Mini review

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# Some new psychoactive substances: Precursor chemicals and synthesis-driven end-products

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**This paper describes some of the new classes of 'designer drugs' being encountered today by forensic scientists and law enforcement agencies in Europe, the United States, and Australia. In particular, it concentrates on new cathinone derivatives, the tryptamines, new-generation phenethylamines, and some of the synthetic cannabinoids. The synthetic approaches towards many of these designer drugs including a discussion of the chemical precursors used in the syntheses are presented. Many of today's so-called designer drugs exist as a result of legitimate research into medical conditions and the natural product chemistry. A link between synthetic approaches published in the open scientific and medical literature and the exploitation of this research by clandestine manufacture of drugs for illicit purposes is drawn.** 

**Keywords:** designer drugs; cathinones; methcathinone; tryptamine; cannabinoids; phenethylamines; psychoactive; precursors

## Introduction

The major drugs of abuse trafficked in the world today remain heroin, cocaine, cannabis, and amphetamine-type stimulants (ATS).[1] $\Delta^9$-Tetrahydrocannabinol and cocaine are essentially fully cultivated drugs requiring little further work following harvesting of the cannabis plant and coca leaf, respectively, and extraction. Heroin is a semi-cultivated drug requiring acetylation of the morphine extracted from opium. The amphetamine type stimulants are fully synthetic drugs and include some very well-known substances such as amphetamine itself, methamphetamine (*N*-methylamphetamine), and 3,4-methylenedioxymethamphetamine (MDMA).

While these three compounds are the most commonly trafficked of the fully synthetic drugs, there are other synthetic substances, both licit and illicit, that are abused and today, there is an increasing trend towards so-called 'designer drugs'. There is no strict definition on what constitutes a designer drug but they are usually molecules that have been modified in such a way that they retain psychoactivity while circumventing legal controls. The main factors determining which substances are abused are market demand, ease of synthesis, and availability of precursor chemicals. Cultivated and semi-cultivated drugs, such as cocaine and heroin, are always in demand and crop production in countries such as Colombia, Peru, Afghanistan, and other politically unstable nations is rarely a problem for those involved in their production and trafficking.[1] The chemicals required to convert the crops into finished products, such as acetic anhydride, hydrochloric acid, potassium permanganate, are produced for legitimate industrial use on a large scale and the diversion of comparatively small amounts for illegitimate use is a major problem for law enforcement agencies.[2] Similarly, the demand for amphetamine, methamphetamine, and MDMA is still very high and these drugs are produced in large quantities to satisfy user demand in the United States, Europe, and Australia.[1] In addition to being popular with users, their production is, from a synthetic viewpoint, quite simple. The major precursor chemicals used for the production of methamphetamine are the pharmaceutical drugs ephedrine and pseudoephedrine and to a lesser extent phenyl-2-propanone (P-2-P) which has some small legitimate industrial use in the flavour and fragrance industries.[2] The immediate precursor for almost all MDMA production is 3,4-methylenedioxyphenyl-2-propanone (3,4-MDP-2-P) which has virtually no legitimate industrial use but is easily made from the essential oil safrole or from the industrial chemical piperonal, both of which are produced for industry in large quantities. There is also a thriving illegal production of safrole in south-east Asia.[2] So for the drugs heroin, cocaine, amphetamine, methamphetamine, and MDMA, there is strong market demand, simple synthetic procedures, and ready availability of precursor chemicals. It is noteworthy, however, that these precursor chemicals and reagents are listed in either Schedule I or II of the 1988 United Nations Convention and are closely watched by National and International law enforcement agencies.[3] However, despite this care taken to prevent the diversion of industrial chemicals and pharmaceuticals for illegitimate use, clandestine drug manufacturers appear to have no difficulty in sourcing them.

The term 'designer drug' was first coined in the 1980s but describes a problem more commonly associated with the twenty-first century. Historically, the age of the designer drug began in 1925 with the International Opium Convention which banned the use of morphine and its diacetyl ester, heroin. This led to alternative esters of morphine, such as dibenzoylmorphine, being manufactured in an attempt to circumvent the Opium Convention which in turn led to the first controls when the League of Nations in 1930 passed analogue resolutions extending control to all esters of morphine.[4] Little more happened until the 1980s when analogues of drugs such as fentanyl appeared. It was during the 1980s that what is probably the classic case of a designer drug appeared although the compound itself had been synthesized many years before. The substance MDMA had been known since its

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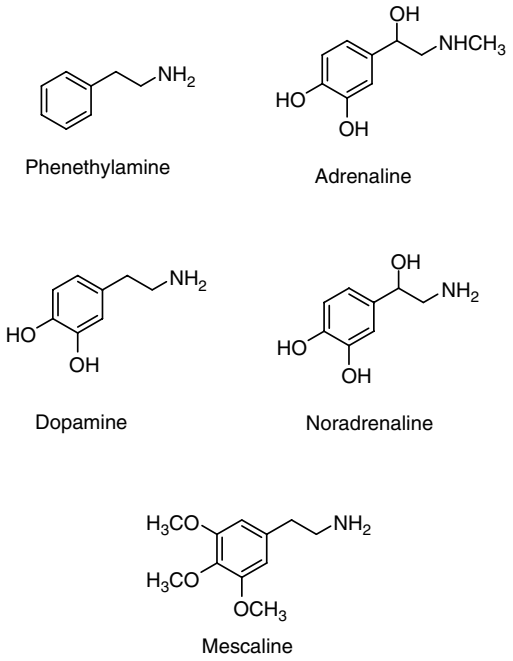



**Figure 1.** Phenethylamine, adrenaline, dopamine, noradrenaline, and mescaline.

synthesis in 1912 at Merck Darmstadt in an attempt to produce an appetite suppressant. From a structural point of view it was simply methamphetamine with a methylenedioxy group on the aromatic ring and it was not illegal until new legislation was enacted.[5]

Since the 1990s, there has been an explosion in the number of new psychoactive substances. The science of organic chemistry has opened up a world of millions of molecules and yet most of the new psychoactive compounds, like the old, belong to a relatively small number of chemical classes with the majority being nitrogenous. A quick glance at the chemical structures reveals many similarities between the synthetic psychotomimetics and the endogenous neurohormonal transmitters, such as dopamine and serotonin. Many of the new designer substances are based on the phenethylamine (Figure 1) structure and include compounds such as the cathinone family analogues.[6–9] Other phenethylamine modifications include compounds developed as part of legitimate chemical and medical research aimed at producing pharmaceuticals to treat a variety of medical conditions.[10] Others still are based on the serotonin like compound tryptamine (Figure 2) and its many analogues.[11–13] Many 'designers' are chemical modifications of currently controlled substances that have similar pharmacological effects and chemically designed to circumvent legislation. Which substance becomes popular with the drug abusing community is again based on a number of factors: (1) popularity with users, i.e. does it produce the desired effects; (2) will it be legal; and (3) is it easy to produce. This paper will address a number of the new classes of psychoactive substances, their synthesis, and precursor chemicals and some of their effects in an attempt to demonstrate how these factors can determine what sort of substance may become popular.

