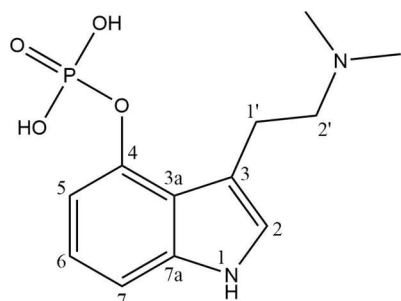


### Introduction

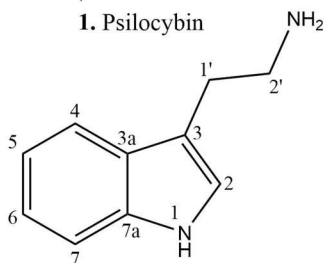
Psilocybin (PY, 4-phosphoryloxy-N,N-dimethyltryptamine or O-phosphoryl-4-hydroxy-N,N-dimethyltryptamine) (**Figure 1, 1**) is an indolamine (**Figure 1, 2**), and the primary ingredient in magic mushrooms. It has been implicated as a treatment for a number of psychological ailments including depression, general anxiety disorder, various addictions, obsessive-compulsive disorder, and post-traumatic stress disorder.<sup>1-4</sup> Because of the drug's re-emerging relevance in clinical applications, and because of its distinctive and informative effects on brain function, it is important to understand the pharmacology and general chemistry underlying its metabolism.

### Psilocybin is a prodrug of psilocin

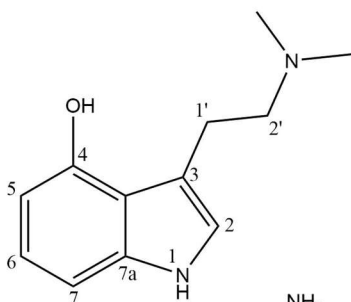
Magic mushrooms, the natural source of psilocybin may refer to several different hallucination-causing fungi, but the most potent of these are found in the genus *Psilocybe*. When ingested, magic mushrooms cause "trips," wherein a user experiences euphoria, colorful hallucinations, and changes in perception, cognition and mood. In the case of "bad trips," a user may experience states of intense panic or paranoia.<sup>5,6</sup> More generally, these trips are sometimes described in terms of psychotic states, and behavioral studies involving psilocybin have demonstrated similarities between the effects of psilocybin and schizophrenia both in subjective experience and in physiological response.<sup>7</sup> While psilocybin is more widely known as the cause behind these effects, it is referred to by researchers as a prodrug, or a biologically



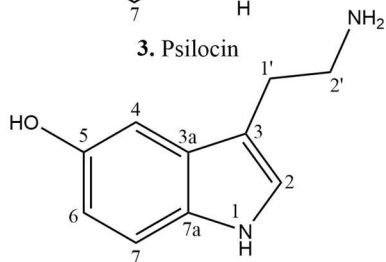
1. Psilocybin



2. Basic Indolamine Structure



3. Psilocin



4. Serotonin (5-HT)

**Figure 1:** Structural reference of indolamines discussed in this review

inactive compound that gives rise to an active drug through metabolism. Psychological effects are caused by psilocin (PI or 4-hydroxy-N,N-dimethyltryptamine) (**Figure 1, 3**), the product of enzymic psilocybin dephosphorylation by alkaline phosphatases in the intestine mucosa.<sup>8</sup> Indeed, it is suggested that psilocybin is unable to cross the blood brain barrier due to its polar charged phosphate group,<sup>9,10</sup> and evidence indicates that psilocybin is dephosphorylated almost completely into the more lipophilic and psychoactive psilocin, which can more easily enter circulation.<sup>8,11,12</sup> Further evidence is that psilocin is around 1.48 times as potent as psilocybin, likely because no metabolism is required for it to cross the blood-brain barrier and exert effects.<sup>13</sup>

