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Designer drugs: a medicinal chemistry perspective

F. Ivy Carroll, Anita H. Lewin, S. Wayne Mascarella, Herbert H. Seltzman, and P. Anantha Reddy

Center for Organic and Medicinal Chemistry, Research Triangle Institute, Research Triangle Park, North Carolina

Address for correspondence: F. Ivy Carroll, Ph.D., Center for Organic and Medicinal Chemistry, Research Triangle Institute, P.O. Box 12194, Research Triangle Park, NC 27709-2194. fic@rti.org

There are numerous medicinal chemistry reports in the literature describing the pharmacological properties of thousands of narcotics, stimulants, hallucinogens, sedative-hypnotic drugs, cannabinoids, and other psychoactive substances as well as synthetic methods for their preparations. This information, while essential for the advancement of science, has been used by clandestine chemists to manufacture and market an endless variety of analogs of so-called designer drugs. In this review, we describe how clandestine chemists used the principles of medicinal chemistry to design molecules, referred to as designer drugs, that elicit the effects of opioids, amphetamine and analogs, cannabinoids, and phencyclidine analogs while circumventing the law.

Keywords: controlled substances; designer drugs; medicinal chemistry; opioids; analgesics; amphetamines; cannabinoids; PCP; stimulants; hallucinogens

Introduction

The manufacture, trafficking, and abuse of clandestinely produced drugs are worldwide problems. In the early years up to the 1960s, the major drugs of abuse were heroin, cocaine, LSD, and amphetamine. Beginning in the late 1970s and early 1980s, clandestine laboratories synthesized substances referred to as designer drugs that produced pharmacologic effects similar to those of controlled substances but were sufficiently different in structure to evade the provisions of national control policies. This problem was addressed, to some extent, in the late 1980s and 1990s by the one-year emergency scheduling authority over chemicals given to the Drug Enforcement Administration (DEA). The Designer Drug Enforcement Act of 1986 defined a designer drug as "a substance other than a controlled substance that has a chemical structure substantially similar to that of a controlled substance in schedule I or II or that was specifically designed to produce an effect substantially similar to that of a controlled substance in schedule I or II." Nevertheless, the manufacture, trafficking, and marketing of clandestinely produced designer drugs through the Internet has increased dramatically in recent years and all continue to be a serious threat to public health and safety.[1–4]

Throughout the drug discovery process, pharmaceutical companies, academic institutions, research institutions, and other organizations publish their studies in scientific journals, books, and patents. This information exchange, which is essential to the legitimate scientific enterprise, can be, and is, used by clandestine chemists who duplicate the technical sophistication used by the research community to manufacture and market a seemingly endless variety of analogs of so-called designer drugs. In this review, we will briefly describe the medicinal chemistry associated with compounds in the opioid, amphetamines, cannabinoid, and phencylidine classes and its possible role in the development of the various designer drugs.

Opioids

Analgesics are compounds that give relief from pain. Narcotic pain medications that have the potential to become addictive are one part of a class of drugs called opioids. Morphine (A1, Fig. 1) is the prototypic opioid analgesic that serves as the standard drug to which all analgesics are compared in

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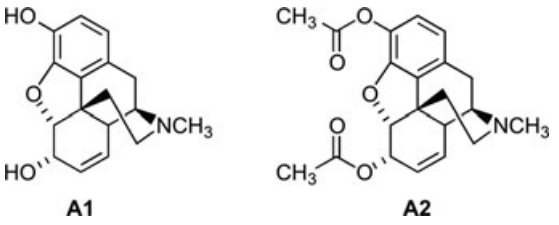


Figure 1. Structures of morphine and heroin.

determining their relative analgesic potency. Thousands of analogs have been synthesized and evaluated with the goal of developing a more potent analgesic devoid of morphine's side effects, such as its euphorigenic and reinforcing properties, which result in addiction. For details see McCurdy and Prisinzano,[5] Foley,[6] and Casy and Parfitt.[7] One early analog developed was 3,6-diacetylmorphine (A2, diamorphine, heroin; Fig. 1). While this compound did not prove to be a better analgesic with fewer side effects, it did become and continues to be the major opioid compound of abuse. However, at times, when heroin could not be produced in sufficient amounts at an acceptable cost in clandestine laboratories, alternative opioids, referred to as "designer drugs," were used to replace heroin. Due to the ease of synthesis and availability of starting materials, the piperidine class of opioids was the dominant "designer drug" developed. Another major factor was that structure–activity relationship (SAR) studies during the 1970s had identified very potent analgesics in the piperidine-based classes.[5,7–10]

This part of the review presents an overview of the piperidine class of opioids including SAR studies that may have led to major opioid "designer drugs." Thousands of synthetic piperidine derivatives have been designed, synthesized, and evaluated in animal pain models.[5,7–10] Several of these compounds have been evaluated in humans, and a few are used clinically. Similar to morphine and heroin, these compounds have rewarding properties in addition to their analgesic activity and, thus, are subject to abuse.

For practical purposes, the piperidines are presented as four classes of analgesics related to the parent drug (Fig. 2): meperidine (A3) (also known as pethidine and Demerol), ketobemidone (A4), picenadol (A5), and fentanyl (A6). Structurally, the meperidine, ketobemidone, and picenadol classes are 4-arylpiperidines having a carbalkoxy, 4-keto, and 4-alkyl substituent, respectively. In contrast, the fentanyl family, which is the most potent of the four classes, has a 4-anilinopiperidine structure. Because the parent drug as well as its analogs are relatively easy to synthesize, all have some degree of abuse potential. For example, changing the *N*-methyl group in meperidine to *N*-substituted normeperidine analogs, such as the *N*-phenylethyl analog (A7, Fig. 3), results in more potent compounds, which have appeared on the streets. However, the most prominent designer drugs resulted from changes in the acyloxy group.

The replacement of the 4-carboethoxy group of meperidine by the 4-propionyloxy ($OCOC_2H_5$) group gives *N*-methyl-4-phenyl-4-propionoxypiperidine (A8, MPPP, Fig. 3), the so-called reversed ester of meperidine. The structure–activity correlations for A8 parallel those of meperidine (A3). However, the reverse ester analogs generally show about a 20-fold increase in analgesic potency relative to the meperidine analogs.[7] Similar to meperidine, replacement of the *N*-methyl by selected *N*-substituents increases analgesic activity and provides the most active compounds in this class. Maximum activity is found with the *N*-(3-phenyl-3-propanol) analog (A9, phenoperidine, Fig. 3), which is more active than meperidine and morphine.[11]

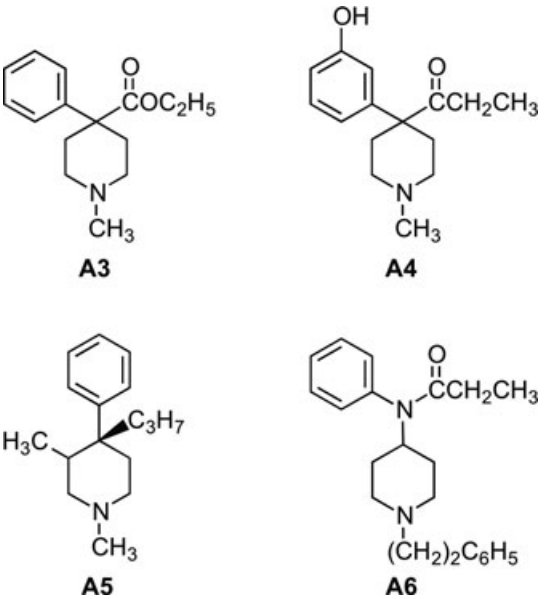


Figure 2. Substituted piperidine analgesics.

