PROJECT CUBENSIA

A World Consciousness Expansion Proposal

Last Update: September 1, 2025

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1. Preface

The Perennial Philosophy

Throughout time and space, humans have developed a multitude of spiritual practices to achieve union with the many words that encompass the totality of existence, whether that term is God, the Universe, Atman, Enlightenment, Nirvana, the Divine, Ultimate Reality, or Absolute Truth. These spiritual practices all arise from different periods of time, cultures, communities, personalities, and traditions, fitting into the circumstances and needs of their period and the individuals that made up their followers.[1]

The common metaphor for how so many variations of spiritual traditions have arisen is that we all begin at different locations at the base of the mountain of spiritual development, whether high or low, to the West or East, or within forests or alongside streams. However, as one climbs the mountain of spiritual attainment, individual experiences of the ineffable become increasingly more similar to one another, until one arrives at the view of the top. There, one can see the entire landscape of reality from one single viewpoint.

That said, even for realized spiritual masters and enlightened beings, teaching the path to the highest level of realization still requires returning down the mountain and supporting those along the path. Hence, paths remain relevant for their circumstances regardless of the full scope of reality and spiritual end point. That said, what brings these practices together at their core has been termed the "perennial philosophy", or the commonalities that exist whether we see spiritual attainment through the lens of Christianity, Islam, Judaism, Buddhism, Hinduism, Taoism, indigenous philosophies, and other traditions.[2]

The most well-cited modern consolidation of the perennial philosophy or wisdom is Aldous Huxley and his major work, *The Perennial Philosophy*, inspired by his use of psychotropic substances and readings of neo-Vendanta by Swami Vivekananda.[2] However, perennialism has its roots in ancient Greek and Roman philosophy as well, and remains a consistent subject of interest through comparative interpretations of spiritual traditions.[3]

Spirituality as Human Technology

Spiritual practices could be considered one of the first human technologies, a compendium of ways of being, acting, and doing that served to enhance the positive traits of human individuals and societies and increase their fitness, resilience, and cooperation in the face of existential

threats. Many traditional practices, such as meditation, breathwork, fasting, and yoga, appear to be strategies to reduce experiences of suffering in the moment, as well as inoculate the human mind against future experiences of suffering. Several scientific studies have verified the veracity of these ancient claims and the influence of these practices on human neurobiology.[4] Doctrines espouse basic heuristic principles of human behavior for strengthening the individual and relationships, whether through means of generosity, empathy, mental fortitude, ethical practice, or foundational contentment. These symbolic behaviors find variations throughout history and have shown to remain consistent means of ensuring human societies, communities, and nations remain intact, while simultaneously improving the individual human condition.

The historical line of many religious, philosophical, and spiritual traditions can be traced back to a single charismatic individual, almost exclusively male. These would include Jesus Christ (Christianity), Siddartha Gautama (Buddhism), Muhammad (Islam), Abraham (Covenant with God), Moses (Judaic Law), Bodhidharma (Zen or Ch'an), Confucius (Confucianism), Padmasambhava (Nyingma Tibetan Buddhism), or Laozi (Taoism). Here, these traditions have relied heavily on the doctrinal teachings of very specific figures, leading to a strong reliance on the living presence or belief in the existence of the individual.

Even in their lifetime, many of these leaders reported a strong dependency of their followers on the leader's existence to continue the practice, often admonishing them for the follower's lack of faith. Increased secularization in the modern era has eroded this substantial faith in an individual leader, leading to a reduction in devotion to spiritual practices. Furthermore, modern gender dynamics and the women's rights movement has further alienated individuals, especially women, from religious organizations that rely on a patriarchal structure to continue existing. The exceptions include Hinduism, which appears to be a persistent, evolutionary, agglomeration of traditions that can be traced back to the Vedic tradition of the Indo-Aryan migrants of the Indus Valley Civilization, as well as the indigenous traditions of the Hmong, Native Americans, Siberian shamans, Māori, and others, which have more inclusion elements of all types of individuals.

