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Recreational drug discovery: natural products as lead structures for the synthesis of smart drugs

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Over the past decade, there has been a growing transition in recreational drugs from natural materials (marijuana, hashish, opium), natural products (morphine, cocaine), or their simple derivatives (heroin), to synthetic agents more potent than their natural prototypes, which are sometimes less harmful in the short term, or that combine properties from different classes of recreational prototypes. These agents have been named *smart drugs*, and have become popular both for personal consumption and for collective intoxication at rave parties. The reasons for this transition are varied, but are mainly regulatory and commercial. New analogues of known illegal intoxicants are invisible to most forensic detection techniques, while the alleged natural status and the lack of avert acute toxicity make them appealing to a wide range of users. On the other hand, the advent of the internet has made possible the quick dispersal of information among users and the on-line purchase of these agents and/or the precursors for their synthesis. Unlike their natural products chemotypes (ephedrine, mescaline, cathinone, psilocybin, THC), most new drugs of abuse are largely unfamiliar to the organic chemistry community as well as to health care providers. To raise awareness of the growing plague of smart drugs we have surveyed, in a medicinal chemistry fashion, their development from natural products leads, their current methods of production, and the role that clandestine home laboratories and underground chemists have played in the surge of popularity of these drugs.

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1 Introduction

Receptors for opiates, cannabinoids, and dopamine, all major doorways to mind-altering substances, have been described in mammals, birds, and amphibians. Indeed, zoophoria, that is the use of intoxicating substances by animals, was already described by Aristotle in pigs and monkeys,[1] and is vividly exemplified by the sight of the Tasmanian poppy cultivations ravaged by hordes of wallabies.[2] However, humans are now increasingly going beyond the simple plundering of the intoxicating natural pharmacopoeia in their quest for, fundamentally, signalling the brain the false arrival of a huge fitness benefit, short-cutting to the pleasant sensation associated of doing something beneficial for our survival and fitness. The existence of pleasure highways in the neurochemical jungle of our brain motivates us to do important things. In this sense, we are all potential addicts, although the vast majority of us become addicted to things one does, like the pleasure of learning, eating, exercising, or loving, rather than to the mind-altering chemicals one takes.

Natural products have always figured prominently among drugs of abuse, and remain popular today. However, just like the medicinal herbal pharmacopoeia was gradually replaced by synthetic medicines that were easier to manufacture and optimized (domesticated) in terms of pharmacodynamic (potency), pharmacokinetic (absorption), and safety compared to their natural prototypes, so the natural intoxicating pharmacopoeia is increasingly being complemented, or even replaced, by a

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variety of synthetic drugs. These, due to an alleged minor risk of acute toxicity and habit-induction, are perceived as safer than hard drugs like heroin or cocaine. Sometimes these new agents combine the recreational profile, but also the toxicity, of distinct chemotypes, creating new appealing blends of psychotropic activity. Due to a wrongly perceived sense of legality and safety, these recreational substances have been dubbed "smart drugs", and are often commercialized as natural despite their synthetic origin. Thus, the ingredients of products like *Spice*, *K2* and *Bath Salts* are synthetic analogues of natural products, and can have dramatic and life-threatening adverse effects. Nevertheless, they are largely perceived by their users as herbal, natural and devoid of risk. Within the published literature on recreational drugs, their analytics and toxicology are taking the lion's share of the attention, and have been extensively reviewed.[3–5] Conversely, information on the way smart drugs were developed from natural product leads and their current ways of production is scant and, to the best of our knowledge, has not yet been systematically reviewed from a medicinal chemistry standpoint. *Natural Product Reports* has recently published an article on the botanical products used as ingredients of smart drugs.[6] Spurred by the growing popularity of their synthetic analogues, we have reviewed the development of synthetic smart drugs from their lead structures, their current methods of production, and the role that clandestine home laboratories and underground chemists have played in the growing popularity and availability of these products.

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2 The advent of psychonauts and the role of "mom and pop" clandestine laboratories

The occasional use of intoxicating compounds by professional chemists and chemistry students was long limited to common compounds like alcohols and hydrocarbons, and the potential of the published biomedical literature to inspire the synthesis of recreational compounds was not apparently realized until the late seventies. In those years, the political turmoil in Afghanistan had caused a worldwide shortage of heroin, triggering its replacement with synthetic opioids and especially fentanyl (**1**). The synthesis of fentanyl was complicated for the technical standards of clandestine drug synthesis of those days, and its supply chain for the street market was therefore limited, being mostly based on material diverted from its mainstream use in hospitals. As a second choice, meperidine (or pethidine) (**2**) was also used as a heroin replacement, but its short duration of activity and more marked side effects never made it very popular. Furthermore, its synthetic preparation, requiring the handling of a nitrogen mustard, was also unsuitable for clandestine synthesis.

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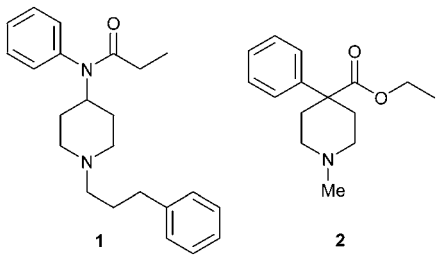

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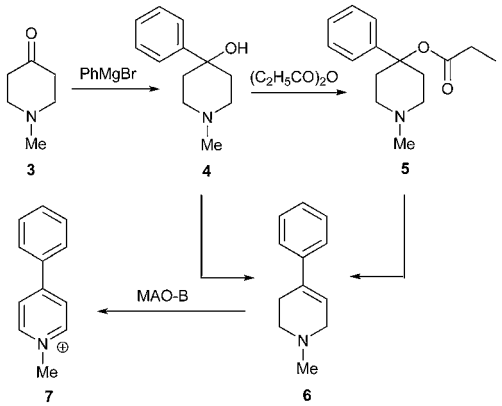
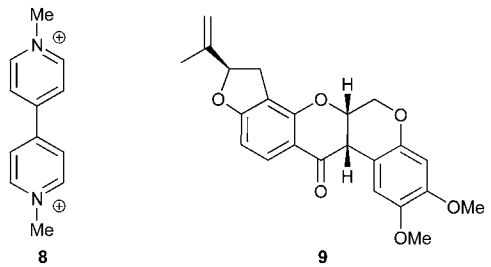
By browsing in the chemical literature, an unknown underground chemist noticed a 1947 publication in the *Journal of Organic Chemistry* where the Hoffmann-LaRoche researcher Albert Ziering described the synthesis of the reverse ester of meperidine (1-methyl-4-phenyl-4-propionyloxypiperidine, MPPP, **5**), that outperforms the parent compound in terms of morphine-like activity.[7] The synthesis of this compound was much simpler than that of fentanyl and meperidine, and it could closely mimic the effects of heroin. In a short time, the use of **5**, dubbed *China White* in the street drugs lingo, spread within the underground chemistry community and then within the street drug market. Barry Kidston, a twenty-three year old chemistry graduate student at the University of Maryland was the first victim of this drug. Interested in recreational drugs, he set up a laboratory in the basement of his parents' house, and, in 1977, he went on synthesizing **5** from *N*-methylpiperidinone (**3**, Scheme 1) for personal use for several months, until he suddenly developed a severe stiffness and difficulty of movement that required hospitalization with the very unusual diagnosis of juvenile Parkinson's disease. *L*-DOPA could, in fact, improve his symptoms, although a tolerance later developed, eventually leading Kidston to commit suicide with a lethal dose of cocaine two years later.[8] His autopsy revealed massive loss of dopaminergic neurons in the *substantia nigra*, the histological hallmark of Parkinson's disease. The extreme rarity of the condition prompted an enquiry by the National Institutes of Health (NIH). A sample of the last batch of the drug Kidston had been injecting was recovered from the splash-guard tube of his rotavapor,[8] and it turned out to be a mixture of **5** and its elimination product, the dehydropiperidine **6** (MPTP). Both compounds proved unable to reproduce the permanent signs of Parkinson's disease in rodents. The disease is very rare in young people, never occurring suddenly, and a paper reporting the unusual case of Barry Kidston was rejected by several major neurology journals, being eventually published in *Psychiatric Research*, a newly established journal.[9]

A few years later, in 1981 and 1982, advanced Parkinson's disease was diagnosed in six relatively young heroin addicts from the Santa Clara County in California who had consumed a sample of **5** manufactured by an underground chemist in Texas, and then brought to the Bay Area. Again, the drug was contaminated by **6**, and the neurologist J. William Langston started to investigate the case. When he looked up the volume of *Journal of Organic Chemistry* reporting the synthesis of **5**[10] at the library of Stanford University, he found the pages cut out, a clear sign that this article was hot in the underground chemistry community.[8] In 1983 Langston published a paper in *Science* reporting the likely association between Parkinson's disease and MPTP, raising interest in this compound.[11] Langston also detailed the discovery of this connection in a popular book, *The Case of the Frozen Addicts*, published in 1995.[8] In 1984 it was found that **6** could indeed rapidly induce Parkinson's disease in primates, with rodents being rather resistant to its activity.[12] What had happened to Kidston and the Texas garage chemist was dehydration during the work up of the addition of phenylmagnesium bromide to *N*-methyl-4-piperidinone (**3**), or, alternatively, overheating during the esterification of the tertiary alcohol **4** with propionic anhydride. In the central nervous system (CNS), MPTP is dehydrogenatively aromatized by MAO (monoamine oxidase)-B of glial cells to the neurotoxic cation 1-methyl-4-phenylpiridium (MPP^+, **7**), a substrate of the dopamine transporter that is accumulated in dopamine-producing neurons where it interferes with complex I of the electron transport chain of mitochondria, eventually inducing cell death. The discovery of a compound capable to induce Parkinson's disease had profound implications on the etiology of this condition, generating an animal model of the disease and suggesting that MPP^+-like compounds in the environment might play a role in the development of the disease.[13] Thus, Parkinson's disease shows an unusually high prevalence in agricultural areas and in people who work with pesticides, and some agents used in agriculture like paraquat (**8**) and the homoisoflavone rotenone (**9**) show indeed MPTP-like activity.[14] Remarkably, the chloride of MPP^+ had even be commercialized in the 1970s as an herbicide against nutsedge (various *Cyperus* species) under the trade name of Cyperquat.



Scheme 1 Synthesis of MPPP (**5**), the reverse ester of meperidine (**2**).



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Since the case of Kidston surfaced in 1979,[9] the level of sophistication of underground chemists has increased

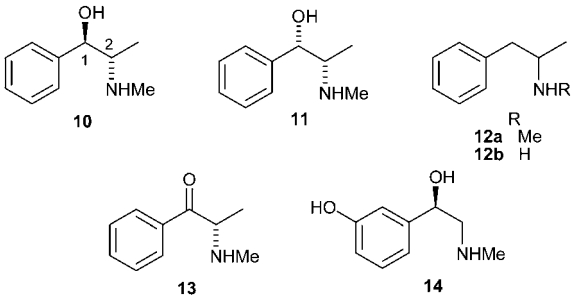
exponentially, and one wonders if, by creating a redundancy of talented people, the downsize of medicinal chemistry in big pharma might have contributed to the expertise upgrade of current clandestine drug synthesis.[15] Thus, compounds like ecstasy and mephedrone were re-discovered by underground designers of psychoactive drugs who popularized their use through the web, in the effort to stay ahead of the legislation, and, sometimes, even of science. On the other hand, quality control in "mom and pop" labs is virtually non-existent, and contamination from by-products and intermediates is not uncommon in final products, potentially leading to tragedies like the one of MPTP.

3 Recreational natural product-based drug discovery

3.1 Ephedrine

The pseudoalkaloid ephedrine (**10**) was first purified from the Chinese medicinal plant *ma huang* (*Ephedra sinica* Stapf.) by Nagayoshi Nagai at Tokyo University in 1887.[16] It was the first important biomedical discovery made in Japan, and Nagai, the founder of the Pharmaceutical Society of Japan (PSJ), established the structure of ephedrine, discovered its facile reductive deoxygenation (the Nagai reaction), and eventually synthesized it as a racemate.[17] Ephedrine was at first considered a biological analogue of atropine, and its first use in medicine was as a short-acting mydriatic agent. Its stellar success started in the early 1920s, when it was unveiled as an orally available and longer acting analogue of epinephrine,[18] the adrenal hormone discovered in 1900 by Jokichi Takamine, a pupil of Nagai. In a few years, ephedrine became the treatment of choice for asthma, reaching its medicinal zenith in the 1950s. Ephedrine is now superseded as an anti-asthmatic agent by synthetic analogues like salbutamol and terbutaline, and, as a nasal decongestant, by its diastereomer pseudoephedrine (**11**).[19] Ephedrine has, nevertheless, re-emerged in the twilight zone of street drugs and nutritional supplements, serving both as a major source for the illicit production of methamphetamine (meth, **12a**) and methcathinone (**13**), and as a mental stimulant and weight loss promoter in dietary supplements.[19]

Ephedrine (**10**) occurs in *ma huang* with its diastereomer pseudoephedrine (**11**), and the literature is rather confusing regarding the configurational descriptors of these compounds. The natural enantiomer of ephedrine has the 1*R*,2*S* configuration, and can be referred to as the *levo*(-), *erythro* or *D*-form. Natural pseudoephedrine is the epimer at the benzylic carbon, has the configuration 1*S*,2*S* and can be referred to as the *threo*- or *L*-form, and is dextrorotatory. Unfortunately, the descriptors *dextro*/*levo* and *D*/*L* are sometimes confused, as is the orientation for their assignment of the Fischer descriptors to these compounds, that requires placing the more oxidized phenyl carbon to the top, and not to the bottom, of the projection. Pseudoephedrine has less pronounced activity than ephedrine on CNS, and has now largely replaced ephedrine in nasal decongestants and cough mixtures. Compared to anti-histaminic decongestants, it does not cause rebound congestion, thus explaining its popularity amongst users. Ephedrine and ephedrine-containing extracts are currently banned in the US healthfood market, where, however, *ma huang* can be regularly commercialized.[19] Ephedrine is also listed as a Table I precursor under the United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances.[19] To curb the supply chain of metamphetamine, the commercialization of nasal decongestants containing pseudoephedrine is regulated, with purchase limits and identification/signature requirements, and pseudoephedrine is increasingly replaced in these products with phenylephrine (**14**), despite growing concerns for the poor efficacy of this compound.[20] Ephedrine has an excellent brain penetration, where it acts mainly at the level of the norepinephrine transporter, reverting its activity from the re-uptake of the neurotransmitter to its secretion in the synaptic cleft, and therefore acting as an indirect sympathomimetic agent.