### Receptor affinities for psilocin

Pharmacokinetic investigations indicate that around 50% of orally administered <sup>14</sup>C-labelled Psilocybin is absorbed by the body.<sup>9,14</sup> Similarly, a 4-6 µg/ml plasma concentration is needed to elicit psychological effects, and full effects occur at

8-25 mg per os doses.<sup>15,16</sup> Psilocybin demonstrates high affinity for the 5-HT<sub>2A</sub> serotonergic receptor, a lower affinity for the 5-HT<sub>1A</sub> receptor, and affinities for some histamine, dopamine, imidazoline, and other serotonin receptors, as well as serotonin transporter protein.<sup>17</sup> Despite these affinities, serotonin receptors are the biggest contributors the drug's effects, evidenced

by ketanserin, a 5-HT<sub>2A</sub> antagonist, and its ability to greatly reduce the hallucinogenic and psychotomimetic, that is, psychosis-mimicking, effects of psilocybin administration.<sup>7</sup> This high affinity is likely due to Psilocin's high structural similarity to serotonin (5-Hydroxytryptamine, 5-HT) (**Figure 1, 4**). It is noteworthy that Psilocin bears little affinity for the D<sub>2</sub> dopaminergic receptor, but pre-treatment with haloperidol, a D<sub>2</sub> antagonist, reduces the drug's effect. Because of this, it is theorized that stimulation of a 5-HT receptor causes stimulation of D<sub>2</sub> receptors, a contributing factor in psilocybin's effects.<sup>18</sup>

