CHAPTER NINETEEN

Emerging Designer Drugs

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1. INTRODUCTION

The consideration of Emerging Designer Drugs seems very topical today. In the past few years, a plethora of relatively obscure compounds have appeared on the illicit drug market, and in some cases, have proven to be quite popular. In many, but not all cases, these new drugs of abuse have turned out to be established research chemicals that have diffused out of laboratories and scientific journals and onto the streets. As novel pharmacological entities, the legal ramifications for selling and possessing these drugs are initially unclear, and enterprising individuals typically exploit the novelty of these substances to make rapid and substantial profits selling them over-the-counter and online. Indeed, emerging drugs of abuse occupy a legal grey area until emergency scheduling powers are invoked, typically first at the municipal and state level, then nationally. Although the proliferation of designer drugs toward the end of the 1990s was likely fueled by the desire to profit off the sale of "legal ecstasy alternatives," the market has since expanded tremendously, and now includes not only potential ecstasy replacements, but a variety of psychedelic phenethylamines and tryptamines, cathinone derivatives with bizarre psychostimulant properties, and synthetic cannabinoids. A few modified ketamine derivatives also have recently appeared, and one might even expect eventually to see some modified salvinorin analogues for sale.

Some years ago, a graduate student in one of our laboratories speculated, "make one drug illegal, and a more dangerous one will take its place." Today, this seems almost axiomatic. Certainly, no knowledgeable person could present a reasonable argument that marijuana is less safe than the new synthetic cannabinoids that are now appearing. It may be a case of unintended consequences of current drug policy that new, untested drugs are proliferating on the black market at an unprecedented rate. One might reasonably believe that if marijuana, LSD, and ecstasy had remained legal, or at least decriminalized, many of these new designer drugs would never have caught on. For example, it is not clear that any of the potential replacements for ecstasy is as satisfactory to users as is the original molecule, MDMA (3,4-methylenedioxy-*N*-methylamphetamine), at least from a psychopharmacology point of view. Similarly, it seems unlikely that the products containing potent synthetic

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cannabinoids would ever have appeared if marijuana and/or its many preparations were legal and readily available. It seems evident that much of the demand for new drugs that is the motivation for illegal manufacture is based on finding new "legal highs" that can be quickly marketed before they are identified and restricted by the various drug control agencies throughout the world.

Similarly, it may be the case that strict controls on the majority of recreational drugs with pronounced reinforcing effects have driven those searching for new compounds to explore the pharmacological "back bench." In that regard, although it is the case that essentially all preclinical evaluations of the abuse potential of psychostimulants (like cocaine or methamphetamine) or opioids (like heroin or alfentanil) detect strong reinforcing effects, many emerging drugs of abuse tend to function as relatively weak reinforcers. In what may be the only case of a compound being released from Schedule I controls after emergency scheduling powers were invoked, 1-[3-(trifluoromethyl) phenyl]piperazine (TFMPP) failed to engender self-administration in rhesus monkeys (Fantegrossi et al., 2005) despite eliciting a hallucinogen-like head twitch response in the mouse, and substituting for (MDMA) in a drug discrimination paradigm (Yarosh et al., 2007). Thus, it may be the case that many emerging drugs of abuse deliver less acceptable rewarding effects than do the drugs for which they are marketed as "legal alternatives."

What are other factors that are driving the explosion of new designer drugs? First of all, the Internet has provided a venue for rapid dissemination of information about drugs. Not only can users search public databases for keywords such as "psychostimulant," "hallucinogen," or "cannabinoid," but numerous blogs now exist where users of new chemicals can describe in detail not only their experiences with these chemicals but also where they can be obtained. Previously, availability of such chemicals was largely limited to aficionados who had contacts with small organic chemistry laboratories. When the desired substance is not actually proscribed, it can be manufactured in laboratories in other countries, particularly China. A recent Google search of "research chemicals" and "China" revealed that most of the popular research chemicals could be shipped "from multiple warehouses: China, EU, USA, Russia, India, and Kazakhstan." "Best Seller" chemicals listed on one site included, for example, the synthetic cannabinoid JWH-018 in 10 g or 50 g lots, the "bath salt" psychostimulant/entactogen methylenedioxypyrovalerone (MDPV) in 5 g lots, and the psychedelic 2C-I in 50 g lots.

Internet marketing sites couple ready access to information about the doses and effects of research chemicals with easy accessibility. Furthermore, the economics of synthetic research chemicals can be very favorable. For example, 10 g of JWH-018 was listed on one Internet site at a cost of only $100! With a smoked dose of 2–5 mg it is about twice the potency of THC, meaning that the intoxicating potential of 10 g of JWH-018 is approximately comparable to one-quarter pound of very high grade (16–18% THC) cannabis. From the user's perspective, such a synthetic cannabinoid is much less expensive than cannabis itself. Amusingly, many internet distributors will include purity analysis of

their drugs, including results obtained using thin layer chromatography or mass spectrometry, and the purity of products from illicit sources often (but not always) rivals that of established research chemical companies. It is often quite difficult to justify the cost of purchasing these drugs from legitimate distributors of research chemicals instead of from overseas clandestine laboratories, but the requirement to disclose the source of all materials in scientific manuscripts and grant applications probably keeps the behavior of most scientists in check.

New research chemicals, in general, do not present significant challenges to competent synthetic chemists. Synthetic cannabinoids require relatively few simple steps. Synthetic hallucinogens typically require three or four synthetic steps. Although the syntheses are not formidable for the typical synthetic chemist, when we consider that small pilot plants may be dedicated to their synthesis in countries such as China, the number of synthetic steps is irrelevant. The cost of starting materials such as substituted benzaldehydes, indoles, and reducing agents is relatively trivial compared with the marketed prices of the final products.

Given that we presently do not have ways to control the appearance of these substances on illicit markets, we shall attempt to identify the emerging trends that seem to be appearing on the current drug scene. Our intention here is to give a survey of the major classes of substances that are appearing, and in some cases, at least, to predict future trends. The reader should be aware, however, that prediction in this game cannot be reliable because someone may serendipitously discover a new molecule that finds tremendous acceptance with potential users, much as what happened with MDMA. It is impossible to predict such random occurrences, and despite our best efforts to offer what we believe are likely trends, the discovery of such a drug would completely derail all of our reasoned arguments.