The growing success of ephedrine as an anti-asthmatic agent, and the political turmoil in China in the 1930s led to a scarcity of the product, triggering the synthesis of simplified and cheaper analogues that could be used for bronchodilation, CNS stimulation, and nasal vasoconstriction.[21] Amphetamine (deoxy-*nor*ephedrine, **12b**) was the first analogue of ephedrine to be commercialized in the 1930s, reaching enormous success as a nasal decongestant when formulated in a plastic inhaler to insert into the nostrils (Benzedrine® Inhaler).[22] The lack of the benzylic hydroxyl not only makes amphetamine a liquid and facilitates its volatilization, but also increases the brain penetration, making it the archetypal stimulant and inducer of the "fight or flight" response. Hundreds of amphetamines have been synthesized, and some of them have still medicinal use in the treatment of attention deficit hyperactivity disorder (ADHD), narcolepsy, and obesity.[22] The use of stimulants boomed during World War II, both on the Allied front (amphetamine, **12b**) and the German side (metamphetamine, **12a**), and it is still permitted today to treat combat fatigue and promote wakefulness in combat, with significant use recorded during the Persian Gulf War.[22] After WW2, the use of amphetamines permeated Western society, and involved a broad segment of the population, including housewives, truck drivers, students and professional, all variously willing to promote wakefulness, improve mood and attention, or losing weight.[23] In 1969 alone, the production of amphetamine tablets in US was at least 8 billion, enough to supply every American with 40 standard 10-mg dosages, and it has been estimated that in 2006 nearly 20 million American were taking some form of amphetamine on a regular, and mostly on prescription, basis.[24] The

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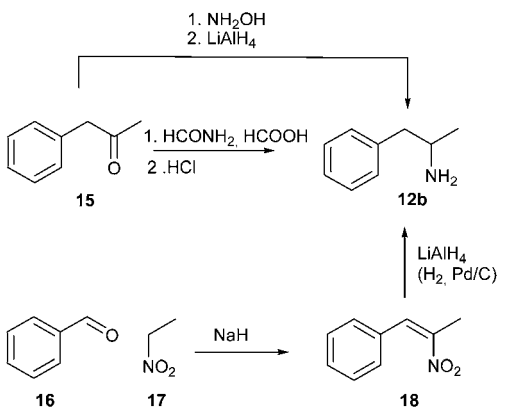
danger and the habit forming potential of amphetamines became evident in the seventies, and now amphetamine and its analogues are either totally banned as medicinal products, like in Japan, or heavily regulated. While ephedrine is mainly active at the epinephrine system, amphetamine and its analogues show also potent dopaminergic action, making them more addictive than ephedrine. The molecular mechanism of action at the dopamine transporter level has been elucidated, and its reverse operation, that is extruding rather than re-uptaking dopamine, has been related to phosphorylation. The current view is that amphetamines behave as a long-acting analogues of endogenous trace amines like phenethylamine, that, unlike amphetamine, are quickly metabolized by MAO.[22]

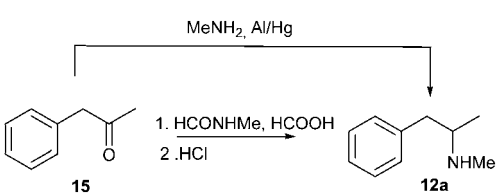
The *D*-(2*S*)-enantiomer of amphetamine, incidentally also dextrorotatory and therefore named dextroamphetamine or dexamfetamine, is a more potent CNS stimulant than its enantiomer, but the illegal synthesis of amphetamine produces the racemic mixture, and in the illegal market amphetamine has been largely replaced by metamphetamine (**12a**), that can be more easily obtained in the more potent *D*-form by deoxygenation of ephedrine. Phenylacetone (phenyl-2-propanone, P2P, **15**) is the most common starting material, and can be converted to amphetamine by reductive amination *via* the corresponding oxime or, most conveniently, by the Leuckart reaction with formamide in the presence of formic acid and next hydrolysis.[25] The synthesis from P2P has substantially superseded the one based on the Henry reaction between benzaldehyde and nitroethane followed by reduction with $LiAlH_4$ or by hydrogenation (Scheme 2).[22]

The illegal market of amphetamines is dominated by methamphetamine (street names: meth, speed, shabu, **12a**), a more potent and quicker acting analogue of the parent compound due to a better brain penetration and an increased stability against enzymatic degradation by MAO.[22] As a result, methamphetamine induces a massive efflux of catecholamines, and especially dopamine, into the synaptic cleft and unnaturally sustains their synaptic presence by inhibiting their reuptake. This increase in monoamine neurotransmission is responsible for the desired effects - energy, sense of well-being, euphoria, wakefulness - as well as the adverse health effects. These effects, although best known in the cardiovascular system (infarction, hypertensive crises), in practice affect all organs, including the well publicized dental decay (meth mouth)[26] and vision loss due to ischemic optic neuropathy. Meth is one of the most addictive recreational drugs, and, potency aside, its popularity is also related to the facility of its synthesis, that can be done by amateur chemist for personal use from easily available products.[27] *N*-methylation increases the difference in potency between the two enantiomers of methamphetamine. Thus, while the *levo* (2*R*) enantiomer has little central stimulating activity and is used in many over-the-counter nasal decongestants, the *dextro* (2*S*) enantiomer (**19**) is used, alone or in combination with a racemate, for the treatment of ADHD, obesity, narcolepsy and depression. Confusion between the two enantiomers was at the basis of the recall of the first alpine skiing medal won by a British athlete.[28] At the Olympic Games in Salt Lake City in 2002, Alain Baxter won a bronze slalom medal, but failed the drug test due to the presence of trace amounts of methamphetamine in his urine. Unaware of the presence of *levo*-methamphetamine in the American, but not the European, version of a Vicks Vaporub inhaler, Baxter had used the product to treat a cold in the days before the games, and had to return his medal. The official anti-doping method of analysis for amphetamine was based on mass spectrometry, and could therefore not distinguish between enatiomeric forms. An appeal backed up by considerable science was, unexpectedly, turned down by the Court of Arbitration in Sport in Lausanne, sparkling considerable controversy.[28] Interestingly, Maradona was booed off Argentina's World Cup team in 1994 for testing positive to ephedrine, present in the American, but not the Argentinian version, of its favourite energy drink (Rip Fuel).

The illegal synthesis of meth was once based on the reductive amination of P2P with methylamine and aluminium amalgam, or on the Leuckart reaction with *N*-methylformamide/formic acid and hydrolysis of the resulting formate (Scheme 3). Both methods afford a racemic compound, and have now been replaced by the deoxygenation of ephedrine and pseudoephedrine, that affords the much more stimulating *dextro*-enantiomer (**19**).[29] Furthermore, phenylacetic acid, the main precursor of P2P is now strictly regulated and difficult to obtain. Two methods, nicknamed Red P and Nazi, neither of which are safe outside a chemical laboratory, are now popular in small "mom and pop" labs, often set up by individuals with no background in chemistry.[22,27] The Red P method is based on the Nagai reaction, while the Nazi method is substantially a Birch reduction. Both rely on



Scheme 2 Synthesis of amphetamine from P2P (**15**) or benzaldehyde (**16**).

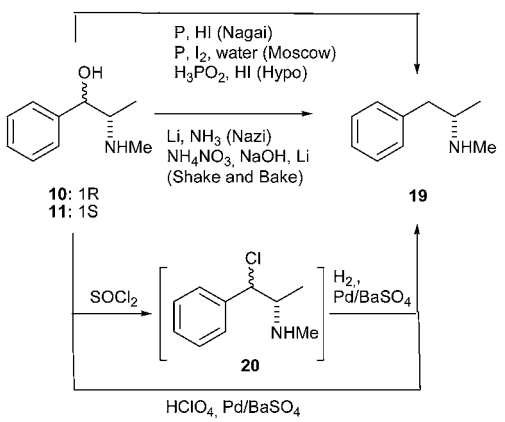


Scheme 3 Synthesis of *rac*-methamphetamine (**12a**) from P2P (**15**).

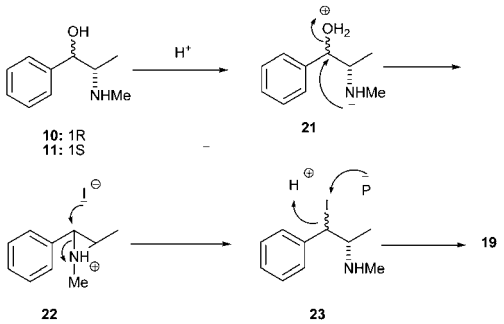
easily available products, and can be performed "on demand", given the facility of the reaction. The starting material for both syntheses is ephedrine from the illegal market (large laboratories) or pseudoephedrine from nasal decongestants (home laboratories). In the original (Nagai) version of the Red P method, ephedrine or pseudoephedrine is treated with hydriodic acid (HI) and red phosphorous (Scheme 4). The mechanism of the reaction has been elucidated (Scheme 5).[29]

The first step is an anchimerically-assisted nucleophilic substitution at the benzylic position. Thus, after protonation of the benzylic hydroxyl, an aziridinium ion is formed, next nucleophilically opened by iodide. The second step is an electrophilic benzylic substitution, where iodine is electrophilically activated by interaction with elemental phosphorous and then displaced by a proton. The reagents required by the classic version of the reaction can be replaced by red phosphorous-containing consumer products, like a matchbook striker, and by a mixture of iodine, a disinfectant for farm animals and the most common agent to sanitize the teats of milk cows, and water, that generates HI *in situ*. This version, known as the Moscow route is particularly dangerous, since the reaction of iodine with red phosphorous generates phosphorous acid, that can further react with red phosphorous to generate phosphoric acids and phosphine, a highly toxic gas.[27] Another variation uses hypophospohrous acid (H_3PO_2) as a replacement for red phosphorous, and has been nicknamed the "hypo" method.

The so called Nazi method [Nazi because it was believed to have been invented by the Nazis (wrong) or because Hitler was receiving daily injections of methamphetamine in the last years of WW2 (true)] uses lithium (from lithium photo batteries), liquid ammonia (an industrial refrigerant and a fertilizer), and toluene (from paint thinners) in the Birch version. It can be also done directly from crushed pseudoephedrine pills in a one-pot "shake and bake" fashion using a plastic soda bottle as a reaction flask. Ammonia is generated *in situ* from ammonium nitrate (from cold compress packs or from fertilizers) and lye (NaOH), lithium comes from photo batteries, and the product is extracted into a hydrocarbon solvent like Coleman fuel, a mixture of pentane, cyclohexane, heptane and octane used for lanterns and camp stoves. Despite the use of household



Scheme 4 Synthesis of *dextro*-methamphetamine (**19**) from ephedrine (**10**) and pseudoephedrine (**11**).



Scheme 5 Mechanism of the Nagai reaction.

"reagents", the shake-and-bake method has considerable risk of explosion and burns, since the container needs to be periodically opened to relieve pressure, with lithium being exposed to the air and potentially starting a fire.[30] The agricultural applications of iodine and ammonia, and the strong odour associated to the synthesis facilitate rural meth production, that has dramatic implications when carried out in an enclosed house or apartment, leading to long-lasting contamination. Fires and explosions are not uncommon, and the synthesis causes the release of noxious gases like phosphine, hydrochloric acid, and ammonia, or vapors (iodine), with considerable environmental damage. In better equipped clandestine laboratories, other deoxygenation methods based on the intermediate formation of 1-deoxy-1-chloroephedrine are used. This compound can be produced by the action of thionyl chloride, on ephedrine (pseudoephedrine), and can then dechlorinated catalytically with $Pd/BaSO_4$ (Emde method).[31] The chlorination and the benzylic hydrogenolysis can be combined in a single step (the Rosenmund method) by treatment with $HClO_4$ in the presence of $Pd/BaSO_4$.

The various methods of synthesis employed can be forensically distinguished based on the impurity profile of the final product. For instance, methamphetamine prepared according to the Nagai method contains as major impurity dimerization products like 1,3-dimethyl-2-phenylnaphthalene.[32] A large series of adulterants have also been detected in seized samples of meth, that in some cases is replaced by a mixture of caffeine and sodium benzoate, that apparently tastes like methamphetamine, and is generally used as the highly crystalline hydrochloride.[33]

The dosage of meth depends on the method of administration. Since tolerance quickly establishes, a chronic user needs 4–5-fold higher dosages than non-regular consumers.[22] An oral dosage of 10–30 mg has effects that last for 3–4 h, with an onset of 20–60 min. The same dosages, when snorted, are active after 5–10 min, and, when smoked or injected, within 2 min. Self-administration *via* anal or vaginal suppository has also been recorded.[22]

The United Nations Office of Drug and Crime estimates that amphetamine stimulants, and methamphetamine in particular, are the second most widely used illicit drug after cannabis.[34] However, methamphetamine abuse is a much more serious public health problem, not only because of the dramatic

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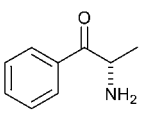
adverse health effects of amphetamine abuse, but also because of the aggressive behavior it induces, quite the opposite of cannabis abuse. It has indeed been argued that amphetamines are no better than caffeine in improving the performance of exhausted troops, but they make them more aggressive and willing to fight.[24] Furthermore, the hazardous and environmental effects of meth labs are devastating, since many of them are located in residential buildings, with exposure to amphetamines and the chemical paraphernalia associated to their production of anyone, including children, living in the same household.