Regardless, as spiritual technologies, the doctrines of wisdom appear to have a very consistent cluster of belief structures, which become updated by subsequent followers and practitioners over centuries to adapt to the ongoing crises that were faced by the societies at the time. These traditions had time to slowly evolve and change, selected for or against if the wisdom-clusters could sufficiently enable the societies to overcome their challenges. In this way, these spiritual traditions were also subject to a question of fitness; could they evolve and survive through time,

or were they subject to decay and destruction over time? That said, most pre-modern challenges were localized in time and space, such as regional war, famine, pestilence, and political instability within nations, and did not pose the wholesale destruction of the human species on a global scale.

Existential Threats to Humanity and Evolution

As modern life and secular technology become increasingly prevalent across the globe, we find that these ways of being, and their associated benefits, are eroding. Despite the many material improvements that digital spaces, social media, and other internet-enabled technologies have offered, the trade-off has been well-documented.[5] We have seen a significant decline in public trust, deterioration of mental health, and the spread of misinformation. These challenges are arising just as many existential crises, that are highly detrimental to the very human condition of the modern era, pose a substantial drop in the experiential quality of human life, if not complete annihilation.[6]

Whether those threats mean climate change, global wars, nuclear armaments, pandemics, food and water insecurity, or malicious artificial intelligence, what remains clear is that humans remain the driver of these scenarios that threaten our existence as a species on this planet. Our abdication of responsibility for resolving the very challenges that we've created speaks to a limitation in awareness and consciousness, rather than an inherent property of anthropogenic design. While historically, biological evolution of emergent traits relied solely on a trial-and-error model that tested the fitness of gene clusters and their expression in living beings over the course of millions of years, humans have demonstrated a remarkable transformation of abilities and traits over short generations, and even within lifetimes, through material, social, and cultural technology. The fitness of humans is heavily tied to our ability to document, share, and improve on artifacts or modes of being and behavior.

We are a species of malleability in the face of destruction.

2. Proposal Description

Background

Psilocybe cubensis, the entheogen mushroom species often associated with spiritual transformation in both ancient and modern iconography, has played a consistent part of human spiritual evolution and appears to support initial spiritual development at its early stages. The primary psychoactive components of *Psilocybe cubensis* are psilocybin and psilocin, the dephosphorylated product of psilocybin. It is believed that psilocybin serves as a prodrug to psilocin and requires the presence of a phosphatase enzyme to achieve its potent entheogenic effect.[8] These mushroom species are relatively straightforward to forage, or grow using modern established microbiological protocols, and provide a highly effective psychosomatic experience for overcoming personal, emotional, and spiritual challenges. Despite growing research literature pointing to the benefits of psilocin and its progenitor psilocybin, the compounds and associated mushroom species remain classified as Schedule I controlled substances and outlawed in the majority of countries.[9]

In 2020, a consortium of researchers from the University of California, San Diego, the Medical College of Wisconsin, and other institutions, studied the structure-activity relationship of 17 psilocybin analogues.[10] While the investigators found that psilocin remained the most potent compared to the analogues, the other 17 structures remain within one to two-fold less potent and thus still retain a significant portion of their bioactivity regardless of their structure. The advantage to these structural analogues, given that they are not Schedule I substances, is that they are not actively deemed illegal by the Drug Enforcement Administration (DEA). While the Federal Analogue Act of 1981 was put into place to allow agents to prosecute possessors of structural analogues of drugs, deeming substances chemically similar enough to Schedule I or II substances to be considered Schedule I or II, the constitutionality of the law has been put under question by Supreme Court Justice Neil Gorsuch on the basis of the Vagueness doctrine.