Finally, it must be kept in mind that it is not only the research chemicals, per se, that present the problems, but also the absence of quality controls used in their manufacture. Unlike the pharmaceutical industry, there is no standard of purity required for research chemicals. Savvy buyers may seek sellers who offer the equivalent of material safety data sheets, or documentation of purity by NMR or IR, but one must first of all trust the integrity of the seller, and that the documentation is actually for the specific lot of chemical that was purchased, when in fact there is no guarantee of that. Indeed, enormous variability in the identity and dose of active constituents has recently been documented both within and between brands of internet-available "legal high" products (Baron et al., 2011; Zuba and Byrska, 2013). Second, manufacturing contaminants may be included and unless it has been definitively established to be safe, a minor contaminant may lead to an adverse reaction. Recall that MPTP, the potent dopamine neurotoxin, was a contaminant generated during the crystallization of a meperidine analogue. Had the final meperidine analogue been pure, and free of the MPTP contaminant, none of the heroin addicts who used it would have been afflicted with severe parkinsonism.

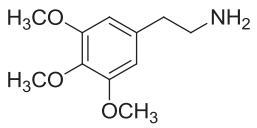
2.1. TYPES OF DESIGNER DRUGS

2.1.1. Phenethylamines

From a chemistry perspective, phenethylamines represent the largest category of current designer drugs, as well as potentially a vast reservoir for new and untested substances. Phenethylamines are probably the largest category because they are the easiest to synthesize, and the possible ring modifications that can be carried out on them are almost uncountable. In addition, depending on what substituents are attached to the aromatic ring of the phenethylamine template, phenethylamines can have psychopharmacological effects ranging from classic hallucinogenic action, to psychostimulant effects, to various molecules that could possess mixtures of direct effects on GPCRs, as well as being either inhibitors or substrates for the three monoamine uptake carrier proteins (See Figure 1). Effects on monoamine reuptake carriers can range from molecules that possess amphetamine- or methamphetamine-like psychostimulant effects, to other compounds that may have more of an MDMA-like or entactogenic effect. The extent to which activity at each of these targets can be "mixed and matched" is unknown, and it is likely that new designer drugs will continually appear that are built upon the phenethylamine scaffold.

2.1.2. Hallucinogens

There are two categories of hallucinogens that have appeared on the street. The first are the phenethylamines, originally inspired by the structure of mescaline (1). A large compendium of active hallucinogenic phenethylamines has been presented in the book PIHKAL, by Shulgin and Shulgin (1991).



Mescaline 1

Despite its historic importance and being the only naturally occurring phenethylamine hallucinogen, mescaline itself is perhaps one of the least potent such substances. Replacing the 4-methoxy with larger alkoxy groups (ethoxy, propoxy, alloxy, methallyloxy) or with alkylthio groups leads to compounds that are significantly more potent than mescaline itself (Shulgin and Shulgin, 1991; Nichols, 2004). Although relatively potent, these molecules have not appeared on the illicit market, and reasoning to explain that can perhaps be found in their more difficult synthesis, compared to other ring substitution patterns, as well as the unfavorable economics of manufacturing and distributing compounds that require relatively large doses (tens of milligrams vs a few

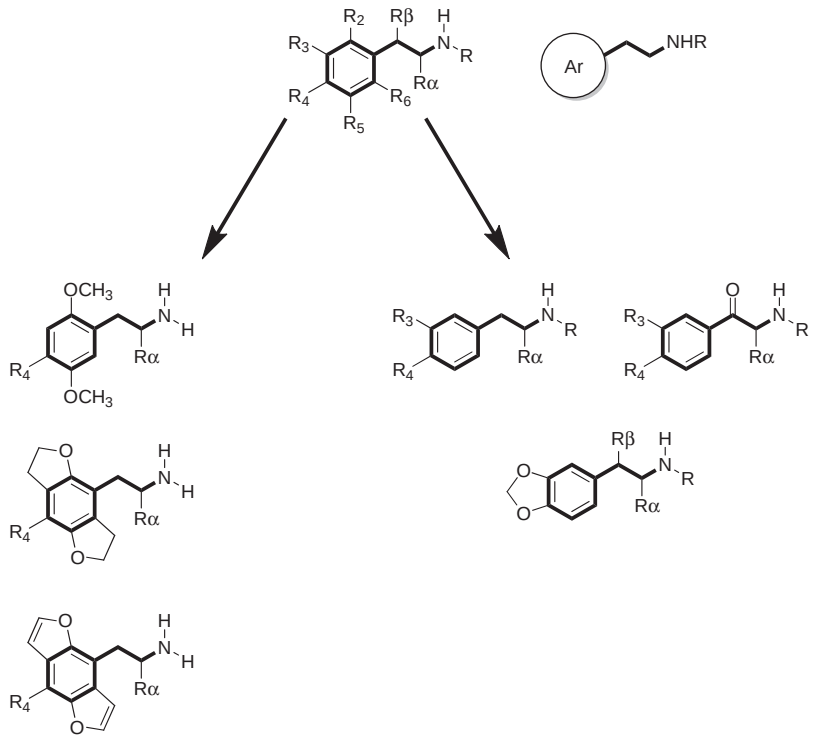


Figure 1 General examples of how the simple phenethylamine template can be modified to produce hallucinogens, illustrated on the left, or molecules that have effects at the monoamine transporters, exemplified on the right.

milligrams or less). It is the author's opinion that molecules closely resembling mescaline (i.e. 3,4,5-trisubstituted phenethylamines) are unlikely to appear on the street in significant quantities.

Transposing the 3- and 5-methoxy groups to the 2,6-positions leads to compounds that also are active, but again the relatively low potency and particularly the significant synthetic challenges in making 2,6-dimethoxy-4-substituted phenethylamines probably mean that these also will not emerge as new problems.

By contrast, transposition of the 3-methoxy of mescaline to the 2-position, leading to a 2,5-dimethoxy substitution pattern, is the most commonly seen type of hallucinogen. Although several of these have the simple two-carbon side chain, such as 2C-D, 2C-B, or 2CT-2 (Figure 2), the most potent have an alpha-methyl attached to the side chain (e.g. DOM, DOB, and Aleph-2). These types of molecules are generally referred to as substituted "amphetamine" hallucinogens, because unsubstituted alpha-methylphenethylamine itself is amphetamine. Only a small set of these compounds is illustrated in Figure 2, because a very large library of similar compounds can be generated