3.2 Cathinone

The pseudoalkaloid cathinone (**24**) is the major stimulant agent from the khat bush (*Catha edulis* Forsk. ex Endl.), whose leaves are consumed in the Horn of Africa and Yemen in much the same way that cocoa leaves are chewed in South America.[35] The economic and social relevance of khat can hardly be underestimated. Its trade represents Ethiopia's fourth bigger export after coffee, leather and seed oils, and in some countries like Yemen, a staggering 80% of the adult male population consumes khat on a regular basis.[36] Khat, a social drug used by people to relax, must be consumed fresh, since cathinone, a primary aminoketone, is not stable in the leaves, and is quickly degraded upon drying, not only because of a predictable self-condensation, but also because of enzymatic reductive depotentiation to its corresponding alcohol, cathine (**25**).[35] Chewing is a slow method of release, and cathinone has a slower brain penetration and milder dopaminergic activity compared to amphetamines.[35] For these reasons, khat is considered one of the least harmful and addictive recreational drugs, and it is not clear if the medical problems associated to its consumption (increase incidence of oral cancers, higher risk of heart attack, marked lowering of the sperm count), are directly related to cathinone and other plant constituents, or, rather, are the result of the concomitant factors, like the associated high consumption of cigarettes in poorly ventilated chewing houses (*mafreshi*), the presence of pesticides on the leaves, generally not washed in fear of decreasing their potency, the association to caffeinated drinks to increase the stimulant effects, or a combination of all these factors.[35] The only mild psychotropic effects, similar to those of a strong coffee, their long onset period (chewing for at least one hour is generally required to feel the first effects), as well as the complexity of the supply chain that involves fresh plant material to be consumed in bulk amounts (>100 g per chewing session), have substantially prevented the diffusion of khat outside its production countries and their national groups, and the trade of khat, now illegal in the US and most of the EU countries, is limited to Ethiopian, Somali and Yemeni migrants living abroad in Western countries.[35]



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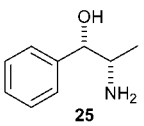

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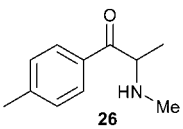

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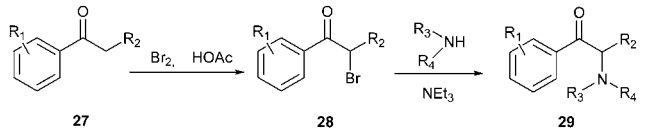
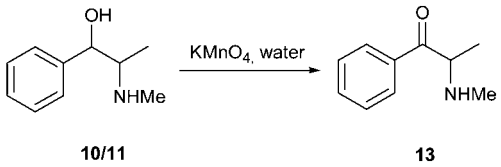
Given the mild biological profile of cathinone, it is surprising that its synthetic analogues, used in products once legally commercialized as "bath salts", are among the most successful recreational drugs ever, as exemplified by mephedrone (4-methylmetcathinone, **26**).[37] Mephedrone is not the first designer cathinone to be introduced into the illegal drug market, but is surely the most successful one. This compound was first reported as an intermediate in the synthesis of *p*-methylephedrine in 1929,[38] and languished in obscurity in the science literature until the past decade. In 2003, an anonymous underground chemist working under the pseudonym of "Kinetic" posted on a website a description of its synthesis, praising the capacity of mephedrone to induce a "fantastic sense of well-being" not unlike the one induced by ecstasy.[39,40] Interest in mephedrone was triggered by the popularity of mixtures of natural cathinones (*hagigat*) as recreational drugs in Israel.[37] When natural cathinones were outlawed in Israel in 2006, these compounds were replaced by totally synthetic analogues, whose availability was apparently related to their investigation as horticultural products. Synthetic cathinones were already present in the illegal drug market of Russia, but mephedrone was first identified in illicit samples in Australia and France in 2007,[37] and took off in popularity in the UK the following year, in the wake of three unrelated but converging events.[40] The first one was the very low quality of cocaine on the UK illegal drugs market, the result of a devaluation of the pound compared to the dollar that led to extensive cutting with less expensive agents; the second one was the shortage of ecstasy due to a spectacular seizure of a 33 tonnes of safrol-rich Selasian wood (*Cinnamomum parthenoxylum* Meisn.) oil in Cambodia,[41] that made this drug rare, expensive, and adulterated. The third one was the ban of benzylpiperazines, a popular class of mildly hallucinogenic agents. These events created a vacuum in the marked, that, backed up by an aggressive web-based marketing, was filled by mephedrone, a compound that can be synthesized easily and that at that time could be imported from abroad (mainly China) legally. In April 2010 mephedrone was banned in UK in the wake of some dubious and exaggerated press reports of fatalities and bizarre behavior associated to its consumption,[37] and most EU countries followed suit. While the actual acute toxicity of mephedrone in cellular and animal experiments is still debated, cases of clear association with toxic and even deadly side-effects have been reported in users,[42] rationalizing a banning decision that was at the time severely criticized by the scientific community due to the inconsistency of the data on which it was based.

Two reasons sustained the meteoric rise in popularity of mephedrone and other designer cathinones in the past years. The first one is the facility of their synthesis from common and legally available chemicals, resulting in an overall low price compared to other illegal drugs. The second one is their pleiotropic profile of activity, reminiscent of ecstasy, cocaine, and the hallucinogenic piperidines, all drugs in short supply at the time of the surge in popularity of mephedrone.[40] Despite a more consistent international control, the major production sites of designer cathinones are still located in China and India, and these compounds can be prepared either by total synthesis or by



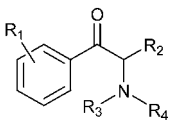
Scheme 6 Synthesis of designer cathinones from phenones (for mephedrone **26**, $R_1 = p$-Me; $R_2 = CH_3$: R_3 = Me; R_4 = H).



Scheme 7 Semisynthesis of methcathinone (**13**) from ephedrinic precursors.

semi-synthesis. The most common way of preparation is the total synthesis from phenones, as already reported in 1929 for mephedrone (Scheme 6).[38]

The process involves the treatment of a solution of a phenone (4-methylpropiophenone for **26**) in acetic acid with bromine, separation of the upper oily fraction of the α-brominated product, and treatment with an amine (methylamine hydrochloride for **26**) and triethylamine in CH_2Cl_2, with final crystallization of the hydrochloride being done from ether. The semisynthesis capitalizes on the availability of different stereochemical versions of ephedrine and pseudoephedrine. Just like amphetamines, also cathinones can be prepared from ephedrine precursors, in this case by oxidation rather than benzylic deoxygenation. An aqueous permanganate oxidation is used to prepare cathinones from ephedrinoids (enantiomeric forms of ephedrine and pseudoephedrine), resulting in a significant contamination from manganese, a toxic heavy metal (Scheme 7).[43] The enantiomeric purity of the resulting cathinones depends on that of the starting ephedrinoids, possibly resulting in variability in activity (see below). The semisynthesis from ephedrines is the preferred method of preparation for methcathinone (**13**), a popular street drug in the former Soviet Union,[42] and a spate of novel analogues has now emerged, involving, compared to the parent lead cathinone (**24**), substitution at three sites, namely the aryl moiety, the α-alkyl carbon, and the amine nitrogen. Since cathinones are oxidized amphetamine, each amphetamine can have its analogue in the cathinone series, with countless possibilities of combining modifications at these three sites. The most popular analogues of mephedrone are summarized by formula **29** (MD = methylendioxy).



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	R_1	R_2	R_3	R_4
Methcathinone	H	Me	Me	H
Methedrone	p-OMe	Me	Me	H
Methylone	3,4-MD	Me	Me	H
Buphedrone	H	Et	Me	H
Pentedrone	H	*n*-Prop	Me	H
Ethcathinone	H	Me	Et	H
α-PPP	H	Me	Me	Pyrr
MDPV	3,4-MD	Et	Pyrrolidil	

Mephedrone was initially commercialized in the form of products not intended for human consumption, like plant feeders and bath salts, making prosecution difficult and generating a sense of security and non-infringement of the law in users.[40] It is sold as a powder or, more rarely, as tablets, and the most common routes of administration are snorting and ingestion, with dosages in the range of 25–75 mg and 150–250 mg and onset of activity in the range of 5–10 min and 45–120 min, respectively.[37] Sometimes the two routes are combined to benefit from the short induction of the nasal administration and the longer duration (up to 4 h) of effect associated to the oral route. The excellent water solubility of the hydrochloride makes it also possible to administer the drug by the intravenous (injection) and the rectal (enema) methods. The most common side effects are headaches, trismus and sweating accompanied by a strong body odor, while the psychiatric and cardiovascular effects are similar to those of amphetamines.[37] Owing to a too short history of use, little is known about the chronic effects of synthetic cathinones, and mephedrone in particular, although cardiac toxicity can be predicted from the type of serotonergic activity (see below).[37] The "high" induced by mephedrone is characterized by stimulant effects (mood enhancement and alertness) combined with hallucinogenic effects, especially at high dosages, and craving is common.[37]

Little is known about the molecular, pre-clinical and clinical pharmacology of mephedrone. User reports and drug-user oriented websites are rife with often inconsistent information, and the outlaw nature of designer cathinones burdens their study with bureaucracy. Mephedrone used for recreational purposes is racemic. Based on the structure–activity relationships of cathinone as an adrenergic agent, one of the two enantiomers is expected to be more active than the other one, since (*S*)-cathinone is much more potent than (*R*)-cathinone. Enantiopure cathinones can be prepared by Friedel-Craft acylation of aromatics with either enantiomers of *N*-trifluoroacetyl aminoacyl chlorides [alanoyl chlorides for methcathinone (**13**)] in the presence of $AlCl_3$ (Scheme 8).[44] The acylation reaction works well with aromatics bearing electron-donating groups, like most substituents present in designer cathinones (as well as amphetamines). The biological profile of the enantiomers of mephedrone is, however, unknown, and might differ from that of the corresponding enantiomers of cathinone, since, due to the different molecular pharmacology of the lead compounds (see below), analogues with the same substitution pattern require individual investigation.

From a pharmacological standpoint, mephedrone is structurally similar to amphetamines and to adrenergic agents,

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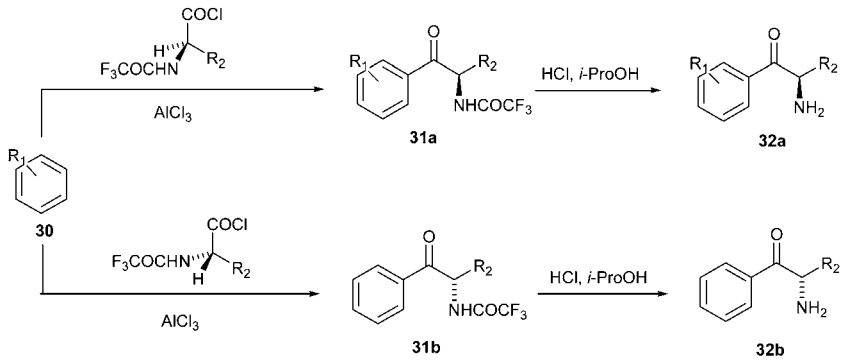
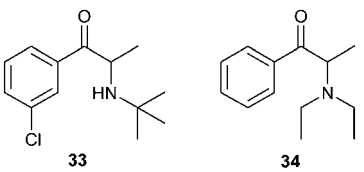


Scheme 8 Enantioselective synthesis of cathinones from *N*-protected aminoacyl chlorides and substituted aromatics.

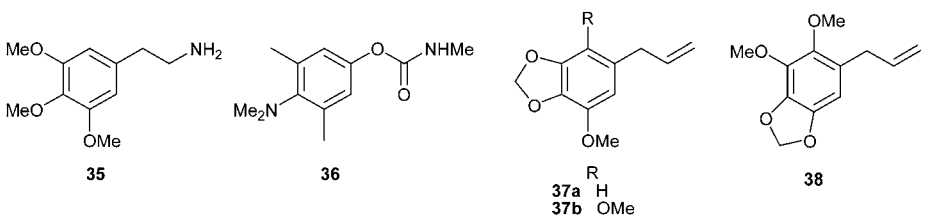
promoting the release of monoamine neurotransmitters from nerve terminals, inhibiting their uptake, and overall acting as a central nervous system stimulant.[45] However, its profile of monoamine targets significantly differs from that of amphetamines, rather resembling that of MDMA because of a potent serotonergic activity. The potentiation of serotonergic signaling has been related to a triple mechanism, namely the direct stimulation of 5-HT_{2b} receptors, the inhibition of the re-uptake of serotonin, and the displacement of serotonin from synaptic vesicles.[45] In general, affinity for 5-HT_{2b} is correlated not only to hallucinogenic properties, but also to the proliferation of cardiac valvular interstitial cells, in line with the observation that chronic consumption of mephedrone is linked to an increased incidence of valvular heart disease, just like that observed for various stimulants used as slimming agents.[42] Surprisingly, and unlike amphetamines, mephedrone is not directly toxic for dopaminergic neurons, although glial toxicity has been suggested.[46] The human metabolism of mephedrone is rather predictable, namely *N*-demethylation, reduction of the keto group to a benzylic alcohol, and stepwise oxidation of the benzylic methyl to the hydroxymethyl and carboxylate stage. Some of these metabolites are then conjugated by sulfation and glucuronidation.[47]

The regulatory status of cathinones is complicated by their similarity to some mainstream drugs, like bupropion (**33**), an atypical antidepressant also used as a smoking cessation aid, and the appetite suppressant amfepramone (**34**). Rigorous application of the American law, that makes automatically illegal all analogues of any controlled substance, would outlaw these popular drugs, while the specification of single structures cannot keep pace with the creativity of the hundreds of clandestine chemists involved in the discovery of new recreational compounds, with over 40 synthetic cathinones having already been identified in the illegal drug market.[42] The amine neurotransmitters selectivity of bupropion and amphepramone is markedly different from that of mephedrone, since bupropion is mainly active on the dopamine transporter, while amfepramone is a selective norepinephrine releasing agent.[48] It is therefore likely that the psychotropic profile of the various designer cathinones of the illegal drug market is not overlapping.



3.3 Mescaline

The hallucinogenic pseudo-alkaloid mescaline (**35**) occurs in significant amounts in peyote [*Lophophora williamsii*](Lemaire ex Salm-Dyck) Coulter], the San Pedro cactus (*Trichocereus pachanoi* Britton et Rose), and the Peruvian torch cactus (*Trichocereus peruvianus* Britton et Rose), succulent plants native to the Eastern deserts bordering the US and Mexico (*L. williamsii*) and to the Andean regions of South America (*T. pachanoi* and *T. peruvianus*).[49] These plants have been used for centuries by Native American in shamanistic ceremonies, consumed as teas or chewed dried. The existence of religious practices involving the use of peyote was already recorded in the XVI century, a few decades after the Cortez conquest of Mexico, and mescaline was isolated in 1897 by Heffter in Leipzig and structurally elucidated and synthesized in 1919 by Späth in Vienna.[50] Mescaline was the first of the hallucinogenic compounds to be characterized and synthesized, and Heffter is considered, along with Lewin, the father of modern studies on this class of compounds.