Table 1. Concentration for each psilocybin derivative required to activate the four relevant neural 5-HT serotonin receptors for entheogenic activity.[10]

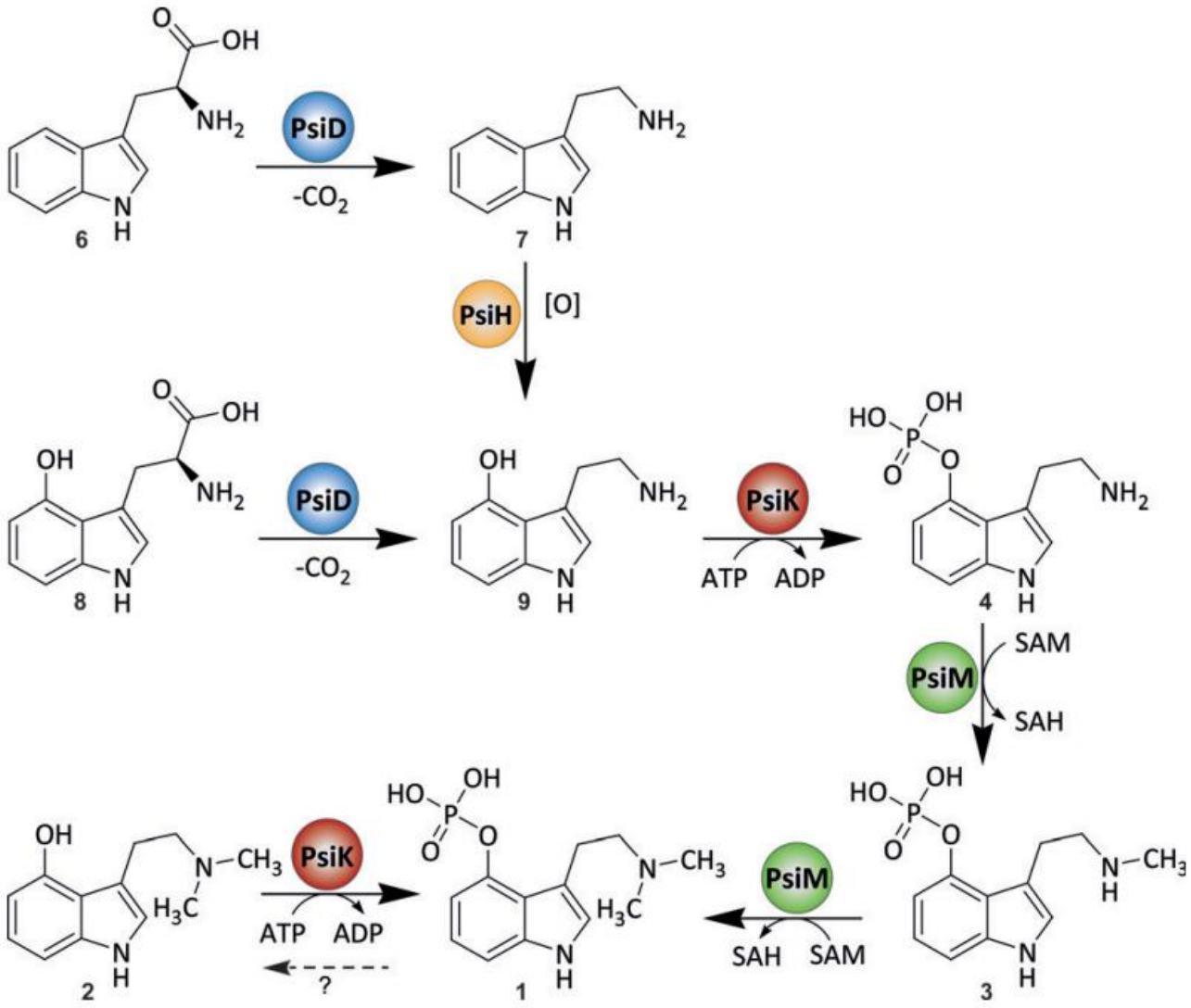
	5-HT$_{2A}$			m5-HT$_{2A}$			5-HT$_{2B}$			5-HT$_{2C}$		
compound	EC$_{50}$ (nM)	pEC$_{50}$ (± SEM)	E_{max}% 5-HT (± SEM)	EC$_{50}$ (nM)	pEC$_{50}$ (± SEM)	E_{max}% 5-HT (± SEM)	EC$_{50}$ (nM)	pEC$_{50}$ (± SEM)	e_{max} % 5-HT (± SEM)	EC$_{50}$ (nM)	pEC$_{50}$ (± SEM)	E_{max}% 5-HT (± SEM)
5-HT	0.26	9.58 ± 0.04	100	0.16	9.81 ± 0.06	100	0.21	9.67 ± 0.03	100	0.25	9.60 ± 0.04	100
psilocin	2.40	8.62 ± 0.05	98.4 ± 1.3	3.21	8.49 ± 0.04	95.7 ± 1.0	2.37	8.63 ± 0.08	39.2 ± 0.8	21.8	7.66 ± 0.07	85.1 ± 1.9
4-HO-MET	4.04	8.39 ± 0.04	96.8 ± 1.1	2.49	8.60 ± 0.04	98.2 ± 1.2	2.64	8.58 ± 0.05	43.8 ± 0.6	29.7	7.53 ± 0.06	90.8 ± 1.7
4-HO-MPT	3.82	8.42 ± 0.04	98.1 ± 1.1	2.85	8.55 ± 0.05	99.9 ± 1.3	3.40	8.47 ± 0.04	58.4 ± 0.7	45.8	7.34 ± 0.07	82.9 ± 2.1
4-HO-MIPT	5.20	8.28 ± 0.04	99.6 ± 1.2	6.51	8.21 ± 0.03	103 ± 1.0	10.3	7.99 ± 0.12	49.1 ± 1.8	166	6.78 ± 0.10	76.2 ± 2.8
4-HO-DET	6.47	8.19 ± 0.04	100 ± 1.2	4.19	8.38 ± 0.04	105 ± 1.1	6.27	8.20 ± 0.04	71.1 ± 0.8	264	6.58 ± 0.04	80.4 ± 1.3
