THE MAGIC MOLECULES
BEHIND PSYCHEDELIC MUSHROOMS

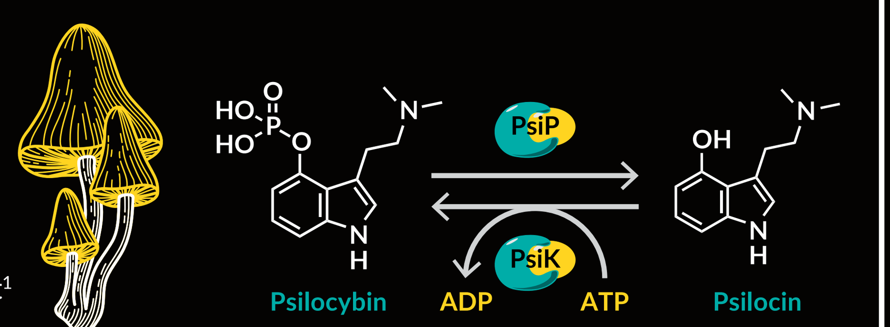
PSYCHEDELIC MUSHROOMS

Mushrooms have been used in medicinal and spiritual practices in Indigenous cultures around the world for several millennia. A wide variety of species of gilled mushrooms under the order of Agaricales contain psychoactive alkaloids. The two most studied genera include *Psilocybe* and *Amanita*. Because of renewed interest in entheogenic plant molecules as therapeutics, there is a large body of research building around the psychedelic effects of alkaloids found in these mushrooms. Presented here are the biosynthetic and metabolic pathways of psilocybin-containing mushrooms.

MUSHROOMS IN POPULAR CULTURE

Psilocybe

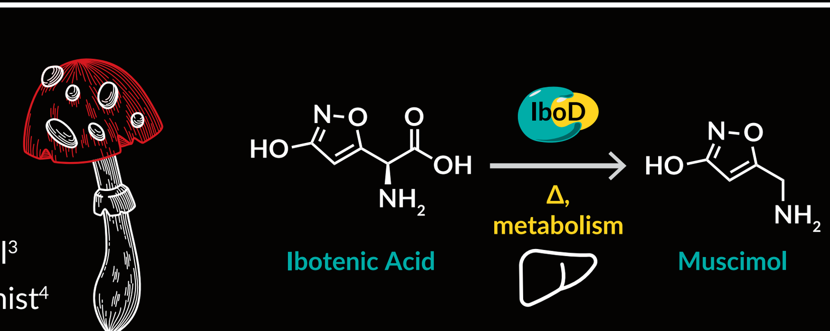
Family: Hymenogastraceae
Genus: *Psilocybe*
Active Psychedelic: Psilocin[1]
Mode of Action: 5-HT_{2A} Agonist[1]



Psilocybe mushrooms produce tryptamine and β-carboline alkaloids that elicit their hallucinogenic effects by acting upon serotonin (5-HT) receptors.[1] Psilocin is currently the most studied tryptamine alkaloid; however, studies show others may also contribute to 5-HT_{2A} activity.[2]

Amanita

Family: Amanitaceae
Genus: *Amanita*
Active Psychedelic: Muscimol[3]
Mode of Action: $GABA_A$ Agonist[4]