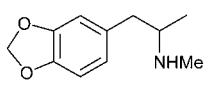


Interest in mescaline, and, in general, in hallucinogenic compounds, peaked in the Fifties, in the wake of the publication of *The Doors of Perception*, an assay where the polymath Aldous Huxley described his experience with this compound. While various artists and writers, including Sartre, experimented with mescaline at that time, by far the most far-reaching effects associated to this cultural climate and to the secularization of mescaline are those related to Alexander Shulgin. After experiencing with mescaline, Shulgin, a Berkeley graduate, developed an active interest in mind-altering drugs and the systematic study of their effect in humans. Shulgin claimed that mescaline made him aware of the existence of a world buried in our spirit, whose "*availability*" was "*catalyzed*" by chemicals. The consequences of these insights were devastating. As an employee of Dow Chemicals, Shulgin developed the successful carbamate mexacarbate (Zectran, **36**), the first biodegradable pesticide, and, as a token of gratitude, he was allowed to freely pursue his research interests. Mescaline bears structural and biosynthetic relationship with oxygenated phenylpropanoids occurring in certain essential oils like nutmeg, parsley, and dill. Since nutmeg consumption has been associated to psychotropic effects, Shulgin wondered if myristicin (**37a**), the major constituent of its essential oil, and the related phenylpropanoids apiol (**37b**) and the isomeric dillapiol (**38**), could be metabolically aminated to hybrid compounds resembling both mescaline (for the oxygenation pattern of the aryl moiety) and amphetamine (for the presence of the C3 side chain). Shulgin reported these investigations in a series of high-profile articles that appeared in *Nature* in the sixties,[51] but by this time his interests had substantially divorced from those of Dow, and in 1965 Shulgin left the company, setting up a home-made laboratory where he systematically investigated the synthesis and psychotropic properties of phenylalkylamines and indolylamines, eventually reporting his findings in two cult books he wrote with his wife, PiHKAL (Phenylethylamines I Have Known and Loved, 206 entries)[52] and TiHKAL (Tryptamines I Have Known and Loved, 55 entries)[53] that were published in the nineties. In the sixties, Shulgin became consulting for DEA, obtaining a license (revoked in 1994, two years after the publication of PiHKAL) that made it possible for him to synthesize and possess any illicit drug. It is ironic that the creator of some of the most widespread and abused illicit drugs authored in 1988 a reference book on controlled substances, received several awards from DEA, and even testified in court as an expert witness.

The name of Shulgin is closely associated to ecstasy (methylendioxymetamphetamine, MDMA, **39**), but this compound was not actually discovered by him, rather having a respectable origin as a mainstream pharmaceutical intermediate.[54] Around 1910–1912, the German company Merck was trying to bypass a Bayer patent on hydrastinine (**40a**), a semi-synthetic derivative of the alkaloid hydrastine endowed with vasoconstrictor and clotting properties. The synthesis of its 3-methyl derivative (**40b**) was investigated *via* a Pictet–Spengler approach that required the preparation of MDMA. Contrary to rumours, Merck was not interested in investigating this compound as a slimming drug, and, under the name methylsafranylamine, it was only mentioned in the patent as an intermediate to **40b**.[54] Shulgin became intrigued by MDMA in the 1976, when he was teaching at Berkeley. One of his students was suffering from stuttering, and, while finding benefits from this compound (presumably synthesized clandestinely by some underground chemist), she also praised its psychotropic properties. Shulgin, who had already synthesized MDMA in the sixties but had not experienced it, was impressed by the activity of MDMA, that he summarized as an "*altered state of consciousness with emotional and sensual overtones*".[52] The following year, he introduced the compound to Leo Zoff, a psychologist nearing retirement, who deferred retirement and started distributing MDMA to psychologists all over US. In a few years MDMDA became popular with underground psychotherapists to relax patients and enhance communication, in accordance with Shulgin's insight, that referred to ecstasy as "*his low-calorie Martini*".[52]

In a surprising twist of indications, in the early 1980 ecstasy, a meditative and relaxing agent for psychologists, emerged as an euphoric clubber drug, first in US and then in Europe. By combining the effects of amphetamines and hallucinogens, ecstasy was perceived as the perfect dance party drug, giving dancers the energy and euphoria necessary to dance for hours, and creating at the same time a feeling of warmth, intensified by an obsessively rhythmical and repetitive loud music. Eventually, MDMDA was classified as a Schedule I controlled substance in US in 1985, and in the same year the WHO recommended its ban.

Ecstasy is taken orally at a dosage of ca 100–120 mg, and its effects are felt 30–60 min after ingestion, peak after 1–2 h, and last for 4–5 h. Other methods of administration, including the rectal one, are less popular. Although lacking avert acute toxicity, the use of ecstasy can induce extreme physical exertion and sweating in dancers, causing fatal dehydration and hyperthermia. Unfortunately, the suggestion of drinking plenty of water to counteract the effects of this ecstasy-sustained behavior was wrongly perceived as an antidote to ecstasy itself, causing fatalities due to hyponatriaemia by water intoxication.[55] Ecstasy is undoubtedly related to fatalities, but the media have shown a disproportionate interest in reporting them, blaming only ecstasy for the dangers associated to rave parties, where thousands of people consume mixtures of drugs and dance to



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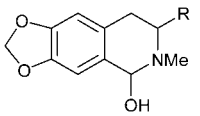
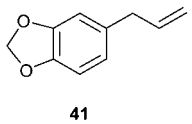


R
40a H
40b Me



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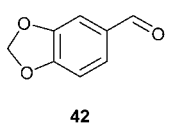

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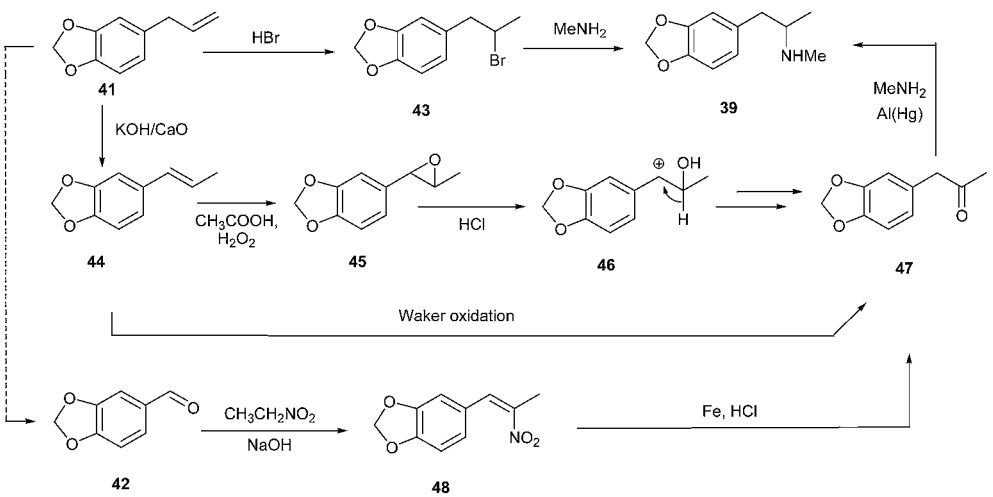
exhaustion. The chronic toxicity of ecstasy is actually highly debated. Following a retraction of a paper claiming the induction of neurotoxicity in primates after a single dosage of the compound, the issue is still substantially unsettled.[55] Just like THC from marijuana, ecstasy also holds a noteworthy medicinal potential, and positive preliminary clinical results have been reported in the treatment of post-traumatic stress disorder and anxiety associated with terminal cancer and addiction.[55]

The most common starting material for the clandestine synthesis of ecstasy is the phenylpropanoid safrole (**41**), used either as such, or *via* piperonal (**42**), its oxidative degradation product. Some essential oils have a high content (>75%) of safrole, and can be directly used as a starting material. The most common source of safrole is the oil of sassafras [*Sassafras* albidum (Nutt.) Nees], banned for human consumption because of the carcinogenicity of safrole, but still used industrially as a starting material for the preparation of piperonal (**42**), an important intermediate for pesticides, fragrances and drugs. Commercially, safrole-rich oils are named sassafras oil regardless of their source. Since the trade and the transport of safrole and piperonal are monitored internationally, an illicit market from wild-growing plants has developed, with considerable ecological damage to the South-Asian rainforests, the source of one of the best sources of safrole, the lauraceous tree *Cinnamomum parthenoxylon* Meisn.[56] After depleting Vietnam of the plant, the safrole mafia moved to Cambodia, operating clandestine distillation factories in the Western Cardamom mountains, the last refuge for some of the world's most threatened animal species, including the Asian elephant, the Indochinese tiger, and the Siamese crocodile. In one single operation, 33 metric tons of safrole-rich oil were destroyed in Cambodia in 2008,[56] eventually triggering the replacement of ecstasy with mephedrone in the illegal drug market in Europe (see above). Overcollection of *Ocotea cymbarum* Kunth made Brazil the major world exporter of safrole until the sixties, but this plant is now included in the IUCN red list of endangered species.[57]

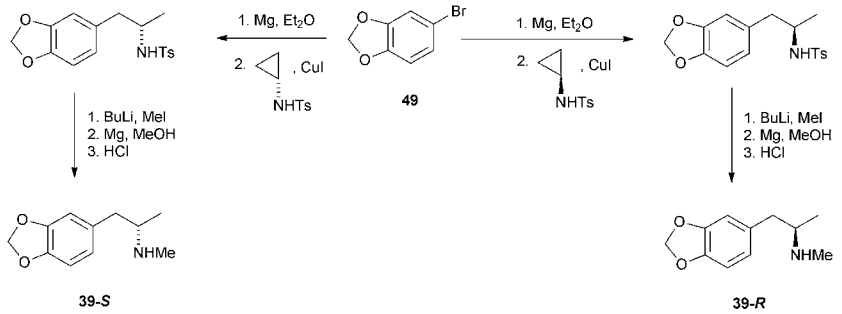
The most direct synthesis of MDMA from safrole (**41**) is the one described in the original Merck patent of 1912. The preparation involves hydrobromination to the homoallylic secondary bromide **43**, then displaced with methylamine (Scheme 9). Alternatively, MDMA is obtained by reductive amination of piperonyl acetone (3,4-methylendioxyphenyl-2-propanone, MDP2P, **47**) with methylamine in the presence of aluminum amalgam. DDP2P can in turn, be prepared from safrole by isomerization in basic medium to isosafrole (**44**), epoxidation to **45** and treatment with acid, by a Waker oxidation in the presence of palladium, or, alternatively, from piperonal (**42**) by a Henry reaction with nitroethane and next reduction of **48** with Fe/HCl.

All these syntheses afford racemic MDMA. The synthesis of enantiopure forms of MDMA is based on the chemo- and stereoselective opening of an alanine-derived chiral tosylaziridine by the Grignard derivative of 4-bromomethylendioxybenzene (**49**) (Scheme 10). The synthesis is completed by a reductive methylation and detosylation.[58] Remarkably, and in contrast with amphetamines, both enantiomers of MDMA show bioactivity, with, however, a different target profile, metabolism and toxicity. The *S*(+) enantiomer (**39-*S***) has dopamine-mediated stimulant-like effects, is more neurotoxic, and is mainly eliminated as glucuronide, while the *R*(-) enantiomer (**39-*R***) is mostly hallucinogenic *via* a potentiation of serotonergic responses, less toxic, and is eliminated by sulfate conjugation.[59-61] Given this peculiar profile of racemic MDMA, only this form is produced in the illegal manufacture.

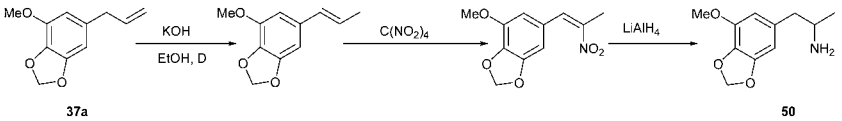
Ecstasy was actually only a latecomer in the spate of psychotropic oxygenated phenylpropanamines that Shulgin developed from phenylpropanoid-containing essential oils.[62] In the early sixties, Shulgin had already described the conversion of myristicine from nutmeg into 3-methoxy-4,5-methylenedioxyamphetamine (MMDA, **50**) (Scheme 11),[51a] a compound 3 times more potent than mescaline, that next served as a lead compound for extensive structure–activity studies. These focused on the length of the aliphatic chain,[63] the



Scheme 9 Synthesis of MDMA (**39**) from safrole (**41**) or piperonal (**42**).



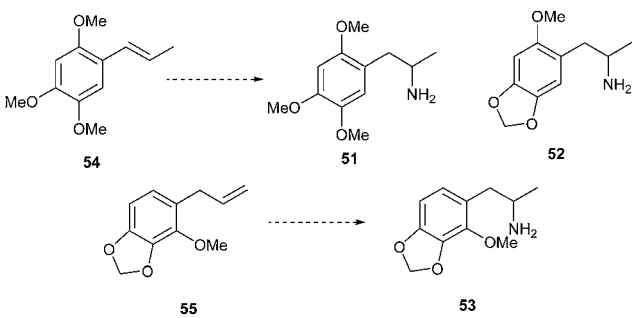
Scheme 10 Asymmetric synthesis of *S*- and *R*- MDMA.