4-HO-EPT	3.15	8.50 ± 0.04	99.5 ± 1.2	1.88	8.73 ± 0.04	101 ± 1.1	4.34	8.36 ± 0.03	89.2 ± 0.7	129	6.89 ± 0.06	89.0 ± 2.1
4-HO-DPT	1.64	8.79 ± 0.04	103 ± 1.0	1.28	8.89 ± 0.04	101 ± 0.9	2.23	8.65 ± 0.03	94.1 ± 0.7	212	6.67 ± 0.06	83.3 ± 2.0
4-HO-DIPT	6.82	8.17 ± 0.04	102 ± 1.3	4.37	8.36 ± 0.04	101 ± 1.1	5.12	8.29 ± 0.02	97.0 ± 0.6	1408	5.85 ± 0.05	91.4 ± 2.6
4-HO-MALT	3.67	8.43 ± 0.04	101 ± 1.2	3.81	8.42 ± 0.04	102 ± 1.2	3.16	8.50 ± 0.05	60.4 ± 0.8	44.2	7.36 ± 0.07	82.7 ± 2.0
4-AcO-DMT	103	6.99 ± 0.02	79.2 ± 0.7	N.T.			100	7.00 ± 0.13	22.1 ± 1.0	268	6.57 ± 0.08	22.8 ± 0.6
4-AcO-MET	92.3	7.04 ± 0.03	94.3 ± 1.1	N.T.			45.7	7.34 ± 0.06	48.9 ± 1.0	575	6.24 ± 0.06	41.2 ± 0.9
4-AcO-MPT	42.4	7.37 ± 0.03	96.0 ± 1.1	N.T.			28.8	7.54 ± 0.06	62.7 ± 1.2	401	6.40 ± 0.05	32.7 ± 0.6
4-AcO-MIPT	43.9	7.36 ± 0.04	93.2 ± 1.4	N.T.			44.7	7.35 ± 0.08	49.1 ± 1.3	542	6.27 ± 0.16	33.7 ± 2.1
4-AcO-DET	184	6.74 ± 0.02	90.7 ± 0.8	N.T.			79.4	7.10 ± 0.07	64.2 ± 1.6	851	6.07 ± 0.04	53.5 ± 1.0
4-AcO-EPT	66.4	7.18 ± 0.03	98.1 ± 0.9	N.T.			24.0	7.62 ± 0.04	95.8 ± 1.2	315	6.50 ± 0.04	87.6 ± 1.4
4-AcO-DPT	23.7	7.63 ± 0.04	100 ± 1.0	N.T.			5.50	8.26 ± 0.06	97.4 ± 1.8	991	6.00 ± 0.05	68.2 ± 1.5
4-AcO-DIPT	70.7	7.15 ± 0.16	74.6 ± 4.3	N.T.			70.8	7.15 ± 0.04	93.0 ± 1.2	1303	5.89 ± 0.06	80.8 ± 2.4