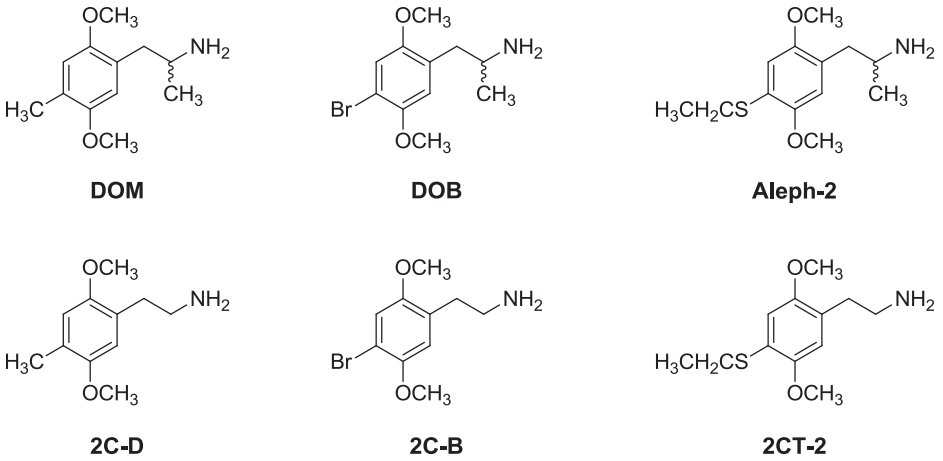


Figure 2 Examples of 2,5-dimethoxy-substituted hallucinogens.

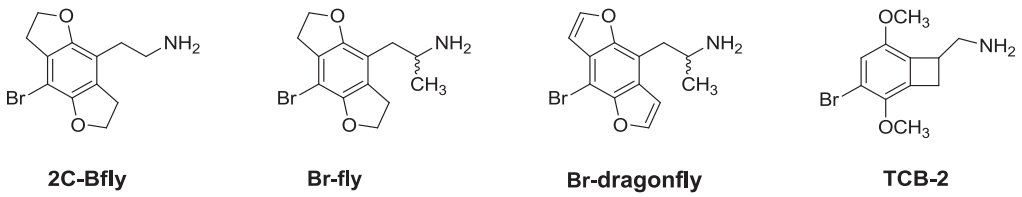


Figure 3 Examples of rigid analogues of hallucinogenic amphetamines with high potency.

simply by changing the 4-substituent. Halogens (other than fluorine), short unbranched alkyl groups, and a variety of alkylthio substituents can be introduced into 4-position of the molecule to give potent compounds, both in the phenethylamine and in the amphetamine series. Interestingly, extending the alpha-methyl in the side chain to the two carbon alpha-ethyl completely abolishes hallucinogenic activity.

Further increases in potency can be obtained by constraining the 2,5-dimethoxy substituents into a dihydrofuran ring (e.g. 2C-Bfly, Br-Fly, and Br-Dragonfly; Figure 3). Indeed, Br-dragonfly approaches the potency of LSD using in vitro or rodent models, and overdose deaths have resulted from its use (e.g. Andreasen et al., 2009). Although the synthesis of these furan-type compounds is slightly more complex than for simple phenethylamines, their higher potency holds economic incentives for illicit laboratories. In principle, a variety of new designer drugs could emerge from this template. For example, 2,5-dimethoxy-4-ethylphenethylamine (2C-E) has been cited as an important hallucinogen with unusual properties (Shulgin and Shulgin, 1991). The corresponding 4-ethyl could be readily prepared for any of the rigid molecules, and indeed 4-propyl, and a variety of 4-alkylthio compounds could safely be predicted to be quite psychoactive. A potent molecule that was developed by constraint of the side chain is TCB-2

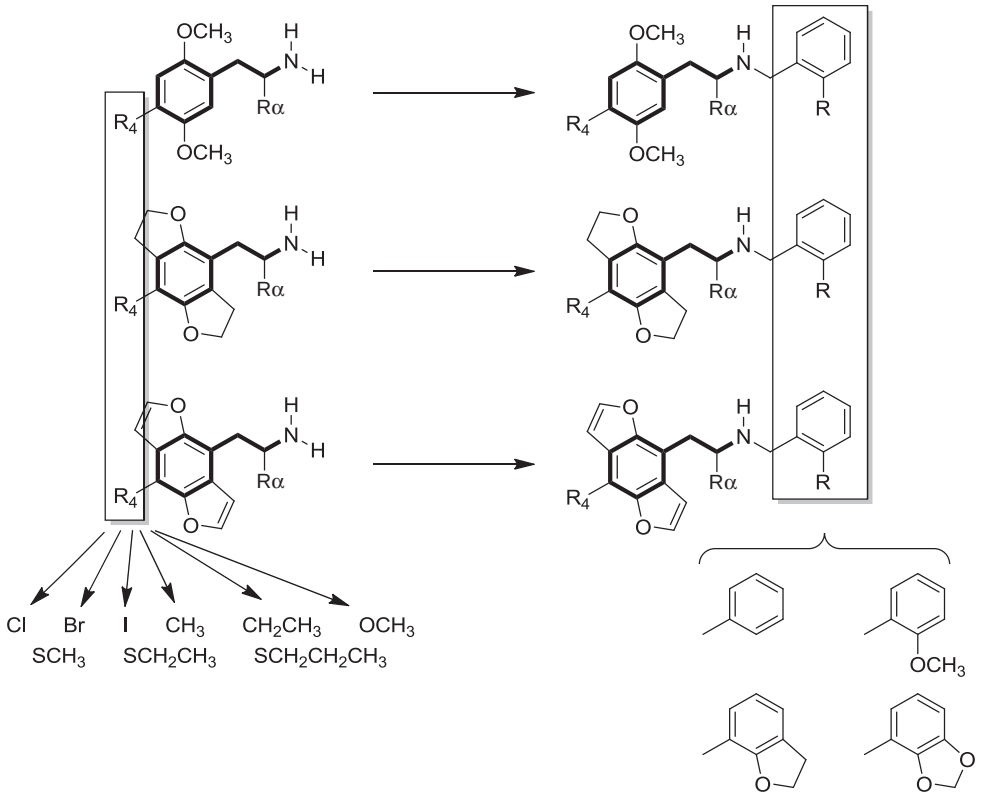


Figure 4 Examples of possible permutations and combinations of *N*-benzylphenethylamines that could appear as new designer drugs.

(McLean et al., 2006), now commercially available as a 5-$HT_{2A/2C}$ agonist for experimental laboratory studies. Although its synthesis is tedious enough to prevent its manufacture from being economical, it does exemplify the fact that relatively modest structural changes can lead to active compounds.

The toxicity of phenethylamine hallucinogens has generally been considered to be low. Nevertheless, deaths are occasionally reported, usually following overdose, and in some cases associated with polydrug abuse. The stimulation of 5-HT_{2A} receptors in the vasculature also can lead to severe vasoconstriction resulting in limb amputation or death (Bowen et al., 1983; Winek et al., 1981).