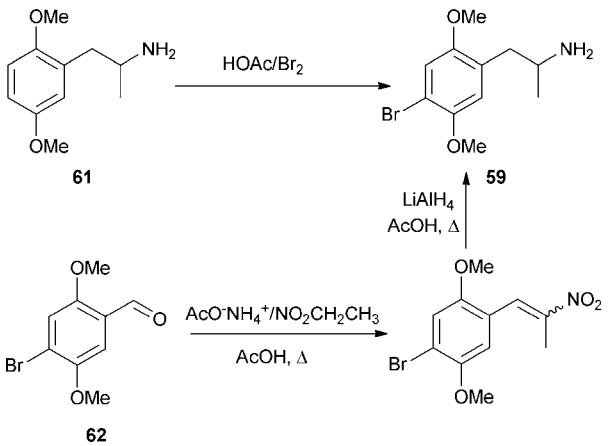
Scheme 11 Synthesis of MMDA (**50**) from myristicine (**37a**).

shift of the *meta*-methoxyl to one of the *ortho*-positions,[64] the increase of the oxygenation pattern of the aryl moiety,[51c] and the introduction of various substituents at the carbon *para* to the alkyl chain.[64]

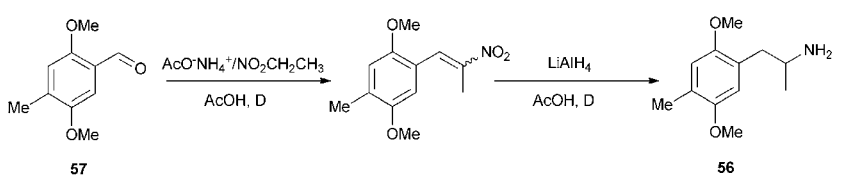
New potent hallucinogenic compounds that emerged from these studies were TMA-2 (**51**), MMDA-2 (**52**) and MMDA-3a (**53**) whose potency in terms of mescaline units was 17, 21 and 18.[51c] With the exception of MMDA-2, the phenylpropanoid precursors of these compounds were obtained from essential oil constituents,[51c] with asarone (**54**) and croweacin (**55**) serving as precursors of TMA-2 and MMDA-3a, respectively.



To improve metabolic stability and avoid demethoxylation and conjugation, Shulgin next replaced the 4-methoxy group of TMA-2 with a methyl group, obtaining 2,5-dimethoxy-4-methylamphetamine (DOM, **56**), known with the acronym STP (*Serenity*, *Tranquillity and Peace*, or, alternatively, *Super Terrific Psychedelic*, or *Stop The Police*, in the street drugs lingo). The active dosage of STP is as low as 5 mg, but it was sold in tablets containing *ca.* 20 mg of active ingredient, triggering severe cases of overdose-related panic and confusion that required hospitalization, a prelude to similar, but deadly, cases that occurred with further analogues.[52] Shulgin published the synthesis of DOM in 1970, using 2,5-dimethoxy-4-methylbenzaldehyde (**57**) as a starting material, capitalizing on a Henry reaction with nitromethane to extend the chain, followed by nitro-to-amine reduction (Scheme 12).[65]



Scheme 13 Synthesis of DOB (**59**) from **61** or **62**.



Scheme 12 Synthesis of DOM (**56**) from **57**.

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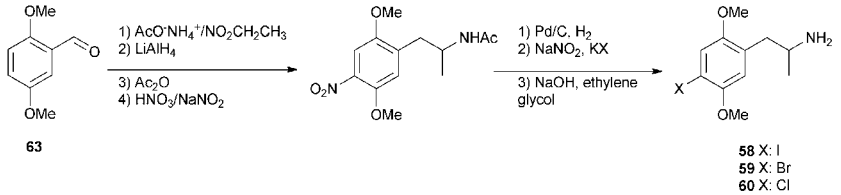
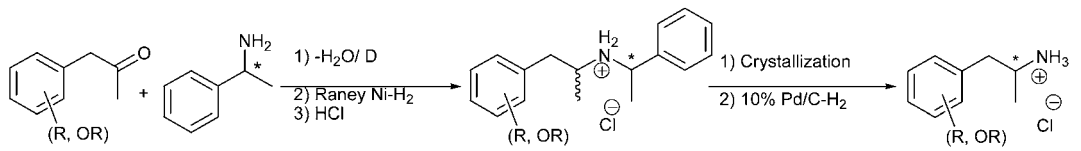


Scheme 14 Synthesis of DOI (**58**), DOB (**59**) and DOC (**60**) from **63**.

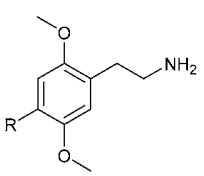


Scheme 15 Synthesis of enantiopure DO(X) entries.

The next step was the replacement of the benzylic methyl of DOM with an halogen atom, either iodine, bromine or chlorine, generating DOI (**58**), DOB (**59**) and DOC (**60**), respectively, active at dosages of 1.5–3 mg and longer acting than DOM. Two different processes for obtaining DOB were published in 1971 by Shulgin[65] and by Barfknecht,[66] starting from 2,5-dimethoxyamphetamine (**61**) and 4-bromo-2,5-dimethoxyaldehyde (**62**), respectively (Scheme 13), while a general entry to all three analogues based on the halogenolysis of a diazonium salt was later developed from 2,5-dimethoxybenzaldehyde (**63**) (Scheme 14).[67]

All these new oxygenated amphetamines were first synthesized as racemates, but the marked difference in activity between the enantiomers of methamphetamine fostered the development of enantioselective synthetic entries. Capitalizing on early work by Weinges and Graab,[68] Nichols reported an efficient asymmetric entry into enantiopure methoxylated amphetamines.[69] The method is based on the formation of a homochiral imine by reaction with an enantiopure α-methylbenzylamine and a ring-substituited phenylacetone. Reduction with H_2 and Ni-RANEY® afforded a diastereomeric mixture, that could be resolved by crystallization or chromatography, eventually providing enantiopure amines after reduction (Scheme 15). As for other psychedelics, the *R* isomer is more active than the racemic mixture, and the *S* is much less active.

The following class of methoxylated amphetamines discovered by Shulgin became known as 2C-x, a shortened version of the previous compounds, characterized by a two-carbon alkyl chain and a *para*-substitution, whose most popular members became known as 2C-I (**64**), 2C-B (**65**), 2C-C (**66**), 2C-T2 (**67**) and 2C-T7 (**68**) with the substituent being, respectively, iodine, bromine, chlorine, and an ethylthio or n-propylthio groups.[70,71]

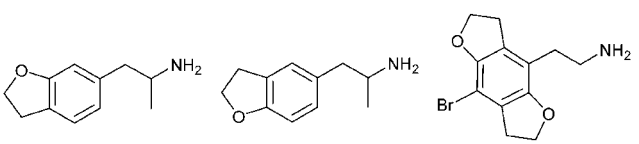


	R
64	I
65	Br
66	Cl
67	-SCH_2CH_3
68	-$SCH_2CH_2CH_3$

A further elaboration of these compounds led to psychotropic agents of the NBOMe series.[72] The 2-methoxybenzyl decoration on the basic nitrogen seems to be due to Nichols, resulting in such an improvement of potency that "*small breezes*, *accidental inhalation*, *or touching the eyes or mouth after handling could result in full-blown effects or dangerous overdoses*".[73] Within these compounds, 2- (25I-NBOMe) (**69**), nicknamed Smiley Paper, Bomb-25 or N-Bomb,[74] became popular with psychonauts. This compound can be prepared in four steps from 2,5-dimethoxybenzadehyde (**63**) (Scheme 16), and its tritiated version was developed by Nichols as a radioligand for human 5-HT_{2A}receptors.[75]

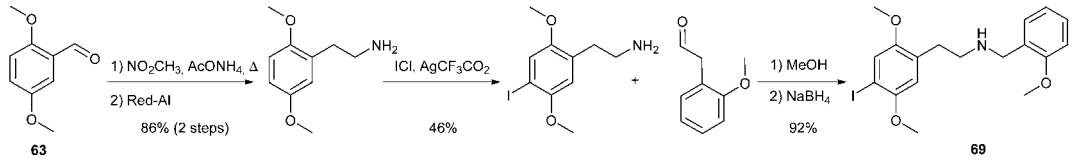
Nichols also developed the aminoindane tethered analogues of the 2C-x compounds, as exemplified by 5,6-methylenedioxy-2-aminoindane (MDAI) (**70**), prepared in two steps from 3,4-methylendioxy-1-indanone (**71**) (Scheme 17),[76] and marketed as "the research equivalent of methylone".

2,3-Dihydrobenzofuran derivatives constitute a further class of psychedelic agents discovered by Nichols. These compounds were developed in the wake of information, from an underground chemist, of their highly potent activity.[77] The first products synthesized were 5–40 times less potent than DOM, but the isosteric replacement of one of the dioxolane oxygens with a methylene in compounds of the C3-x series gave highly potent compounds with a reduced neurotoxicity compared to their lead structures, as exemplified by 6-APDB (**72**) and 5-APDB (**73**).[78]

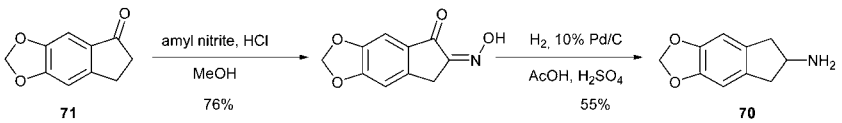


72 **73** **74**

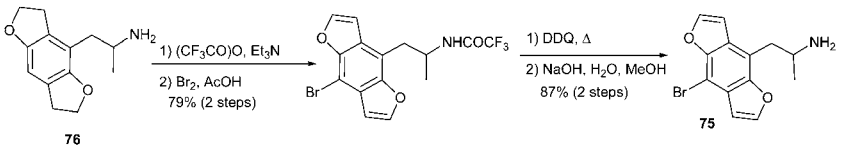
Further tinkering on the structure of 2C-x compounds afforded analogues of the 2C-x-FLY series, where x defines the substituent at position 8 and FLY the presence of two dihydrofuran rings protruding from the oppositely sides of the benzene ring. The compound with a bromine substituent found



Scheme 16 Synthesis of 25I-NBOMe (**69**) from **63**.



Scheme 17 Synthesis of MDAI (**70**) from 3,4-methylendioxy-1-indanone (**71**).

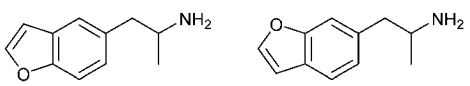


Scheme 18 Synthesis of bromo-dragonFLY (**75**) from **76**.

widespread use as a recreational drug under the name 2C-B-FLY (**74**), and has been associated with causalities in Denmark and California because of confusion with less potent analogues.[79]

Aromatization of the dihydrofuran moieties of 2C-x-FLY led to a class of ultrapotent analogues of mescaline, nicknamed dragonFLYs because their structures appear reminiscent of the homonymous insect.[80] Many of these compounds outperform the natural product by at least two orders of magnitude, rivalling LSD in terms of potency. The bromo-dragonFLY (**75**) is the most (in)famous member of this class of hallucinogens. It is active at dosages as low as 500 μg, and its effects last up to 2–3 days.[81] Unsurprisingly, bromo-dragonFLY has been involved in severe side-effects and the death of users, also because of the difficulty of dosing with the often rudimental equipment of clandestine laboratories. Bromo-dragonFLY (**75**) is prepared from the FLY precursor **76** by protection of the primary amino group, bromination, aromatization with DDQ, and deprotection (Scheme 18).[82] An asymmetric version of the synthesis has also been published by Nichols, and the biological evaluation of the two enantiomers in terms 5-HT_{2A} and 5-HT_{2C} binding showed only modest selectivity, although a higher potency for the *S*-enantiomer was found in functional studies (phosphoinositide hydrolysis).[83] These results are broadly in line with the general observation that the enantioselectivity of action is more marked in the adrenergic activity of unsubstituted phenethylamine compared to the serotonergic activity of their oxygenated analogues.

The benzofuran analogues of MDA known as 5-APB (**77**) and 6-APB (**78**)[84] (nicknamed Benzo Fury) are recent additions to the illegal drugs market, and are often confused with 5-APDB (**72**) and 6-APDB (**73**) with dramatic effects on users because of the different potency of compounds from the two classes.



When seen from a medicinal chemistry perspective, the tolerance to chemical modification of the mescaline framework is amazing. The key to the improvements in potency seems the conformational constraint associated to the methoxy groups and the alkylamine moiety. In the case of the *ortho*-dimethoxy groups, this conformational constraint is associated to a reduced mesomeric interaction between the phenolic oxygen atoms and the aromatic ring, since closure of the 5-membered ring leads to a deviation from planarity between the oxygen lone-pairs and the aromatic π-system. Finally, while the methylendioxy motif is common in plant phenylpropanoids, it rarely occurs in arylalkyl amines, leaving to human ingenuity the unnatural marriage of these structural elements.

3.4 Tryptamines

Owing to their close structural similarity with the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT), tryptamines can promiscuously interact with various 5-HT receptor subtypes, including 5-HT_{2A} and 5-HT_{2C}. The stimulation of these receptors in the brain is associated with hallucinogenic sensations, but, due the widespread distribution of 5-HT receptors and to the adrenergic traits of some of them, this is generally accompanied by peripheral symptoms like tachycardia, hypertension, nausea/vomiting, and tremors. In otherwise healthy individuals, the hallucinogenic tryptamines are rarely lethal *per se*,[85] but can induce life-threatening behaviors as well as a series of long-term impairments of cerebral performances.

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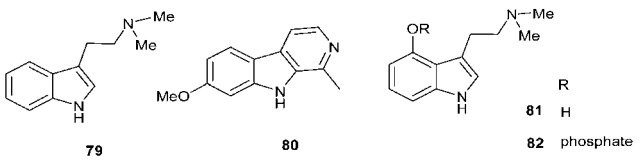
The most widespread tryptamine is *N*,*N*-dimethyltryptamine (DMT, **79**), a compound present in plants, insects and amphibians as well as in human plasma and brain. The role of endogenous DMT is controversial. It was initially suspected to induce schizophrenic behaviors in patients having abnormally low platelet MAO levels, but this association was questioned in later studies.[86] The hallucinogenic properties of **79** are quenched *in vivo* by a MAO-mediated rapid metabolism, but combination with MAO-inhibitors can indeed lead to potent hallucinogenic mixtures. The most famous of these combinations is Ayahuasca, a South-American beverage containing the stems of *Banisteriopsis caapi* (Malpighiaceae) and the leaves of *Psychotria viridis* (Rubiaceae) that has recently made headline news because of the development of a Ayuhasca-based "hallucinogenic tourism" in Peru. *B. caapi* contains the β-carboline alkaloid harmine (**80**), a potent MAO-inhibitor, while the leaves of *P. viridis* contain large amounts of DMT, about 7.50 mg g^{-1} of dry weight.