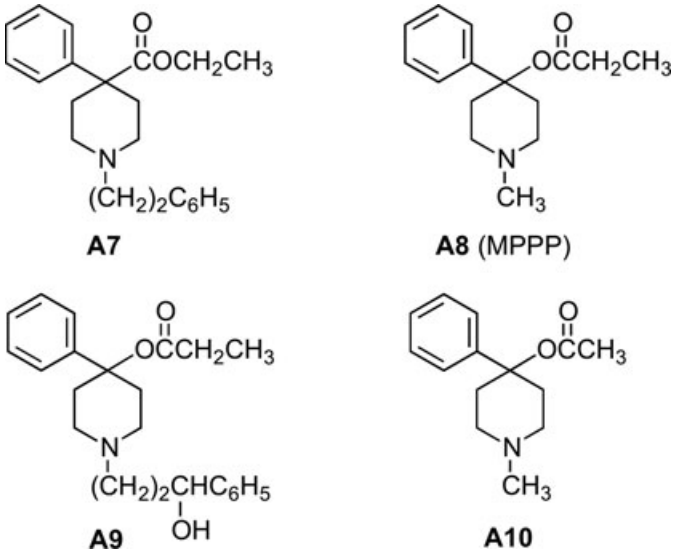


Figure 3. Structure of meperidine analogs.

With this structure–activity information readily available in the literature, along with well-described synthetic procedures that showed that compounds of the reverse ester class were much easier to synthesize than the merperidine type, it was not surprising that A8 as well as *N*-methyl-4-acetyloxypiperidine (A10, Fig. 3) showed up as "designer drugs."[12] Unfortunately, many of those who used A8 developed an irreversible Parkinsonian-like syndrome due to the presence of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (A11, MPTP, Fig. 4) as an impurity. It was later found that, in the body, MPTP was converted to a neurotoxin MPP^+ (A12, Fig. 4) that destroys dopamine neurons, which are the same neurons lost due to aging and possibly to other factors in Parkinson's disease.[13,14]

Even though ketobemidone is reported to be commonly abused in Europe, to our knowledge no ketobemidone analogs have been associated with major abuse problems in the United States. The *N*-cinnamyl analog of ketobemidone (A13, Fig. 5) is reported to be more than 250 times as potent as ketobemidone in mice.[15,16] An Internet site called OPIOPHILE[17] refers to finding this information in an article, apparently Ref. 16, implying that this information was used to select and synthesize this analog.

To our knowledge, picenadol is the only 4-alkylpiperidine agonist that has received clinical evaluation. Due most likely to its partial agonist activity, it has not been subject to abuse, and thus, to our knowledge no designer drugs have been developed from this class of analgesics.

Of the four classes of piperidine analgesics, the fentanyl class has provided the most potent compounds. An enormous number of fentanyl analogs have been prepared, many of which are substantially more potent than morphine. The fact that fentanyl (A6) and two of its analogs, alfentanil (A14) and sufentanil (A15), were well-known opioid drugs on the market commonly administered intravenously (IV) made this class of opioids attractive to clandestine laboratories (Fig. 6). It seems highly likely that a SAR study reported from Janssen Pharmaceutica[7,18] was used by the clandestine

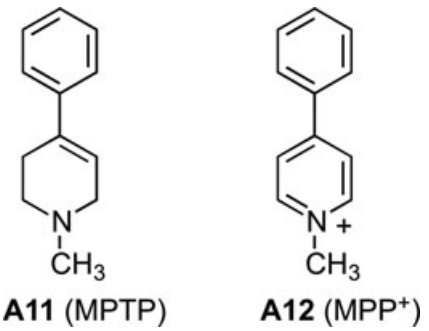
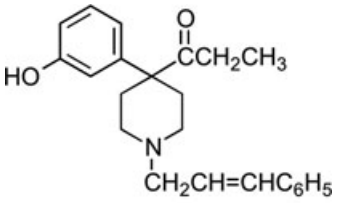


Figure 4. Structures of MPTP (A11) and MPP^+ (A12).



A13

Figure 5. Structure of a ketobemidone analog.

chemist in choosing *N*-[(2-methyl-2-phenylethyl)-4-piperidyl]-*N*-phenylpropanamide (A16, α-methylfentanyl), referred to as "China white," and *N*-[3-methyl-1-(2-phenylethyl)-4-piperidyl]-*N*-phenylpropanamide (A17, 3-methylfentanyl) as designer drugs. Compound (±)-A16, which differed from fentanyl (A6) by having an extra methyl group on the *N*-(2-phenylethyl) substituent, was reported to have about the same potency as fentanyl (A6) in the rat tail withdrawal test.[18] The (±)-*cis*- and (+)-*cis*-isomers of A17, which have a methyl group on the piperidine 3-position, were reported to be 6- and 19-times more potent than fentanyl (A6) in the rat tail withdrawal test.[18] In a comparison study, (+)-*cis*-A17 was reported to be up to 6684 times more potent than morphine. The study concluded that A17 also had a fast onset of action, a shorter duration of action than morphine, and an unusually high safety margin. Based on this study, it is not surprising that clandestine laboratories chose A16 and A17 as their designer drugs to be used in place of heroin. The unusually high potency of A17 relative to fentanyl (A6) may have contributed to the first opioid designer drug sold as China white being reported as containing A17.[19]

Even though A16 was chemically and pharmacologically almost identical to fentanyl (A6), it was not on any schedule of the U.S. Controlled Substances Act (CSA) and, therefore, not a controlled substance. It was not surprising that A16 (China white) was followed by the appearance of the highly potent A17 as the next opioid designer drug. Although A17 disappeared almost as quickly as it appeared, new fentanyl analogs continue to appear on the streets.[20–22]

In addition to fentanyl (A6), α-methylfentanyl (A16), 3-methylfentanyl (A17), and other common fentanyl drugs such as alfentanil (A14) and sufentanil (A15), a number of fentanyl analogs were detected analytically in overdose victims or in street samples confiscated from drug busts (Fig. 6).[21,22] Similar to α-methylfentanyl (A16) and 3-methylfentanyl (A17), clandestine chemists could find published reports of the potent analgesic activity of β-hydroxyfentanyl and β-hydroxy-3-methylfentanyl (A18 and A19, respectively).[23,24] Literature searches using PubChem, Reaxys, and SciFinder indicated that some, but not all, of the other fentanyl analogs had been reported. Thus structures A20–A29 appear to be fentanyl analogs designed by combining published information with typical medicinal chemistry principles. Since a thiophene ring is a well-known bioisostere of a phenyl ring,[25] it is not surprising that the clandestine chemist(s) synthesized A20–A24, where a thiophene ring had replaced the phenyl ring in fentanyl (A6), α-methylfentanyl (A16), 3-methylfentanyl (A17), β-hydroxyfentanyl (A18), and β-hydroxy-3-methylfentanyl (A19), respectively. Compound A25 is an analog of A21, which has an extra 3-methyl group. Based on the data reported for A16 and A17, one might predict that A25 would be a more potent analgesic. Compound A26 is a bioisostere of fentanyl (A6), where the amide carbonyl oxygen has been replaced by a sulfur atom,[25] and compound A27 is a fentanyl (A6) analog where a fluoro group has replaced the para-hydrogen of the *N*-phenyl group of fentanyl. Compounds A28 and A29 are analogs of A16 where the *N*-propionyl group has been replaced by an acetyl and an acryl group, respectively. Based on general medicinal chemistry principles, one might expect that compounds A26 and A27 would have analgesic activity similar to that of fentanyl (A6) and that compounds A28 and A29 would have activity similar to that of α-methylfentanyl (A16). While expected analgesic and rewarding activity played an important role in the design of the compounds, the ease of synthesis and availablity of starting materials undoubtedly were important factors in the selection of compounds.

Even though opioid designer drugs are not presently a major problem, it is safe to predict that if the heroin supply again becomes less available to clandestine chemists, opioid designer drugs will be back as drugs of abuse. Based on information presently available, it seems likely they will appear as fentanyl analogs.