***N*-Benzylphenethylamines**. Following earlier studies by Elz (2002) and Heim (2003) *N*-benzylphenethylamines are now recognized to be highly potent 5-HT_{2A} receptor agonists, with potential as hallucinogens (Braden et al., 2006). Although to date, only the 2,5-dimethoxy-4-iodo and 2,5-dimethoxy-4-chlorophenethylamines with *N*-(o-methoxybenzyl) groups seem to have gained any popularity as recreational drugs, it is possible to construct a large library of *N*-benzylphenethylamines

that might be expected to have activity, as illustrated in Figure 4. Once the phenethylamine is in hand, it is a trivial matter to add the *N*-benzyl substituent from readily available benzaldehydes. These compounds do not appear to have oral activity, and the few blogs describing them generally report administration either rectally or by buccal absorption. These compounds are the most potent 5-$HT_{2A/2C}$ agonists known, with picomolar receptor affinities. Unfortunately, it also appears that their high potency can easily lead to overdose, and in some cases death (Geller, 2012; Araiza, 2012).

The second category of hallucinogens is comprised of the tryptamines, which would include LSD, a semisynthetic ergoline derivative. LSD is an extremely potent compound, with a typical minimum active human dose of about 0.05 mg. The subjective effects resulting from LSD ingestion can last up to 12 h and include alterations of mood, perceptual changes, and cognitive impairment. Thus, any novel analogues maintaining this high potency and relatively long duration could be problematic to new users not familiar with appropriate dosing. As it happens, however, no structural analogues have been developed that retain the unique psychopharmacological characteristics of LSD. Although it is relatively easy to produce lysergic acid amides other than the diethylamide seen in LSD, none of the ones that have been tested show potencies comparable to LSD. The methyl group on the basic nitrogen of LSD can be replaced with an ethyl to afford a quite potent analogue of LSD, but the economics of producing LSD, and then transforming it to the (N6)-ethyl compound are unfavorable.

The core structure of tryptamines is comprised of a bicyclic indole ring system with an aminoethyl moiety attached at the 3-position. The basic structure for all the tryptamines is derived from tryptophan, which serves as an essential amino acid in some animals. Enzymatic decarboxylation of tryptophan then leads to tryptamine. The biosynthesis of various endogenous tryptamines proceeds through differential modification of the tryptophan structure. For example, serotonin biosynthesis commences with hydroxylation at the 5-position of tryptophan by tryptophan hydroxylase and then proceeds through decarboxylation of the side chain by aromatic amino acid decarboxylase. The production of other endogenous tryptamines such as melatonin proceeds through different biosynthetic sequences, but all tryptamines contain the basic indole ring system, and one can consider them all to be structurally similar to serotonin. The bicyclic indole ring system contains six positions (not counting the site where the tryptamine side chain is attached) that are available for chemical modification; however, the majority of medicinal chemistry efforts have thus far focused on modification of the 4- and 5-positions. One reason for that is because it has been shown that modification of either the 6- or 7-positions significantly reduces or abolishes the psychoactive effects of the resulting compound. The addition of untested functional groups could potentially change this view, however, perhaps one day giving rise to novel 6- or 7-position substituted tryptamines that retain pharmacological activity.

2.2. PSYCHOSTIMULANTS

2.2.1. MDMA and Its Replacements

The unique psychoactive properties of MDMA have so far not been discovered in any other molecule, although various substances are claimed to have "similar" effects. Research chemicals that have been marketed as possible MDMA-replacements include several structures illustrated in Figure 5, including 4-fluoroamphetamine and 4-fluoromethamphetamine, as well as 4,5-methylenedioxy-2-aminoindan (MDAI), 5-iodo-2-aminoindan (5AI), 5,6-methylenedioxy-2-aminotetralin (MDAT), and the dihydrofuran compound 6-(2-aminopropyl)-2,3-dihydrobenzofuran (6-APB) (Figures 6, 7).

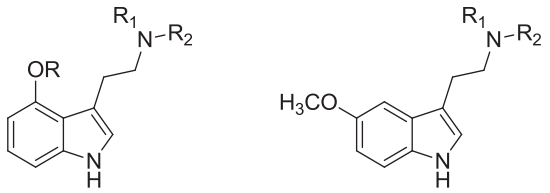


Figure 5 General structural features of simple hallucinogenic tryptamines.

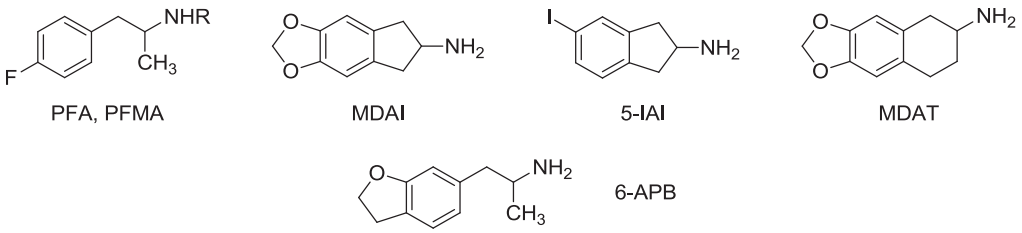


Figure 6 MDMA-related "research chemicals."

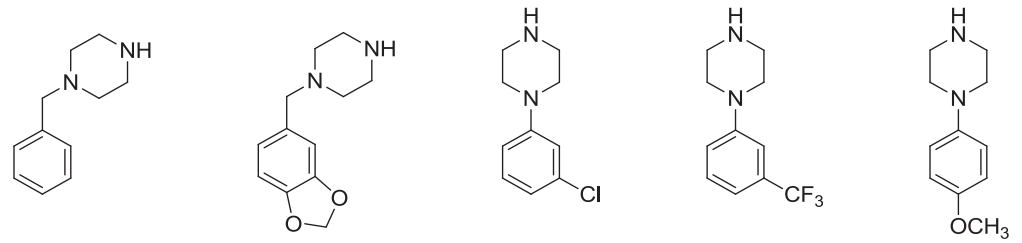


Figure 7 Substituted piperazine compounds with abuse potential.