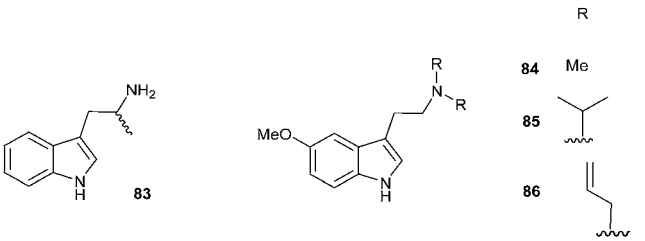


Another DMT-rich plant is *Mimosa hostilis* (Leguminosae), known as jurema in Mexico and Brazil, where its root barks are used to prepare an hallucinogenic infusion. However, due to the MAO metabolism, this plant exerts mild effects when consumed alone. It is possible to find on the internet several examples of association with *Peganum harmala*, another plant containing MAO inhibiting β-carbolines. These mixtures are often referred as *Ana*huasca (meaning *analogue* of ayahuasca).[87]

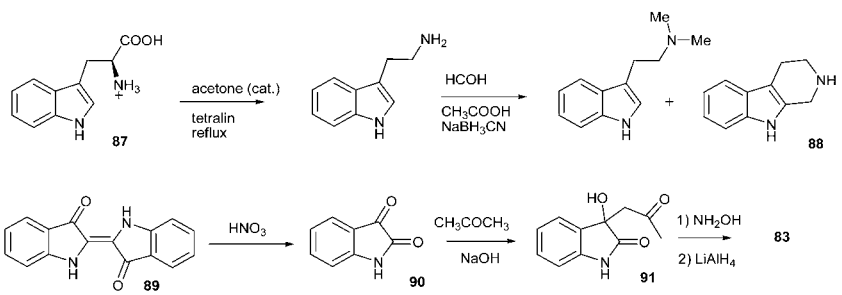
Secondary metabolites structurally similar to DMT are contained in the skin of the toad *Bufus marinus* (5-hydroxy-DMT), and in psychoactive fungi of the genus *Psilocybe* known as "magic mushrooms" [psilocin (**81**) and psilocybin (**82**)]. These mushrooms are still available on the recreational market. Rather than purchasing the illegal isolated active principles, consumers prefer to buy home-grow kits of spores and cultivate them to get the hallucinogenic fruit bodies, that next are eaten raw or used to prepare a tea.

Most natural tryptamines and their plant sources show only moderate psychotropic effects, and are either illegal or heavily regulated. This, and the lack of structural sophistication of many of them, has fostered their replacement with synthetic analogues. According to the United Nations Office on Drugs and Crime World Drug Report, until mid-2012, 10% of the identified synthetic recreational drugs were tryptamines, after cannabinoids (23%), amphetamines (23%), and cathinones (18%), respectively.[34]

Synthetic tryptamines act as serotonin analogs, showing *in vitro* affinity for the 5-HT_{2A} receptor, the most important receptor that mediates their hallucinogenic effects, but also for the 5-HT_{1A} and 5-HT_{2C} receptors.[88] In addition, some of them could act as competitive inhibitors of the serotonin re-uptake transporter, thus increasing the amount of circulating serotonin.[89] Within the many psychotropic tryptamines described by Shulgin in TIHKAL,[53] *rac*-α-methyltryptamine (AMT, **83**), and three *N*,*N*-disubstituted 5-methoxytryptamines [*N*,*N*-dimetyl- (5-MeO-DMT, **84**), *N*,*N*-diisopropyl- (5-MeO-DIPT, **85**, street name: *foxy methoxy*) and *N*,*N*-diallyl- (5-MeO-DALT, **86**)] are the most widely used. The case of 5-MeO-DALT (**86**) is interesting from a regulatory standpoint. This compound is legal in UK, because the allyl group does not fall into the category of alkyl groups, which the law requires for a tryptamine to be included into the Class A of the tryptamines controlled by the Misuse of Drugs Act 1971. Conversely, the compound is regulated in other European countries and Japan.



The α-methyl substitution of AMT slows down its inactivation by MAOs, resulting in a longer-lasting action, while the oxygenation of the indole phenyl ring increases its potency at 5-HT_{2A},[90] the main mechanism underlying the psychoactive effects.[91] The common dose to induce hallucinations is about 1 mg Kg^{-1} by parenteral administration or inhalation. Users' experiences reported on Erowid (www.erowid.org) confirm the existence of significant differences in the duration of the psychedelic effects, with AMT producing longer-lasting effects compared to the other compounds. Just like ecstasy, AMT can be sniffed, injected intravenously, smoked or also ingested orally, with the onset of the psychedelic experience varying according to the administration route ranging from a few seconds (inhalation) to 30 min (oral ingestion). AMT is obtained by clandestine chemists as a racemic mixture (see Scheme 19),



Scheme 19 Synthesis of tryptamines from tryptophan (top) and from indigo (bottom).

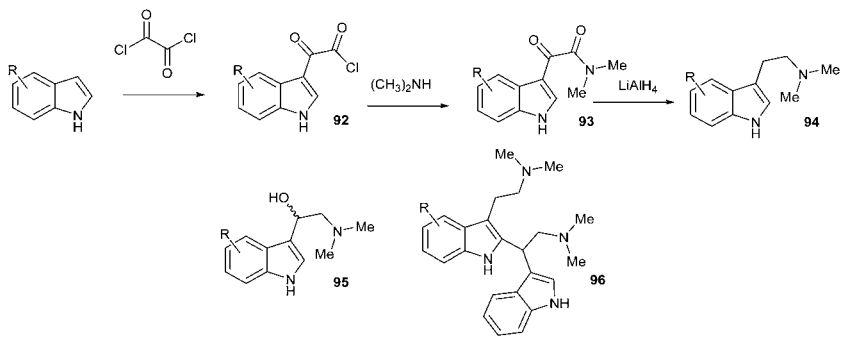
but, just like with amphetamines, one of the enantiomers (the *S*- in this case) is 3–4 times more potent than the other one.[53] This trend was confirmed also for the 5-methoxy and 4-hydroxy derivatives of AMT. Neither the resolution of racemic **83** nor its asymmetric synthesis are trivial, and its street version is essentially the racemate.

The synthesis of the 3-(2-ethylamine)indole nucleus of hallucinogenic tryptamines is relatively easy from an organic chemistry perspective, and clandestine chemists likely experience little problems in their work, given the easy availability of precursors. A countless number of possible synthetic routes are reported on the internet and in this paragraph only a general account will be provided. The purity profile of the final products put into the market is another very important issue to be considered; indeed, many indole-containing derivatives show biological activity, and the presence of intermediates or by-products within a poorly purified product could have potential clinical implications that are practically unknown.

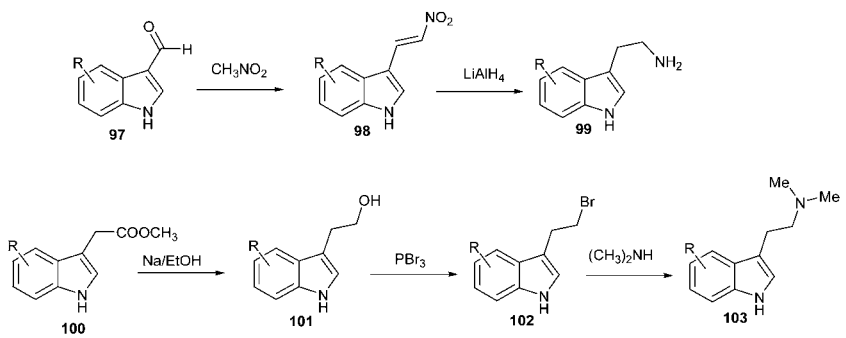
Tryptamine can be easily obtained by decarboxylation of the proteogenic amino acid tryptophan (**87**, Scheme 19), easily available in the market as a dietary supplement.[92] The procedure involves the use of high-boiling solvents (as tetralin), and the rate of the reaction can be increased in presence of catalytic amounts of carbonyl derivatives, presumably due to the formation of the corresponding Schiff bases. The most used and economically affordable decarboxylation auxiliary is acetone, but other variants are also popular, including essential oils rich in carbonyl derivatives, like spearmint oil that contains up 80% *R*-carvone. The alkylation of tryptamine by treatment with alkyl halides is not a practical route since, as expected, it affords mixtures of polyalkylated products, including the corresponding quaternary ammonium salts. Reductive amination in acidic conditions (sodium cyanoborohydride, glacial acetic acid, formaldehyde) can give DMT in moderate to good yields, but care is required to avoid the Pictet–Spengler cyclocondensation of the intermediate Schiff base to tetrahydrocarbolines (**88**). This reaction also plagues the use of essential oils as decarboxylation promoters, leading to contamination with β-carboline derivatives.[93] Despite these drawbacks, this synthesis is still very popular in the underground chemistry community, in whose lingo it is referred to as "*the breath of hope synthesis*".[93]

The industrial dye indigo (**89**) is also used as a starting material for the synthesis of AMT. After oxidative cleavage with nitric acid (or oxygen/ozone in NaOH) to isatin (**90**), aldol reaction with acetone affords the oxindole **91** that, after formation of the oxime and reduction with $LiAlH_4$ gives racemic AMT *via* a combined reduction of the amide carbonyl and the oxime double bond.

The alternative routes can be broadly divided into two classes, depending on the starting material (indole or substitutes indoles *vs.* aniline derivatives). One popular route belonging to the first class is based on the venerable Speeter–Anthony synthesis of triptamines (Scheme 20).[94] Indole is acylated with oxalyl chloride to **92**, next followed by amide **93** formation and global reduction with an excess of $LiAlH_4$ to **94**. The hypotensive[95] pseudo-benzylic alcohol **95** and its dimerization product **96**, whose biological profile is completely



Scheme 20 The Speeter–Anthony method for synthesis of tryptamines.



Scheme 21 Tryptamine synthesis starting from indole-3-carbaldehydes (**97**) and esters of indole-3-acetic acids (**100**).

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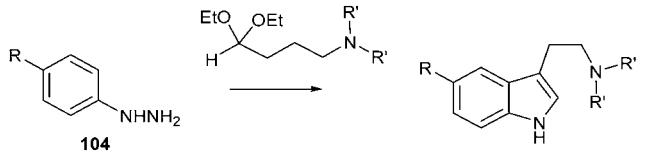


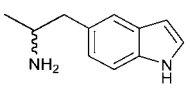
Scheme 22 General Fischer synthesis of tryptamines.

unknown, are the most common by-products formed in the reaction, and often contaminate the street drug.

Another convenient starting material is indole-3-carbaldehyde(s) (**97**) that can be condensed with nitromethane (or nitroethane to obtain AMT) in the presence of weakly basic catalysts (Henry reaction) to give nitroethenyl indoles (**98**), next reduced to tryptamines **99** with $LiAlH_4$. Since nitroethenyl indoles are the substrates for Michael additions with 3-unsubstituted indoles, a certain amount of dimeric by-products can be formed during the synthesis. An alternative route starts from the indole-3-acetic acids that, as methyl esters (**100**), are reduced with Na/EtOH to tryptophol (**101**). This is converted to substituted tryptamines **103** *via* conversion to the bromine derivatives **102** with PBr_3 followed by reaction with secondary amines (Scheme 21).

Due to the higher reactivity of the pyrrole moiety of indole, 4- 5- or 6-substituted indole derivatives are generally obtained from suitably substituted benzene derivatives rather than from their corresponding unfunctionalized indole derivatives. A wide range of substituted phenyl hydrazines (**104**) can readily give rise to the indole ring *via* a Fischer synthesis with protected aldehydes (4-aminobutyraldehydes) or ketones (5-substituted pentan-2-ones) (Scheme 22).

Synthetic tryptamines, such as 5-MeO-DALT, have similar UV spectra compared to naturally occurring tryptamines, and this may lead forensic toxicologists to overlook the possibility of their ingestion. Analysis for the determination of natural alkaloids such as harmine and DMT in several human fluids (blood, urine, bile, *etc.*) are usually carried out through GC-MS or LC-MS systems. A common pattern of fragmentation has been generalized for tryptamine derivatives and this can be very useful to guide the mass spectral interpretation of these simple compounds.[96] A liquid chromatography-linear ion trap mass spectrometry method has been very recently validated for the detection and quantification of tryptamine derivatives in human plasma.[97]



105

Compared to other classes of recreational compounds, "innovations" are less frequent with tryptamines. A recent example is 5-(2-aminopropyl)indole (**105**), a positional isomer of AMT that has been linked to numerous fatalities. AMT and **105** can be differentiated on the basis of the mass fragmentation pattern and the UV spectrum.[98]

3.5 Cannabinoids

The ten-year old story of the introduction and diffusion of Spice in the recreational drug community exemplifies the difficulties associated with the regulation and control of the illegal market of synthetic drugs.

The name Spice was created by the now disappeared company Psyche Deli for a line of herbal products sold into brightly coloured bags and containing a few grams (1–3 g) of mixtures of dried and crushed plant parts (flowers, stems, leaves) from various aromatic species. These complex blends became known as "herbal incense" in smoke shops and convenience stores. Their composition was highly variable, and included parts of fully "legal" plants like *Leonotis leonurus*, *Pedicularis densiflora*, *Scutellaria nana*, *Nymphacea caerulea*, and *Canavalia maritima* rumoured to be endowed with mild psychoactive properties. These products are advertised as 'exotic incense blend which releases a rich aroma' and 'not for human consumption', but are commonly smoked through conventional cannabis pipes or wrapped up as cigarettes, inducing euphoric effects similar to those associated to the consumption of cannabis products.

Starting from 2004, and thanks mainly to the internet, Spice invaded first Europe and next the US, where it is now considered to be among the most frequently used illicit substances after cannabis. Additional brand names were given to the same or similar products, such as K2, Bombay Blue, Yucatan Fire, Bliss, Blue Lotus, Black Mamba and many others, testifying to the great imagination of both producers and consumers and also the intensity of the high a consumer might experience.

At the beginning of 2009, several academic and forensic analyses revealed that the herbal products contained in Spice were actually laced with mixtures of psychotropic compounds mainly, but not exclusively, composed by synthetic agonists of CB_1 receptors, the same receptor activated by Δ^9-tetrahydrocannabinol (Δ^9-THC, **106**) contained in marijuana, and by its endogenous biological analogues (*e.g.* anandamide, 2AG).[99] Although these compounds are structurally unrelated to the phytocannabinoids, their interaction with brain cannabinoid receptors triggers psychotropic effects that closely mimic and outperform those provoked by phytocannabinoids.

