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# Doors of deception – The diaspora of designer drugs

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*If the doors of perception were cleansed, everything would appear to man as it is, infinite*

*For man has closed himself up, till he sees all things thro' narrow chinks of his cavern.*[1]

William Blake – The Marriage of Heaven and Hell

Aldous Huxley derived the title for his short tome, *The Doors of Perception,*[2] describing his experiences following controlled administration of mescaline, from William Blake.

Huxley brilliantly summarized his experience: 'There are things known and unknown and in between are the doors.' Jim Morrison, who named his band *The Doors* after reading Huxley's book, would have informed him that – after a less controlled mescaline experiment – the known and unknown lie within the doors.

Ingestion of perception-altering substances dates back millennia, when they may have been used routinely as a dietary source of neurotransmitters,[3] which are energetically expensive to synthesize. Sullivan and Hagen suggest that there is a 'deep-time' relationship (co-evolution) between hominids and psychotropic plants, their premise based on the synthesis by plants of defensive chemicals that mimic mammalian neurotransmitters, and the ability of mammals to metabolize and/or utilize these phytochemicals to their advantage. Ingestion of these compounds as a routine component of early hominid diets, even if this is no longer necessary, may explain in part the current propensity for the widespread use/abuse of these compounds.

Almost all recreational drugs (cocaine, nicotine, amphetamines, tetrahydrocannabinol [THC]) are plant toxins that induce changes in dopaminergic circuitry.

Marijuana is widely recognized as the most used recreational drug, at least in Europe and North America;[4] however, this is a generalization when dealing with specific countries, regions, or neighborhoods. For instance, members of the Los Angeles and San Francisco Police Department Narcotics Divisions confirmed that in many neighbourhoods in those cities the impact of *Cannabis* is minimal compared with crack, methamphetamine, and/or heroin. This is undoubtedly true for many neighborhoods in major metropolitan areas in the USA and elsewhere.

It is generally accepted that the addiction potential of the psychoactive components (primarily THC) of *Cannabis* is limited to psychological habituation, although heavy users may experience slight to moderate short-term physical withdrawal symptoms. There are, to my knowledge, no documented instances of mortality due solely to *Cannabis* poisoning. Most adverse health effects involve respiratory problems due to ingestion of particulates and other components associated with heavy smoking of any substance, psychoactive or not; nevertheless, legal and illegal use of THC and analogs has and will continue to have a significant impact on society. Even with current restrictions in the USA, the medicinal marijuana market is estimated to be 1.7 billion dollars in 2011, 92% accounted for by California and Colorado. This is dwarfed by estimates of the illicit market, for example, a commonly quoted figure from the US Drug Enforcement Agency (DEA) is $35 billion.

When was the last (first?) report of which you are aware involving violence purportedly due to marijuana (rather than alcohol, steroid, methamphetamine. . .) intoxication? Statistics from the NHTSA/FARS (US National Highway Traffic Safety Administration/Fatality Analysis Reporting System) from 2009 state that 32% of all traffic fatalities in the USA (33,808) could be directly attributed to alcohol impairment, while those involving use of marijuana are essentially identical to those in which no drug use is suspected. This is not an anomaly.[5] This is not a defense of using cannabinoids and their mimetics, or a denigration of current laws regulating their use; rather, it is to emphasize the need for a rational approach to drug enforcement policies which can be abetted in part by increased understanding of the physiological and psychological bases of their effects on human behaviour.

There is a grey area when dealing with many recreational drugs including cannabinoids, steroids, opiates, and tropane alkaloids (scopolamine, atropine), since they have legitimate medicinal uses. This spotlight article explores the current knowledge of THC receptors, computational approaches to development of THC receptor analogues and other designer drugs for medicinal and recreational use, and the unexpected synergistic effects of tropane (belladonna) alkaloids on smoking cannabinoids.