It is perhaps important to note that MDMA itself, as well as a few of its analogues, has a chiral carbon, giving rise to stereoisomers. That is not particularly uncommon among drugs of abuse: for example, the psychostimulant methamphetamine and the psychedelic DOI are both phenethylamine derivatives with chirality in their side chains, although the stereochemistry is reversed for psychostimulants and hallucinogens. In most cases, however, one enantiomer is more biologically active, whereas the other will be either inactive, or "functionally inactive" due to a markedly decreased potency. That is not the case with MDA, MDMA, and perhaps several other analogues. Indeed, the S-(+)- and R-(−)- enantiomers of MDA and MDMA are both active at approximately the same dose, although their biological effects appear to be qualitatively distinct from one another. In that regard, we observe stimulant-like reinforcing and discriminative stimulus effects with S-(+)-MDMA that we do not see with the R-(−)- enantiomer (Fantegrossi et al., 2005). Similarly, in animal models, hallucinogen-like effects of R-(−)-MDA and R(−)-MDMA are not induced by their S-(+)- enantiomers. In humans, S-(+)-MDMA appears to be responsible for the unique psychopharmacology of racemic MDMA, but the pure S enantiomer did not completely reproduce the effects of the racemate, suggesting some contribution from the R enantiomer (Anderson III et al., 1978).

Although some reasonably efficient stereoselective syntheses for substituted amphetamine isomers are known, thus far, no chiral products have been seen on the illicit market (other than S-(+)-methamphetamine). The economics of a stereoselective synthesis are very unfavorable, as is postsynthesis resolution of individual enantiomers, but it may be the case that some novel pharmacological entity may appear where one enantiomer has desirable properties, but the racemate has undesirable effects or has some toxic effect. In such a case, we might expect one day to see the appearance of two new drugs of abuse, with perhaps very different pharmacological effects, that turn out to be enantiomers of one another. Current drug-scheduling regulations, at least in the United States, cover all stereoisomers of a specific controlled substance.

2.2.2. Benzyl- and Phenylpiperazines

Following the appearance of *N*-benzylpiperazine (BZP) in the United States in 1996 (Austin and Monasterio, 2004), a number of substituted *N*-substituted piperazines appeared as drugs of abuse (Arbo et al., 2012). Although these molecules have not been as popular as some other types of drugs, they still represent a distinct class of designer drugs, and one might surmise that a variety of aromatic ring substituents can be introduced to provide new substances that might have abuse potential. Molecules that have so far appeared on the illicit market include the following.

Substituted piperazines often have been sold as ecstasy or ecstasy replacements with names such as A2, Bliss, Charge, Frenzy, Herbal Ecstasy, and Rapture, among others. These preparations often consist of 1-benzylpiperazine (BZP) and 1-(3-trifluoromethylphenyl) piperazine (TFMPP) in a 2:1 ratio, as estimated by the DEA System to Retrieve Information From Drug Evidence (STRIDE) program. It was have reported that a mixture of

BZP and TFMPP can mimic the effect of MDMA in humans. Similarly, drug users have posted experiences with meta-chlorophenylpiperazine (mCPP) to internet sites specializing in the dissemination of drug information, such as erowid.org and lycaeum.org, and the drug has been used as a positive control for MDMA in human studies (Tancer and Johanson, 2001, 2003). Interestingly, some cocaine (Buydens-Branch et al., 1997), alcohol (Benkelfat et al., 1991), and MDMA abusers (McCann et al., 1999) have reported "euphoric" responses to mCPP, perhaps explaining its recreational use.

Perhaps not surprisingly, based on their illicit use, piperazines are reported to have substrate activity at the dopamine and serotonin reuptake transporters, DAT and SERT, respectively, a pharmacology that is shared with MDMA and other psychostimulants. We have previously investigated the reinforcing and discriminative stimulus effects of BZP and TFMPP in rhesus monkeys (Fantegrossi et al., 2005). In these studies, BZP was self-administered and amphetamine-like in drug discrimination, whereas TFMPP was not self-administered and did not have amphetamine-like interoceptive effects. An extensive review on patterns and motivation of BZP use, target populations, legal status around the world, pharmacology, toxicology, kinetics and new developments in analytical and detection techniques has recently been published (Monteiro et al., 2013). In accordance with these studies, stimulant-like effects of BZP have been demonstrated in humans Campbell et al., 1972 (Campbell et al., 1972), rats (Baumann et al., 2005), and mice (Yarosh et al., 2007). The binding profile of TFMPP at various serotonin receptors is complex, as similar potencies have been reported for TFMPP at 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2C} receptors (Schoeffter and Hoyer, 1989). Additional studies have suggested that TFMPP may be either an antagonist (Conn and Sanders-Bush, 1987) or a weak partial agonist (Grotewiel et al., 1994) at 5-HT_{2A} receptors as well. This promiscuous pattern of binding to 5-HT receptors and monoamine transporters likely provides quite a bit of room for optimization of novel pharmacological entities built upon the piperazine scaffold. It seems likely that piperazine-like designer stimulants, psychedelics, and perhaps drugs of mixed action will appear as new drugs of abuse in the future.

2.2.3. Substituted Cathinone Derivatives

A variety of ring- and sidechain-substituted cathinones (β-ketophenethylamines) have appeared over the years. Initially, only cathinone and methcathinone were seen on the illicit market. More recently, mephedrone has been widely used, and its effects have been compared to those of MDMA. Mixtures of mephedrone and pyrovalerone have been marketed as "bath salts," although that is nothing but a marketing ploy, because they have no value in bathing or cleaning. One frequent constituent of these products is 3,4-methylenedioxypyrovalerone (MDPV), which is structurally similar to both MDMA and methamphetamine. MDPV surprisingly acts as a cocaine-like reuptake inhibitor at dopamine transporters (Baumann et al., 2013), although it has MDMA- and methamphetamine-like actions in mice (Fantegrossi et al., 2013). By inspection of the structures in Figure 8 it can be surmised that a variety of side chain lengths and amines