Before their use in Spice preparations, these synthetic and semi-synthetic cannabinoids were available only in academia and in pharmaceutical research centres, where they had been developed to decipher the complex pharmacology of cannabinoid receptors. The role of synthetic and semi-synthetic cannabinoids in the discovery of cannabinoid receptors and their endogenous ligands can hardly be overestimated. Because of a much higher affinity for their biological targets compared to THC, these compounds undergo less nonspecific binding. Using a tritiated versions of CP55940, it was, indeed, possible to demonstrate the presence of specific binding sites in rat brain membranes,[100] while the displacement of ([^{3}H]HU243) from rat brain membranes provided the first evidence for the existence endogenous versions of THC in biological fluids. Synthetic tritiated cannabinoids are still an indispensable pharmacological tool for cannabinoid research.

Due to their restricted availability and difficult preparation, synthetic cannabinoids were not included in the lists of illegal substances, and they were therefore transparent to the forensic methods used to detect cannabinoids, namely GC-MS/HPLC screening or immunological assay. However, this scenario changed dramatically with the discovery in the nineties that some simple pyrrole and indole derivatives act as potent cannabinomimetic agents, leading to their widespread use as an alternative to marijuana. Over the years, international agencies became increasingly concerned about the danger posed by synthetic cannabinoids, as testified by the detailed overview on this topic published in 2011 by United Nations Office on Drugs and Crime (UNODC).[101] Currently, several detections methods are available, and the whole class of synthetic cannabinoids has been banned from commercialization.

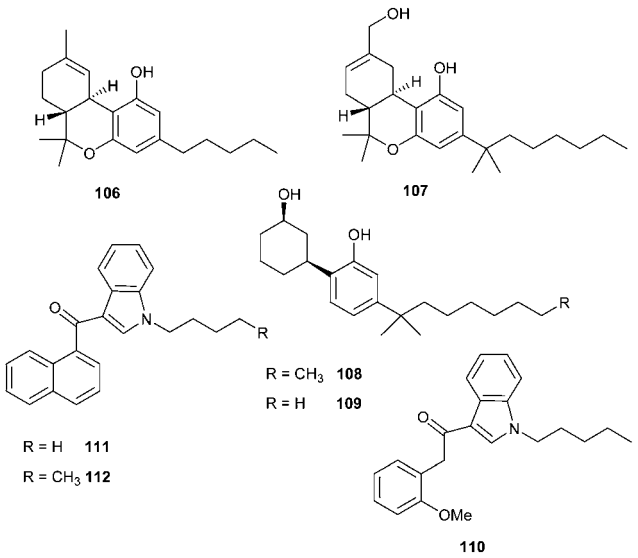
The class of synthetic cannabinoids is structurally heterogeneous, including more than 100 different compounds, many of which have been included in Spice and similar blends, whose composition is continuously changed to dodge detection. The most important synthetic cannabinoids can be grouped into four main structural classes, whose archetypal compounds are presented below:

i) classical cannabinoids (*e.g.* HU-210, **107**);[102]

ii) cyclohexylphenols (*e.g.* cannabicyclohexanol, **108**, and CP-47,497, **109**);[103]

iii) phenylacetylindoles (*e.g.* JWH-250, **110**);

iv) naphthoylindoles (*e.g.* JWH-073, **111**, and JWH-018, **112**).



The abbreviation HU stands for Hebrew University (Raphael Mechoulam, working at this University, has been a pioneer in the study of cannabinoids), while JWH stands for John Williams Huffman, a now retired researcher at the Clemson University, South Carolina, USA, who developed all the compounds marked with his initials. CP-47,497 (**109**) was initially developed at Pfizer in 1980s, while its 1,1-dimethyloctyl analogue, named cannabicyclohexanol (**108**), has been "invented" by the producers of a Spice product and detected for the first time in the January 2009 at the University of Freiburg, Germany.

The common chemical traits of these compounds are the lipophilicity and a relatively high volatility. These properties make it possible to spray them on mixtures of herbs, and, once inhaled when heated, they eventually reach the brain, with a rapid onset of a marijuana-like effect. Structurally, all the compounds of these classes are invariably characterized by an alkyl chain reminiscent of the pentyl side chain of Δ^9-THC, a critical element for the interaction with the cannabinoid receptors.[100] Indeed, a decrease in the length of this side chain results in a reduction of potency and in the appearing of dose-dependent antagonist behaviour,[104] while an increase to C_7 or C_8 results in a systematic increase in affinity. Longer chains cause again a loss of efficacy. In addition, a single or a double methyl branching on this side chain, such as those shown by HU-210 (**107**) and CP47,497 (**109**), considerably increases the affinity for the G-protein coupled CB_1 receptor.[105] Intriguingly, the octyl-derivative cannabicyclohexanol turned out to be several times more potent than the Pfizer heptyl-derivative CP47,497, and this is a surprising result if we consider that in the class of classical cannabinoids, HU-210 is more potent than its octyl analogue.

As often happens for scientific progresses, the invention of non-classical cannabinoids was the result of serendipitous discoveries. It can be dated back to the 1980s, when Sterling-Winthrop, an American pharmaceutical company, was working on analgesic and anti-inflammatory drugs inspired by indomethacin (**113**). They found that one of their products, pravadoline (**114**, WIN 48,098), as expected, inhibited prostaglandin synthesis acting through inhibition of the enzyme cyclooxygenase (COX). However, the strong antinociceptive effects exhibited by pravadoline were not explainable with the simple COX inhibition and, at the same time, the involvement of the opioid system was excluded by the evidence that naloxone and other opioid antagonists were not able to block this effect. At the beginning of 1990s, the characterization of the cannabinoid receptor CB_1 offered to the Sterling researchers the solution to the pravadoline enigma, leading to the discovery that these aminoalkylindoles could bind to the same receptor as Δ^9-THC and its analogues.[106]

The exploration of the structure-activity relationship (SAR) of aminoalkylindoles for this receptor and the areas of potential overlap with previously established cannabinoid SAR constituted the starting point of the research activity of J. W. Huffman in this field, begun about 20 years ago and financed by National Institute of Drug Abuse (NIDA). At that time, the most popular model for the interpretation of cannabinoid ligand–receptor interaction was the 3-point model elaborated a few years before by Thomas *et al.*[107] In the light of this model and using the naphthoyl derivative WIN55,212-2 (**115**), another Sterling product, as a starting point, Huffman hypothesized that the attachment location for the morpholino group could correspond to the pentyl side chain of Δ^9-THC. To test this hypothesis, the Huffman group prepared a series of naphthoyl indole derivatives where a simple alkyl group took the place of the oxazine and morpholine rings and the methyl group was eliminated from the indole ring. The high potency of these derivatives clearly demonstrated that a cyclic amino group at that

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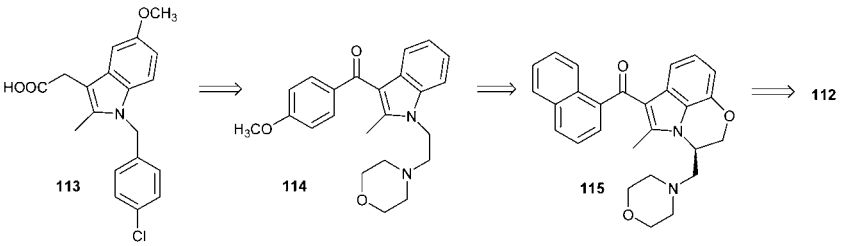


Scheme 23 The ancestors of JWH naphthoylindole cannabinoids.

position was not necessary for CB_1 agonism and the derivative bearing an n-pentyl group (JWH-018, **112**, Scheme 23) was the most active in this series of compounds.[108] Interestingly, some less potent analogues of JWH-018 described in the first publication from the Huffman's group have been recently found in some Spice products sold in USA.[109]

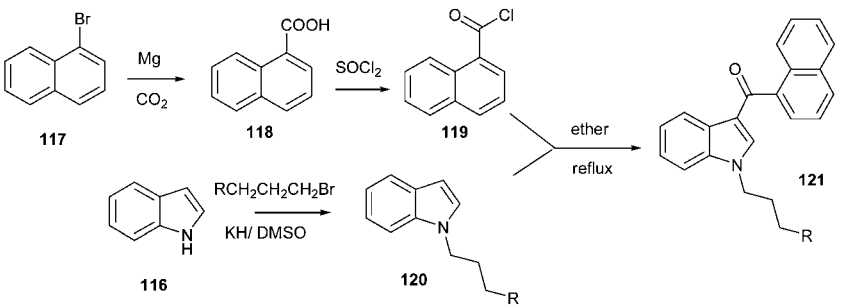
Since that first publication, the Huffman group explored in great detail the chemical space around this new class of CB_1 agonists. The conversion of the original naphthoylindoles into naphthoylpyrroles resulted in compounds with markedly reduced CB_1 receptor affinities; similarly, the role of the naphthoyl residue in the aromatic stacking with the receptor (see below) was evidenced by the reduced CB_1 affinity and *in vivo* potencies of indole compounds bearing the simplified phenylacetyl group. Nevertheless, trying to dodge the detection systems, these compounds have been included in Spice products by "illegal" chemists.

Unlike Δ^9-THC (**106**), which is a partial agonist at the CB_1 receptor, many of the synthetic cannabinoids of the JWH family are full agonists and many of them outperform THC in terms of affinity for CB_1, with picomolar K_i values (8–200 pM), much lower than those of the psychotropic principle of marijuana, that shows a two-digit nanomolar affinity for CB_1 (K_i *ca.* 40 nM). Docking studies have clearly indicated that the affinity of these polyaromatic ligands for CB_1 is associated to aromatic π–π stacking, with a highly variable CB_1/CB_2 selectivity. In this context, CP47,497 (**109**) and JWH-250 (**110**) are almost pure CB_1 receptor agonists.

The lack of detailed, pharmacokinetic, pharmacological and toxicological studies on humans and the intrinsic high affinity for CB_1 exhibited by many of these synthetic cannabinoids make them potentially very harmful. Some of the effects triggered by these compounds are unrelated to those associated to phytocannabinoids or even opposite, like those of pressure and heart rate, and the pharmacological basis for these differences are unknown. For example, the indole derivatives could in some way interact with one or more serotonin receptors, a completely unexpected activity for classical cannabinoids. Moreover, the potential for addiction is probably much higher, due to a quick development of tolerance, and the complete lack of knowledge about the possible interaction between synthetic cannabinoids and other plant products present in the Spice blends is a further issue of concern.

As cannabinoid-receptor full agonists, synthetic cannabinoids present serious dangers to the user when overdosed. JWH-018 (**112**) has been associated to intense anxiety, agitation, and, in rare cases (generally with non-regular JWH users), with the induction of seizures and convulsions due to inhibition of GABA neurotransmission, an effect that is marginal for THC. There is clearly an urgent need for further research on the effects of synthetic cannabinoids, not only to better understand the human pharmacology of the cannabinoid system, so far explored only with Δ^9-THC, a low-efficacy partial agonist, but, above all, to manage their adverse effects.

A few synthetic cannabinoids included in the Spice mixture are directly available on the market and the following companies are those selling some of these products: Cayman Chemical Company (Ann Arbor, USA); LGC Standards (Teddington, UK); Tocris Bioscience (Bristol, UK); Chiron AS (Trondheim, Norway). However, the majority of these compounds needs to be synthesized following the methodologies reported in the original scientific papers. It elicits a strange feeling to imagine these papers passionately consulted by these "garage chemists" trying to commit a crime by following the synthetic procedure there described! As clearly stated in the UNODC document[34] "*A creative chemist would be able to easily synthesize hundreds of similar*



Scheme 24 General strategy for the synthesis of naphthoylindoles.

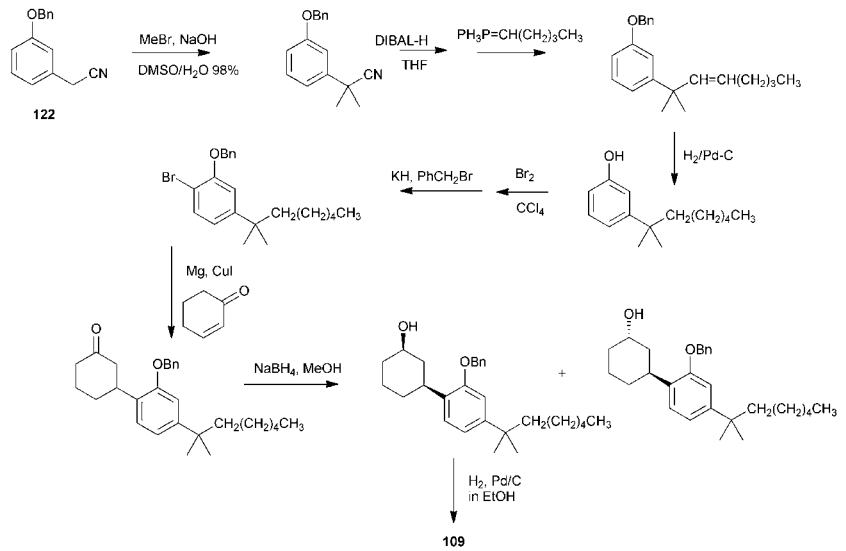
compounds with a high probability of showing cannabimimetic action by the addition of a halogen, alkyl, alkoxy or other substituents to one of the aromatic ring systems. Other small changes such as variation of the length and configuration of the alkyl chain can also be made". This is a major difference compared to the acetylation of morphine to obtain heroin or the preparation of ecstasy from safrol, since the chemistry is complicated enough to need the intervention of a specialist with a sound background in organic chemistry.

The general synthetic strategy for indole derivatives (exemplified in Scheme 24 for naphthoylindoles) involves *N*-alkylation and chemoselective Friedel–Crafts acylation at C-3. Alkylation is generally performed first, avoiding *N*-acylation in the following step, and using conditions typical for *N*-alkylation, namely a poorly interacting counter ion (potassium, sodium) and a highly polar solvent like DMSO. In these conditions, charge localization on nitrogen overcomes the inherent higher nucleophilicity of the C-3 carbon, guaranteeing excellent regioselectivity of alkylation. All reagents are easily available from specialized sellers, and the syntheses require only standard laboratory equipment.

