. all researched and wrote sections of this review.

Funding

NIH and NIMH (MH082867).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank William K. Warren, Jr., and the William K. Warren Foundation who funded the William K. Warren Jr. Chair in Medicine (to C.W.L.).

■ ABBREVIATIONS

PCP, phencyclidine; LSD, lysergic acid diethylamide; THC, tetrahydrocannabinol; MDMA, 3,4-methylenedioxymethamphetamine; PCC, 1-N-piperidinocyclohexylcarbonitrile; PCA, 1-(1-phenylcyclohexyl)amine; PCE, N-ethyl-1-phenylcyclohexylamine; PCMo, 1-(1-phenylcyclohexyl)morpholine; AE, adverse event; RC, research chemical; MXE, methoxetamine; NMDA, N-methyl-D-aspartate; NFL, National Football League; DEA, Drug Enforcement Administration; SAR, structure–activity relationship; ER, emergency room; FDA, Food and Drug Administration; CSA, Controlled Substance Act; DAWN, Drug Abuse Warning Network; NIDA, National Institute of Drug Abuse; IUPAC, International Union of Pure and Applied Chemistry; LogP, partition coefficient; BBB, blood–brain barrier; CNS, central nervous system; CNS MPO, central nervous system multiparameter optimization; I.V., intravenous; P.O., *per os*, oral administration; $t_{1/2}$, half-life; V_d , volume of distribution; CYP, cytochrome P₄₅₀; GSH, glutathione; NAC, N-acetyl cysteine; K_i, inhibitory dissociation constant (affinity); IC₅₀/EC₅₀, potency; GABA, gamma-aminobutyric acid; DA, dopamine; NE, norepinephrine; nAChR, nicotinic acetylcholine receptor; SERT, serotonin transporter; GPCR, G-protein coupled receptor; NET, norepinephrine transporter; Q/R/N site, glutamine, arginine, asparagine site; rCBV, relative cerebral blood volume; pHMRI, pharmacologic magnetic resonance imaging; EEG/qEEG, (quantitative) electroencephalogram (or electroencephalography); PFC, prefrontal cortex; PD, pharmacodynamics; [³H]-PCP, tritiated PCP; DS, discriminative stimulus; 3-OMe-PCP, 3-methoxyphencyclidine; LD₅₀, lethal dose, 50%; MDD, major depressive disorder; mGlu_{2,3,5}, metabotropic glutamate receptor 2, 3, or 5; M_{1,4}, muscarinic acetylcholine receptor 1 or 4; MK-801, dizocilpine; DAAO, D-amine acid oxidase; GlyT1, glycine transporter 1; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; PAM, positive allosteric modulator; DRL, differential-reinforcement-of-low-rate; ICSS, intracranial self-stimulation; 3-OH-PCP, 3-hydroxyphencyclidine; TCP, tenocyclidine; TCE, trichloroethylene

■ REFERENCES

- (1) Morgan, J. P., and Kagan, D. (1980) The Dusting of America: The image of phencyclidine (PCP) in the popular media. *J. Psychedelic Drugs* 12, 195–204.
- (2) TV: On a deadly drug. New York Times (1979), page C18, October 29, 1979; <https://nytimes.com/1979/10/29/archives/tv-on-a-deadly-drug.html>.
- (3) Carter, M. N. (1977) Its name is heavenly, but angel dust can be a deadly high. *AP Wire Story*, November 10, 1977.
- (4) Ogelsby, E. W., Faber, S. J., and Faber, S. J. (1979) *Angel dust: What everyone should know about PCP*, Lega-Books.
- (5) Garey, R. E. (1979) PCP (phencyclidine): An update. *J. Psychedelic Drugs* 11, 265–277.
- (6) Petersen, R. C., and Stillman, R. C. (1978) Phencyclidine: An overview, in *Phencyclidine Abuse: An Appraisal*. NIDA Res. Monogr 1, 1–17.
- (7) Linder, R. L., Lerner, S. E., and Burns, R. S. (1981) *PCP, the Devil's Dust: Recognition, Management, and Prevention of Phencyclidine Abuse*, Wadsworth Publishing Company, CA.
- (8) Lerner, S. E., and Burns, R. S. (1978) Phencyclidine use among youth: History, epidemiology, and acute and chronic intoxication. *NIDA Res. Monogr.* 21, 66–118.
- (9) The PCP Story – a film (1977) *Clin. Toxicol.* 10, 365–366.