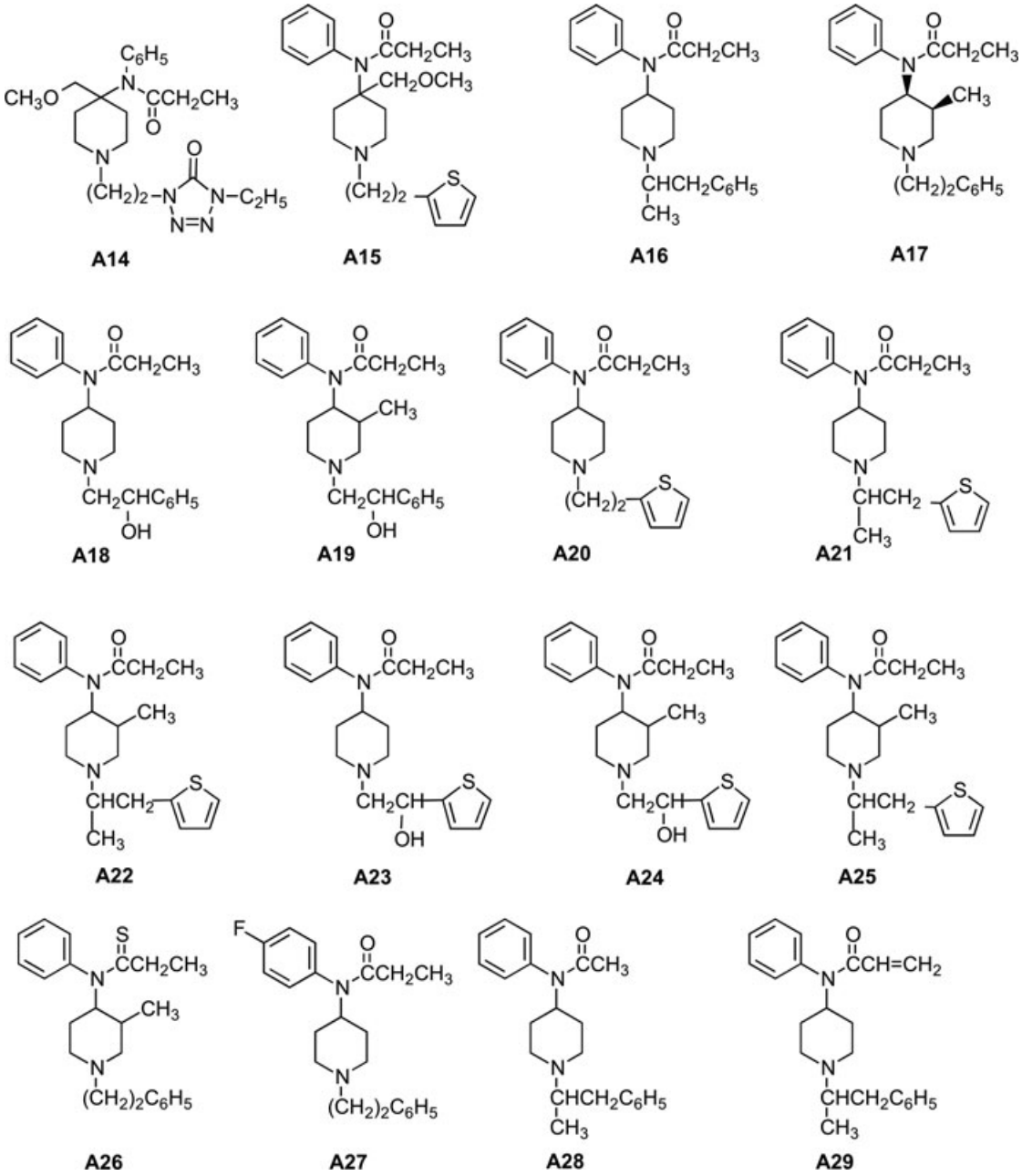


Figure 6. Structures of fentanyl analogs.

Amphetamines and their analogs

Amphetamine analogs (see Table 1) have been described as being the most popular and extensively studied designer drugs.[26] An example would be the street drug "ecstasy" (MDMA, B1),[27] the structure of which contains the β-phenethylamine (β-PEA, B2) backbone. The latter, a metabolite of phenylalanine, is present in the mammalian brain and is known to produce multiple neurobehavioral actions including hyperactivity,[28,29] induced place preference conditioning,[30] conditioned taste aversion,[31] and to possess rewarding and reinforcing properties.[31] MDMA could thus be considered a

Table 1. Compound numbers, structures, and names

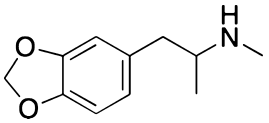
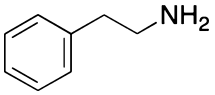
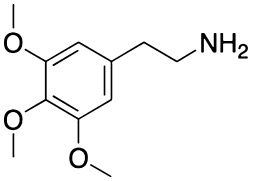
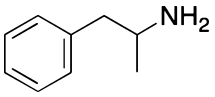
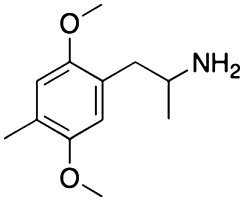
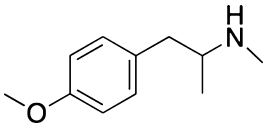
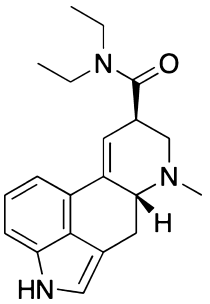
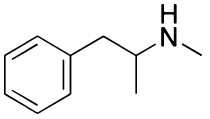
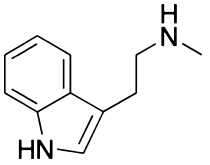
Number	Structure	Name		
		Common	Abbreviated	Street
B1		3,4-Methylenedioxy-methamphetamine	MDMA	Ecstasy, XTC, adam, empathy, E, X
B2		β-Phenethylamine	β-PEA	
B3		Mescaline		
B4		Amphetamine		
B5		2,5-Dimethoxy-4-methylamphetamine	DOM	STP
B6		p-Methoxy-methamphetamine	PMMA	
B7		Lysergic acid diethylamide	LSD	Acid
B8		Methamphetamine	METH	Ice
B9		Methyltryptamine		

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Table 1. *Continued*

Number	Structure	Name		
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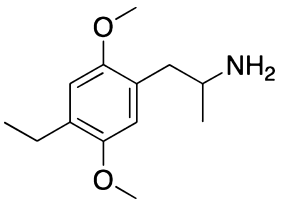
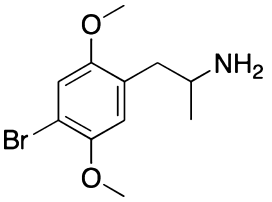
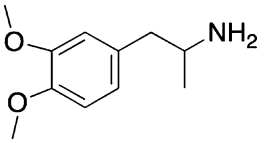
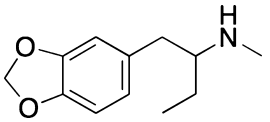
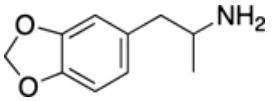
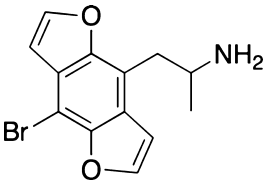
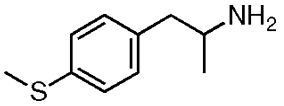
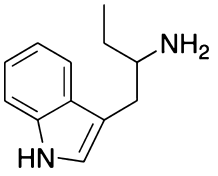
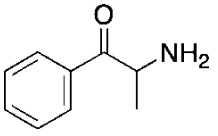
B10		2,5-Dimethoxy-4-ethylamphetamine	DOEt	
B11		4-Bromo-2,5-dimethoxy-amphetamine	DOB	
B12		3,4-Dimethoxy-amphetamine	3,4-DMA	
B13		Methylbenzo-dioxolylbutanamine	MBDB	
B14		3,4-Methylenedioxy-amphetamine	MDA	Love drug
B15		Bromobenzodifuranyl isopropylamine	Bromo-DragonFLY	
B16		4-Methylthioamphetamine		MTA
B17		α-Ethyltryptamine	etryptamine	α-ET, Love pearls
B18		Cathinone		Khat