Indole (**116**) is a very cheap reagent (ca 0.1 $/g). It has interesting ormesic olfactory properties. At medium concentrations it has a fecal odor and, indeed, it is component of human faeces, but at very low concentrations it has a flowery smell and it is used as a orange-like fragrance constituent of many flower scents. Indole has a pK_a of 21 in DMSO, thus, very strong bases such as sodium- and potassium hydride are required for complete deprotonation. These bases are pyrophoric, but easier to handle compared to alkyl lithium reagents or Grignard reagents, that would also favor C-alkylation. Naphthalene is even cheaper than indole. It is a major constituent of coal tar (average 10%) and is easily available from mothballs, although its use in these products is being phased out for toxicological reasons. Indeed, naphthalene has a great toxic potential, and extensive exposure has been associated to hemolytic anemia, as dramatically evidenced in people who have accidentally, or intentionally for suicidal purposes, ingested mothballs or deodorant blocks containing naphthalene. In addition, the International Agency for Research on Cancer (IARC) classifies naphthalene as possibly carcinogenic to humans and animals (Group 2B).[110] The IARC also points out that acute exposure causes cataracts in humans, rats, rabbits, and mice, and that hemolytic anemia can occur in children and infants after oral or inhalation exposure or after maternal exposure during pregnancy.

Naphtalene is more reactive than benzene in electrophilic aromatic substitution, and the reaction of naphthalene with bromine in boiling CCl_4 or $CHCl_3$ yields the desired α-bromonaphthalene (**117**) in good yields (>60%) and with good regioselectivity, since position α is kinetically favoured. Minor amounts of dibromonaphthalene are also obtained. The α-bromonaphthalene can be thus easily purified and treated with magnesium in ether to obtain the Grignard reagent which, treated with CO_2, gives the α-naphthoic acid (**118**) in good yields. As an activated heterocycle, indole is highly reactive in electrophilic aromatic substitutions, with a *ca.* 10^{13} higher reactivity than benzene in the Friedel–Crafts reaction. The coupling with α-naphthoyl chloride (**119**) is therefore high yielding, and the β-position of indole is also kinetically favoured, with the reaction at C-2 being, essentially, non-competing. Recrystallization of the crude reaction mixture is generally sufficient to purify the final compound **121**.

The synthesis of cyclohexylphenols is much more demanding, and requires precursors like [3-(benzyloxy)phenyl] acetonitrile (**122**) that are not commercially available, and need to be prepared ad hoc. The synthesis of CP47,497 (**109**, Scheme 25) exemplifies these issues. The synthesis involves the reduction of the cyano group to aldehyde followed by a Wittig reaction, a β-alkylation on a cyclohex-2-enone, reduction of the ketone functionality and deprotection to give racemic CP47,497. Even more sophistication is required for the synthesis of the enantiopure and active enantiomer. This synthesis is clearly much more elaborate and complex compared to that of the



Scheme 25 The published synthesis of CP47, 497 (**109**).

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naphthoylindole derivative, since it also involves separation of diastereomers and then of enantiomers. It seems very unlikely that "garage chemists" could have interest, equipment, and expertise to reproduce this complex synthetic scheme; thus, CP47,497 (**109**) found in Spice formulations has seemingly leached from industrial sources.

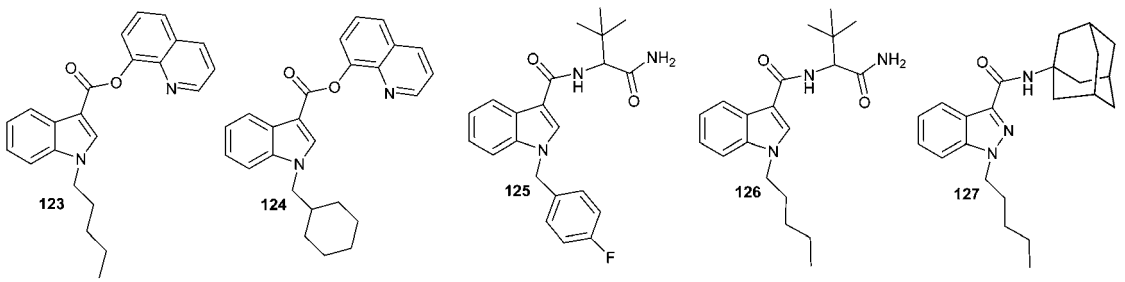
Since the beginning of 2011, the use and possession of all the synthetic cannabinoids has been made illegal in Europe and in USA. The Synthetic Drug Abuse Prevention Act has been signed by President Obama and became effective in July 2012, banning the compounds more frequently found in synthetic marijuana. However, the continuous race between smart drug producers and regulatory agencies is fuelled by the introduction of chemical differences compatible with activity that make these designer drugs invisible to mainstream forensic detection, that is focused on the detection of specific compounds. For example, soon after the prohibition of JWH-018 (**112**) and the development of protocols for its detection in drug samples, this compound was replaced by its non-regulated close analogue JWH-073 (**111**), transparent to the detection system based on the molecular weight and chromatographic properties of JWH-018.

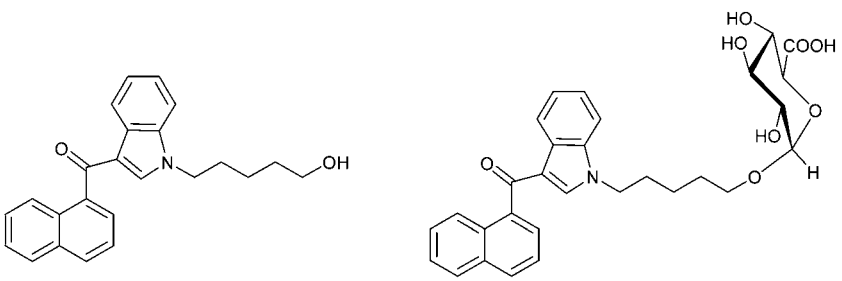
Combinations of synthetic cannabinoids are also used, lowering the concentration of all single constituents to on the verge of detection. For instance, a recent analysis of a Japanese Spice sample[111] purchased on the Internet, identified a mixture that included, along with a series of common synthetic cannabinoids of the JWH series, two cannabimimetic quinolyl carboxylates (**123–124**) and two cannabimimetic carboxamide derivatives (**125–126**), one of which (**125**) had been reported by Pfizer in 2009 as a potent CB_1 agonist but never detected before in illegal products. Interestingly, the related AKB48 (**127**) has been recently detected in an Italian Spice sample.[112] Pharmacological/toxicological data on these compounds are completely lacking and their abuse, or even the simple use, should be considered as potentially extremely dangerous.

The detection of new designer drugs remains an analytical challenge because of the ability of manufacturers to rapidly substitute closely related analogues for banned substances, thus creating a constantly moving analytical target. Highly refined analytical techniques are, in general, needed to detect the presence of small amounts of recreational drugs in herbal mixtures or to identify the presence of their metabolites in the fluids of the consumers. With Spice, the situation is compounded by the high potency of the compounds, unparalleled in the illegal market of non-psychedelic recreational agents, and by the use of mixtures to complicate detection. Currently, phytocannabinoids are detected using immunoassays tests performed on the urine of the suspected consumers. This method is unsuitable for compounds structurally unrelated to phytocannabinoids, and there is an urgent need to develop and validate analytical methods capable to detect synthetic cannabinoids *via* biological fluids (plasma, urine).

During the first few hours after use, serum concentrations of synthetic cannabinoids are generally in the 1–10 μg L^{-1} range. Generally, no unchanged compound is found in the urine of consumers and thus a detailed study on their metabolism in humans is needed for each compound. Hydroxylation and formation of the glucuronides (for example, affording **128** and **129** from JWH-018), operated by hepatic cytochrome P450, seem to be the main metabolic reactions, but also *N*-dealkylation and other oxidations have been observed.

A detailed study has been carried out on the pharmacokinetic of JWH-018, and the detection of its urinary metabolites. The major metabolites are glucuronic acid conjugates, and these can be reliably detected by LC–MS/MS (drug at concentrations of 6–50 μg L^{-1}). Interestingly, ω-hydroxylated JWH-018 (**128**) and its glucuronide (**129**) have a different pharmacological





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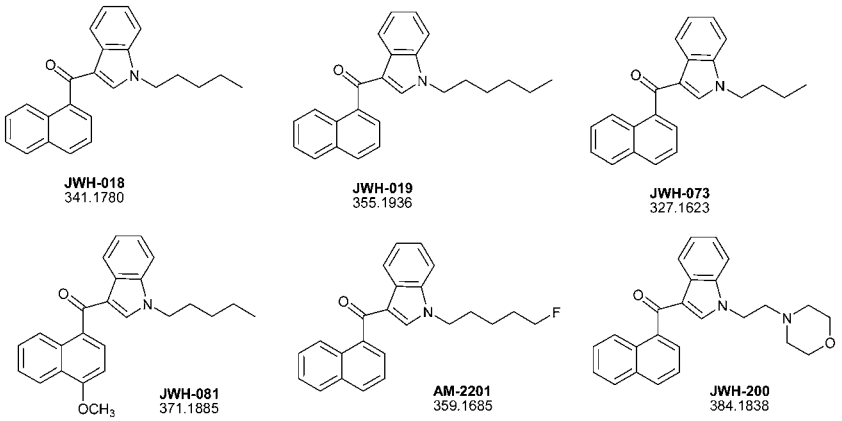

Fig. 1 The exact masses of some products of the JWH family.

profile. While the former is a full and potent activator of CB_1, the glucuronide is a competitive antagonist.[113] As a result, the glucuronide may potentially attenuate the pharmacological properties of JWH-018 *in vivo*, urging consumers to increase the dosage needed to achieve the same level of intoxication. Furthermore, if the half-life of the glucuronide were longer than that of JWH-018, chronic use of Spice products containing JWH-018 would potentially foster continuous abuse, leading to tolerance and dependence.

It is unrealistic that the sophistication of the pharmacokinetic studies carried out on JWH-018 could be replicated for each of the new analogues that are continuously introduced on the market of recreational drugs, but there has been progress in broad-spectrum LC-MS/MS based methods to detect whole classes of compounds directly in oral fluids[114] and hair.[115] The ingenious Grabenauer method[116] pools classes of compounds together based on the mass defect of their molecular formula, that is, the mass loss associated to the formation of chemical bonding. Despite structural diversity, mass defects are relatively constant within a class of analogues, and, by using a MS/MS filtering system focused on mass defects, selective detection of compounds of a specific structural type can be achieved regardless the difference in molecular weight. For example, this technique has been applied to JWH-018 derivatives (Fig. 1). The majority of compounds in this family have mass defects between 0.13 and 0.23 mDa. A mass defect filter centered at 0.185 with a window of $\pm$50 mDa would capture approximately 75% of the currently known structures (Fig. 1). The small population of compounds with mass defects less than 0.13 mDa is primarily composed of halogenated (with Cl, Br, or I) derivatives. This problem can be overcome by taking advantage of the isotopic peaks or scouting for precursor ions of common fragment ions that should enable the detection of compounds with mass defects that fall outside the range of mass defect filter parameters.

In conclusion, research aimed at clarifying the pharmacology and toxicology of synthetic cannabinoids and at improving the methods for their detection in herbal matrices and human fluids are strongly needed, and their development should be encouraged by public and private funding agencies. Because of their easy synthesis and alleged natural nature and safety, these compounds will increasingly permeate the market of recreational drugs. Some beneficial clinical uses of cannabinoids, like their anti-emetic and anti-glaucoma properties, were serendipitously discovered because of their recreational use in patients. Synthetic cannabinoids are making us aware of the flip side of the coin, that is the toxicity of this class of compounds.

4 Conclusions

The popularity of psychotropic agents boomed in the sixties as a cultural icon of resistance to authority and a spiritual quest, while nowadays the sheer pursuit of pleasure permeates the drug culture, fundamentally secularized and hedonistic. Behaviours useful for survival were encouraged during evolution by associating pleasure to them. Eating delivers energy and sex creates offspring, but psychotropic compounds highjack these associations, short-circuiting thousands of years of evolution. Their use is therefore intrinsically non-natural, providing a moral support to banning policies based on concerns over their acute and/or long-term detrimental health effects. On the other hand, the replacement of little toxic natural agents like mescaline, psilocybin and marijuana with more potent synthetic analogues is often quoted as a vivid example of the global failure of repressive anti-drug politics. Thus, while the consumption of the classic natural products-based intoxicants (marijuana, cocaine, heroin) is steady, that of their synthetic analogues has boomed, to the point that amphetamine-type stimulants are now second only to cannabis-based products (marijuana, hashish, hemp oil) in popularity.[34] In this context, there is no guarantee that a softer regulation on natural intoxicants would have prevented the illegal development of "smart" analogues, and what is surprising is, rather, that these synthetic compounds, most of which have never been tested in rodents or humans, are promoted as natural, benign, and "more legal" than their plant prototypes. Designer drugs can induce bizarre and violent behaviour, their lethal dosage is unknown, as are the treatment of their overdosage and their effects on pregnancy. Sadly, much of what we know on many of them comes only from self-experimentation reports posted on websites like Erowid (Earth Wisdom) and Bluelight by people

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who want to explore or alter their conscious state. The critical role of the internet in the "virtualization" of the smart drugs market can hardly be underestimated, with the first recorded act of e-commerce being indeed a drug deal, the sale of a marijuana sample between the student of Stanford and MIT in 1971 or 1972.[117] Furthermore, while the manufacture of illicit drugs was a sort of hidden science, nowadays there is no shortage of web sites entirely dedicated to their manufacture, with "explorers of the inner space" like Alexander Shulgin, Steve Preisler (Uncle Fester), Jeffrey Jenkins (Eleusys) and Hobart Huson (Strike) having achieved a stellar status in the underground chemistry community.

Most of the street analogues of natural intoxicants were first described in the mainstream chemical literature, and were then rediscovered by psychonauts, who began to experiment with home-produced recreational agents. These activities have rarely directly involved academic laboratories, but recreational drug designers get inspiration for new agents by scanning the scientific literature, focusing on researchers known for studying mind-altering substances and on journals reporting their studies.[118] J. Robert Oppenheimer, the father of the atomic bomb, claimed that "*Scientists are not delinquents. Our work has changed the conditions in which men live*, *but the use made of these changes is the problem of governments*, *not of scientists*".[119] Chemists can indeed be like Prometheus, who stole the fire of the Gods and gave it to the humans, or like his brother Epimeteus, the careless keeper of the Pandora's box of human tribulations. The interior expeditions of psychonauts have allowed the recreational synthetic genie out of the bottle, and now society has to find the most suitable way to put it back in.

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