- (10) Petersen, R. C., and Stillman, R. C. (1978) Phencyclidine abuse: an appraisal. *Natl. Inst. Drug Abuse Res. Monogr.* 21, 1–17.
- (11) Luisada, P., and Reddick, C. (1975) *An epidemic of drug-induced schizophrenia*, 128th Annual Meeting of the American Psychiatric Association, Anaheim, CA. May, 5–9.
- (12) <https://drugabuse.com/library/pcp-history-and-statistics/>.
- (13) <https://www.encyclopedia.com/medicines/encyclopedias-almanacs-transcripts-and-maps/pcp-phencyclidine>.
- (14) Rainey, J. M., and Crowder, M. K. (1974) Prevalence of phencyclidine in street drug preparations. *N. Engl. J. Med.* 290, 466–467.
- (15) Lundberg, G. D., Gupta, R. C., and Montgomery, S. H. (1976) Phencyclidine: Patterns seen in street drug analysis. *Clin. Toxicol.* 9, 503–511.
- (16) <http://hallucinogens.com/pcp/pcp-streetnames>.
- (17) Maddox, V. H. (1981) The historical development of phencyclidine. In *PCP (Phencyclidine): Historical and Current Perspectives* (Domino, E. F., Ed.), pp 1–8, NPP Books: MI.
- (18) Kotz, A., and Merkel, P. (1926) Hydroaromatische Alkamine. *J. Prakt. Chem.* 113, 49–77.
- (19) Bruylants, P. (1924) Contribution a l'etude de la reaction des composés organo-magnésien sur les nitriles. *Bull. Soc. Chim. Belg.* 33, 467–478.
- (20) Kursanov, N. (1907) Phenyl derivatives of naphthenes, second paper, some derivatives of phenylcyclohexane. *Zh. Russ. Fiz.-Khim. Ova.* 38, 1295–1297.
- (21) Chiavarelli, S., Rogers, E. F., and Marino-Bettolo, G. B. (1953) Researches on synthetic products with erythrina alkaloids as a model. *Gazz. Chim. Ital.* 83, 347–350.
- (22) Chen, G., Ensor, C. R., and Bohner, B. (1969) The pharmacology of 2-(ethylamino)-2-(2-thienyl)-cyclohexanone-HCl (CI-634). *J. Pharm. Exp. Ther.* 168, 171–179.
- (23) Morris, H., and Wallach, J. (2014) From PCP to MXE: a comprehensive review of the non-medical use of dissociative drugs. *Drug Test. Anal.* 6, 614–632.
- (24) *PCP (Phencyclidine): Historical and Current Perspectives* (Domino, E. F., Ed.), NPP Books: MI, 1981.
- (25) Chen, G. (1981) The neuropharmacology of phencyclidine. In *PCP (Phencyclidine): Historical and Current Perspectives* (Domino, E. F., Ed.), pp 9–15, NPP Books: MI.
- (26) Chen, G., Ensor, C. R., Russell, D., and Bohner, B. (1959) The pharmacology of 1-(1-phenylcyclohexyl)piperidien-HCl. *J. Pharm. Exp. Ther.* 127, 241–250.
- (27) Parcell, R.F. Heterocyclic amine compounds (to Parke, Davis and Co.). U.S. Patent 2 921 076 (January 12, 1960).
- (28) Parke, Davis and Co. Heterocyclic amine compounds. United Kingdom Patent 836 083 (June 1, 1960).
- (29) Parke, Davis and Co. Phenylcyclohexane compounds. United Kingdom Patent 837 747 (June 15, 1960).
- (30) Parke, Davis and Co. Heterocyclic compounds for use as central nervous system depressants. United Kingdom Patent 838 748 (June 22, 1960).
- (31) Parke, Davis and Co. Cyclohexylamine compounds. United Kingdom Patent 851 782 (October 19, 1960).
- (32) Maddox, V. H., and Godefroi, E. F. Methods of producing heterocyclic amine compounds (to Parke, Davis and Co.). Canadian Patent 780 870, March 19, 1968.
- (33) Greifenstein, F. E., Yoshitake, J., DeVault, M., and Gajewski, J. E. (1958) A study of 1-aryl cyclohexylamine for anesthesia. *Anesth. Analg.* 37, 283–294.
- (34) Lear, E. (1968) Intravenous anesthesia: A survey of newer agents. *Anesth. Analg.* 47, 154–159.