## Cathinones

Cathinone (Figure 3) is a powerful stimulant of the central nervous system and occurs naturally in the fresh leaves of *Catha edulis*

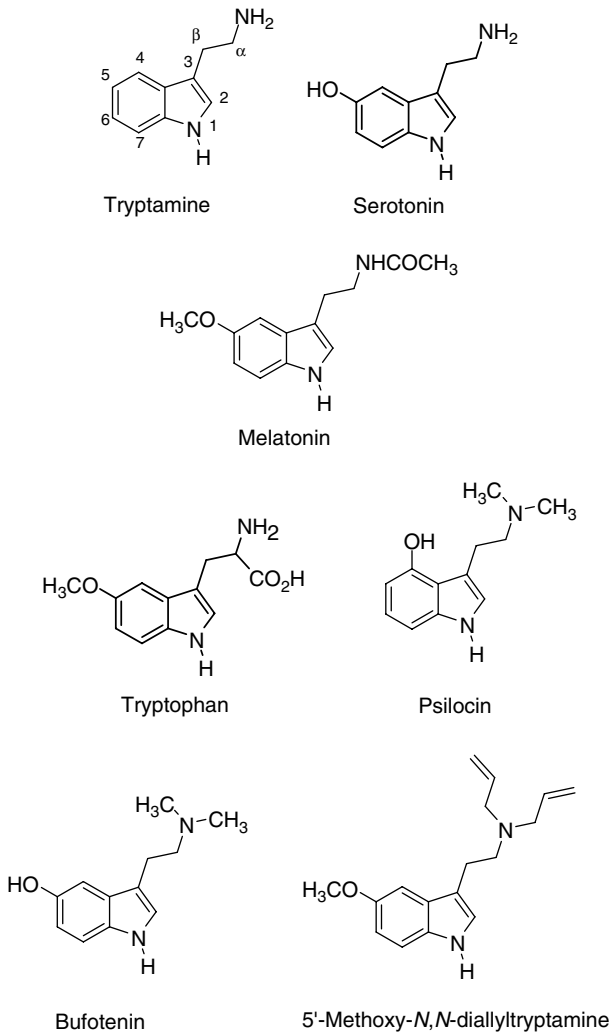



**Figure 2.** Tryptamine and some related compounds.

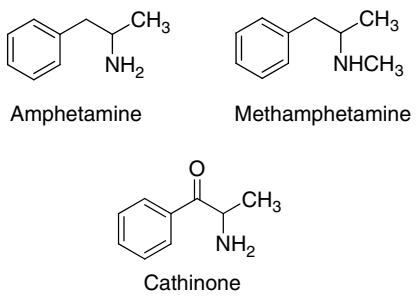



**Figure 3.** Cathinone, amphetamine, and methamphetamine.

(khat). The plant is a native to many East African countries and has been used for its pharmacological effects since the eleventh century.[14,15] Chemically, cathinone is structurally similar to amphetamine (Figure 3) but is unstable. It is scheduled in the United Nations 1971 Convention on Pyschotropic Substances.

### Synthesis of methcathinone

The *N*-methyl derivative of cathinone, methcathinone (Figure 4), was first identified in the Soviet Union in 1982 and referred to

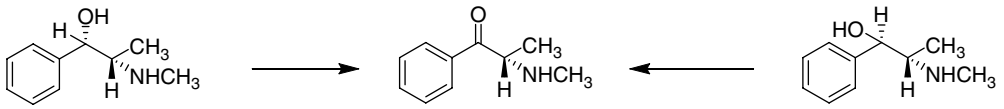


**Figure 4.** Synthesis of methcathinone by oxidation of ephedrine or pseudoephedrine.

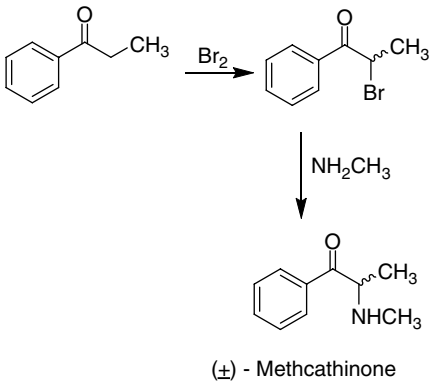



**Figure 5.** Preparation of racemic methcathinone from propiophenone.

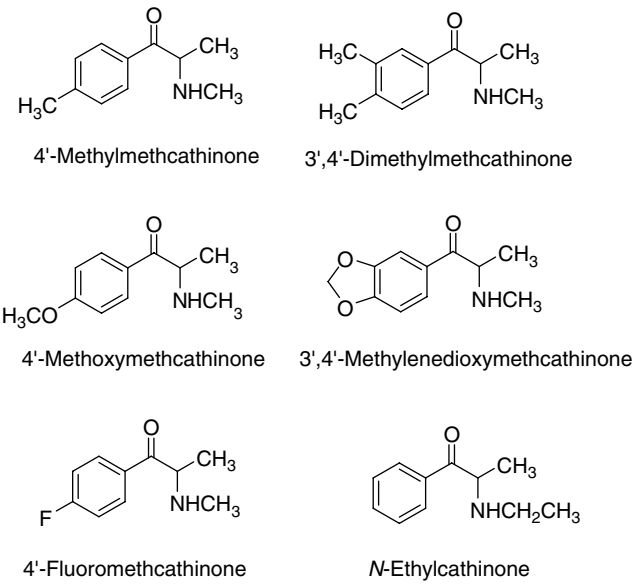



**Figure 6.** Some ring- and nitrogen-substituted cathinones.

as 'ephedrone'.[6] It was first produced in the United States in 1988 and hundreds of clandestine methcathinone laboratories have been found since then. The synthesis of methcathinone is comparatively simple with the easiest approach being the oxidation of the readily available pharmaceuticals pseudoephedrine and ephedrine (Figure 4).[9,16] The major stimulant activity is associated with the *S*-(−)-isomer of methcathinone which may be produced by the oxidation of the 1*R*, 2*S*-(−)-ephedrine or the 1*S*, 2*S*-(+)-pseudoephedrine with Jones reagent or potassium permanganate. Oxidation of the benzylic hydroxyl group to a ketone removes chirality at the benzylic position but proceeds with retention of stereochemistry at the 2 position producing the more active *S*-(−)-methcathinone. Another synthetic approach to methcathinone and its analogues employs propiophenone or substituted propiophenones as the immediate precursor (Figure 5).[17] This synthesis will always produce racemic methcathinone in the absence of asymmetric influence. Despite the fact that ephedrine and pseudoephedrine are more closely monitored by law enforcement than propiophenone – for example, they are Schedule 1 chemicals under the United Nations Office of Drugs and Crime (UNODC) 1988 Precursor Convention – they are still easily diverted for illegitimate use as is evidenced by their massive diversion for methamphetamine manufacture. They are produced in large quantities for use as nasal decongestants and although they are gradually being replaced by other drugs for this purpose, such as phenylephrine, there is currently enough available for diversion into the clandestine methamphetamine industry and certainly enough for methcathinone production.

### Synthesis of methcathinone analogues

Today there are many analogues of methcathinone appearing on the drug scene which is particularly dynamic at the moment. Most of these involve substitution of the aromatic ring or at the amino group (Figure 6). In these cases it is not feasible, from a synthetic viewpoint, to begin with ephedrine or pseudoephedrine. However, analogues or designers of methcathinone may be synthesized by using the appropriate ring-substituted propiophenones as the starting material.[6,17] A good example of this approach is the synthesis of 4′-methylmethcathinone also known as mephedrone (Figure 7), which results in a racemic mixture. The same approach may be used to produce other ring-substituted methcathinone analogues, i.e. commence with the appropriate ring-substituted propiophenone. To prepare different nitrogen-substituted cathinone analogues, it is necessary to use the appropriate amine in the amination step.[6] Propiophenone and its ring-substituted derivatives are relatively easy to obtain without attracting too much attention and so the opportunities to clandestinely produce an entire range of methcathinone analogues are many and this is indeed what is occurring at present. In the author's laboratory alone, nine analogues of methcathinone have been submitted by law enforcement agencies during the last two years. Where standards have not been available identification has been made by $^{1}H$ and $^{13}C$ NMR spectroscopy.

