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REVIEW ARTICLE

Metabolism of psilocybin and psilocin: clinical and forensic toxicological relevance

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ABSTRACT

Psilocybin and psilocin are controlled substances in many countries. These are the two main hallucinogenic compounds of the “magic mushrooms” and both act as agonists or partial agonists at 5-hydroxytryptamine (5-HT)_{2A} subtype receptors. During the last few years, psilocybin and psilocin have gained therapeutic relevance but considerable physiological variability between individuals that can influence dose-response and toxicological profile has been reported. This review aims to discuss metabolism of psilocybin and psilocin, by presenting all major and minor psychoactive metabolites. Psilocybin is primarily a pro-drug that is dephosphorylated by alkaline phosphatase to active metabolite psilocin. This last is then further metabolized, psilocin-O-glucuronide being the main urinary metabolite with clinical and forensic relevance in diagnosis.

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Introduction

Hallucinogens are compounds that in low doses alter a person's perception of reality often in dramatic and unpredictable ways, thought, or mood, without causing marked psychomotor stimulation or depression and preserving alertness, attentiveness, memory and orientation (Cody, 2008). Although they mainly cause auditory, visual and tactile distortions, gustatory and olfactory alterations may also be present. These sensory distortions are referred to as synesthesia, meaning that sounds are “seen” or colors are “heard”, etc. (Chan & Mendelson, 2014). Although called hallucinogens, hallucinations (i.e., such as manifestations of something non-existent or dream-like episodes in awake humans) are not always present and therefore psychedelics (“mind revealing”) or “psychotomimetics” (psychosis mimicking) are alternative preferred designations (Nichols, 2004; Osmond, 1957). These compounds differ from most other psychoactive drugs since they induce neither dependence nor addiction nor are used for prolonged periods; in other words, these drugs do not interfere with the mesolimbic rewarding system and are considered physiologically safe (Katzung et al., 2012; Nichols, 2004). One of the possible classification schemes divide hallucinogens as (i) serotonin (i.e.,

5-hydroxytryptamine [5-HT]) like such as psilocybin, psilocin and lysergic acid diethylamide [LSD]; and (ii) catecholamines (i.e., dopamine, noradrenaline and adrenaline) like such as mescaline (Figure 1).

Psilocybin (*O*-phosphoryl-4-hydroxy-*N,N*-dimethyltryptamine; Figure 2) and psilocin (4-hydroxy-*N,N*-dimethyltryptamine) are tryptophan indole-based alkaloids distributed worldwide in mushrooms of the genus *Psilocybe*, *Panaeolus*, *Conocybe*, *Gymnopilus*, *Stropharia*, *Pluteus* and *Panaeolina* (Cody, 2008; Derosa & Maffioli, 2014; Tyls et al., 2014). Both are tryptamines, i.e., have an indole ring structure, a fused double ring comprising of a pyrrole ring and a benzene ring, joined to an amino group by a two carbon side chain (Tittarelli et al., 2015). They are commonly referred as “magic”, “hallucinogenic”, “psychedelic”, “entheogenic”, “medicinal”, “neurotropic”, “psychoactive”, “sacred” or “saint” mushrooms (Guzmán, 2008). Psilocin and psilocybin are typically used as recreational drugs by eating the mushrooms, which contains them at concentrations of up to 0.5% and 2% (m/m), respectively (Pedersen-Bjergaard et al., 1997). Nevertheless, these concentrations show a large variation depending on the species, origin, mushroom sizes, growing and drying conditions, and age (van Amsterdam et al., 2011). Although both