- (35) Pradhan, S. N. (1984) Phencyclidine (PCP): Some human studies. *Neurosci. Biobehav. Rev.* 8, 493–501.
- (36) Domino, E. F. (1964) Neurobiology of phencyclidine (Sernyl), a drug with an unusual spectrum of pharmacological activity. *Int. Rev. Neurobiol.* 6, 303–347.
- (37) Stevens, C. L., Klundt, I. L., Munk, M. E., and Pillai, M. D. (1965) Amino ketone rearrangements. IV. Thermal rearrangements of o-amino methyl ketone. *J. Org. Chem.* 30, 2967–2972.

- (38) Stevens, C. L. Ketamine synthesis (to Parke, Davis and Co.). U.S. Patent 3 254 124 (June 12, 1966.)
- (39) Domino, E. F., Chodoff, P., and Corssen, G. (1965) Pharmacological effects of CI-581, a new dissociative anaesthetic, in man. *Clin. Pharmacol. Ther.* 6, 279–291.
- (40) Domino, E. F. (2010) Taming the ketamine tiger. *Anesthesiology* 113, 678–684.
- (41) Tyler, M. W., Yourish, H. B., Ionescu, D. F., and Haggarty, S. J. (2017) Classics in chemical neuroscience: ketamine. *ACS Chem. Neurosci.* 8, 1122–1134.
- (42) Luby, E. D., Cohen, B. D., Rosenbaum, G., Gottlieb, J. S., and Kelley, R. (1959) Study of a new schizophrenomimetic drug – Sernyl. *Arch. Neurol. Psychiatry* 81, 363–369.
- (43) Anis, N., Berry, S., Burton, N., and Lodge, D. (1983) The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-D-aspartate. *Br. J. Pharmacol.* 79, 565–575.
- (44) Lodge, D., and Anis, N. A. (1982) Effects of phencyclidine on excitatory amino acid activation of spinal interneurons in the cat. *Eur. J. Pharmacol.* 77, 203–204.
- (45) Lodge, D., Davies, S. N., Jones, M. G., Millar, J., Manallack, D. T., Ornstein, P. L., Verberne, A. J., Young, N., and Beart, P. M. (1988) A comparison between the *in vivo* and *in vitro* activity of five potent and competitive NMDA antagonists. *Br. J. Pharmacol.* 95, 957–965.
- (46) Lodge, D., and Mercier, M. S. (2015) Ketamine and phencyclidine: the good, the bad and the unexpected. *Br. J. Pharmacol.* 172, 4254–4276.
- (47) Javitt, D. C. (2007) Glutamate and schizophrenia: phencyclidine, N-methyl-D-aspartate receptors, and dopamine-glutamate interactions. *Int. Rev. Neurobiol.* 78, 69–108.
- (48) Moghaddam, B., and Javitt, D. (2012) From revolution to evolution: The glutamate hypothesis of schizophrenia and implications for treatment. *Neuropsychopharmacology* 37, 4–15.
- (49) Mori, A., Noda, Y., Mamiya, T., Miyamoto, Y., Nakajima, A., Furukawa, H., and Nabeshima, T. (2001) Phencyclidine-induced discriminative stimulus is mediated via phencyclidine binding sites on the n-methyl-d-aspartate receptor-ion channel complex, not via signal receptors. *Behav. Brain Res.* 119, 33–40.
- (50) Domino, E. F. (1992) Chemical dissociation of human awareness: Focus on non-competitive NMDA receptor antagonists. *J. Psychopharmacol.* 6, 418–424.
- (51) Javitt, D. C., and Zukin, S. R. (1991) Recent advances in the phencyclidine model of schizophrenia. *Am. J. Psychiatry* 148, 1301–1308.
- (52) Willetts, J., Balster, R. L., and Leander, J. D. (1990) The behavioral pharmacology of NMDA receptor antagonists. *Trends Pharmacol. Sci.* 11, 423–428.
- (53) Weickert, C. S., Fung, S. J., Catts, V. S., Schofield, P. R., Allen, K. M., Moore, L. T., Newell, K. A., Pellen, D., Huang, X. F., Catts, S. V., and Weickert, T. W. (2013) Molecular evidence of N-methyl-D-aspartate receptor hypofunction in schizophrenia. *Mol. Psychiatry* 18, 1185–1192.
- (54) Wang, C., McInnis, J., Ross-Sanchez, M., Shinnick-Gallagher, P., Wiley, J. L., and Johnson, K. M. (2001) Long-term behavioral and neurodegenerative effects of perinatal phencyclidine administration: implications for schizophrenia. *Neuroscience* 107, 535–550.