Another class of cathinone-related compounds is the pyrovalerones, some of the more common ones being shown in Figure 8. Pyrovalerone itself was synthesized as far back as 1964 and marketed legitimately for therapeutic use as an appetite suppressant and in the treatment of chronic fatigue.[18] The ring-substituted compound 3,4-Methylenedioxypyrovalerone, or MDPV as it has come to be known, was first synthesized along with other stimulants in 1969.[18] It has some similar effects to methamphetamine and is also said to increase libido and anxiety levels. MDPV is now widely available mainly through Internet purchases where it has been marketed as 'bath salts' and as 'plant food' in an attempt to avoid medicines or other legislation. The syntheses of many pyrovalerone derivatives have been well described in a publication by Meltzer *et al.*[18] and their synthesis of MDPV is shown in Figure 9. The syntheses are comparatively easy and in most cases the starting materials are commercially available

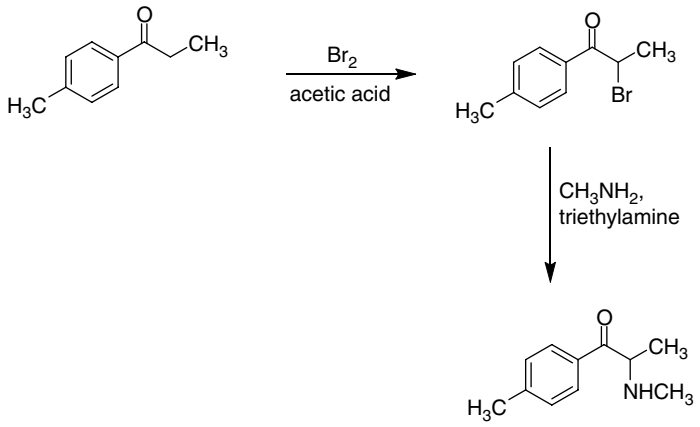



**Figure 7.** Synthesis of racemic 4′-methylmethcathinone from 4′-methylpropiophenone.

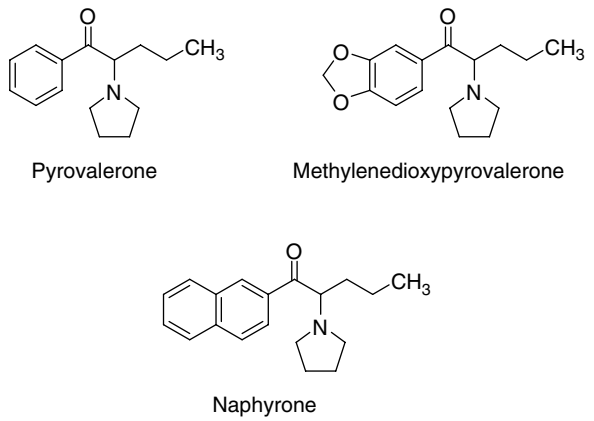



**Figure 8.** New-generation legal highs related to methcathinone.

industrial chemicals that may be easily obtained without raising any concerns among law enforcement agencies.

## Tryptamines

Tryptamine (Figure 2) is a primary amine alkaloid based on the heterocycle indole. The basic tryptamine structure is found widely in nature in both the plant and animal kingdoms.[13,19–22] Serotonin, a naturally occurring tryptamine, is a neurotransmitter and local hormone in humans and its biosynthesis proceeds by the metabolism of the essential amino acid, tryptophan.[23] It has many receptors in both the central and the peripheral nervous systems and its pharmacological effects are profound. Another naturally occurring tryptamine with an important pharmacology is melatonin. It is biosynthesized in the pineal gland by *N*-acetylation and *O*-methylation of serotonin. Bufotenin,[22,24] a tryptamine closely related to serotonin, was originally found by the German Nobel Chemistry laureate, Heinrich Wieland in the parotid gland of toads in 1934.[25] Interestingly, 20 years later, it was discovered again by his son Theodor Wieland in toadstools. The substance 5-Methoxy-*N*,*N*-dimethyltryptamine, present in several species of jungle trees of the genus *Virola,* is the active ingredient of a number of snuff powders prepared from the resin of *Virola* species by the Waika Indians of the Upper Orinoco in Venezuela and Rio Negro in Brazil. It is also a component of the dart poison used by the Yanoama Indians of the Upper Orinoco.[19,22]

The hallucinogenic activity of these naturally occurring tryptamines has long been exploited by humans. One of the most potent naturally occurring hallucinogens that contain the tryptamine structure is psilocybin, the phosphate ester of psilocin, found in various hallucinogenic mushrooms, particularly *Psilocybe mexicana*. The structures of psilocin and psilocybin were confirmed

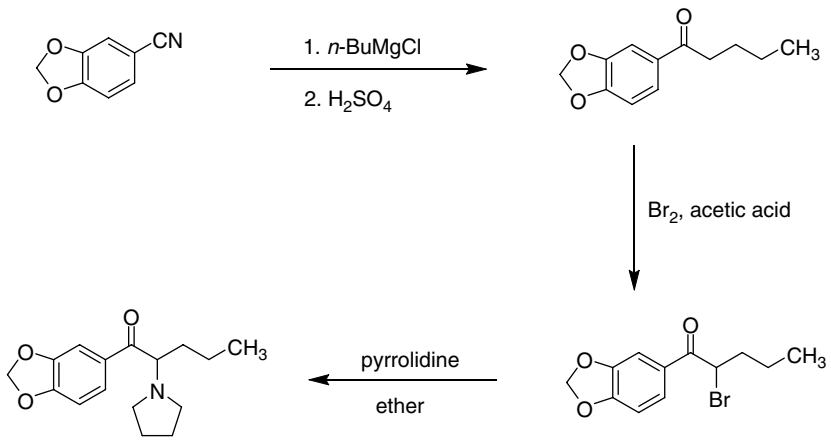
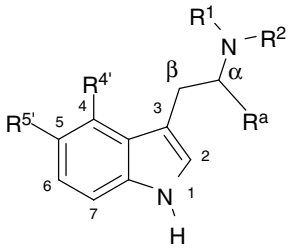



**Figure 9.** Synthesis of MDPV.

**Table 1.** Some natural and synthetic tryptamines




| Common Name | Full Name | Origin | $R^1$ | $R^2$ | $R^{4'}$ | $R^{5'}$ | $R^a$ |
|---|---|---|---|---|---|---|---|
| Serotonin | 5-hydroxytryptamine | Natural | H | H | H | OH | H |
| Melatonin | 5-methoxy-N-acetyltryptamine | Natural | COCH3 | H | H | $OCH_3$ | H |
| Psilocin | 4-hydroxy-N,N-dimethyltryptamine | Natural | $CH_3$ | $CH_3$ | OH | H | H |
| Tryptophan | $\alpha$-carboxyltryptamine | Natural | H | H | H | H | $CO_2H$ |
| Bufotenin | 5-hydroxy-N,N-dimethyltryptamine | Natural | $CH_3$ | $CH_3$ | H | H | H |
| 5-MeO-DMT | 5-methoxy-N,N-dimethyltryptamine | Natural | $CH_3$ | $CH_3$ | H | $OCH_3$ | H |
| 5-MeO-DALT | 5-methoxy-N,N-diallyltryptamine | Synthetic | $CH_2$=CH-$CH_2$ | $CH_2$=CH-$CH_2$ | H | $OCH_3$ | H |
| 5-MeO-DiPT | 5-methoxy-N,N-diisopropyltryptamine | Synthetic | $CH(CH_3)_2$ | $CH(CH_3)_2$ | H | $OCH_3$ | H |
| Sumatriptan | 5-methylaminosulfonamide-N,N-dimethyltryptamine | Synthetic | $CH_3$ | $CH_3$ | H | $SO_2NHCH_3$ | H |
| 5-MeO-AMT | 5-methoxy-$\alpha$-methyltryptamine | Synthetic | H | H | H | $OCH_3$ | $CH_3$ |
| DET | N,N-diethyltryptamine | Synthetic | $CH_2CH_3$ | $CH_2CH_3$ | H | H | H |

by Albert Hoffmann *et al*. in the Basel laboratories of Sandoz in 1959.[20,21]