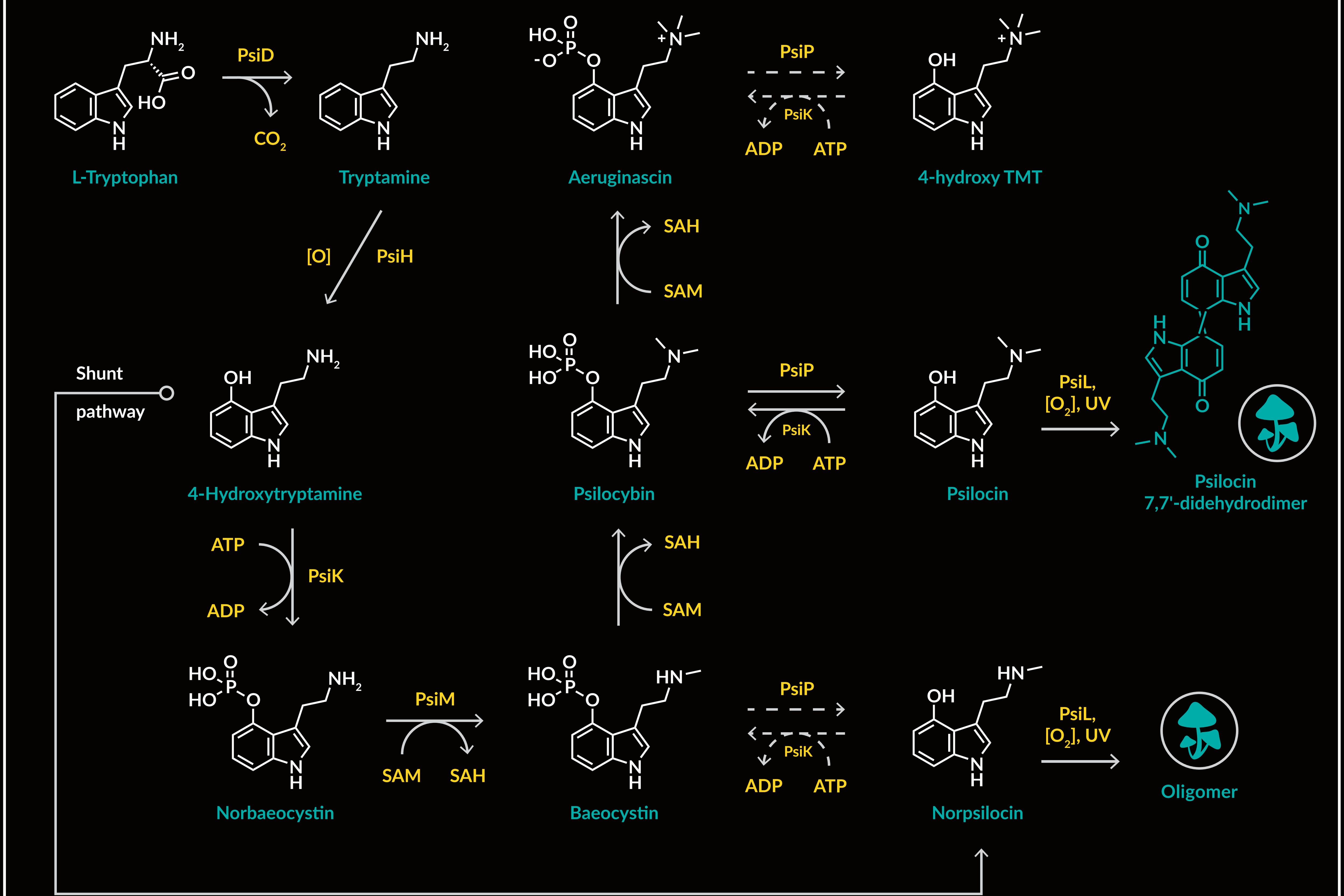
Amanita mushrooms are often portrayed as the icon of psychedelic mushrooms in media and pop culture with their characteristic vivid red and white spotted toadstool. However, their active alkaloids are ibotenic acid and muscimol which act upon a distinctly different set of neurotransmitters than their *Psilocybe* counterparts.[3,4]

VIEW PSYCHEDELIC MUSHROOM RESOURCES AT
WWW.CAYMANCHEM.COM/MUSHROOMS

- References used to compile poster
- Research tools for psychoactive mushroom components & their metabolites
- Articles, webinars, & more