Despite a history of being used for thousands of years, and the subject of numerous chemical investigations dating back to the 1800s,[6] it wasn't until 1964 that the correct structure for THC was identified.[7] THC is the major psychoactive component of ca. 85 estimated cannabinoids synthesized by *Cannabis sativa*.[8–10] Like the majority of popular recreational drugs – including nicotine, cocaine, amphetamines, and opiates – THC is a plant neurotoxin that affects dopaminergic circuitry primarily through G protein-coupled receptors (GPCR).[11]

Receptors for cannabinoids were difficult to identify due to the highly lipophilic nature of THC. During the 1980s, Pfizer embarked on a major effort to synthesize analogues based on the THC structure, one of which, CP55,940, a high affinity CB1 ligand, led to identification of two receptors for THC in the early 1990s. CB1 is primarily localized in the central nervous system,[12] and CB2 in cells associated with the immune system;[13] however,

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there are exceptions,[14,15] and tentative evidence for additional receptors.[16] Identification of these receptors renewed efforts to synthesize THC analogues, to date numbering over 3000,[17] with the goals of enhancing activity and/or specifically targeting either CB1 or CB2. Primary contributors include C. Huffman (Clemson University); R. K. Razdan (Virginia Commonwealth University; A. Makriyannis (Northeastern University); Abbot, Eli Lilly, Roche, and Merck Canada (C. Huffman, personal communication).

Although a general topic of interest in the 1990s, designer drugs first made international headlines in 2003 with the Bay Area Laboratory Co-operative (BALCO) scandal involving the widespread use by athletes of tetrahydrogestrinone (THG), which was synthesized by Patrick Arnold by hydrogenation of gestrinone. This simple reaction created a potent agonist for androgen and progesterone receptors whose presence could not be detected by standard multiple reaction monitoring (MRM) methods used by anti-doping laboratories for steroid detection. Subsequent characterization of this steroid derivative by Catlin *et al*.[18] led to US federal prosecution of many involved with BALCO, culminating in March 2011, with the most high profile case so far, involving the former San Francisco Giant (US Major League Baseball) Barry Bonds. Bonds has recently been found guilty of felony obstruction of justice (April 2011).

Synthetic organic chemistry can be traced back to 1865 when Friedrich August Kekule published two theoretical papers on the structure of aromatic organic molecules.[19,20] What should we make of his later explanation of the discovery of the structure of the benzene ring?[21]

*The atoms were gambolling before my eyes. This time the smaller groups kept modestly in the background. My mental eye, rendered more acute by the repeated visions of the kind, could now distinguish larger structures of manifold confirmation: long rows, sometimes more closely fitted together all twining and twisting in snake like motion. But look! What was that? One of the snakes had seized hold of its own tail, and the form whirled mockingly before my eyes. As if by a flash of lightning I awoke; and this time also I spent the rest of the night in working out the rest of the hypothesis. Let us learn to dream, gentlemen, then perhaps we shall find the truth. . .*

Was he ingesting magic mushrooms, an obsessed chemist, or simply tweaking his audience? Whatever the source of his dreams, Kekule's theory led to focused research on coal-tar derivatives by IG Farben among others – arguably the birth of modern synthetic organic chemistry.[22]

Paul Ehrlich postulated in the early 1870s that differences in chemoreceptors between micro-organisms, parasites, and cancer cells from those in host cells could be exploited for therapeutic purposes.[23] In the absence of current ligand-based and receptor-based molecular design techniques, there were limited approaches to identify minor structural changes in biologically active compounds that would enhance selectivity and/or potency of therapeutic molecules.