### Synthesis of tryptamine analogues

Many naturally occurring tryptamines have been synthesized in the course of chemical research into the molecular structures of natural products. A number of synthetic analogues have been legitimately produced to combat medical conditions, for example, sumatriptan used to treat migraines. Other tryptamines have been clandestinely synthesized in attempts to exploit powerful pharmacological effects of the tryptamine structure (Table 1). Synthesis of tryptamine analogues is not difficult and there have been a number of successful synthetic approaches.[24,26,27] The dimethyl derivative, *N*,*N*-Dimethyltryptamine, was first synthesized in 1931 by Manske.[26] Obviously, the easiest approach for some simple *N*,*N*-dialkyl tryptamines is to begin with tryptamine itself and exhaustively alkylate the primary amino group. An example of this approach is the preparation of *N*,*N*-dimethyltryptamine (DMT) shown in Figure 10. Tryptamine is treated with excess methyl iodide and the intermediate quaternary ammonium salt is then reduced to DMT. If however tryptamine is not available or if it is desired to produce more complex tryptamines, i.e. tryptamines containing substituents on the aromatic ring, other approaches may be tried. Starting with indole, or a ring-substituted indole, the Speeter-Anthony synthesis[27] gives good yields of tryptamines. An example of the applicability of this synthesis is 5′-methoxy-*N*,*N*-diisopropyltryptamine, whose psychoactive properties are well known. Its synthesis by this method is shown in Figure 11. By varying the amine used in the second step, a variety of tryptamines may be prepared. Generally the Speeter-Anthony approach is an ideal way to produce various tryptamines if indole or a ring-substituted indole is available as the precursor. More recently Professor David Nichols' team at Purdue University has prepared a number of novel tryptamine derivatives as part of their research into the serotonin receptor sites in the brain.[28–31]

If indole or an indole derivative is not available, it can be easily synthesized using a range of methods. The Fischer indole synthesis is a well-known procedure that gives good yields of substituted indoles, although not indole itself. However, indole, for use as a precursor may be easily prepared from ortho-nitrobenzaldehyde by a nitro-aldol condensation with nitromethane to give 1-(2-nitrophenyl)-2-nitroethane followed by cyclization to indole. The organic chemistry of indole, first prepared in 1866, is comprehensive and well documented. The importance of the pharmacology of naturally occurring tryptamines, such as the endogenous molecule serotonin, whose structure was first elucidated in 1948, is also well established. It is not surprising then that those with an eye to the main chance should draw the connection between the psychoactive properties of serotonin – or its relatives found in certain mushrooms – and the ease of synthesis of tryptamines, and embark on production of a new range of psychoactive designer drugs. The precursors are readily available or easily prepared and the synthetic chemistry required to prepare tryptamines is comparatively simple.

## Phenethylamines

The relationship that exists between endogenous compounds, such as serotonin, and naturally occurring compounds, such as psilocin, and the many synthetic, psychoactive tryptamines may be extended to the general class of compounds often referred to as phenethylamines (Figure 1). The phenethylamine (PEA) moiety is embedded in the structures of many psychoactive drugs such as mescaline and dopamine, etc. Indeed amphetamine derives its common name from a methyl derivative of phenethylamine, i.e. **a**lpha-**m**ethyl**ph**en**et**hyl**amine**. By extension, the PEA structure is present in methamphetamine, MDMA, and other amphetamine-type stimulants.

The structural relationship between compounds such as mescaline, which occur naturally in peyote, and the endogenous

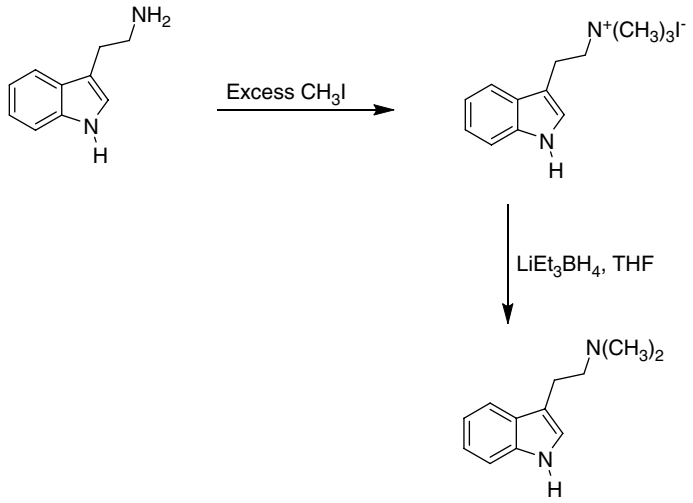



**Figure 10.** Synthesis of *N*, *N*-dimethyltryptamine (DMT) from tryptamine.

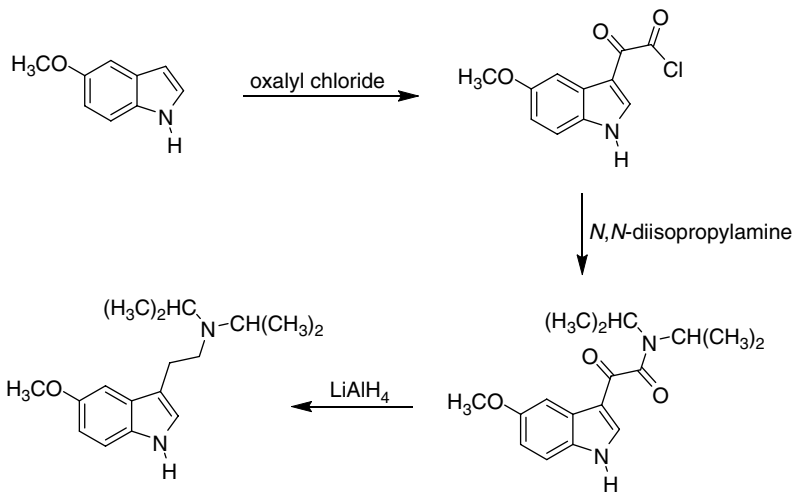



**Figure 11.** Synthesis of 5-methoxy-*N*, *N*-diisopropyltryptamine.

catecholamine neurotransmitters, such as dopamine, adrenaline, and noradrenaline, is obvious (Figure 1). The pre-Colombian Mexican Indians practiced a religion based on the worship of a small cactus with powerful hallucinogenic properties attributed to the alkaloid mescaline.[32,33] Mescaline was first isolated from the peyote cactus, *Lophophora williamsii* in 1896 by Heffter[34] and its structure was confirmed by total synthesis (Figure 12) in 1919 as 3,4,5-trimethoxyphenethylamine by Ernst Spath.[35] Beginning with gallic acid (3,4,5-trihydroxy benzoic acid) Spath prepared 3,4,5,-trimethoxybenzaldehyde which was then condensed with nitromethane and the resulting nitrostyrene was reduced in two steps to mescaline. The peyote cactus grows in a narrow area along the Texas side of the Rio Grande and into Mexico, mainly within the Chihuahuan desert. It has been used by the indigenous peoples of these lands for millennia for sacramental rites.[36] The word 'mescal' has been incorrectly applied to refer to the peyote cactus where in fact the word is only used in Mexican Spanish to refer to the *Agave tequilana* plant which when fermented produces the famous drink tequila. So, when Heffter isolated the active ingredient of the peyote cactus. it was given the common name 'mescaline'.[22] Although the most abundant psychoactive alkaloid in peyote, 3,4,5-trimethoxyphenylethylamine is not alone with at least an additional five alkaloids being present in smaller amounts.[37] However, the psychoactive properties of these substances are largely undetermined. Mescaline itself is quite weak when compared to other psychoactive substances, but it has frequently been used as a means to rate compounds for their psychic properties. It has been determined that a dose of 350 mg of mescaline sulfate is the minimum required to produce a psychic response and this has been rated at one 'mescaline unit'. Considering the structure of mescaline and its similarity to endogenous molecules such as dopamine, adrenaline, and serotonin, it is perhaps not surprising that it should have powerful pharmacological effects. It has now been well established that many hallucinogenic drugs owe their pharmacological activity to their ability to activate the 5-$HT_{2A}$ or serotonin-2A receptor site in the brain. Many drug classes seem to have this effect including amphetamine derivatives, tryptamines, and some ergot alkaloids. Amongst the ergot alkaloids should also be counted the synthetic drug lysergic acid diethylamide (LSD). Much of the research aimed at understanding the 5-$HT_{2A}$ receptor site has been carried out using the simple