Designer drugs based off derivative 4-AcO-DMT (psilacetin), which was first synthesized by Albert Hoffmann and his colleague Franz Troxler in 1961,[11] are often freely available for sale. The remaining analogues were first synthesized and personally tested by Alexander and Ann Shulgin and are similarly available for sale as research chemicals.[12] That said, their purity and safety have always been questionable. Designer drugs based on tryptamine chemical structures have been known to contain the presence of substantial toxins, byproducts, and metals that make their use deleterious to health. Additionally, while substantially easier to synthesize than psilocybin, these chemical analogues remain inaccessible without institutional approval or substantial access to chemical research laboratories and associated synthesis knowledge. Thus, there remain substantial barriers to entry to access these legally available chemical entities.

Biosynthesis of Psilocybin Analogues

Federally, the possession and manufacture of *Psilocybe cubensis* are considered illegal due to the presence of psilocybin and psilocin, as Schedule I substances, within the tissue structure. However, given that *Psilocybe cubensis* spores do not actively contain these substances, they are freely available for purchase so long as the state in question has not outlawed their possession or sale. This can be seen in the popularity of mushroom vendors who legally sell *Psilocybe cubensis* spores, so long as they put a disclaimer that the spores are only for microscopic visualization purposes. While this bypass in the legal structure of the DEA allows individuals to freely produce entheogenic mushrooms for personal consumption, the sale and distribution of larger quantities of the mushrooms remain suspect in the eyes of the law.

Figure 1. Biosynthesis of psilocybin in *Psilocybe cubensis* from tryptophan (6) or hydroxytryptophan (8).[13]



Psilocybin biological production begins with the amino acid tryptophan. The full biosynthesis itself is relatively straightforward, requiring only four enzymes and five chemical steps, in which the final two steps are two intermolecular methylations.[13] The construction of analogous species would require the inhibition of putative kinase PsiK followed by the insertion of a gene sequence of a relevant acetylase, such that no phosphate-bearing chemical group is produced within the genetically modified *Psilocybe cubensis*. This would yield the 4-AcO-DMT analogue. Other analogues could be biosynthesized by deactivating the endogenous putative

methyltransferase and inserting the gene sequence for an ethyltransferase or even a prenyltransferase in its stead.