Hamett made the first significant contribution relating structure to activity of small organic compounds with his study correlating electronic properties of organic acids and bases with reaction rates and equilibrium constants, focusing on benzoic acid derivatives.[24] Moving beyond the linear free energy relationships provided by the Hammett equation, the next major development was the introduction of quantitative structure-activity relationships (QSAR) by Corwin Hansch *et al*. in two seminal papers in the early 1960s,[25,26] providing a new tool to systematically relate molecular descriptors (electronic, steric, topological, and hydrophobic indices) to biological activity. These early efforts concentrated on naturally occurring plant hormone mimics, and relied on statistical analysis of published accounts of the biological activity of phenoxyacetic acid derivatives and other plant growth regulators. Electronic indices were found insufficient for QSAR of biological systems; rather, a measure of lipophilicity (classically measured as an octanol-water partition coefficient) was essential to predict targeting of compounds to specific tissues, cells or organelles, and subsequent biological activity.[27] While there are limitations to Hansch analysis, it allows modelling of complex biological systems using simple parameters. John Topliss developed a method to automate QSAR;[28,29] however, it is of limited utility in many experimental systems and ignores possible interactions between multiple substituents.

QSAR remains a dynamic tool for drug design and optimization.[30,31] Although attempts have been and continue to be made to adapt QSAR to prospective analyses, it is almost exclusively retrospective, i.e. a series of compounds with a targeted biological activity has been previously characterized, and QSAR is then used to optimize activity by systematically altering minor structural features. Approximately 15 years ago, pharmaceutical companies realized that existing screening libraries were inadequate for newly developed high-throughput efforts for lead drug design. The challenge has been to balance size and structural diversity of new libraries against screening cost, while maintaining affinity and selectivity against a portfolio of targets. Two major approaches have emerged: fragment-based screening (FBS)[32,33] and diversity-oriented synthesis (DOS).[34] The first relies on iterative screening of small molecular weight compounds that direct synthesis of subsequent fragments for testing, with theoretically as few as 1000 fragments representing the chemical diversity of tens of millions of larger MW drug-like compounds. DOS requires a much larger screening library, but proponents claim that FBS favours flat aromatic compounds while biological systems operate in a three dimensional world favoured by DOS analysis. Despite major advances in chemical screening and synthesis, discovery of new drugs is difficult, expensive, and the efficacy of target-based drug discovery has been questioned.[35] One option goes beyond individual genes and proteins, instead focusing on signalling pathways based on multiple criteria requiring cell-based assays.[36] There are further complications when dealing with multi-cellular organisms, and these are addressed below with specific reference to recreational drugs.

QSAR and related combinatorial chemistry approaches provide powerful tools to direct synthesis of biologically active drugs. Since over 3000 compounds that bind to CB1 and/or CB2 have been synthesized,[17] it is not surprising that some of these have been exploited for recreational drug use. There are four main classes of cannabinoid mimetics: analogues of endogenous ligands related to anadamide[37] (N-arachidonylethanolamine), especially oleamide; THC analogues based on the dibenzopyran ring, including HU-210 with reported 100 times the potency of THC; the cyclohexylphenol series (Pfizer), for example CP 47497; and the JWH series named after the eponymous John W. Huffman, a structurally diverse group that includes indenes, indoles, and pyrenes.

Cannabinoid analogs first became a significant market in Europe sometime in the mid-2000s (and in the USA several years later) with the emergence of Spice, K2, Green Buddha and similar products marketed as 'exotic incense blends'.[37] Spice and its spin-offs consist of mixtures of up to 10 or 12 dried herbs (on-label) and (apparently) one or more designer drugs (including compounds from the four groups listed previously) added for

the psychoactive effects. Sometime between 2006 and 2008, Spice and its cousins triggered notice from the Psychonaut Web Mapping Project and the Early Warning System (EWS), which are coordinated by the European Monitoring Centre for Drugs & Drug Addiction. EWS links police, customs, regulatory agencies, and other illegal drug specialists, while Psychonaut (now defunct) trawled the Web for novel recreational drugs. After a significant delay due to the absence of standards and analytical techniques, the complex matrix (dried herbs) in which the mimetics were embedded, and masking agents, regulatory agencies from Germany and Austria were able to characterize JWH-018, and CP 47,497 and several homologs from a number of products. Specific mimetics have subsequently been banned or otherwise regulated in European and Scandinavian countries beginning in 2009.[37] While animal models and ligand-receptor experiments supported the psychoactivity of many of these compounds, the direct correlation of these results administering well-characterized compounds to human subjects was limited. Auwarter *et al*. filled this gap by self- experimentation,[38] adding the information that JWH-018 effects last for a shorter period of time (1–2 hours) than THC, and the C8 analog of CP 47,497 longer (5–6 hours).