BIOSYNTHETIC PATHWAY TO PSILOCYBIN

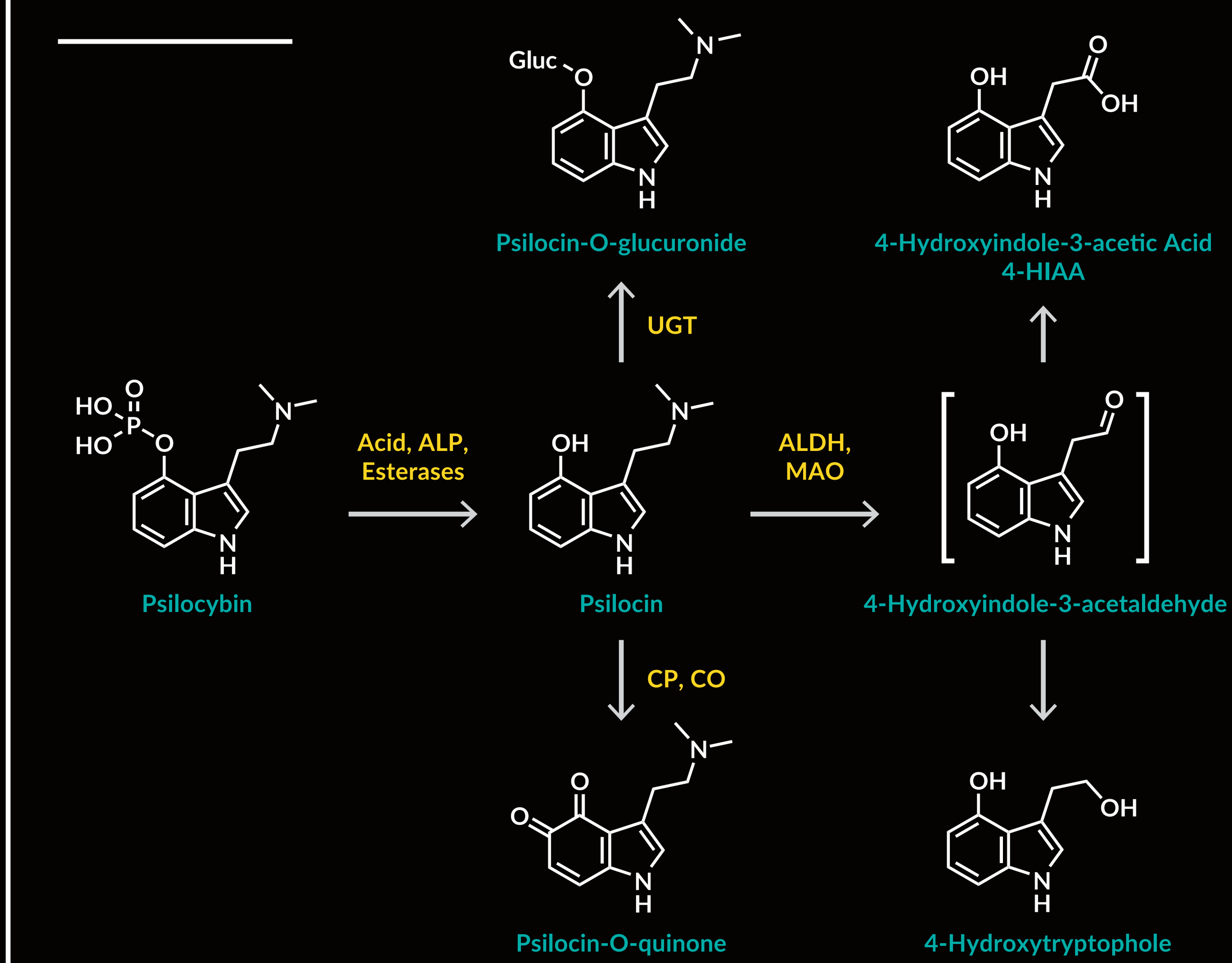
The biosynthetic pathway of psilocybin has been elucidated from the amino acid tryptophan.[5,6] Tryptophan is decarboxylated by L-tryptophan decarboxylase (PsiD) to form tryptamine, which is then oxidized by indole 4-monooxygenase (PsiH) to 4-hydroxytryptamine. 4-Hydroxytryptamine is then phosphorylated by a kinase (PsiK) to form norbaeocystin, which is then methylated by N-methyltransferase (PsiM) to form baeocystin (monomethylation) and psilocybin (dimethylation). A third methylation to form aeruginascin, previously thought to only occur in *Inocybe* species, was observed for the first time in *Psilocybe cubensis* in 2020. There is also a shunt pathway that was observed where 4-hydroxytryptamine is methylated to form norpsilocin.[6]



ENZYMATIC TRANSFORMATIONS		
L-Tryptophan decarboxylase (PsiD)	Kinase (PsiK)	N-Methyltransferase (PsiM)
Indole 4-monooxygenase (PsiH)	Laccase (PsiL)	Phosphatase (PsiP)

Psilocybin is dephosphorylated by phosphatase (PsiP) to psilocin. Rapid oxidation of psilocin then forms oligomeric structures that contribute to the bluing that occurs in freshly cut and aging fruiting bodies.[7-9] The 7,7'-didehydrodimer of psilocin appears to be the primary contributor to the blue chromophore.[9] The oligomeric structures are hypothesized to be a defense mechanism against pests and predators.[6] It has been demonstrated that PsiK is able to re-phosphorylate psilocin to psilocybin. This process is thought to be a protective mechanism to repair the cell from the liberation of phenolic tryptamines. Dashed arrows indicate hypothesized protective mechanism.

HUMAN METABOLISM OF PSILOCYBIN



METABOLIC TRANSFORMATIONS		
Alkaline phosphatase (ALP)	Cytochrome oxidase (CO)	Glucuronosyltransferase (UGT)
Aldehyde dehydrogenase (ALDH)	Ceruloplasmin (CP)	Monoamine oxidase (MAO)

Psilocybin is metabolized to the psychoactive metabolite psilocin. Psilocin is then metabolized by monoamine oxidase (MAO) and presumably aldehyde dehydrogenase (ALDH) to 4-hydroxyindole-3-acetic acid (4-HIAA) and 4-hydroxytryptophole. Phase II metabolism by glucuronosyltransferase (UGT) results in the major metabolite psilocin-O-glucuronide.[1] Minor oxidation pathways have also been described.

β-CARBOLINE ALKALOIDS

β-Carboline alkaloids in *Psilocybe* mushrooms are also biologically active. Several act as monoamine oxidase inhibitors (MAOIs), which potentiate the psychedelic effects of the tryptamine alkaloids by inhibiting their metabolism.[10]