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Table 1. *Continued*

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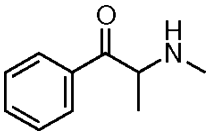
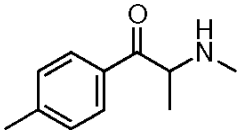
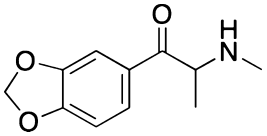
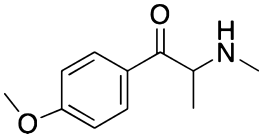
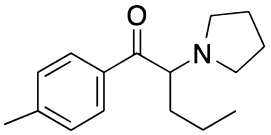
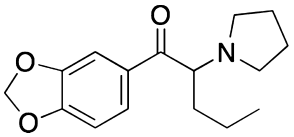
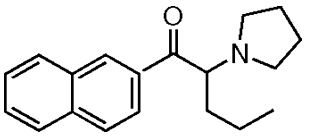
B19		Methcathinone, Ephedrone		
B20		Mephedrone		
B21		Methylone	Arlone	
B22		p-Methoxymethcathinone	PMMC	
B23		Pyrovalerone	Methedrone	
B24		Methylenedioxypyrovalerone	MDVP	
B25		Naphyrone		

"designed" analog. In fact, the effects of structural modifications of β-PEA were extensively explored by Alexander Shulgin[32,33] well before the term "designer drugs" was coined. Starting with the 3,4,5-trimethoxy analog of β-PEA (mescaline, B3), a natural product found in peyote that has been used for 3,000 years by Native Americans, Shulgin systematically modified the number and positions of the methoxy substituents. He eventually introduced additional substituents and modified the ethylene chain to produce a large number of analogs, many of which produce neurobehavioral actions. Systematic animal studies tended not to utilize ring-substituted β-PEA analogs because of their rapid turnover due to oxidative deamination.[34] However, the analogous phenylisopropylamines (e.g., amphetamine, B4) have been studied extensively. Animal studies to determine the effects of these agents soon revealed modification of the substitution pattern on the aromatic ring to have profound effects on potency and to lead to distinct effects. Specifically it was recognized that some phenylisopropylamines were hallucinogens, producing LSD-like effects, while others were stimulants like amphetamine. Additional studies led to the definition of three distinct effects (Fig. 7)—central stimulant action (S),

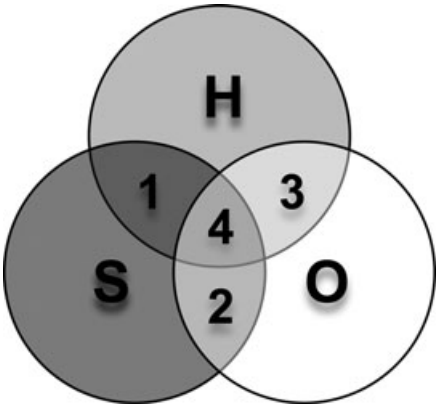


Figure 7. **Venn diagram, classifying drugs as central stimulants (S), hallucinogens (H), or other (O).**

hallucinogenesis (H), and "other psychoactive action" (O)[35]—and to the recognition that phenylisopropylamines with abuse potential could produce one or more of these effects (Fig. 7). The prototypical compounds for the three classes were the central stimulant (+)-amphetamine ((*S*)-B4), the LSD-like agent 2,5-dimethoxy-4-methylamphetamine (DOM, B5), and, p-methoxymethamphetamine (PMMA, B6),[36] which apparently elicits MDMA-like responses in humans.[37]

Early work by Shulgin also revealed different effects of the optical antipodes of each phenylisopropylamine.[38] For the LSD-like phenylisopropylamines, the activity was found to reside in the (*R*)-enantiomer, leading to the widely accepted pharmacophoric hypothesis in which the aryl ring of phenylisopropylamines is superimposed on ring A in LSD (B7, Fig. 8), the amino functionality overlays N(6) in LSD,[39] and the asymmetric center of the phenylisopropylamine is homochiral with C(5) in LSD (as shown for methamphetamine (B8). Of course, the pharmacophoric elements of *N*-methyltryptamine (B9, Fig. 9) are also present in LSD and, indeed, tryptamines may be viewed as β-PEA (B2, Table 1) analogs; they are widely abused.

Generalization studies in rodents have led to classification of commonly abused drugs into three overlapping groups as illustrated in Figure 7. Thus, amphetamine (B4) and methamphetamine (B8) generalize only to (+)-amphetamine ((*S*)-B4) (group S); DOM (B5), DOEt (B10), and DOB (B11) generalize to racemic DOM (B5) (group H) and not to (+)-amphetamine ((*S*)-B4)[40] or PMMA (B6);[35] drugs like 3,4-DMA (B12) and MBDB (B13)[41] generalize only to PMMA (B6) (group O); racemic MDA (B14) generalizes to all three categories (group 4);[36] and racemic MDMA (B1) generalizes to (+)-amphetamine ((*S*)-B4) and to PMMA (B6) (group 2), but not to DOM (B5).[35] Academic studies to determine the optimal conformation to elicit LSD-like effects identified constrained analogs of the compounds in class H with potencies in rodents exceeding that of LSD (B7).[42] Shockingly, these strictly synthetic products that were used as probes in academic research were found to be abused as early as 2008.[43] Recreational drug use of the DOB (B11) analog Bromo-DragonFLY (B15) has been reported to result in seizures[44] as well as fatal poisonings.[45,46] Similarly, 4-methylthioamphetamine (MTA, B16), identified in academic research as an analog recognized by MDMA-trained rats in drug discrimination studies,[47] rapidly appeared on the streets as an MDMA (B1) substitute. This compound disappeared from the clandestine market as soon as

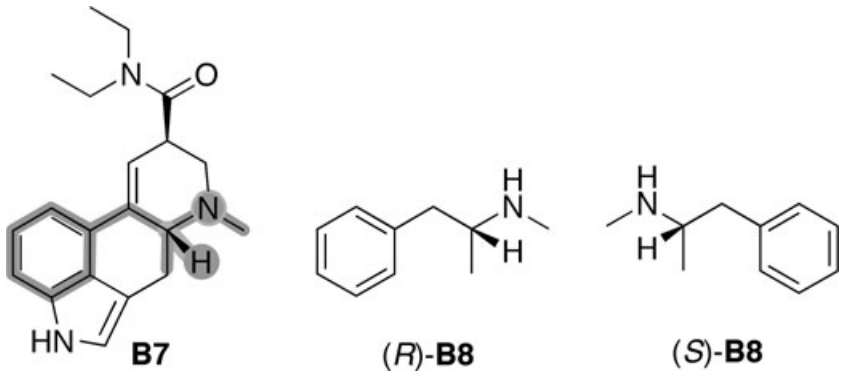


Figure 8. **Chirality of methamphetamine and the pharmacophoric relationship to LSD.**

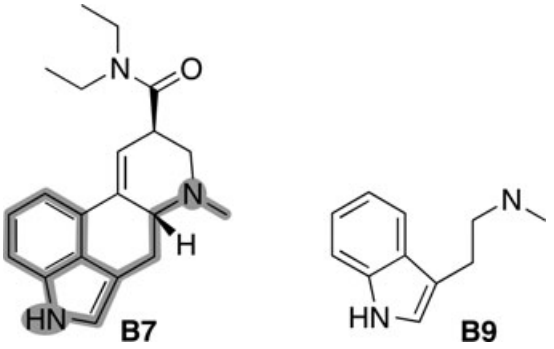


Figure 9. *N*-Methyltryptamine and the pharmacophoric relationship to LSD.

it appeared due to its severe side effects, including several deaths.[48]

As mentioned above, tryptamines, the structural elements of which can be identified in LSD (B7) (Fig. 9) may also be considered as designer drugs. The generalization of tryptamines to DOM (B5, Table 1) and to LSD (B7) has been reported. For example, α-ethyltryptamine (α-ET, B17), which was introduced by Upjohn in 1961 as an antidepressant (Monase) and quickly withdrawn due to side effects, appeared in the clandestine market in the 1980s as a novel designer drug (e.g., "Love Pearls," "ET")[49] shortly after the publication of studies reporting the generalization of tryptamines to DOM (B5).[50] Studies of this series of compounds have shown the (*S*)-enantiomer to be more potent than the (*R*)-enantiomer,[51] in agreement with expectation based on the pharmacophoric hypothesis.[39] Generalization studies have found α-ET (B16) to be MDA-like in that rodents recognize the more potent (*S*)-enantiomer to possess hallucinogenic and PMMA-like properties (group 1) and the (*R*)-enantiomer to produce central stimulant and PMMA-like effects (group 2).[52]

The leaves of *Catha edulis* Forsk, khat, are commonly chewed as a recreational and socializing drug in Eastern Africa and the Arabian Peninsula as they have been for centuries.[53,54] The active principal, *S*(−)-α-aminopropiophenone (cathinone, B18), was found to have a pharmacological profile closely resembling that of amphetamine (B4). In fact, drug-conditioned rodents were unable to distinguish between cathinone (B18) and amphetamine (B4), and clinical experiments in humans have shown B18 to produce amphetamine-like effects.[55] Considering the structural similarity to LSD (B7, Fig. 10), these observations may not be surprising. In recent years, abuse of khat (B18) has spread into European countries, and "designed" analogs of B18 have appeared on the Internet and in the clandestine market.