A preliminary notice was issued in late 2010 that the US DEA intended to invoke an emergency clause of the Controlled Substances Act enacted in 1984 for several synthetic cannabinoids. When sufficient evidence exists for a possible imminent public health crisis, a preliminary reassignment of specific compounds to Schedule I (briefly, a compound with high abuse potential and no accepted medical use) is permitted for a period of one year, making it illegal to be in possession of these compounds. A formal announcement moving five compounds – JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol – to Schedule I was issued 1 March 2011. (HU-210, one of the most potent cannabinoids, was already Schedule I due to its structural similarity to THC). A number of states in the USA have subsequently drafted legislation banning these and, in some instances, additional compounds.

Anticipating the 1 March date, I visited eight head/smoke shops in Los Angeles and San Francisco in late January 2011, all of whom had Spice and usually other options (Green Buddha, Arctic Synergy. . .). Several vendors mentioned that steady customers included police, firemen, and members of the military, i.e. those subject to periodic tests for THC. Visiting the same vendors four weeks after the 1 March ban, all were quite aware of the new law, and all but one either already had or would soon have alternatives that (they claimed) were legal and undetectable. One was particularly proud of his chocolate cookie product, which was based on his mother's home recipe. This was a predictable consequence of the ban, surprising only by the speed at which it occurred. The detailed methods for synthesis readily available in the literature for literally thousands of compounds, as well as the limited number of regulatory facilities available for their routine analysis, make it virtually impossible for this ban to have appreciable effect on sale and use of these products.

An interesting convergence of opinion was manifested while interviewing John Huffman, who has been active in the synthesis of cannabinoid mimetics for over 15 years for medical purposes, and Paul Armentano, Deputy Director of NORML (National Organization for the Reform of Marijuana Laws), the most influential non-profit organization dedicated to legalizing the use of non-medical marijuana. Huffman emphasized that cannabinoid receptors have roles in nausea, mood, pain, inflammation, appetite regulation, osteoporosis, and some types of cancer, and mimetics synthesized in his lab and others are intended solely for medical use. Armentano stated that if marijuana was legalized, there would be no market for the mimetics. Coming from obviously diverse backgrounds, they both concluded that the health effects/toxicity of these compounds to humans have not been evaluated – with little or no quality control of source, purity or concentration – making this the strongest argument against their recreational use.

While there is a major conundrum for cannabinoid regulation because of their sheer number and structural diversity, problems with detection and analysis of designer drugs are by no means limited to this compound class. Indeed, the classical example involves Alexander Shulgin, a brilliant synthetic chemist known in some circles as the Grandfather of Ecstasy. While working for Dow Chemical he synthesized one of the first biodegradable insecticides, Zectran, in 1962. A highly profitable product, he waived patent rights and left Dow to set up an independent lab in 1965, obtaining a DEA-issued Schedule I research license, which he held for over 20 years. He established a close relationship with Bob Sager, head of the DEA Western Laboratories, giving pharmacological lectures to field agents, synthesizing and providing specific compounds to the DEA upon request, and writing a definitive law enforcement book on controlled substances.[39]