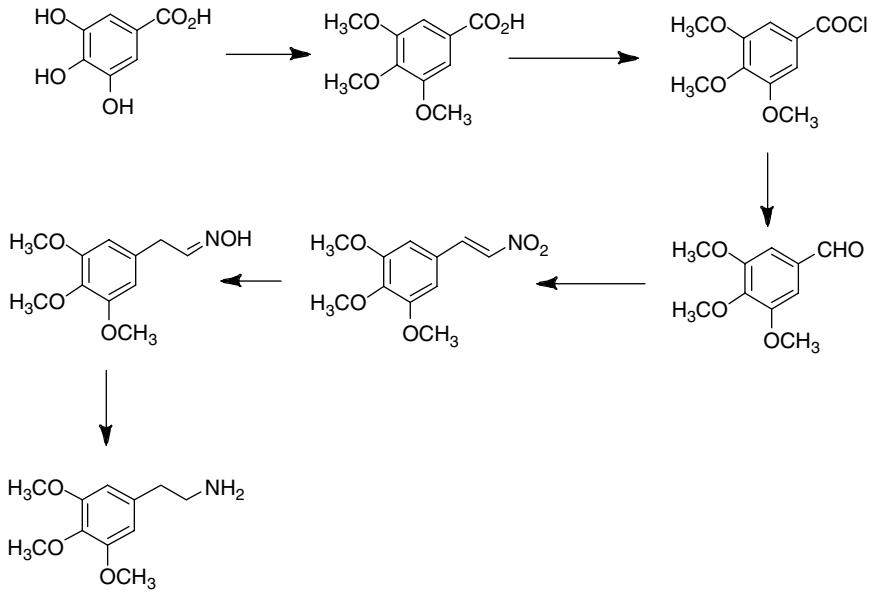



**Figure 12.** Spath's 1919 synthesis of mescaline from gallic acid.

amphetamine compounds presumably because of their easy synthesis/availability.

This similarity between the structure-activity relationships of mescaline and the endogenous catecholamines no doubt prompted the synthesis of many phenethylamines containing structures. Extensive structure-activity relationship (SAR) work has been performed using molecules where the position and number of the methoxyl groups in the mescaline molecule were varied and other substituent groups added to the molecule. In particular a range of 2, 5-dimethoxy-4-substituted phenethylamines and 2, 5-dimethoxy-4-substituted amphetamines have been carefully studied. In the 1980s and 1990s, researcher Alexander Shulgin, his wife and friends tested many such compounds by taking them personally and describing their effects. The results of their investigations were eventually published in a book entitled *PIHKAL: Phenethylamines I have known and loved*.[38] The book also describes original literature syntheses of many of the compounds. Some of the synthetic approaches for 2,5-dimethoxy-4-substituted phenethylamines and 2,5-dimethoxy-4-substituted amphetamines used chemistry similar to that employed by Spath in his synthesis of mescaline (Figure 12). If the appropriate aromatic aldehyde, with methoxy groups in the desired positions is available, the molecule may be developed to give the desired phenethylamine or amphetamine. An aromatic aldehyde may be easily condensed with a nitroalkane to produce nitrostyrene derivative in a variation of the Knoevenagel reaction known as the Henry reaction.[39] The nitrostyrene is then reduced to the corresponding phenylalkylamine. Figure 13 shows the reaction between 2,5-dimethoxybenzaldehyde and nitromethane to give the intermediate nitrostyrene derivative which on reduction gives 2,5-dimethoxyphenylethylamine (2C-H). The analogous 2, 5-dimethoxyphenylisopropylamine series may be prepared similarly by using nitroethane instead of nitromethane thereby producing a range of ring-substituted amphetamines. Today these synthetic pathways are easy to carry out with the methoxylated benzaldehyde precursors and nitromethane and nitroethane being readily available. There are also an increasing number of reducing agents such as lithium aluminum hydride that may be easily obtained.[40] Halogenated analogues of 2C-H are easily prepared from 2C-H itself. For instance, treatment of 2C-H with hydrogen bromide and hydrogen peroxide, or with elemental bromine, gives fair yields of 2,5-dimethoxy-4-bromophenethylamine (2C-B; aka 'NEXUS') (Figure 14).[41] The analogous iodo compound, 2, 5-dimethoxy-4-iodophenethylamine (2C-I) may be prepared from 2C-H by first protecting the amino group as a phthalimide and then treating it with iodine monochloride to give *N*-[2-(2,5-dimethoxy-4-iodophenyl)ethyl]phthalimide. The protecting group is then easily removed to afford 2C-I. Although the Henry variation of the Knoevenagel procedure, i.e. the so-called 'nitrostyrene' route, has been the most commonly employed method to prepare phenethylamines, other routes have been explored particularly when the nitrostyrene route has failed to give satisfactory yields. The Mannich reaction has been employed to create benzylamines from phenols. Nitriles have been produced via reductive alkylation of cyanide ion and the nitriles have then been reduced to phenethylamines.[42]

### Some new-generation phenethylamines

These simple variations of the mescaline molecule produced some powerful hallucinogenic compounds. One well known street

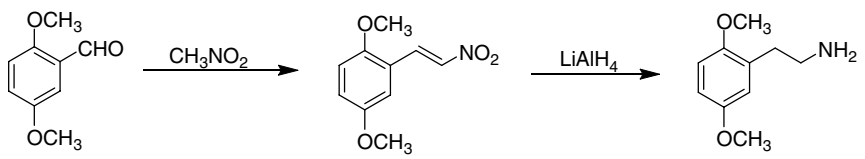
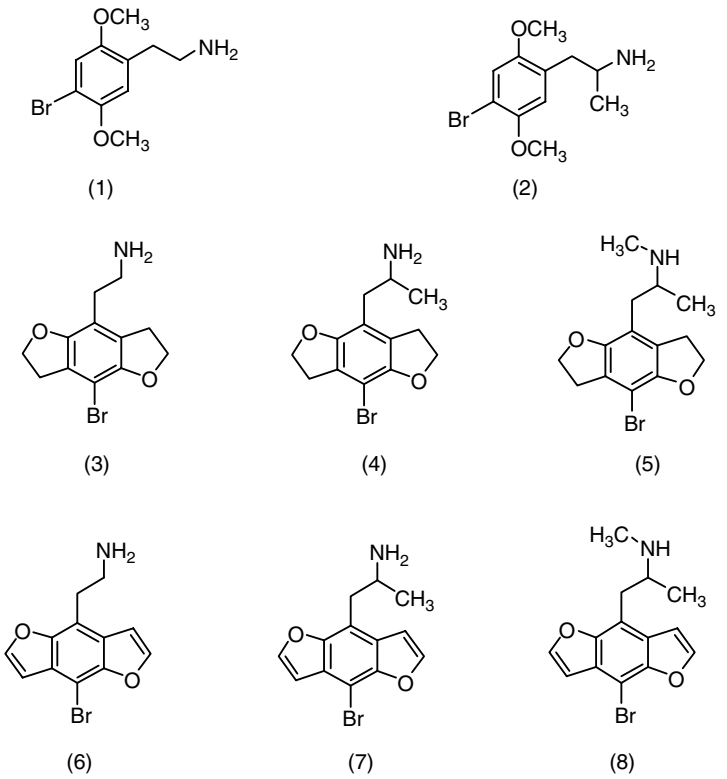