- (55) Morris, B. J., Cochran, S. M., and Pratt, J. A. (2005) PCP: from pharmacology to modelling schizophrenia. *Curr. Opin. Pharmacol.* 5, 101–106.
- (56) Javitt, D. C. (2012) Twenty-five years of glutamate in schizophrenia: are we there yet? *Schizophr. Bull.* 38, 911–913.
- (57) Domino, E. F., and Luby, E. D. (2012) Phencyclidine/schizophrenia: one view toward the past, the other to the future. *Schizophr. Bull.* 38, 914–919.
- (58) Coyle, J. T. (2012) NMDA receptor and schizophrenia: a brief history. *Schizophr. Bull.* 38, 920–926.
- (59) Jentsch, J. D., and Roth, R. H. (1999) The neuro-psychopharmacology of phencyclidine: from NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology* 20, 201–225.
- (60) Moghaddam, B., and Krystal, J. H. (2012) Capturing the angel in ‘angel dust’: twenty years of translational neuroscience studies of NMDA receptor antagonists in animals and humans. *Schizophr. Bull.* 38, 942–949.
- (61) The Terminator (1984) https://www.imdb.com/title/tt0088247/?ref_=fn_al_tt_1.
- (62) Walk Hard: The Dewey Cox Story (2007) <https://www.imdb.com/title/tt0841046/>.
- (63) <https://www.mirror.co.uk/news/real-life-stories/rapper-killed-girlfriend-chewed-up-11566075>.
- (64) Szalavitz, M. (2013) Myths and facts about angel dust: did PCP drive Aaron Hernandez to commit murder? *Time Magazine*, August 28, 2013.
- (65) <http://healthland.time.com/2013/08/28/myths-and-facts-about-angel-dust-did-pcp-drive-aaron-hernandez-to-commit-murder/>.
- (66) <http://ew.com/article/1996/09/13/pcp-laced-chowder-derails-titanic-filming/>.
- (67) <https://www.mysanantonio.com/news/state/article/PCP-seizure-called-DEA-s-largest-ever-852770.php>.
- (68) <https://www.reuters.com/article/us-pcp-bust-idUSTRE6B155M20101202>.
- (69) <http://articles.latimes.com/2012/feb/17/local/la-me-pcp-bust-20120218>.
- (70) <https://www.dea.gov/divisions/la/2014/la021214.shtml>.
- (71) <https://www.justice.gov/usao-cdca/pr/task-force-investigation-pcp-trafficking-leads-federal-charges-against-producers-and>.
- (72) <https://www.samhsa.gov/data/sites/default/files/DAWN143/DAWN143/sr143-emergency-phencyclidine-2013.pdf>.
- (73) Domino, E. F. (1980) History and pharmacology of PCP and PCP-related analogs. *J. Psychedelic Drugs* 12, 223–227.
- (74) Labianca, D. A. (1981) 1-(1-Phenylcyclohexyl)piperidine hydrochloride: A profile of an abused drug. *J. Chem. Educ.* 58, 664–667.
- (75) Lindsley, C. W. (2017) Call for papers: DARK classics in chemical neuroscience. *ACS Chem. Neurosci.* 8, 1812.
- (76) Wager, T. T., Hou, X., Verhoest, P. R., and Villalobos, A. (2016) Central Nervous System Multiparameter Optimization Desirability: Application in Drug Discovery. *ACS Chem. Neurosci.* 7, 767–775.
- (77) Shulgin, A. T., and MacLean, D. E. (1976) Illicit synthesis of phencyclidine (PCP) and several of its analogs. *Clin. Toxicol.* 9, 553–560.
- (78) Allen, A. C., Robles, J., Dovenski, W., and Calderon, S. (1993) PCP: A review of synthetic methods for forensic clandestine investigation. *Forensic Sci. Int.* 61, 85–100.
- (79) Maddox, V. H., Godefroi, E. F., and Parcell, R. F. (1965) The synthesis of phencyclidine and other 1-arylcyclohexylamines. *J. Med. Chem.* 8, 230–235.
- (80) Zarantonello, P., Bettini, E., Paio, A., Simoncelli, C., Terreni, S., and Cardullo, F. (2011) Novel analogues of ketamine and phencyclidine as NMDA receptor antagonists. *Bioorg. Med. Chem. Lett.* 21, 2059–2063.