At the same time, Shulgin was synthesizing the first of what would be over 200 tryptamine and phenethylamine derivatives, the former compound class including DMT and psilocybin, and the latter MDMA (ecstasy) and mescaline. His avowed goal was to synthesize compounds that would escape detection by professional research laboratories. As early as 1960 he set up an elite group including his wife, Ann, to bioassay (self-test) potentially psychoactive substances. This resulted in the Shulgin Rating Scale commonly used today, a subjective rating system that requires a precise description of the chemical ingested, dosage, time after ingestion, and descriptive narrative, including a 5-point psychoactive scale ranging from +/− (threshold response) to ++++ (transcendental state). A colleague of mine who was a graduate student at the University of California, Berkeley in the 1970s, was involved in this group. After ingesting a tryptamine derivative that sent him into an extended episode during which he was convinced he was a bone washed upon a beach, he declined further participation. Potentially dangerous, *in vivo* testing in humans remains the definitive bioassay system for new drugs, a paradigm established and practiced by Shulgin.

Conflict was inevitable; Shulgin ultimately lost his Schedule I license, and shifted from mainstream scientific journals to self-publishing the results of his subsequent research in two books, *PiHKAL (Phenethylamines I Have Known and Loved: A Chemical Love Story)*[40] and *TiKHAL*,[41] a similar tome on tryptamines. A combination of autobiography, philosophy, and organic chemistry, these books are considered by drug enforcement agencies as 'cookbooks' for the synthesis of these psychotropic substances.

Dogma supports THC content as determining the potency of different strains of *Cannabis*; however, numerous studies suggest that compounds synthesized by *Cannabis sativa* and *C. indica* including other cannabinoids, terpenoids and flavonoids have a significant effect on psychoactivity.[42–44] Some strains of *Cannabis* have a significant muscle relaxing effect (CB2-mediated), while others are almost entirely euphoric (CB1-mediated). Since THC has similar binding affinities for CB1 and CB2, synergistic compounds have to be invoked to explain these differences.

**Figure 1.** The Treeman (Venice Beach, California) emerging from a clump of *Brugmansia spp.* flowers.

A recent phenomenon confirmed by four independent sources in southern California is the increasing use of dried flowers from *Brugmansia spp*. (Angel's trumpet), a beautiful ornamental plant common in southern California, (Figure 1) and *Datura stramonium* (Devil's weed, Jimson weed), which are documented sources for belladonna alkaloids,[45] to enhance the effects of smoking marijuana. I first encountered this practice in the early 1970s at Camp Pendleton, California, while interacting with colleagues in the United States Marine Corps returning from Vietnam. At that time the potency of marijuana strains available in Vietnam relative to those available on the west coast of the United States (as was also the case with heroin street formulations) was much higher, so options were explored to enhance the psychoactivity.

Belladonna[46] alkaloids, for example atropine, scopolamine and hyoscyamine, are anti-cholinergics that bind to muscarinic acetylcholine receptors. It is difficult to definitively tease apart the physiological bases of this synergy between THC and alkaloids. It is possible that there is not synergy but completely independent psychoactive effects of compounds binding to different receptor classes; however, the experiences of my sources suggest that THC binding affinity increases – an interesting area for research since both THC and belladonna alkaloids have therapeutic value.

Using QSAR and other tools, designer drugs will become ever more prevalent.

*We are faced with a harmonized collectivity of consciousnesses equivalent to a sort of super-consciousness. The idea is that of the Earth not only becoming covered by myriads of grains of thought, but becoming enclosed in a single thinking envelope so as to form, functionally, no more than a single vast grain of thought on the sidereal scale, the plurality of individual reflections grouping themselves together and reinforcing one another in the act of a single unanimous reflection.*[46]

This could well be a quotation from the famously drug-addled Gonzo journalist Hunter S. Thompson, or Timothy Leary, the high priest of LSD. Instead it is from Pierre Teilhard de Chardin, a French paleontologist, philosopher, and Jesuit priest. Humans will always seek zones of comfort whether through religion, meditation, or drugs. It is imperative that regulatory agencies crawl out of their cocoons, recognize this as inherent in human nature and, instead of catering to special interests, implement policies that minimize harm to individuals and society.

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