**Figure 13.** Synthesis of 2, 5-dimethoxyphenethylamine.




**1**. 2C-B; **2**. DOB; **3**. 2C-B-FLY; **4**. DOB-FLY; **5**. *N*-Methyl-3C-B-FLY; **6**. 2C-B-DragonFLY; **7**. Bromo-dragonFLY; **8**. *N*-Methyl Bromo-dragonFLY

**Figure 14.** Some benzodifuranyl compounds and related phenethylamines.

drug, 2,5-dimethoxy-4-bromophenethylamine (2C-B) (Figure 14), is substantially more potent than mescaline while 2,5-dimethoxy-4-bromoamphetamine is rated at 400 mescaline units. The obvious structural features that 2C-B and other psychoactive phenethylamines had in common were the primary amine moiety separated from the aromatic ring by four angstrom units, i.e. two aliphatic carbon atoms, the methoxyl groups, and a hydrophobic substituent in a position *para* to the amine side chain. Based on this knowledge that both mescaline, 2C-B and others like them are potent agonists of the serotonin receptors research groups began probing deeper the affinity of certain-shaped molecules for the serotonin receptor sites.

Professor David Nichols's research group at Purdue University has produced a range of new generation phenethylamines in the course of research into the $5HT_{2A}$ receptor site. This work was born of the knowledge of the hallucinogenic properties of mescaline and the 2,5-dimethoxylated phenethylamines and phenylisopropylamines and aimed at revealing the three-dimensional structure of this receptor site.[43] The Nichols research group was very active over several decades in the synthesis of phenethylamine and phenylisopropylamine analogues and SAR studies in relation to the serotonin $5\text{-}HT_{2A}$ receptor.[44,45] Serotonin or 5-hydroxytryptamine (5-HT), a neurotransmitter with many human receptors is linked to many human mental processes.[46] The Nichols group studied indole-based hallucinogens such as LSD (lysergide) and psilocybin, and naturally occurring phenethylamine hallucinogens such as mescaline and quickly noted that the potency of synthetic analogues of mescaline such as 2C-B and 1-(2, 5-dimethoxy-4-bromo phenyl) isopropylamine (DOB) greatly exceeded many of the naturally occurring hallucinogens.[43] The Nichols group conducted SAR studies with the aim of learning more about the three-dimensional structure of the serotonin receptor site. They synthesized many new compounds based on what they knew about mescaline and 2C-B in attempts to 'probe' the receptor sites. By building molecules of known geometry, including three-dimensional conformation, and determining their potency, they inferred knowledge of the serotonin 5-HT receptor's 3-dimensional structure.[47]

In the course of the work by the Nichols research group, many new compounds were produced and some proved to be very potent hallucinogens. In particular, a range of rigid benzodifuranyl compounds were synthesized and proved most useful in assisting with the SAR studies. Several of these compounds have since gained a degree of notoriety as drugs of abuse and are shown in Figure 14. The rigid benzodifuranyl compounds shown in Figure 14 have become widely known as the so-called 'FLY' compounds because of the resemblance of the molecular models of these compounds to the common housefly. The synthetic approaches to these compounds are published in the scientific and medical literature and involve easily obtained precursors. The first step in the production of some FLY compounds is to produce the basic skeleton of the benzodifuran compounds as shown in Figure 15. This was achieved by the Nichols group using the procedures of Parham, beginning with benzoquinone as starting material.[48] Once an efficient synthesis of the rigid benzodifuran skeleton i.e. the 2,3,6,7-tetrahydrobenzo[1,2-*b*:4,5-*b*']difuran was developed it then remained to develop the alkylamino sidechain. This was achieved by the series of reactions shown in Figure 16 involving

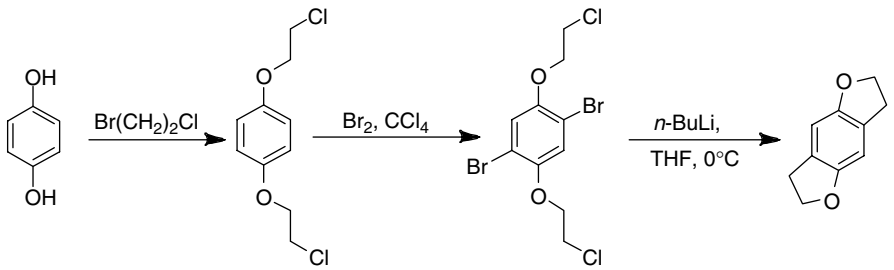



**Figure 15.** Synthesis of 2,3,6,7-tetrahydrobenzo[1,2-*b*:4,5-*b*′]difuran.

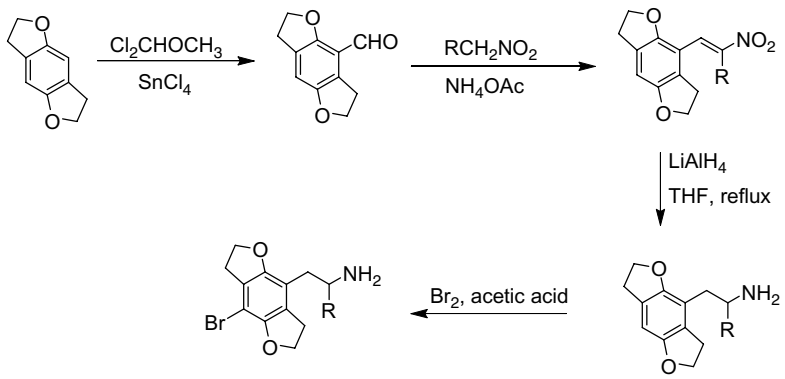
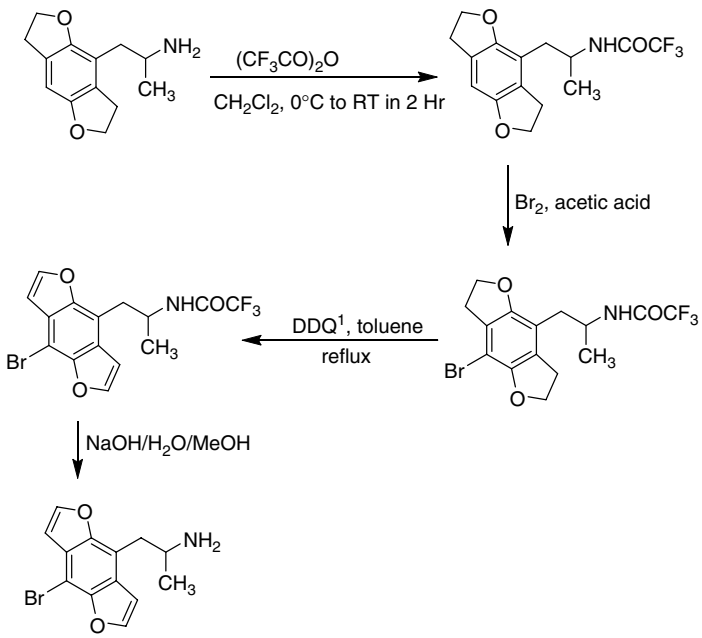