- (81) Kalir, A., Edery, H., Pelah, Z., Balderman, D., and Porath, G. (1969) 1- Phenylcycloalkylamine derivatives. II. synthesis and pharmacological activity. *J. Med. Chem.* 12, 473–477.
- (82) Kalir, A., Teomy, S., Amir, A., Fuchs, P., Lee, S. A., Holsztynska, E. J., Rocki, W., and Domino, E. F. (1984) N-allyl analogues of phencyclidine: chemical synthesis and pharmacological properties. *J. Med. Chem.* 27, 1267–1271.
- (83) Geneste, P., Kamenka, J. M., Ung, S. N., Herrmann, P., Goudal, R., and Trouiller, G. (1979) Conformational determination of phencyclidine derivatives in view of structure-activity correlation. *Eur. J. Med. Chem. - Chim. Ther.* 14, 301–308.
- (84) Geneste, P., Herrmann, P., Kamenka, J. M., and Pons, A. (1975) Nouvelle voie d'accès aux isomères des phenyl-1-cyclohexylamines substituées au cyclohexane. *Bull. SOL. Chim. Fr.* 7–8, 1619–1626.

- (85) Thurkauf, A., Hillery, P., Mattson, M. V., Jacobson, A. E., and Rice, K. C. (1988) Synthesis, pharmacological action, and receptor binding affinity of the enantiomeric 1-(1-phenyl-3-methylcyclohexyl)-piperidines. *J. Med. Chem.* 31, 1625–1628.
- (86) Laurenzana, E. M., and Owens, S. M. (1997) Metabolism of phencyclidine by human liver microsomes. *Drug Metab. Dispos.* 25, 557–563.
- (87) Jushchyshyn, M. I., Wahlstrom, J. L., Hollenberg, P. F., and Wienkers, L. C. (2006) Mechanism inactivation of human cytochrome P450 2B6 by phencyclidine. *Drug Metab. Dispos.* 34, 1523–1529.
- (88) Shebley, M., Jushchyshyn, M. I., and Hollenberg, P. F. (2006) Selective pathways for the metabolism of phencyclidine by cytochrome P450 2B enzymes: identification of electrophilic metabolites, glutathione and N-acetyl cysteine adducts. *Drug Metab. Dispos.* 34, 375–383.
- (89) Shebley, M., and Hollenberg, P. F. (2007) Mutation of a single residue (K262R) in P450 2B6 leads to a loss of mechanism-based inactivation by phencyclidine. *Drug Metab. & Dispersion* 35, 1365–1371.
- (90) Goodman, C. B., Thomas, D. N., Pert, A., Emilien, B., Cadet, J. L., Carroll, F. I., Blough, B. E., Mascarella, S. W., Rogawski, M. A., Subramaniam, S., et al. (1994) RTI-4793–14, a new ligand with high affinity and selectivity for the (+)-MK801-insensitive [³H]1-(2-thienyl)cyclohexylpiperidine binding site (PCP site 2) of guinea pig brain. *Synapse* 16, 59–65.
- (91) Rothman, R. B. (1994) PCP site 2: a high affinity MK-801-insensitive phencyclidine binding site. *Neurotoxicol. Teratol.* 16, 343–53.
- (92) Rothman, R. B., Reid, A. A., Monn, J. A., Jacobson, A. E., and Rice, K. C. (1989) The psychotomimetic drug phencyclidine labels two high affinity binding sites in guinea pig brain: Evidence for n-methyl-D-aspartate coupled and dopamine reuptake carrier-associated phencyclidine binding sites. *Mol. Pharmacol.* 36, 887–896.
- (93) Roth, B. L., Gibbons, S., Arunotayanun, W., Huang, X.-P., Setola, V., Treble, R., and Iversen, L. (2013) The ketamine analog methoxetamine and 3- and 4-methoxy analogues of phencyclidine are high affinity and selective ligands for the glutamate NMDA receptor. *PLoS One* 8, e59334.
- (94) Alam, S., Lingenfelter, K. S., Bender, A. M., and Lindsley, C. W. (2017) Classics in Chemical Neuroscience: Memantine. *ACS Chem. Neurosci.* 8, 1823–1829.
- (95) Vyklícký, Y., Korinek, M., Smeejkálová, T., Balik, A., Krausová, B., Kaniakova, M., Lichnerová, K., Cerný, J., Krusek, J., Dittert, I., Horak, M., and Vyklícký, L. (2014) Structure, function and pharmacology of NMDA receptor channels. *Physiol. Res.* 63, S191–203.