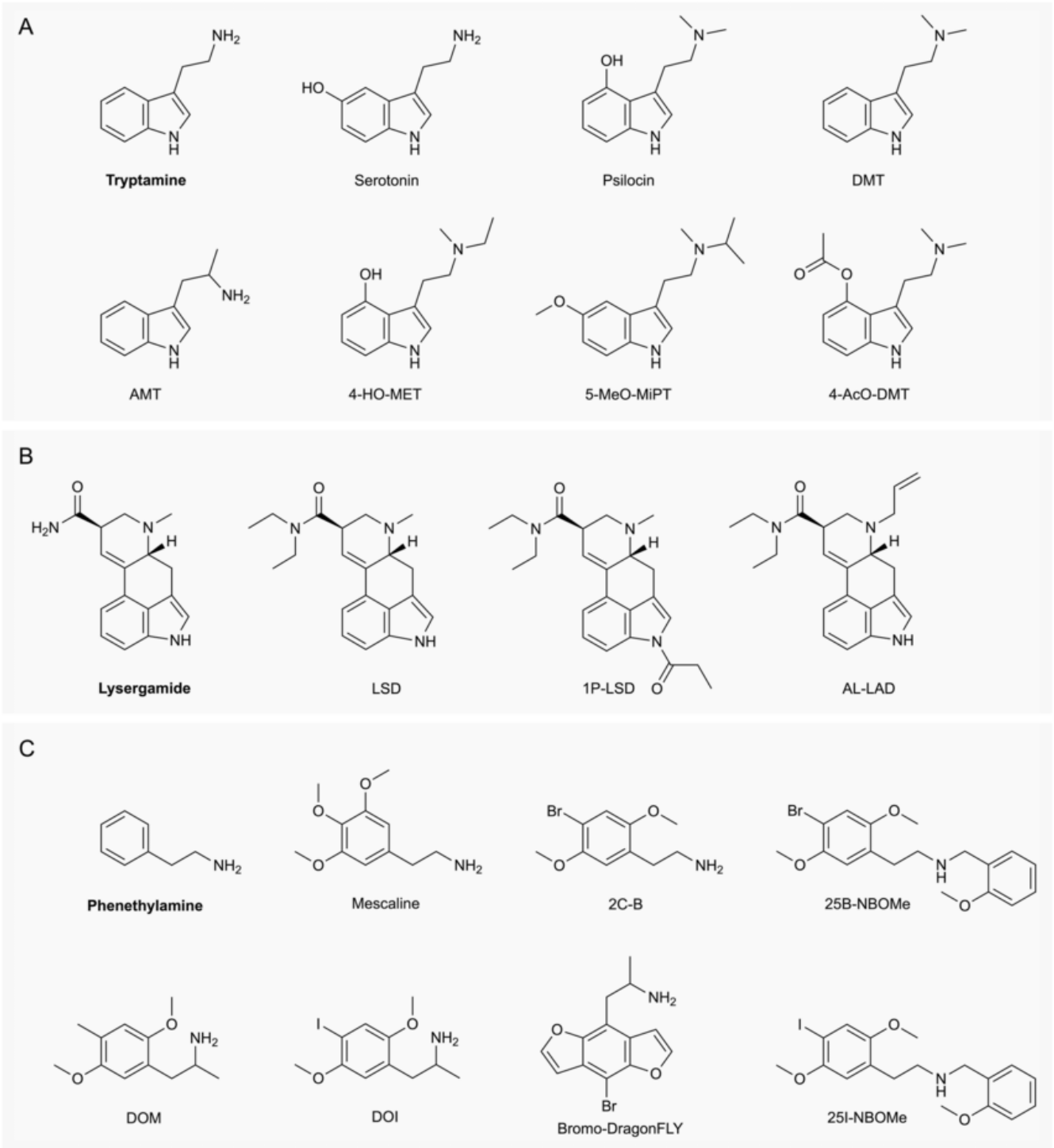
With the arrival of the novel genetic engineering platform, CRISPR-Cas9, the ability to modify organisms has become increasingly more available to research practitioners.[14] Modern research laboratories at academic centers have easily adapted the CRISPR-Cas9 system to filamentous fungi, accelerating research in the field, where historically filamentous fungi were considered challenging to modify using conventional gene-editing techniques.[15]

So long as the gene sequence of the enzymes in question are known or can be adapted from other biosimilar species, a plethora of analogous chemical entities could be produced using the *Psilocybe cubensis* organismal platform. The complete gene sequence of *Psilocybe cubensis* and gene cluster associated with the production of psilocybin and other entheogenic derivatives was recently published in 2024, with a more detailed and complete evolutionary history of the psilocybin gene cluster.[16] More complete work will be necessary to further understand the exact nature of the enzyme biosynthetic cascade and how modifications can be applied to the gene cluster to yield new molecular entities.

Indeed, many of these compounds would not be normally accessible using conventional organic synthesis techniques that would have been the staple chemical strategies used by the organic chemist Alexander Shulgin and his early investigations into tryptamine and phenylalanine derivatives. Given the potential novel structure of biosynthetic tryptamines, these compounds could have novel effects not yet known to the scientific and amateur entheogenic communities. Since these structures have not yet been tested, extensive animal and human testing would be required to evaluate the biological safety of these chemical entities. The author poses to experiment with these substances on himself to establish a first-pass subjective review of the compounds, much as Alexander and Ann Shulgin did themselves.