Specifically, cathinone analogs with substitution patterns reminiscent of those found in phenylisopropylamines that are subject to abuse are found in the agents identified as "bath salts." For example, modification of cathinone (B18) paralleling the conversion of amphetamine (B4) to methamphetamine (B8) produces methcathinone (ephedrone) (B19) and replacement of the 4-position aromatic hydrogen by a methyl group gives mephedrone (B20), which has become the best-publicized cathinone derivative due to its ready availability and reports of serious toxicity following its use.[56] Modification of the aromatic moiety of cathinone (B18) by the addition of a 3,4-methylenedioxy group produces the MDMA (B1) analog methylone (B21), which has been found to generalize to MDMA (B1) in rats[57] and modification paralleling the conversion of amphetamine (B4) to PMMA (B6), produces p-methoxymethcathinone (methedrone) (PMMC, B22).[58] Another example of "designed" analogs in the cathinone family is MDVP (B24) and naphyrone (B25), whose structures are based on that of the psychostimulant drug pyrovalerone (B23). The latter, B25, which had been identified in 2006 as a potent and selective inhibitor of dopamine and norepinephrine transporters with no significant affinity at serotonin receptors,[59] was reported to have been advertised as a "legal" substitute for mephedrone (B20) as soon as B20 was banned in April 2010.[60]

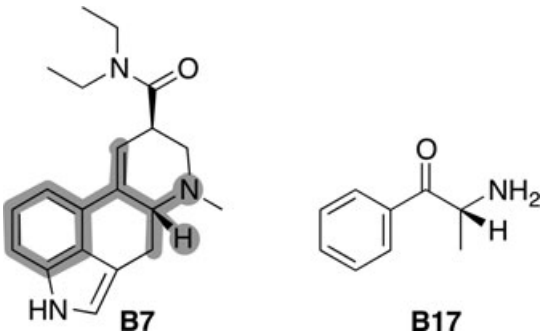


Figure 10. Cathinone and the pharmacophoric relationship to LSD.

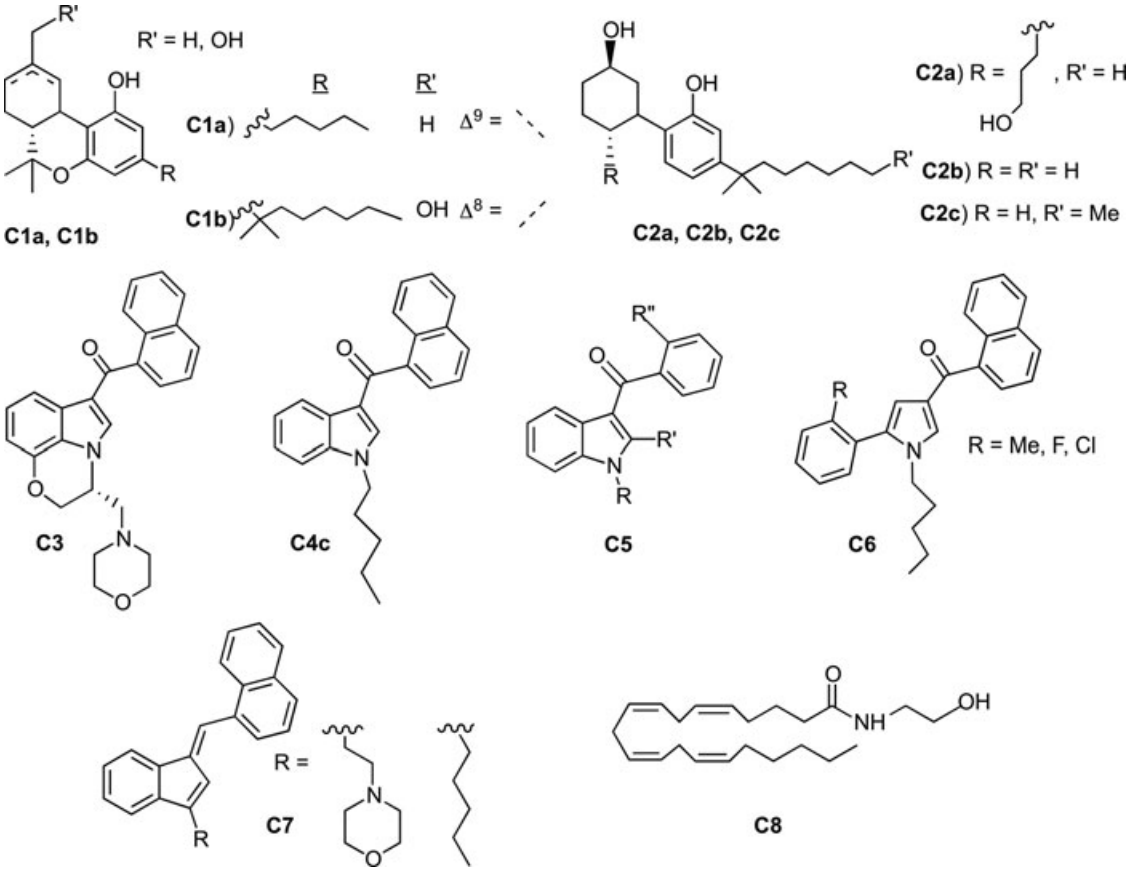


Figure 11. Representative structures of cannabinoid agonists.

Cannabinoids

Overview

Marijuana, which is the most widely used illicit drug in the United States,[61] elicits euphoric effects and is generally without acute dire consequences. In the decades since the structure elucidation of its active constituent, Δ^9-tetrahydrocannabinol (Δ^9-THC) (C1a, Fig. 11),[62] other families of compounds (collectively referred to as cannabinoids) that result in the constellation of effects associated with marijuana have been discovered and designed. The cannabinoid agonists activate the CB1 and CB2 receptors and produce the central nervous system (CNS) effects via the CB1 receptor. These families of compounds include analogs of Δ^9-THC (C1a),[63–66] nonclassical cannabinoids (C2a–c),[67–71] aminoalkylindoles (AAIs) (C3),[72–74] indoles (C4, Table 2; C5),[75,76] pyrroles (C6),[77] indenes (C7),[78,79] and eicosanoids (C8) (endogenous cannabinoids and their analogs).[80] Until recently, these compounds were almost exclusively designed and used to understand their health effects and the nature of drug abuse, to develop the medical potential of cannabinoids, and to study the function and mechanism of action of the cannabinoid signaling system.