- (96) Zhou, Q., and Sheng, M. (2013) NMDA receptors in nervous system diseases. *Neuropharmacology* 74, 69–75.
- (97) Paoletti, P., Bellone, C., and Zhou, Q. (2013) NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. *Nat. Rev. Neurosci.* 14, 383–400.
- (98) Gozzi, A., Large, C. H., Schwarz, S., Bertani, S., Crestan, V., and Bifone, A. (2008) Differential effects of antipsychotic and glutamatergic agents on the pHMRI response to phencyclidine. *Neuropsychopharmacology* 33, 1690–1703.
- (99) Sebban, C., Tesolin-Decros, B., Ciprian-Ollivier, J., Perret, L., and Spedding, M. (2002) Effects of phencyclidine (PCP) and MK801 on the EEGq in the prefrontal cortex of conscious rats; antagonism by clozapine and antagonists of AMPA-, σ 1- and HT_{2a} receptors. *Br. J. Pharmacol.* 135, 65–78.
- (100) Rainey, J. M., Jr, and Crowder, M. K. (1975) Prolonged psychosis attributed to phencyclidine: Report of three cases. *Am. J. Psychiatry* 132, 1076–1078.
- (101) Allen, R. M., and Young, S. J. (1978) Phencyclidine-induced psychosis. *Am. J. Psychiatry* 135, 1081–1084.
- (102) Hertzman, M., Reba, R. C., and Kotlyarove, E. V. (1990) Single photon emission computerized tomography in phencyclidine and related drug abuse. *Am. J. Psychiatry* 147, 255–256.
- (103) Krystal, J. H., Karper, L. P., Seibyl, J. P., Freeman, G. K., Delaney, R., Bremner, J. D., Heninger, G. R., Bowers, M. B., Jr, and Charney, D. S. (1994) Subanesthetic effects on noncompetitive NMDA receptor antagonists, ketamine in humans: Psychotomimetic, perceptual, cognitive and neuroendocrine responses. *Arch. Gen. Psychiatry* 51, 199–214.
- (104) Cosgrove, J., and Newell, T. G. (1991) Recovery of neuropsychological functions during reduction in use of phencyclidine. *J. Clin. Psychol.* 47, 159–169.
- (105) Breier, A., M. Malhorta, A. K., Pinals, D. A., Weisenfeld, N. I., and Pickar, D. (1997) Association of ketamine-induced psychosis with focal activation of the prefrontal cortex in healthy volunteers. *Am. J. Psychiatry* 154, 805–811.
- (106) Verma, A., and Moghaddam, B. (1996) The role of excitatory amino acids in prefrontal cortical function as assessed by spatial delayed alternation performance in rats: Modulation by dopamine. *J. Neurosci.* 16, 373–379.
- (107) Jentsch, J. D., Elsworth, J. D., Redmond, D. E., Jr, and Roth, R. H. (1997) Phencyclidine increases forebrain monoamine metabolism in rats and monkeys: Modulation by the isomers of HA966. *J. Neurosci.* 17, 1769–1775.
- (108) Heale, V., and Harley, C. (1990) MK-801 and AP-5 impair acquisition, but not retention, of the Morris milk maze. *Pharmacol., Biochem. Behav.* 36, 145–149.
- (109) Jones, K. W., Bauerle, L. M., and DeNoble, J. V. (1990) Differential effects of sigma and phencyclidine receptor ligands on learning. *Eur. J. Pharmacol.* 179, 97–102.
- (110) Kesner, R. P., and Dakis, M. (1993) Phencyclidine disrupts acquisition and retention performance within a spatial continuous recognition memory task. *Pharmacol., Biochem. Behav.* 44, 419–424.
- (111) Murray, T. K., and Ridley, R. M. (1997) The effect of dizocilpine (MK-801) on conditional discrimination learning in the rat. *Behav. Pharmacol.* 8, 383–388.
- (112) Fraser, C. M., Fisher, A., Cooke, M. J., Thompson, I. D., and Stone, T. W. (1997) Purine modulation of dizocilpine effects spontaneous alternation. *Psychopharmacology* 130, 334–342.
- (113) Geyer, M. A., Segal, D. S., and Greenberg, B. D. (1984) Increased startle responding in rats treated with phencyclidine. *Neurobehav. Toxicol. Teratol.* 6, 161–164.