Artificial intelligence and machine learning may be used in this context to evaluate structures with potentially higher 5-hydroxytryptamine$_{2A}$ (5-HT$_{2A}$), the primary agonist of psilocin, and other 5-HT receptor affinities. These technologies may also have use in constructing gene sequences for more novel modified enzymes, not yet found in nature, that could construct chemical structures of even more unique architecture as well. This process would greatly accelerate the ability of the project to evade potential legal consequences of distributing these substances, as these tools could be used to continue to optimize and improve upon new chemical structures that would require significant bureaucratic resources to legislate against.

Figure 2. Chemical structures of the main classes of serotonergic psychedelics and example derivatives, compared to endogenous serotonin.[17]



3. Community Impact

The legality of drug use puts significant stress on individuals and communities that practice entheogenic transformation, especially those from underserved, risk-averse, or marginalized communities where the need is greater due to the accumulation of generational and individual trauma. These individuals are more likely to be prosecuted with the possession of illegal substances. Known designer drug analogues may be more easily legislated against, however, the design of biosynthetic novel compounds that have no known parallel in the research literature would require federal and state authorities to put legal resources into building a case against each individual chemical species and biological specimens.

In time, new novel structures would be produced before the previous versions are considered illegal by these authorities, following the progress of any legal cases. Annual "updated" versions of the modified mushroom species could be distributed to vendors and manufacturers to ensure legal compliance with the status of specific psilocybin derivatives.

The spores of basidiomycetes species are easily propagated and stored for later use. Using the *Psilocybe cubensis* organismal platform, genetically modified specimens could continue to produce genetically identical or similar spores that would be available for later production. This would reduce the dependency of communities on vendors and potential traceback by authorities if the legality of these modified species were reviewed by the federal and state governments.

Spore kits containing these genetically modified variants will be distributed to residential and commercial growers of *Psilocybe cubensis* through standard commercial distribution methods at cost. The gene sequences will be made available for free through the Creative Commons Attribution-ShareAlike 4.0 International (CC BY-SA 4.0) license to allow anyone, anywhere in the world, to adapt and modify the *Psilocybe cubensis* species and circumvent drug restriction laws. The goal will be to increase access to community-clusters that most need it.

4. Potential Challenges

Basidiomycetes and other filamentous molds are known to undergo mutations and genetic drift due to their rapid growth rate. It is possible that the genetic transformation is rejected, and the mutated species reverts to the original psilocybin bioproduction. These transformations will need to be monitored, as the minute presence of any psilocybin would render the biomaterial illegal in the eyes of legal authorities.

Additionally, certain genetic transformations could potentially decrease or abolish the production of the desired entheogen variant, either endogenously or through limited growth rate of the mushroom itself. Genetic modification could render specimens more susceptible to diseases during spawning, fruiting, and harvesting. That said, one approach would be to insert an additional gene sequence that increases the fitness and mold resistance of the mycelium. Regardless, these biological factors will need to be considered as specimens are evaluated for their entheogenic potential.

5. Conclusions

The growing recognition of the psychotherapeutic potential of psilocybin and derivatives has the potential to improve the state of the human condition through the individual and cultural-level expansion of consciousness. According to a survey conducted by RAND, 12 percent of adults in the United States have reportedly used entheogenic mushrooms, with nearly three percent of adults using them in 2023 alone. With that, entheogenic mushrooms are the most consumed psychotropic substances in the United States. However, legal structures that greatly limit the use of entheogens will remain an impediment to the wider adoption of these spiritually transformative substances.

To achieve national and globally significant spiritual modification to the human species, we hypothesize a more substantial population of humans will need to have some spiritually transformative experience to address the monumental challenges we face as a species. With the expansion of more modern spiritually transformative experiences, communities, events, and technologies, the need for humans to adopt more relevant strategies in our time is increasingly important to our survival.[18]

Here, we present a biosynthetic strategy to circumvent the artificially imposed restrictions on the use, manufacture, and distribution of these spiritually important substances. As we face the existential threat of extinction, we must use the entire toolbox of human technology to facilitate a rapid evolutionary change for the sake of our progeny and their future, or be rendered nothing more than a bleak moment in natural history along with all the other species we have brought into extinction by our own hands.

May our legacy as a species be of Eros and not of Thanatos.

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