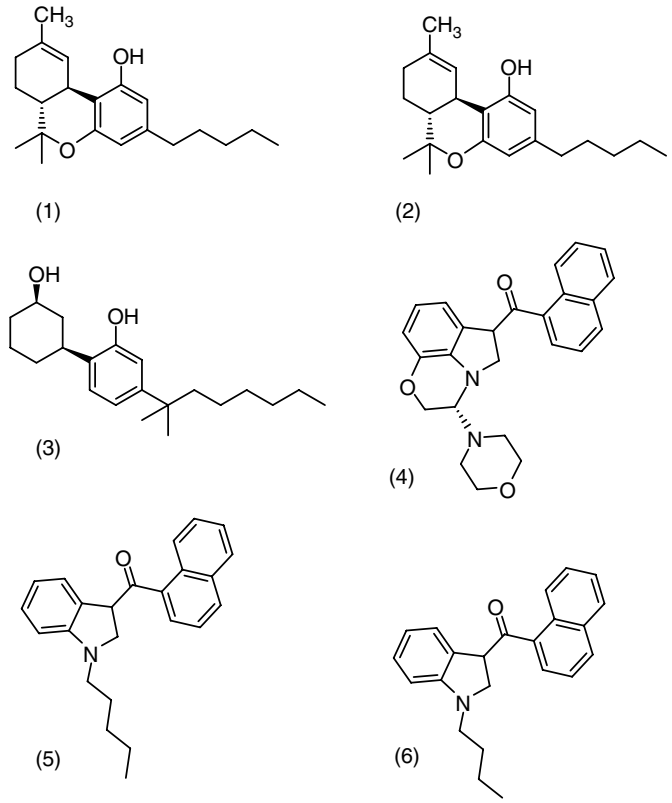

**Figure 16.** Formylation and subsequent elaboration of the benzodifuran nucleus.

formylation to give the aldehyde which could then be subjected to the same type of reactions used by Spath to prepare mescaline and used much later by many others to prepare simple phenylethylamine compounds with potent hallucinogenic properties.[44,49] If nitromethane is used in the second step R will equal hydrogen and the product will be 1-(8-bromo-2,3,6,7-tetrahydrobenzo[1,2-*b*;4,5-*b*′]-difuran-4-yl)-2-aminoethane better known by its street name, 2C-B-FLY. If nitroethane is used then R equal methyl and the analogous amphetamine series is produced, i.e. 1-(8-bromo-2,3,6,7-tetrahydrobenzo[1,2-*b*;4,5-*b*′]-difuran-4-yl)-2-aminopropane which is known by its street name of DOB-FLY. Another of the FLY compounds created by the Nichols research group has the street name 'Bromo-DragonFLY' and its synthesis is shown in Figure 17. Like the other rigid benzodifuranyl




1. 2,3-Dichloro-5,6-dicyanobenzoquinone

**Figure 17.** A synthesis of Bromo-DragonFLY.




(1) $\Delta^9$THC; (2) HU-210; (3) CP 47,497; (4) WIN 55,212; (5) JWH-018; (6) JWH-073

**Figure 18.** Some cannabinoid receptor agonists.

compounds, it was prepared for structure-activity relationship studies and turned out to have a particularly high potency for the serotonin 5-$HT_{2A}$ receptor. There were many dozens of the benzodifuranyl and benzofuranyl compounds prepared for these studies but it is beyond the scope of this article to discuss the ease of synthesis of them all.

## Synthetic cannabinoids

The synthetic cannabinoid class of drugs is some of the most recent of the so-called designer drugs. Although many of the molecules in this class were created in the laboratory over the last 20 years it is only in the last few years that they have been introduced into the drug scene. There has long been available a range of products generally referred to as 'herbal highs'. These products are usually plant materials with little psychoactive effects and have tended to receive little attention from law enforcement agencies. They may present as liquids, dried vegetable matter, or live matter and may contain a wide range of extracts from substances such as peyote, salvia, and kava. While the peyote cactus for instance does indeed contain some very potent substances, for example, mescaline, the amount present in the herbal highs is usually very small.

During the early to mid-2000s a new range of products appeared, also marketed as herbal highs or legal highs and marketed mainly by the Internet as the 'Spice' range.[50,51] It was always maintained that these substances were nothing more than the herbal highs that were already well-known and largely ignored by law enforcement because of their low psychoactive potency. Typical plants represented by the Spice drugs were supposed to include the 'Lion's Ear (*Leonitis leonuris*), the 'Blue Lotus' (*Nymphaea caerulea*) and the 'Sacred Lotus' (*Nelumbo nucifera*). These products were known to have minimal psychoactive effects, but sufficient to be attractive enough for sale by internet. However, it soon became apparent that users thought this range of Spice drugs were really very excellent at producing a high, i.e. they contained some very potent psychoactive substance or substances. These experiences by users attracted attention from the forensic chemistry community and law enforcement agencies. However, initial chemical analyses failed to detect any of the 'usual suspects' known to produce psychoactive effects and the general feeling was that the users were overstating the effects of the Spice products. However, some suspicions regarding the supposed herbal nature of the Spice drugs arose when the chemical analyses also failed to detect any of the compounds that would be expected to be seen in a plant extract, for example, phytosterols. In late 2008, chemists at the German THC Pharmaceuticals Company identified a research chemical, JWH-018 (Figure 18), and in early 2009 scientists at the University of Freiberg,[50] the National Institute of Health Sciences in Japan,[52,53] and the Bundeskriminalamt in Wiesbaden also identified JWH-018 and another research chemical designated CP 47,497 (Figure 18). While new to the drug-abusing community, these research chemicals had been developed within universities as part of legitimate chemical research designed to combat certain medical conditions.

A large volume of medical and scientific research has been carried out over several decades into the mechanism of cannabis activity. By the early 1980s, two cannabinoid receptors had