- (114) Tricklebank, M. D., Singh, L., Oles, R. H., Preston, C., and Iversen, S. D. (1989) The behavioral effects of MK-801: A comparison with antagonists acting noncompetitively and competitively at the NMDA receptor. *Eur. J. Pharmacol.* 167, 127–135.
- (115) Jentsch, J. D., Tran, A., Taylor, J. R., and Roth, R. H. (1998) Prefrontal cortical involvement in the phencyclidine-induced activation of the mesolimbic dopamine system: Behavioral and neurochemical evidence. *Psychopharmacology* 138, 89–95.
- (116) Jentsch, J. D., Redmond, D. E., Jr, Elsworth, J. D., Taylor, J. R., Youngren, K. D., and Roth, R. H. (1997) Enduring cognitive deficits and cortical dopamine dysfunction in monkeys after long-term administration of phencyclidine. *Science* 277, 953–955.
- (117) Schlemmer, R. F., and Davis, J. M. (1983) A comparison of three psychotomimetic-induced models of psychosis in nonhuman primate social colonies. *Prog. Clin. Biol. Res.* 273, 273–279.
- (118) Shi, W. X., and Zhang, X. X. (2003) Dendritic glutamate-induced bursting in the prefrontal cortex: further characterization and effects of phencyclidine. *J. Pharmacol. Exp. Ther.* 305, 680–687.
- (119) McQuinn, R. L., Cone, E. J., Shannon, H. E., and Su, T. P. (1981) Structure-activity relationships of the cycloalkyl ring of phencyclidine. *J. Med. Chem.* 24, 1429–1432.
- (120) Chaudieu, I., Vignon, J., Chicheportiche, M., Kamenka, J.-M., Trouiller, G., and Chicheportiche, R. (1989) Role of the aromatic group in the inhibition of phencyclidine binding and dopamine uptake by PCP analogs. *Pharmacol., Biochem. Behav.* 32, 699–705.
- (121) McQuinn, R. L., Cone, E. J., Shannon, H. E., and Su, T.-P. (1981) Structure-activity relationships of the cycloalkyl ring of phencyclidine. *J. Med. Chem.* 24, 1429–1432.

- (122) Moriarty, R. M., Enache, L. A., Zhao, L., Gilardi, R., Mattson, M. V., and Prakash, O. (1998) Rigid phencyclidine analogues. Binding to the phencyclidine and σ_1 receptors. *J. Med. Chem.* 41, 468–477.
- (123) Kroemer, R. T., Koutsilieri, E., Hecht, P., Liedl, K. R., Riederer, P., and Kornhuber, J. (1998) Quantitative analysis of the structural requirements for the blockade of the N-methyl-D-aspartate receptor at the phencyclidine binding site. *J. Med. Chem.* 41, 393–400.
- (124) Cook, C. E., Brine, D. R., Jeffcoat, A. R., Hill, J. M., Wall, M. E., Perez-Reyes, M., and Di Guiseppi, S. R. (1982) Phencyclidine disposition after intravenous and oral doses. *Clin. Pharmacol. Ther.* 31, 625–634.
- (125) McMahon, B., Ambre, J., and Ellis, J. (1978) Hypertension during recovery from phencyclidine intoxication. *Clin. Toxicol.* 12, 37–40.
- (126) Bey, T., and Patel, A. (2007) Phencyclidine intoxication and adverse effects: A clinical and pharmacological review of an illicit drug. *Cal. J. Emerg. Med.* 8, 9–14.
- (127) Olney, J. W., Labruyere, J., and Price, M. T. (1989) Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. *Science* 244, 1360–1362.
- (128) Spiewoy, C., and Markou, A. (2003) Withdrawal from chronic phencyclidine treatment induces long-lasting depression in brain reward function. *Neuropsychopharmacology* 28, 1106–1116.
- (129) Lachenmeier, D. W., and Rehm, J. (2015) Comparative risk assessment of alcohol, tobacco, cannabis and other illicit drugs using the margin of exposure approach. *Sci. Rep.* 5, 8126.
- (130) Landauer, M. R., and Balster, R. L. (1982) The effects of aggregation on the lethality of phencyclidine in mice. *Toxicol. Lett.* 12, 171–176.
- (131) Ramsey, A. J. (2009) NR1 knockdown mice as a representative model of the glutamate hypothesis of schizophrenia. *Prog. Brain Res.* 179, 51–58.
- (132) Bridges, T. M., LeBois, E. P., Hopkins, C. R., Wood, M. R., Jones, J. K., Conn, P. J., and Lindsley, C. W. (2010) Antipsychotic potential of muscarinic allosteric modulation. *Drug News Perspect.* 23, 229–240.