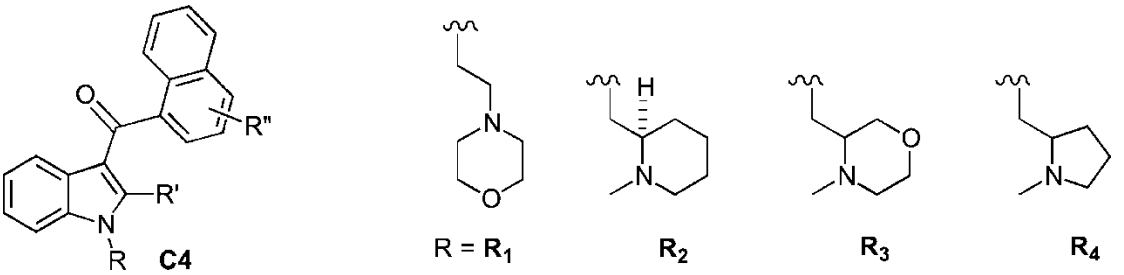
In recent times (from 2006 and possibly earlier), clandestine "labs" (believed to be in China) have co-opted a number of these compounds, many of which were neither controlled nor illegal substances, and provided them for the production of "synthetic marijuana" preparations for lucrative sale. These co-opted synthetic cannabinoids started to appear in the United States in late 2008.[81] Because of absent legal controls and the ability to readily detect these compounds in euphorigenic products using commonly employed drug screening methods (MS and immunoassay), coupled with a risk-tolerant clientele, products abounded. These preparations, which

have been sold as incense and claiming "not for human consumption" under many brands (i.e., Spice, K2, Serenity Now, Tribal Warrior, Spike99, exSES, etc.),[82] are herbal mixtures that act as a carrier for chemically synthesized active cannabinoid agonists. Typically, they are smoked to intake the active volatilized ingredient.

First family

The initially identified and currently dominant compounds found in Spice and other preparations were the series of 1-alkyl-3-(1-naphthoyl)indoles (Table 2) known as JWH compounds (named by Professor John W. Huffman who developed these ligands on NIDA-funded grants for basic

Table 2. Naphthoyl indole CB1 receptor potencies (K_i)



Compound number	Common ID	*R*	*R′*	*R″*	K_i (nM)
C4a	JWH 072	*n*-Pr	H	H	1050
C4b	JWH 073	*n*-Bu	H	H	8.90
C4c	JWH 018	*n*-Pn	H	H	9.00
C4d	JWH 019	*n*-Hx	H	H	9.80
C4e	JWH 020	*n*-Hp	H	H	128
C4f	AM 2201	*n*-5F-Pn	H	H	1.0
C4g	Compd 98[74]	R_1	H	H	7.8[a]
C4h	JWH 122	*n*-Pn	H	4-Me	0.69
C4i	JWH 210	*n*-Pn	H	4-Et	0.46
C4j	JWH 182	*n*-Pn	H	4-*n*-Pr	0.65
C4k	JWH 240	*n*-Pn	H	4-*n*-Bu	14
C4l	JWH 081	*n*-Pn	H	4-MeO	1.2
C4m	JWH 267	*n*-Pn	H	2-MeO	381
C4n	JWH 153	*n*-Pn	Me	6-MeO	250
C4o	JWH 164	*n*-Pn	H	7-MeO	6.6
C4p	JWH 198	*n*-Pn	Me	4-MeO	4.5
C4q	Compd 142[74]	R_1	H	1,2,3,4-H_4	38[a]
C4r	Compd 143[74]	R_1	H	5,6,7,8-H_4	97%@1000 nM[b]
C4s	JWH 015	*n*-Pr	Me	H	164
C4t	–	*n*-Bu	Me	H	22
C4u	JWH 007	*n*-Pn	Me	H	9.5
C4v	–	*n*-Hx	Me	H	48
C4w	–	*n*-Hp	Me	H	>10,000
C4x	–	*n*-Bu	H	4-Me	–

[a] IC_{50}.
[b] % Inhibition of 0.5 nM [^{3}H]WIN 55,212-2 binding.

cannabinoid research). This series evolved from a computational and visual melding of structural features of Δ^9-THC with those of the previously developed aminoalkylindoles (AAI) to arrive at *N*-alkyl-2-methyl-3-(1-naphthoyl)indoles to test the hypothesized structural correspondence.[83] While the thinking on the SAR of indoles has expanded beyond an atom-to-atom correspondence with Δ^9-THC, it provided a successful guide for developing compounds that contributed to the understanding of the structural features related to cannabinoid receptor activation as discussed below. The structures of the cannabinoids to be discussed are found in Figure 11 and Tables 2 and 3.

The first analog of the JWH series to appear in designer drug preparations was JWH 018 (1-pentyl-3-(1-naphthoyl)indole) (C4c). A combination of high activity and easy synthesis[72,75,83–85] helped drive its selection. Its structure evolved from looking for a common structural motif for the classical cannabinoids (C1) and the AAIs (C3), wherein the aminoalkyl morpholinoethyl of C3 and the pentyl chain of C1 were equated.[83] For example, replacing the morpholinoethyl chain in analog C4g with the *n*-pentyl chain gave JWH 018 (C4c), a full agonist (see section "Metabolites and analysis") at the cannabinoid CB1 receptor (versus the partial agonism of Δ^9-THC) with potency fourfold that of Δ^9-THC (C1a, Table 3).[86]

A study of the effect of N1-alkyl chain length on receptor affinity[87] of 1-alkyl-3-(1-naphthoyl)indoles (C4) shows a clustering of high affinity (low nM K_i at CB1) with *n*-butyl, *n*-pentyl, and *n*-hexyl side chains and a significant loss of affinity with larger and especially smaller side chains (compounds C4a–C4e, Table 2). The potential of modified alkyl side chains of the indole nitrogen can be seen from the improved affinity of AM 2201 (C4f) (with a 5-fluoropentyl side chain).[88]

Other side chains in the aminoalkyl series have also been shown to have good affinity at the CB1 receptor. Thus, in addition to the archetype 1-[2-(4-morpholino)ethyl]indole group R_1 (C4g), the 1-(1-methylpiperidin-2-yl-methyl)indole group R_2, the 1-(4-methylmorpholin-3-yl-methyl) indole group R_3, and the 1-(1-methylpyrrolidin-2-yl-methyl)indole group R_4 also exhibited high affinities.[89] Consistent with these analogs, the general observation has been that amino alkyl groups on the indole nitrogen need to be part of a heterocycle with the amine nitrogen separated from the indole nitrogen by two carbons for optimal activity.

Table 3. Reference cannabinoid agonists

Standard cannabinoids		
Compound number	Common ID	K_i CB1 (nM)
C1a[a]	Δ^9-THC	41, 10[b]
C2a[a]	CP 55,940	0.35
C3[a]	WIN 55,212-2	1.9, 9.9[b]

[a]See Fig. 11 for structure.
[b]K_is from different sources.

The 3-position of the indoles is typically acylated, most often with a naphthoyl, a benzoyl, or a phenyl acetyl group. The unsubstituted 1-naphthoyl group (i.e., C4c) is routinely active and easily synthesized. Substituting an alkyl group in the 4-position of the naphthoyl ring significantly increases CB1 affinity for 4-methyl through 4-*n*-propyl (C4h–C4j) in the N1-pentyl series and returns to the affinity of the unsubstituted analog for the 4-*n*-butyl compound C4k.[75] An alkyl group in the 7-position of the naphthoyl ring, mimicking the vinyl methyl of Δ^9-THC in the overlap hypothesis of the latter with WIN 55,212-2, has little effect on affinity in the N1-*n*-pentyl series. Methoxyl-substituted naphthoyl rings in the examples studied generally reduce affinity at CB1 versus C4c; 2-methoxy and separately the 6-methoxy analog on *n*-pentyl indoles (indole C-2 H, C4m and C-2 Me, C4n, respectively) have poor affinity (K_i 381–250 nM), while 7-methoxy C4o has affinity comparable to that of Δ^9-THC (C1a). The 4-methoxy-substituent increases CB1 affinity in C-2 H indoles (see C4l)[84] and in C-2 Me indoles (C4p).[76]

Modeling and CB1 receptor affinity studies of indole analogs with an indole 3-position linkage via a carbonyl (1-naphthoyl) (C4l) or without the carbonyl oxygen (1-naphthylmethane), and with indene analogs, concluded that unlike Δ^9-THC, receptor interaction with an oxygen was not at play in the binding of naphthoyl indoles and that aromatic stacking interactions were responsible for binding.[79,84] Support for this binding mode was found in the binding of two tetrahydronaphthoyl AAIs wherein the proximal and the distal benzene rings were separately reduced, eliminating a region of aromatic stacking.[74] Compared to the fully aromatic naphthyl AAI (C4g), the proximally reduced

analog C4q lost only a modest amount of affinity while the distally reduced analog C4r lost substantial affinity, suggesting the involvement of the distal benzene ring of the naphthyl group as the aromatic stacking region. This is further argued by the generally lower CB1 affinities of 3-benzoyl substituted indoles (versus the 1-naphthoyl analogs), such as the pravadoline analogs.[73] However, in stark contrast to this generality is the 80 pM CB1 affinity of 1-(5-fluoropentyl)-3-(2-iodobenzoyl)indole, AM 694 (C5, R = 5F-C_5H_{10}, R′ = H, R″ = 2-I).[88] As drug design goes, this argues that receptor affinity is not simply modular as regards substituents, groups, and scaffolds; changes in one molecular sector effect the interactions in another of the sectors.