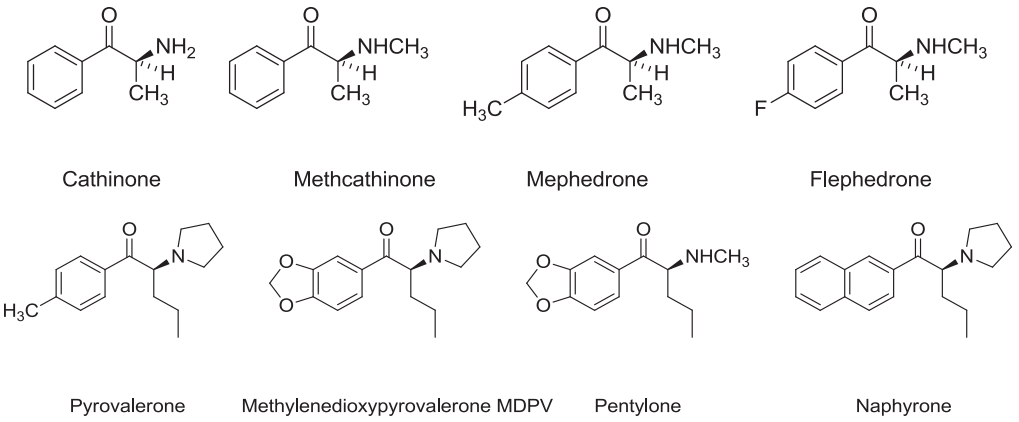


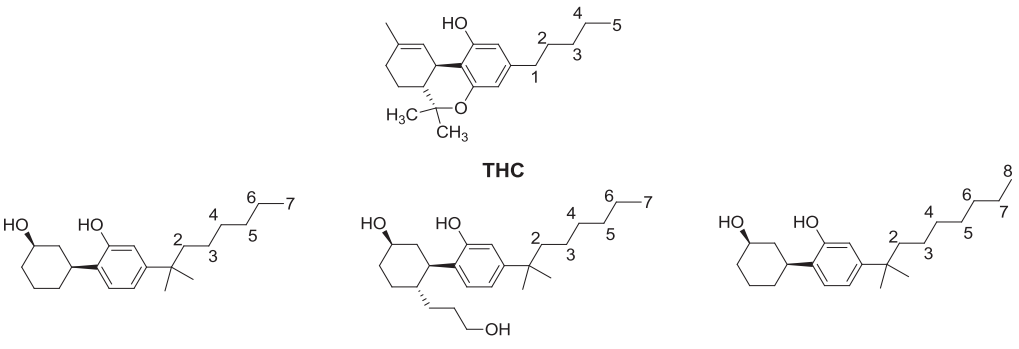
Figure 8 Examples of substituted cathinone derivatives.

can be used to create new compounds that likely will have similar pharmacology. And, as was noted for some phenethylamines, the presence of one or more chiral carbon atoms allows for stereoisomerism among the cathinones. Of all the designer drugs to have appeared recently, these may have some of the most serious reported adverse effects, primarily affecting the heart and cardiovascular system (see e.g. Warrick et al. (2012)). The reader should consult the chapter in this volume by Richard Glennon for a more detailed discussion of substituted cathinone derivatives.

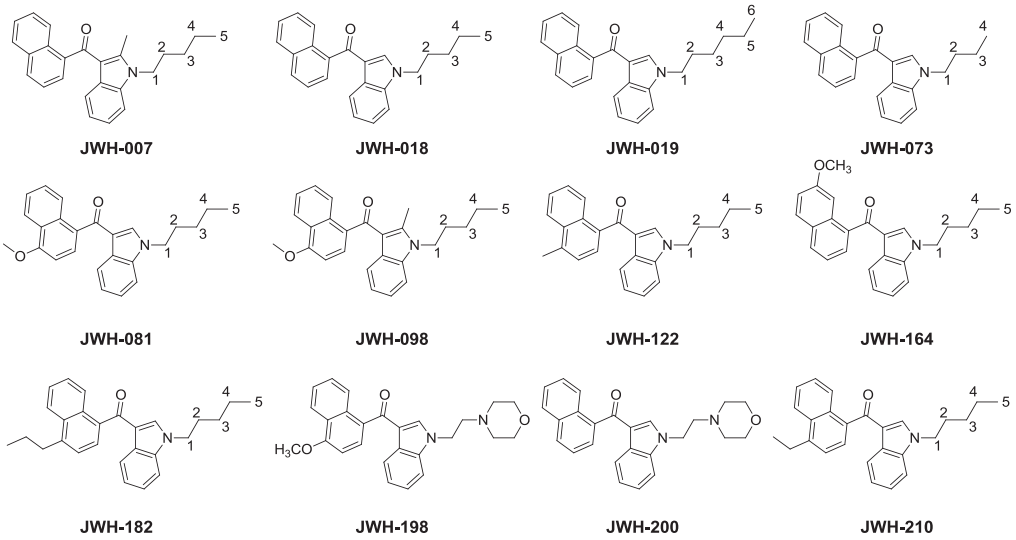
2.3. SYNTHETIC CANNABINOIDS

2.3.1. Overview

Although structure-activity studies of the psychoactive component of marijuana (THC) have been carried out for decades, it is only recently that synthetic cannabinoids have become popular as recreational drugs. These compounds clearly are the result of mining the literature on cannabimetics.



The structurally dissected synthetic cannabinoids CP 47,497 and CP 55,940 were originally developed by Pfizer, and took advantage of earlier work showing that the 1,1-dimethylhelptyl alkyl chain provided optimum activity in THC congeners.



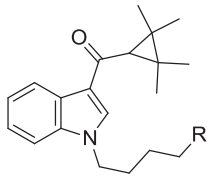
In recent years, products sold as incense in "head shops" have commonly been referred to as "K2" or "Spice" and have been shown to contain one or more of these synthetic cannabinoids. Although marketed as "natural" herbal blends, K2 products are usually comprised of nonpsychotropic plant matter adulterated with various mixtures of these chemicals, most of which are aminoalkylindoles (AAIs) of the JWH family (a series of WIN-55,212-2 analogues created in 1994 by Dr John W. Huffman for structure-activity relationship studies of the cannabinoid receptors). They, along with other synthetic cannabinoids, such as CP-47,497 and HU-210, were first discovered to be in "natural" herbal smoking blends in 2008. One particular AAI, JWH-018, is quite prevalent across many different brands and batches of K2 products. JWH-018 and other cannabinoids, such as Δ9-tetrahydrocannabinol (Δ9-THC), the major active constituent in marijuana, produce their psychoactivity by binding and activating, to varying degrees, cannabinoid 1 receptors (CB1Rs) in the CNS, which are Gi/o-protein coupled receptors (GPCRs).

Although the desired effects of K2 products are probably those that are generally similar to marijuana, the frequency and severity of adverse effects caused by synthetic cannabinoids certainly seems to be much greater than that of marijuana, which has been used for millennia and is the most commonly abused illegal drug in the U.S. Although smoking or oral consumption of marijuana acutely produces relatively mild and tolerable side effects in most users, such as appetite stimulation

and orthostatic hypotension, it very rarely causes the adverse effects observed rather commonly with similar use of K2 products, such as hypertension, agitation, hallucinations, psychoses, seizures, and panic attacks. In one case, seizures and supraventricular tachycardia were characterized after ingestion of pure JWH-018; it should be noted, however, that the afflicted user dissolved "a spoonful" of compound in a mug of warm ethanol in order to swallow the drug in a presumably very large bolus dose. In extreme THC overdose cases, similar symptoms can be observed but they are not generally associated with marijuana use. In addition to acute adverse effects produced by K2, one case report indicates that chronic abuse may also result in a severe withdrawal and dependence syndrome. The use of K2 has even been causally linked to at least one death by overdose and has been implicated for likely involvement in several other fatalities, resulting in over 2500 calls to poison control centers in 2010 alone and numerous visits to emergency departments across the United States and in Europe.