- (133) Menniti, F. S., Lindsley, C. W., Conn, P. J., Pandit, J., Zagouras, P., and Volkmann, R. A. (2013) Allosteric modulation for the treatment of schizophrenia: Targeting glutamatergic networks. *Curr. Top. Med. Chem.* 13, 26–54.
- (134) Lindsley, C. W., Shipe, W. D., Wolkenberg, S. E., Theberge, C. R., Williams, D. L., Jr., Sur, C., and Kinney, G. G. (2006) Progress towards validating the NMDA receptor hypofunction hypothesis of schizophrenia. *Curr. Top. Med. Chem.* 8, 771–785.
- (135) Grannan, M. D., Mielnik, C. A., Moran, S. P., Gould, R. W., Ball, J., Bubser, M., Ramsey, A. J., Abe, M., Cho, H. P., Nance, K. D., Blobaum, A. L., Niswender, C. M., Conn, P. J., Lindsley, C. W., and Jones, C. K. (2016) Prefrontal cortex-mediated impairments in a genetic model of NMDA receptor hypofunction are reversed by the novel M_1 PAM VU6004256. *ACS Chem. Neurosci.* 7, 1706–1716.
- (136) Bubser, M., Bridges, T. M., Thorbeck, D. D., Gould, R. W., Grannan, M., Noetzel, M. J., Niswender, C. M., Daniels, J. S., Melancon, B. J., Tarr, J. C., Wess, J., Duggan, M. E., Brandon, N. J., Dunlop, J., Wood, M. W., Wood, M. R., Lindsley, C. W., Conn, P. J., and Jones, C. K. (2014) Selective activation of M_4 muscarinic acetylcholine receptors reverses MK-801-induced behavioral impairments and enhances associative learning in rodents. *ACS Chem. Neurosci.* 5, 920–942.
- (137) Ghoshal, A., Rook, J., Dickerson, J., Roop, G., Morrison, R., Jalan-Sakrikar, N., Lamsal, A., Noetzel, M., Poslunsey, M., Stauffer, S. R., Xiang, Z., Daniels, J. S., Niswender, C. M., Jones, C. K., Lindsley, C. W., and Conn, P. J. (2016) Selective potentiation of M_1 muscarinic receptors reverses deficits in plasticity and negative and cognitive symptoms in repeated phencyclidine treated mouse model of schizophrenia. *Neuropsychopharmacology* 41, 598–610.
- (138) Cadinu, D., Grayson, B., Podda, G., Harte, M. K., Doostdar, N., and Neill, J. C. (2017) NMDA receptor antagonist rodent models for cognition in schizophrenia and identification of novel drug treatments, an update. *Neuropharmacology*, DOI: 10.1016/j.neuropharm.2017.11.045.
- (139) Muir, K. W. (2006) Glutamate-based therapeutic approaches: clinical trials with NMDA antagonists. *Curr. Opin. Pharmacol.* 6, 53–60.
- (140) Monaghan, D. T., Irvine, M. W., Costa, B. M., Fang, G., and Jane, D. E. (2012) Pharmacological modulation of NMDA receptor activity and the advent of negative and positive allosteric modulators. *Neurochem. Int.* 61, 581–592.
- (141) Berman, R. M., Cappiello, A., Anand, A., Oren, D. A., Heninger, G. R., Charney, D. S., and Krystal, J. H. (2000) Antidepressant effects of ketamine in depressed patients. *Biol. Psychiatry* 47, 351–354.
- (142) Zarate, C. A., Jr., Singh, J. B., Carlson, P. J., Brutsche, N. E., Ameli, R., Luckenbaugh, D. A., Charney, D. S., and Manji, H. K. (2006) A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch. Gen. Psychiatry* 63, 856–864.
- (143) Hillhouse, T. D., Porter, J. H., and Negus, S. S. (2014) Comparison of antidepressant-like and abuse-related effects of phencyclidine in rats. *Drug Dev. Res.* 75, 479–488.
- (144) Wohleb, E. S., Gerhard, D., Thomas, A., and Duman, R. S. (2016) Molecular and cellular mechanisms of rapid-acting antidepressants ketamine and scopolamine. *Curr. Neuropharmacol.* 15, 11–20.
- (145) Jenkins, P. (1999) *Synthetic Panics: The Symbolic Politics of Designer Drugs*, New York University Press, New York.