Additionally, 3-phenylacetyl replacements, mimicking the distal aromatic benzene ring of the 1-naphthoyl group (C5, Fig. 11), maintained comparable CB1 affinity to the latter analogs, especially when substituted in the 2-position of the phenyl ring by halogen, methoxy, or methyl substituent, both supporting the interpretation of aromatic stacking and evolving yet a new family of cannabimimetics.[90]

Substituents on the indole nucleus, such as 2-methyl in lieu of the 2-H, have been probed as well. The 2-methyl generally has a minimal (lowering) effect on CB1 affinity versus the unsubstituted analogs of AAIs[74] (C4g, q, r). The N1-alkyl indoles show no effect with N1-n-pentyl (C4u vs C4c), decreasing affinity with minimally smaller and larger side chains (C4t, v, w vs C4b, d, e) and marked increasing affinity for the N1-propyl side chain (C4s vs C4a).[83] The 2-ethyl moiety greatly reduces CB1 affinity relative to unsubstituted indoles.[74,84] Substituents on the benzene ring of the indole were covered as nitrogen-linked moieties (i.e., N_3, NO_2, NH_2, NCS) and have shown minimal effects on CB1 affinity.[88] Analogs such as 6-iodoindole-3-(1-naphthoyl) bearing 5-fluoropentyl or 5-hydroxypentyl N1-chains exhibited high CB1 affinity (K_i = 1.1 and 3.1 nM, respectively).

Metabolites and analysis

Detection of the drug of abuse or its metabolites in bodily fluids such as urine by commonly used analytical methods is pivotal in both scientific and forensic pursuits. Assays have been reported wherein JWH 018 was not detected in urine, while some of its metabolites were.[91] The identification of these metabolites, therefore, becomes essential for forensic purposes and informative for medical and scientific purposes. Five metabolites of JWH 018, hydroxylated separately on the 4–7 positions of the indole ring and the 5-position of the *n*-pentyl side chain, have been identified, and their pharmacology has been demonstrated.[92] Two of the metabolites exhibit affinity to CB1 similar to that of JWH 018 and three with affinity similar to that of Δ^9-THC. JWH 018 is a full agonist at CB1 (E_{max} = 0.29 pmol/mg) (compare to full agonist CP 55,940 = 0.28 pmol/mg and partial agonist Δ^9-THC = 0.06 pmol/mg), and the 4-hydroxyindole metabolite has an E_{max} = 0.19 pmol/mg. This metabolite activity profile suggests that JWH 018 exhibits a polypharmacology that could account, in part, for its diverse effects. Effects at other receptors are as yet unknown, adding to issues of safety.

On the streets

Since 2004, when "synthetic marijuana" started to appear in Europe and then in 2008 in the United States, the number of products and components has risen dramatically, challenging the capacities of forensic labs.[81] The cannabimimetics in current use are predominantly in the classes of indoles and classical and nonclassical cannabinoids. The indoles showing up in forensic labs are mostly N1-alkyl indoles (mostly pentyl with some butyl and hexyl homologs) with a 3-(1-naphthoyl) or 3-(4-substituted-1-naphthoyl) moiety including JWH 015, JWH 018, JWH 019, JWH 073, JWH 081, JWH 122, JWH 210, JWH 398 (C4 where R = *n*-PN, R′ = H, R″ = CI), and AM 2201 (Table 2).[93,94] Indoles with a 3-(2-substituted-phenylacetyl) include JWH 250, JWH 251, RCS-8 (C5, R = 2-cyclohexylethyl, R′ = H, R″ = OMe), a 1-butyl analog of RCS-8, and JWH 203. RCS-4 (1-pentyl-3-(4-methoxybenzolyl)indole) and its 1-butyl analog have also been identified, as has AM 694

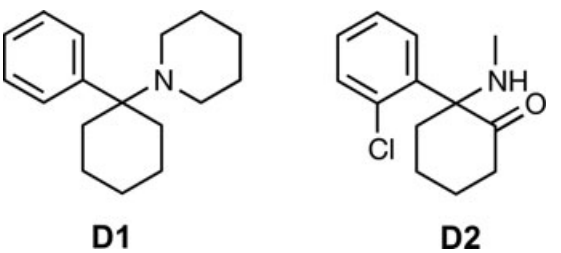


Figure 12. **Structures of phencyclidine (PCP) and ketamine (KET).**

(described in "First family" section). AAIs are WIN 55,212 (C3) and JWH 200 (C4g). The classical cannabinoid (structurally similar to Δ^9-THC, C1a) being found is HU 210 (C1b), its difficult synthesis being offset by its high activity. The nonclassical cannabinoids (the bicyclic analogs similar to CP 55,940, C2a, from Pfizer Pharmaceuticals, and their analogs) are the more readily synthesized CP 47,497 C2b or cannibicyclohexanol C2c, the octyl homolog of the heptyl side chain CP 47,497 (Fig. 11).[93,94]

The wide range of structural variation that exhibits high cannabimimetic activity discussed in the above sections suggest that further reformulation of "synthetic marijuana" is available to clandestine operations in their effort to attempt to confound detection and slip outside legal barriers. A recent report identifying a previously unreported compound, 1-butyl-3-(1-(4-methyl)naphthoyl)indole (C4x), in an herbal mixture seized in Germany supports this concern that further structure modification is in progress for street products.[95] Compound C4x can be recognized as a hybrid of the high-affinity JWH 073 (C4b) and JWH 122 (C4h).

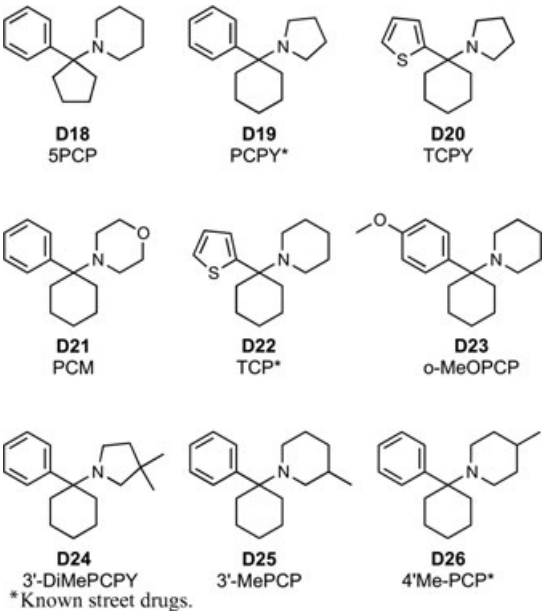
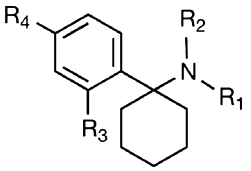


Figure 13. PCP analogs.