### **Interactions of 5-HT<sub>2A</sub> Agonists**

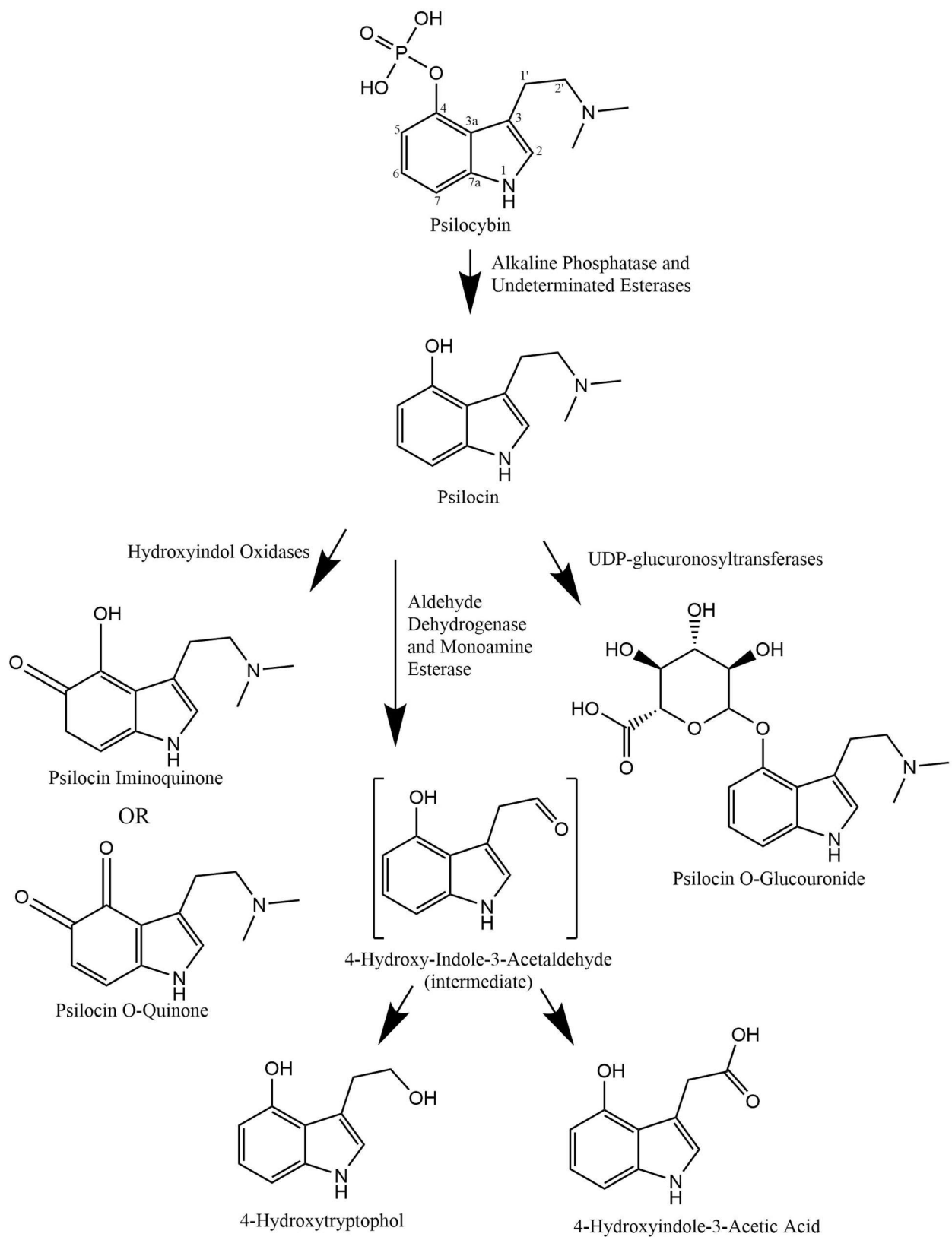
While psilocin exhibits affinity for a wide variety of receptors, 5-HT<sub>2A</sub> receptor antagonists are best able to inhibit its hallucinogenic effects. Because of this, it is believed that the 5-HT<sub>2A</sub> receptor is primarily responsible for psilocin's psychoactive effects, and there has been notable research into the receptor's complex binding mechanism. Specifically, it is suggested that psilocin's aromatic group is stabilized during binding by Phe340 and Phe339 of a 5-HT<sub>2A</sub> receptor through a  $\pi$ - $\pi$  interaction. Phe339 appears responsible for interacting with N-substituted phenethylamines and, by extension, indolamines like psilocin or serotonin. This is evidenced by only miniscule affinity changes for N-unsubstituted phenethylamines following F339L mutation, but massive effects on N-substituted phenethylamine affinity. In contrast, F340L mutation greatly affects affinity for all 5-HT<sub>2A</sub> ligands, though the ligand will still bind to a lesser degree.<sup>19</sup> Serines 239 and 242 are also implicated in stabilizing indolamines, with Ser239, a hydrogen bond donor, engaging oxygen substituents in the 4' (e.g. psilocin) and 5' (e.g. 5-HT) positions. While Ser242 may be engaged by polar ring-substituted tryptamine ligands, other tryptamines may orient such that this residue is not engaged.<sup>20</sup>

The 5-HT<sub>2A</sub> receptor is a metabotropic, excitatory G<sub>q/11</sub> protein linked receptor. It functions through the action of increased concentrations of diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP<sub>3</sub>) generated from the hydrolysis of Phosphatidylinositol 4,5-bisphosphate (PIP<sub>2</sub>) by Phospholipase C.<sup>21</sup> A 5-HT<sub>2A</sub> receptor agonist generally causes neuronal excitation, enhanced memory and learning, bronchial and gastric smooth muscle contraction, and increased production and release of oxytocin, along with a number of other hormones. 5-HT<sub>2A</sub> receptors are rapidly downregulated following hallucinogen administration. This is likely a standard physiologic response to overstimulation, but the result is tachyphylaxis, or acute and sudden decrease in responsiveness, to psilocin. After an initial dose, receptor sites will return to 50% of their usual binding potential after three to seven days and will return to normal after one to four weeks. The 5-HT<sub>2C</sub> receptor, for which psilocin has a similarly high affinity, modulates the release of hormones responsible for appetite and response to stressful stimuli.<sup>22,23</sup> While 5-HT<sub>2C</sub> receptors are sometimes discussed in the context of psilocin's mechanism of action, it should be noted that highly specific 5-HT<sub>2C</sub> antagonists do not inhibit Psilocin's effects in the same way that 5-HT<sub>2A</sub> antagonists do. Ketanserin, which halts psilocin's effects, binds the 5-HT<sub>2A</sub> receptor with much greater affinity than 5-HT<sub>2C</sub>.<sup>24,7</sup> these findings cast doubt on 5-HT<sub>2C</sub>'s importance in inducing psilocin's effects.