The rapid increase in recreational use of synthetic cannabinoids, their current inability to be detected by standard drug urine tests, and the constant introduction of new structurally similar products of unknown content pose a significant risk to public health. Most importantly, the pharmacological and toxicological profiles of these products are virtually unknown, and the mechanisms underlying the discrepancies in the frequency and severity of K2 adverse effects relative to the well-established cannabis have yet to be elucidated.

Internet sites may sell either "herbal" blends (plant material impregnated with active compound) or the pure drugs themselves. In one case, interested potential users were offered instructions in how to make their own smoking blend. After purchasing 1 g of JWH-018 ($50–$70 on various websites), they were told to obtain mullein or marshmallow leaves as a substrate, acetone to dissolve the pure compound, and an acetone-proof spray bottle to distribute the drug solution. Users were instructed to dissolve 1 g JWH-018 in 4 ml acetone and place the resulting solution into the spray bottle. The instructions continued, "Now this is the most dangerous part. You must spray the leaves as evenly as possible, or you can get "hotspots" or localized areas in your mixture that have much higher concentrations of JWH-018 that can be dangerous." Indeed, we have detected these "hot spots" even in commercial preparations, where different extractions from a single divided sample can contain 2–3 times the amount of active compound (data presented by Cindy Moran, Arkansas State Crime Laboratory, at the 2011 College on Problems of Drug Dependence.) Similarly, there is no consistency within a given "brand" of these commercial preparations, as the amount of compound varies from lot to lot, and even the identity of the active compounds themselves can change over time. All of these factors could easily lead to overdose, even by the most cautious user.



UR-144: R = CH_3

XLR-11: R = CH_2F

Recently, a few novel cannabinoid compounds have emerged with structures that differ from those of Δ^9-THC or the AAIs. These compounds would not likely be captured by current analogue scheduling laws that require "substantial chemical similarity" between the novel compound and a previously scheduled drug of abuse, which may explain their sudden emergence onto the drug scene. Examples of such compounds include (1-pentylindol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methanone (UR-144), and its 5″-fluoro analogue (1-(5-fluoropentyl)-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (XLR-11). Both UR-144 and XLR-11 have recently been detected in herbal smoking blends, first in New Zealand, but now in the US as well. Interestingly, UR-144 (and presumably XLR-11 as well) acts as a selective and highly efficacious agonist at cannabinoid CB2 receptors, and has substantially lower affinity for the CB1 receptor (Frost et al., 2010). This finding challenges the notion that CB1 receptors are the primary site of action for psychoactive cannabinoids, and perhaps implies that new compounds of this class may specifically target CB2. Indeed, users describing their experiences with these compounds on various internet forums report that UR-144 produces a "less freaky, wired high than JWH-081" or "a nice high similar to THC/Cannabis."

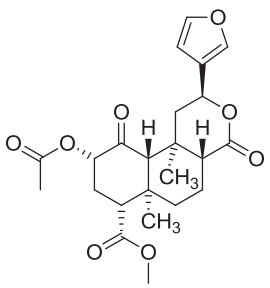
Health problems associated with the use of "Spice" products are reported to be similar to those after cannabis use. For some particular products, however, e.g. "Lava Red", increasing numbers of users have been hospitalized with severe intoxications. A potential problem to be aware of is the unknown cumulative toxic effects these compounds or their metabolites may have. In this regard, we have recently reported that several phase I hydroxylated metabolites of JWH-018 and JWH-073 retain high affinity for cannabinoid CB1 receptors, and display a range of efficacies from neutral antagonism, to partial agonism, to full agonism. Similar results have been published with the fluorinated analogue of JWH-018, which is also a prevalent constituent of K2/'Spice' products, AM-2201 (Chimalakonda et al., 2013). More recently, other phase I metabolites of these same synthetic cannabinoids were demonstrated to act as agonists at cannabinoid CB2 receptors, where they induce qualitatively and quantitively distinct signaling events, as compared to traditional cannabinoids (Rajasekaran et al., 2013). Finally, a phase II glucuronidated metabolite of JWH-018 exhibiting antagonist affinity at CB1 receptors has been described (Seely et al., 2012). Liver metabolism of

xenobiotics is highly variable across the population, so the effects of these active metabolites might be expected to blunt (in the case of antagonist metabolites) or enhance (in the case of high-efficacy metabolites) the effects of the parent drug, depending on one's individual liver enzyme profile, perhaps resulting in wildly unpredictable effects across individuals using the same drug supply.

2.3.2. Toxicity of Synthetic Cannabinoids

Recent reports of acute kidney injury following the use of synthetic cannabinoids (Thornton et al., 2013), particularly XLR-11 (CDC, 2013), as well as reports of seizures following administration of AM-2201 (McQuade et al., 2013) or various compounds from the JWH series (Hermanns-Clausen et al., 2013) raise concerns about the potential toxicity associated with use of these substances. One may speculate that the compounds containing the naphthyl moiety could have carcinogenic potential but without broad screening across a large library of receptors and channels one cannot know what potential for severe or even life-threatening intoxications might exist, particularly in overdose. Further, a pattern of chronic use for these compounds increases concerns about toxicity. It also might be noted that some of these compounds, such as HU-210, CP-55,940 and WIN-55,212-2 are full agonists at the CB1 receptor, whereas THC acts only as a partial agonist. Recently, an increase in the number and severity of symptoms observed in hospitalized persons after consumption of herbal mixtures containing JWH-122, e.g. "Lava Red" and "OMG", has been reported in Germany and Italy. Some of these patients suffered from generalized muscular spasms and/or loss of consciousness that required artificial ventilation. Such severe symptoms had not been reported with JWH-018, emphasizing the fact that slight changes in molecular structure can lead to a dramatic increase in toxicity.