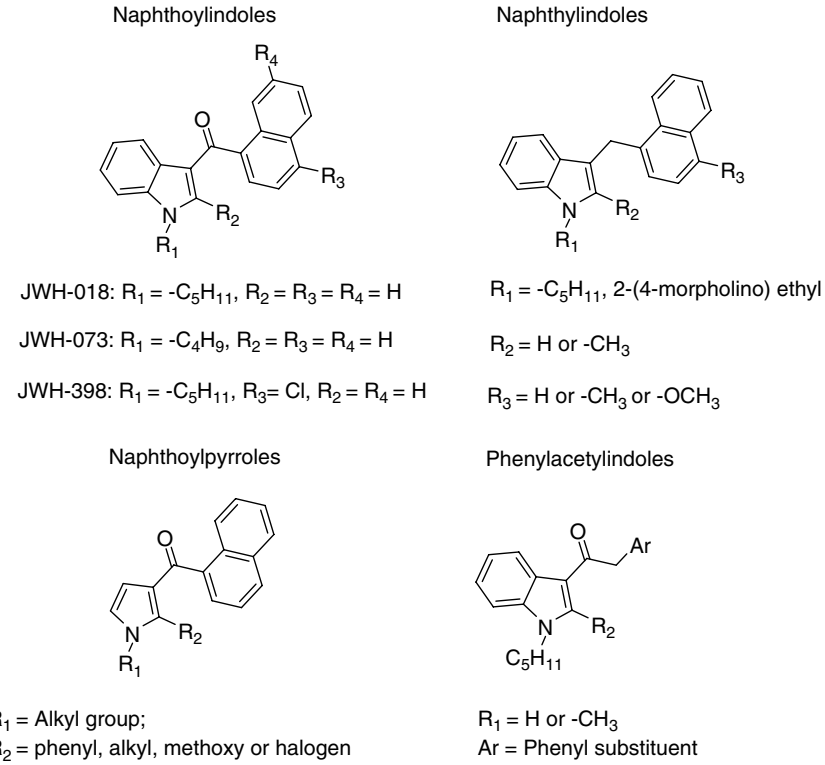


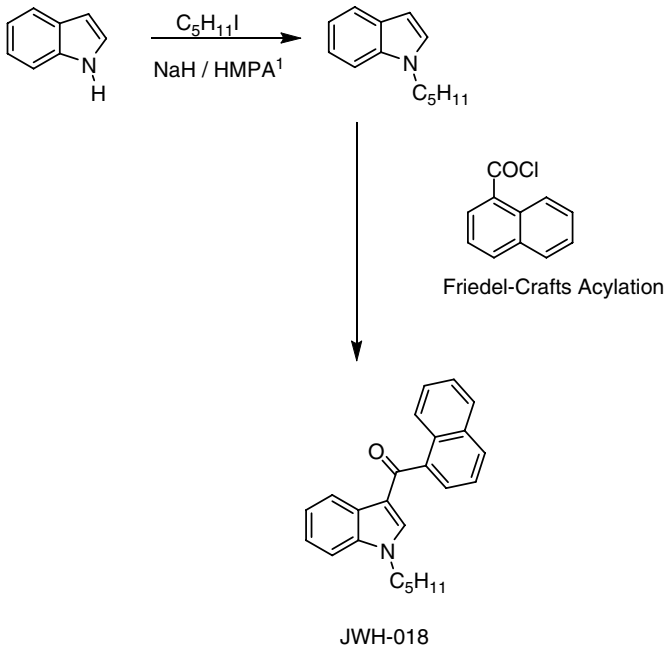

**Figure 19.** Some JWH compounds.

been identified by medical researchers, one in the brain and the central nervous system ($CB_1$ Receptor) and the other in the immune system ($CB_2$ Receptor). In addition to the receptor sites, a number of endogenous receptor agonists were also identified. The identification of the receptor sites spurred on research efforts to investigate the structures of the cannabinoid receptors and also to produce molecules that might behave similarly to $\Delta^9$-THC. One group of cannabinoid receptor agonists is the phytocannabinoids, such as $\Delta^9$-THC itself. A, by now well-known synthetic counterpart to $\Delta^9$-THC – HU-210 (Figure 18) – was synthesized in Israel in 1988 by Raphael Mechoulam and his research group at the Hebrew University[54] (hence the 'HU'). This particular synthetic cannabinoid is reported to have a potency of at least 100 times that of $\Delta^9$-THC. HU-210 has been investigated for its possible use in preventing inflammation caused by amyloid proteins thought to be involved in the onset of Alzheimer's disease. It is also has very potent analgesic properties. However it has been detected in Spice products seized by US Customs.

A second group of agonists are the cyclohexylphenols which are analogues of $\Delta^9$-THC that do not contain the pyran ring moiety in their structure such as 2-[(1R, 3S)-3-hydroxycyclohexyl]-5-(2-methyloctan-2-yl)phenol (Figure 18), more usually referred to as CP 47,497.[55] This compound is reported to be at least 3 times as potent as $\Delta^9$-THC and possibly up to as much as 28 times as potent depending on the route of administration. It displays analgesic, motor depressant, and anticonvulsant properties.[55] The cyclohexylphenols, or 'CP' compounds were developed as potential analgesics during the 1980s by Pfizer. A number of homologues of CP 47,497 have been prepared including the 1, 1-dimethyloctyl homologue, or CP 47,497-C8 which is several times more potent than CP 47,497 itself.[56] In 2009, at the University of Freiburg the CP 47,497-C8 analogue was detected in the Spice range of products. German authorities then placed a ban on the CP 47,497 range with alkyl sidechains of $C_6$ to $C_9$. A third group of cannabinoid agonists is the naphthoylindoles exemplified by WIN 55,212 (Figure 18). All of these agonist groups were of interest and some importance because it appeared likely to some physicians that molecules such as $\Delta^9$-THC and other molecules that interact with the cannabinoid receptors might assist with a wide range of medical conditions such as pain relief and Parkinson's disease.

One of the most active research teams in the field was that of Professor John Huffman at Clemson University, South Carolina. Over the course of two decades, Huffman's research group has looked at the development of pharmaceuticals based on the molecular structure of the cannabinoid agonists and explored the three-dimensional configuration of the cannabinoid receptors. In the course of this research, his group has produced a large number of molecules that are potent cannabinoids and have often been named with the letters JWH – for example, JWH-018. These compounds included naphthoylindoles, naphthylmethylindoles, naphthoylpyrroles, naphthylmethylindenes, and phenylacetylindoles (Figure 19).[57–60] Structurally these compounds do not resemble the $\Delta^9$-THC molecule itself but many are potent cannabinoid receptor agonists.[61] Probably the best known of these is JWH-018 (Figure 18) which is about three times as potent as $\Delta^9$-THC. When it was detected along with CP 47,497-C8 as an active ingredient in Spice products in Germany, it was banned. However, within a month of the ban, JWH-073 (Figure 18), which has an *N*-butyl group instead of the *N*-pentyl group, appeared.

While the clandestine preparation of compounds such as HU-210 and CP 47,497 requires enantioselective synthesis techniques the JWH range of compounds, such as the naphthoylindoles, are quite easy to prepare. There are no stereochemistry issues to face and the synthesis relies on well known synthetic procedures,




1. Hexamethylphosphoramide

**Figure 20.** Synthesis of JWH-018 from indole.

primarily modifications of the Friedel Crafts acylation reaction. As an example a synthesis of JWH-018 is shown in Figure 20. It involves either obtaining the appropriate *N*-alkyl indole commercially, in this case 1-pentylindole, or synthesizing it which is not difficult. The compound 1- Naphthoic acid is then converted to the acid chloride and a Friedel Crafts acylation between the acid chloride and the alkyl indole is performed to give the product. It is clear that if one member of this series is legislated against it is an easy matter to produce another, e.g. JWH-073 instead of JWH-018, by commencing with a different alkyl indole, in this case 1-butyl indole.

## Conclusions

The modern scourge of designer drugs is a problem that is unlikely to disappear quickly. In the twentieth century, the major drugs of abuse were heroin, cocaine, methamphetamine, cannabis, and more latterly MDMA or 'Ecstasy'. These drugs are still a major problem across the world. Today, however, we also face a new range of psychoactive substance abuse albeit based on chemistry that was developed during the second half of the twentieth century. When specific substances have been scheduled, molecular structure variants that avoid specific legislation have soon appeared. Often new molecules developed during the course of legitimate medical or chemical research efforts have later been exploited as psychoactive substances for sale to drug abusers. It is a dilemma faced by scientists involved in such research, including synthetic organic chemistry; that their work will be published in learned journals and therefore will be open to scrutiny by anyone. In today's world, it is very easy to obtain Internet access to relevant journals. It is also just as easy to commission custom syntheses of compounds offshore in parts of the world where few questions are asked. Again, the Internet may be used to market the final product for sale in countries where it is not illicit. By the time appropriate legislation has been passed, small fortunes can be made. Syntheses of the majority of these compounds is really quite easy and the precursor chemicals, unlike those for the drugs such methamphetamine, are either not scheduled or very easy to obtain. The new designer compounds also pose a problem for those forensic scientists engaged in analysis. Most forensic chemistry analysis is based on the need for comparison of the 'unknown' with reference materials, i.e. substances of known identity and purity. This is typified in chromatographic analysis where a retention time and mass spectrum of the unknown is compared with retention times and mass spectra of a large range of reference materials. But what does the forensic chemist do when no reference material is available? Today, this situation is becoming a common occurrence as more and more designer drugs, such as the JWH compounds, are appearing. These compounds cannot be easily purchased as reference materials. Today more than ever before the first principles approach employing techniques such as $^{1}H$ and $^{13}C$ nuclear magnetic resonance spectroscopy must be used to determine the molecular structure of the unknown.

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