Table 4. PCA analogs



Compound number	Name	R_1	R_2	R_3	R_4
D3	PCA	H	H	H	H
D4	NMPCA	Me	H	H	H
D5	*o*-MeNMPCA	Me	H	Me	H
D6	PCDMA	Me	Me	H	H
D7[a]	PCE	Et	H	H	H
D8	*m*-MePCE	Et	H	H	Me
D9	PCDEA	Et	Et	H	H
D10[a]	NPPCA	*n*-Pr	H	H	H
D11	NIPPCA	*i*-Pr	H	H	H
D12	NAPCA	Allyl	H	H	H
D13	NNBPCA	*n*-Bu	H	H	H
D14	NSPCA	*s*-Bu	H	H	H
D15[a]	PCMPA	$(CH_2)_3OMe$	H	H	H
D16[a]	PCMEA	$(CH_2)_2OMe$	H	H	H
D17[a]	PCEEA	$(CH_2)_2OEt$	H	H	H

[a]Known street drugs.

Phencyclidine and analogs

Phencyclidine [1-(phenyl-1-cyclohexyl)piperidine; PCP; D1, Fig. 12] was a serendipitous discovery first synthesized in 1956 as part of a Parke-Davis research program seeking new analgesics of the meperidine class.[96] The pharmacological characterization of PCP found it to be a remarkably powerful CNS depressant.[97,98] PCP initially showed great promise as a relatively potent but safe anesthetic as it did not significantly affect respiration, cardiac function, blood pressure, or body temperature; it was introduced for clinical studies under the name *Sernyl*. However, during early clinical trials, a spectrum of psychological side effects was reported including delirium, euphoria, hallucinations, and violent or manic behavior. These effects resulted in PCP being classified as a psychotomimetic or schizophrenomimetic somewhat comparable to LSD.[99,100] Eventually the incidence of these alarming side effects resulted in PCP being declared "clinically unacceptable"[101] and subsequently withdrawn from further clinical study in 1965. Two years later, PCP was reintroduced as the veterinary anesthetic *Sernylan*.[97] At about the same time, PCP was first discovered by recreational users

Table 5. PCP-analog drug discrimination in PCP-trained rats[113,116,117]

Compound number	Name	Relative potency
D7[a]	PCE	5.79
D11	NIPPCA	2.86
D22[a]	TCP	1.31
D10[a]	NPPCA	1.09
D4	NMPCA	1.02
D1[a]	PCP	1.00
D19	PCPY	0.97
D20	TCPY	0.87
D9	PCDEA	0.83
D3	PCA	0.60
D6	PCDMA	0.60
D25	3′-MePCP	0.32
D13	NNBPCA	0.30
D26[a]	4′-MePCP	0.10
D21	PCM	0.10
D2[a]	KET	0.10

[a]Known street drugs.

under street names such as "PeaCe Pill," "Hog," "Angel Dust," and numerous others.[102] The manufacture of legal PCP-containing products was discontinued altogether in 1978 when PCP was designated a schedule II–controlled substance by the DEA.[103]

The SAR of PCP-like compounds was extensively examined in an effort to optimize the useful anesthetic properties while minimizing undesirable psychotomimetic side effects. More than 300 analogs were eventually prepared, but none were found to have significantly improved pharmacology over the parent compound PCP, and further development was not pursued.[96,104] During this early search for useful PCP analogs, a Parke-Davis consultant prepared a series of 2-phenylcyclohexanone derivatives. This work lead to the discovery of ketamine (KET, D2) in 1962.[104–107] Ketamine has a somewhat improved pharmacological profile compared to PCP and found application as a battlefield anesthetic during the Vietnam War. However, like PCP, ketamine entered the illicit market and was eventually regulated as a controlled substance (CSA Schedule III).[106]

Besides PCP and ketamine, 22 phenylcyclohexylamine (PCA) and PCP analogs were found by these early studies to have significant PCP-like pharmacology (Table 4, D3–D16 and Fig. 13, D18–D25). Of these known active PCP analogs, eight have appeared on the streets as abused drugs: PCP, D1 (1966); ketamine, D2 (1968); PCE, D7 (1969); TCP, D22 (1972); PCPY, D19 (1975); NPPCA, D10 (1999); PCMEA, D16 (1999); and PCMPA, D15 (1999).[108–110] One PCP analog, which published reports had designated as "inactive," 4′Me-PCP, (D26) also appeared on the streets in 1982.[111] In addition, a novel and previously unknown PCP analog, PCEEA (D17), was reported in 1999. This compound may represent a true PCP designer drug analog based on the known PCP ether-analogs PCMEA (D16) and PCMPA (D15).[112]

Rather than the typical designer drug pattern of the synthesis of new compounds to avoid law enforcement or to explore new pharmacology, the appearance 4′Me-PCP on the streets was likely the result of an opportunistic synthesis. Controls on the purchase of piperidine were making this PCP starting material increasingly difficult to obtain, and a clandestine lab resorted to a close analog, 4-methylpiperidine, even though it had been established that this would produce a much less-active PCP analog.

Although several *in vitro* assays for specific PCP binding to CNS receptors were developed, *in vivo* drug discrimination testing was found to be more predictive of overall PCP-like behavioral effects.[113–115] PCP-like drug discrimination data (in rats) available for known active PCP-analogs or analogs, which have appeared on the streets, are shown in Table 5.[113,116,117] It is interesting to note that, although these *in vivo* data were in most cases not available at the time, the compounds selected for synthesis by clandestine labs (other than 4′Me-PCP, as noted above) have a relative potency nearly equal to or greater than the parent compound, PCP.

Summary and concluding remarks

The scientific literature abounds with articles describing in detail the pharmacological properties of thousands of narcotics, stimulants, hallucinogens, sedative-hypnotic drugs, cannabinoids, and other psychoactive substances and provides procedures for their preparation. In the late 1970s, clandestine chemists made use of this information to synthesize various drugs of abuse that were exempt from control by the DEA. In addition, in some cases, sophisticated basic medicinal chemistry

principles were used to synthesize new, not previously reported analogs of drugs with abuse properties similar to those of known drugs on the market or reported in the scientific literature. However, unlike drugs developed by pharmaceutical companies, these clandestine-produced materials do not undergo analysis for purity and identity or prehuman-use pharmacology and toxicology evaluation. In effect, they are tested in populations of drug-addicts, of individuals looking to avoid detection in job-place screens and possession of illegal substances, and of the curious experimenter, to whom they are sold, which in some cases has led to serious consequences including death.

This very serious problem of the so-called designer drugs was brought under some control with the Anti-Drug Abuse Act of 1986 and the 1988 Chemical Diversion and Trafficking Act (CDTA), which regulated the precursors and essential chemicals needed for synthesizing these illegal designer drugs. Even though these two acts brought the designer drug problem under a degree of control, the use of these materials continues and has even increased in recent years.

The foregoing reviews four of the most prominent classes of designer drugs. For each class, we have presented how medicinal chemistry guided clandestine chemists in the design, development, and marketing of designer drugs to mimic the effects of opioids, amphetamines and analogs, cannabinoids, and phencyclidine analogs. While designer drugs have existed even prior to the coining of the term, the specific classes, as well as individual substances within a class, have changed over time to meet the market that exists for these compounds and to avoid compounds that would be covered under the CSA. Thus, although abuse of compounds in the PCP and amphetamine analog classes started at least as early as the mid-1970s (see sections "Phencyclidine and analogs" and "Amphetamines and their analogs"), and PCP and opioid analogs posed major designer drug problems in the late 1970s and 1980s, as pointed out in sections "Phencyclidine and analogs" and "Opioids," respectively, the latter two classes of designer drugs have become less of a problem in recent years. At the same time, as described in section "Amphetamines and their analogs," the recreational use of the stimulant mephedrone and of other amphetamine analogs has increased, and the "JWH" (see section "Cannabinoids") compounds have become the newest major cannabinoid designer drugs.

While legislators and law enforcement groups struggle to control this epidemic, it remains for the scientific community to provide insights to the understanding of the immediate and long-term effects of acute and chronic exposure to these substances. Such efforts have been underwritten largely by the National Institute on Drug Abuse (NIDA) through support of intramural and extramural research programs, publications, and outreach programs. As listed on its website, NIDA's mission has two critical components: the first is the strategic support and conduct of research across a broad range of disciplines, and the second is ensuring the rapid and effective dissemination and use of the results of that research to significantly improve prevention and treatment and to inform policy as it relates to drug abuse and addiction.

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Conflict of interest

The authors declare no conflicts of interest.

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