2.4. SALVINORIN

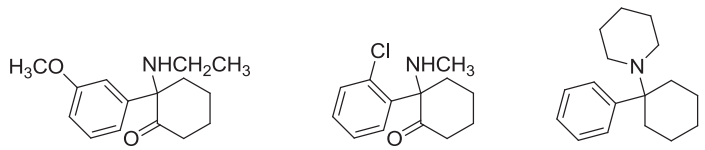


Salvinorin A (SVA) is one of several diterpenes isolated from the Mexican mint Ska Maria Pastora (*Salvia divinorum*). This plant has been used by indigenous peoples in the Oaxaca region of Mexico for hundreds of years (Valdes III et al., 1983; Sheffler and

Roth, 2003), presumably for its psychoactive effects. Both the plant and SVA extracts are now widely available via the internet, where they are marketed as legal short-acting hallucinogens. In this regard, the psychoactive potency of SVA rivals that of lysergic acid diethylamide, although the intoxication induced by SVA is reported to be qualitatively different from that produced by the classical serotonergic hallucinogens (Siebert, 1994). Interestingly, the mechanism of action for SVA was unknown until Roth and colleagues (2002) demonstrated that this compound binds as a potent and selective κ-opioid receptor agonist. The agonist effects of SVA at κ-opioid receptors were further elaborated when in vitro in studies demonstrated that this compound functions as a full agonist at this receptor (Chavkin et al., 2004). SVA is thus the first naturally occurring exogenous κ-opioid receptor agonist to be discovered. Similarly, SVA is the only non-nitrogenous compound known to bind to opioid receptors. The structure of SVA is lipid-like, completely distinct from those of all previously identified opioid ligands, and thus defines a new structural class of κ-opioid receptor selective drugs. The action of SVA is extremely brief, yet a number of analogues of SVA are now known that have a longer duration of action. There are synthetic challenges to making longer-acting SVA analogues, and the only economical approach is to start with SVA itself, so the likelihood that any of them might appear on the street seems low. Nevertheless, given the high potency of SVA, and the fact that *S. divinorum* can be grown on a relatively large scale, it is not inconceivable that a long-acting analogue of SVA could appear on the street. Given the tendency of SVA to cause disorientation and loss of insight, a longer acting version of SVA could be very problematic.

2.5. DISSOCIATIVES

Although this category has so far not expanded like the others, the potential still exists for the creation of a number of new designer drugs to emerge. To date, the only member of this class to gain popularity is methoxetamine (Mket; MXE) (Corazza et al., 2012). It is a structural analogue of PCP (phencyclidine) and ketamine, which are non-competitive NMDA antagonists, and high affinity binding of methoxetamine to this same receptor has recently been demonstrated in vitro (Roth et al., 2013).



Methoxetamine Ketamine Phencyclidine

Methoxetamine has noticeable effects after a 20 mg sublingual dose, and higher doses lead to a disconnection from reality, with loss of motor coordination and sensory

distortions. A dose of 60 mg and higher can produce feelings of floating or falling into another place that is different from normal reality. The hallucinations can be realistic and frightening, although they may not be well remembered after the drug effect wears off. The drug can cause bizarre and reckless behavior. Adverse effects seen in emergency room situations can include hypertension, tachycardia, and agitation. More extreme effects can also be observed after high doses or in combination with other drugs, including apparent reversible cerebellar toxicity (Shields et al., 2012) or even death (Wikström et al., 2013). The psychoactive effects of methoxetamine are longer-lasting than for ketamine, and can be unpredictable. Ketamine can lead to addiction, and there are some suggestions that methoxetamine also may present risk of addiction.

There are at least two locations in the molecule where structural modifications could be made relatively easily by clandestine chemists. In particular, the aromatic ring could be substituted by a variety of substituents, and the starting materials, substituted benzonitriles, are generally available commercially. The method of synthesis precludes the production of anything other than a secondary amine, but one would certainly expect that propylamine could be employed to give an active congener. In addition, although phencyclidine (PCP) is not a popular substance, substitutions on the aromatic right might lead to more acceptable materials that would technically be "legal."

Legal Control Issues

The first attempt to regulate new "designer drugs" arose as a result of illicit production in the early 1980s of 4-methylfentanyl, an opiate that was about 30 times more potent than fentanyl itself. Marketed as "China White," it had resulted in a number of overdose deaths. At that time, any substance that was controlled had to be explicitly named, and the chemical structure had to be known. Realizing that there were a number of similar modifications of fentanyl that could be produced with equally serious properties, but unable to predict which of them might arise, Congress enacted the Controlled Substance Analogue Enforcement Act of 1986. This Act sets out the following definition of a "controlled substance analogue" as:

1. the chemical structure of which is substantially similar to the chemical structure of a controlled substance in schedule I or II;
2. which has a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in schedule I or II;
3. or with respect to a particular person, which such person represents to have a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in schedule I or II.

The first point (1) is considered necessary, but either (2) or (3) may serve to define the activity and relate to point (1). Thus, the act has two "prongs," each of which must be

satisfied. It served for about two decades to give enforcement agencies authority to arrest and prosecute manufacturers and distributors of new "designer drugs" as quickly as the structures could be identified. This act was particularly useful in controlling a number of simple chemical analogues of MDMA. With the plethora of new structures that began to appear in the 1990s, however, this law did not prove to be comprehensive enough. In particular, the synthetic cannabinoids did not fulfill the first prong of the act (1), in that they had no similarity to THC or to the chemical structures of other controlled substances. Furthermore, legal issues also had frequently arisen in interpreting what was meant by "substantially similar."

When the illicit market started to overflow with new and unknown drug molecules, additional regulation was clearly warranted. This action took the form of H.R. 1254, the Synthetic Drug Control Act of 2011. This new law amended the earlier Controlled Substances Act by adding a specific provision to schedule "cannabimimetic agents," defined as "any substance that is a cannabinoid receptor type 1 (CB1 receptor) agonist as demonstrated by binding studies and functional assays within any of the following structural classes." and then listing five very broad chemical types, and explicitly naming 15 distinct compounds within those classes. The specification that the molecules should have cannabimimetic pharmacology offers the possibility of including new molecules that might arise that were not included within the five broad chemical types specified.

The new law goes on to include a number of "Other Drugs," and includes all of the substituted cathinones that have made an appearance or seem likely to appear on the market, as well as one MDMA-like compound (e.g. MDAI). The new law also then schedules a series of hallucinogenic phenethylamines (not amphetamines, which were covered by the earlier act) that includes 2C-E, 2C-D, 2C-C, 2C-I, 2C-T-2, 2C-T-4, 2C-H, 2C-N, and 2C-P. Although some of these have never had a significant presence on the black market, the DEA is perhaps attempting to anticipate possible problems. Importantly, with these compounds now explicitly described in the amended law, it broadens the range of substances covered in the original Controlled Substance Analogue Enforcement Act that will be considered "substantially similar." Interestingly, for all practical purposes 2C-H is inactive, but it is the precursor to several of the newly restricted compounds.

3. CONCLUSIONS

In summary, although underground chemists mining the scientific literature have a vast database from which to identify potential new "research chemicals," it will be increasingly difficult for them to market them as "legal highs." In the meantime, one hopes that some new chemical will not emerge that proves to have unexpected toxicity, with disastrous consequences for the adolescent and young adult population who are the main consumers of these "research chemicals."

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