### **Metabolism**

Because psilocybin is a prodrug, its half-life in plasma is much greater than psilocin, the T<sub>½</sub> for both compounds being about 160 minutes and 50 minutes, respectively.<sup>15,25</sup> Rodent studies of psilocybin metabolism indicate that 75% of psilocybin is converted to psilocin, while the rest is excreted unaltered. Psilocin is excreted primarily in urine (65%), but also in bile and

feces (15-20%). This occurs within 8 hours after oral mushroom administration. Only 10-20% of converted psilocin remains beyond this point, though detectable amounts of the drug may be found in urine samples up to 10 days after ingestion.<sup>26</sup> Psilocin is processed by both phase-I (<20%) and phase-II (>80%) metabolism.<sup>27</sup> In phase-I metabolism, psilocin may be oxidized to produce 4-hydroxyindole-3-acetaldehyde or 4-hydroxyindole-3-acetic acid or reduced to produce 4-hydroxytryptophol. It may also be converted to psilocin iminoquinone or psilocin O-quinone by hydroxyindol oxidases. In phase-II metabolism, psilocin is processed primarily by UDP-glucuronosyltransferases and formed into an O-glucuronide conjugate. These products are excreted renally.<sup>9,27,28</sup> This Process is detailed in **Figure 2**.



**Figure 2:** Summary of psilocybin metabolism.

## Conclusion on Value of Psilocin Research

It is generally accepted that research into psilocin is greatly underdeveloped due to its schedule I status.<sup>9,16,29</sup> Preliminary reassessment of psilocybin's abuse potential suggest that it be downgraded to schedule IV status in the event the drug is approved for medicinal use.<sup>30</sup> However, most clinical research is from the 1960s. These studies often work with Indocybin, an artificially synthesized psilocybin patented by Sandoz, a Swiss Laboratory, and marketed for use in treating depression, only to be banned in 1966 due to public fear of its use as a narcotic.<sup>31,32</sup> For this reason, most reviews call for more, larger, and more modernized research into psilocin's effects and metabolism. Despite limited research into its therapeutic effects, Psilocybin demonstrates promise in safely treating a number of mental illnesses.<sup>29</sup> For example, in patients experiencing treatment-resistant depression high-dose (10 mg and 25 mg, one week apart) psilocybin administration led to decreased depressive symptoms, measured by the Quick Inventory of Depressive Symptoms (QIDS), as well as reduction in both anxiety and anhedonia. These reductions were sustained over the course of a 3-month pilot study,<sup>33</sup> and results were supported by a subsequent 6-month follow-up study.<sup>34</sup> It is important to mention that the hypothesized mechanism of psilocybin's amelioration of depression involves a supervised environment in which patients can productively work through their emotions.<sup>4</sup> Additionally, very few negative effects have been documented in clinical settings, with negative effects including transient headaches, and dysphoria.<sup>29</sup> Studying the effects of psilocin may also allow researchers to gain more insight into the function of psilocin-binding receptors, notably 5-HT receptors, and their mechanisms of action. This was the case in Vollenweider et al's 1999 study uncovering the relationship between 5-HT and Dopamine receptors.<sup>18</sup> Research of this kind may

bring new treatment options to light for the variety of mental illnesses stemming from improper functioning of these receptors.



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