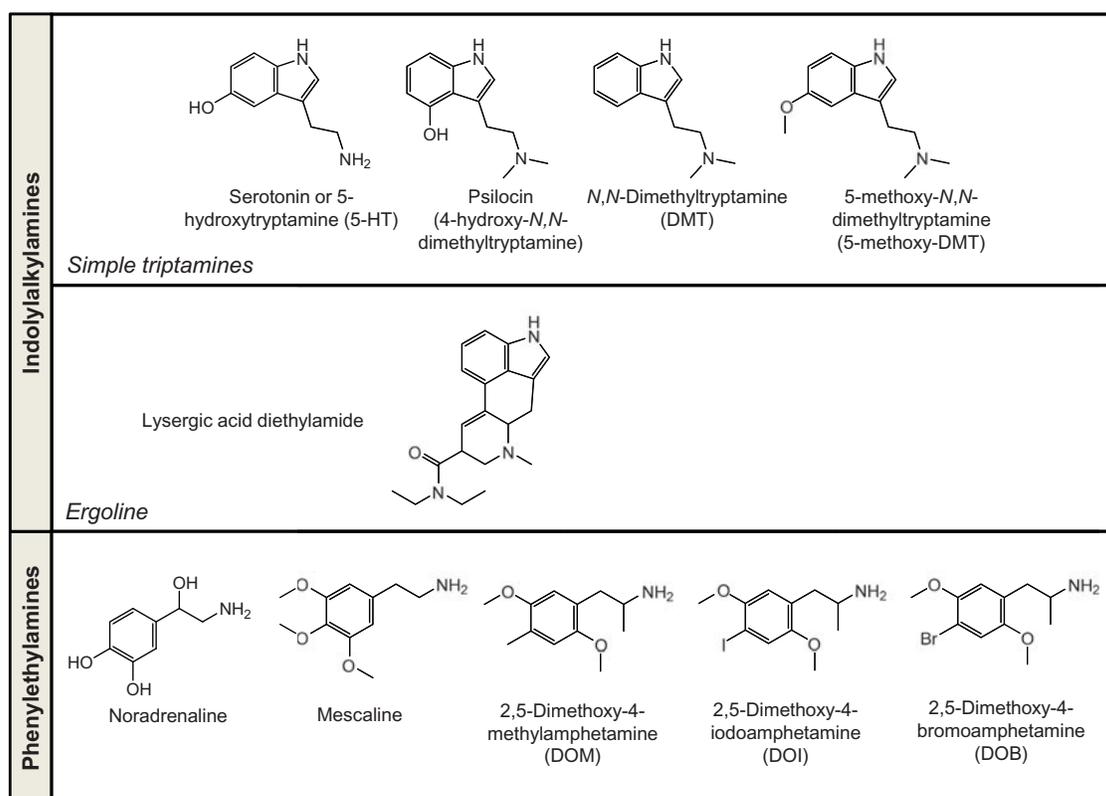


Figure 1. Chemical structures of hallucinogens. This class is divided in two major groups: (i) indolylalkylamines or triptamines or serotonin like and (ii) phenylethylamines or phenethylamine or β -phenylethylamine (2-phenylethylamine) or catecholamines (i.e., dopamine, noradrenaline and adrenaline) like such as mescaline and 2,5-dimethoxy-4-methylamphetamine (DOM), 2,5-dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-bromoamphetamine (DOB). Indolylalkylamines include two subgroups: simple tryptamines with considerable conformational flexibility such as *N,N*-dimethyltryptamine (DMT), 5-methoxy-DMT, psilocybin and psilocin, and the relatively rigid analogs ergolines such as lysergic acid diethylamide (LSD).

are naturally occurring compounds, psilocin and psilocybin can also be chemically synthesized (Hofmann et al., 1958, 1959; Shirota et al., 2003).

Although generally considered of low toxicity ($LD_{50} = 280$ and 285 mg/kg for rats and mice, respectively; a 60-kg person would need to ingest up to 1.7 kg of fresh mushrooms to reach this dose), several acute toxic effects have been reported to be related to psilocybin and psilocin exposure in all organ systems (Isbell, 1959; Lim et al., 2012; van Amsterdam et al., 2011): (i) cardiovascular (tachycardia, hypertension and hypotension); (ii) neurological (headache, confusion, euphoria, muscle weakness, hallucinations, panic attacks, derealization, illusions, synesthesia, convulsions, alterations of thought and time sense, vertigo, anxiety, agitation and significant tolerance with repeated use without causing dependence); (iii) respiratory (transient hypoxemia); (iv) gastrointestinal (nauseas); (v) acute renal failure; (vi) ocular (mydriasis); (vii) hematological; and (viii) fatal accidental cases due to a strong emotional destabilization or hallucinations that predisposed to risky behaviors such as the belief of the ability to fly (Muller et al., 2013). No specific antidote is available, and treatment is

mainly supportive. Most probably, the higher risk associated with hallucinogen administration is “bad trip”, which is characterized by anxiety, fear, panic, dysphoria and paranoia (Johnson et al., 2008). Early single-blind experiments showed cross-tolerance of psilocybin and LSD (Isbell et al., 1961). More recently, and due to its safety profile (little or no affinity for receptors that mediate vital functions) and non-addictive effects, psilocin has emerged as having therapeutic potential namely in psychotherapy as an anxiolytic, antidepressant and to control symptoms of the obsessive-compulsive disorder, and in the treatment of headaches, alcohol dependence and smoking cessation (Grob et al., 2011; Moreno et al., 2006; Sewell et al., 2006; Tyls et al., 2014).

One of the objectives of metabolomics is the characterization of all xenobiotic metabolites and their qualitative and quantitative changes over time (Barbosa et al., 2016; Dinis-Oliveira, 2014, 2015, 2016a, c, d). The focus of this manuscript is to present all the available metabolic data regarding psilocybin and psilocin focusing on major and minor metabolites and discussing their pharmacological and toxicological relevance.

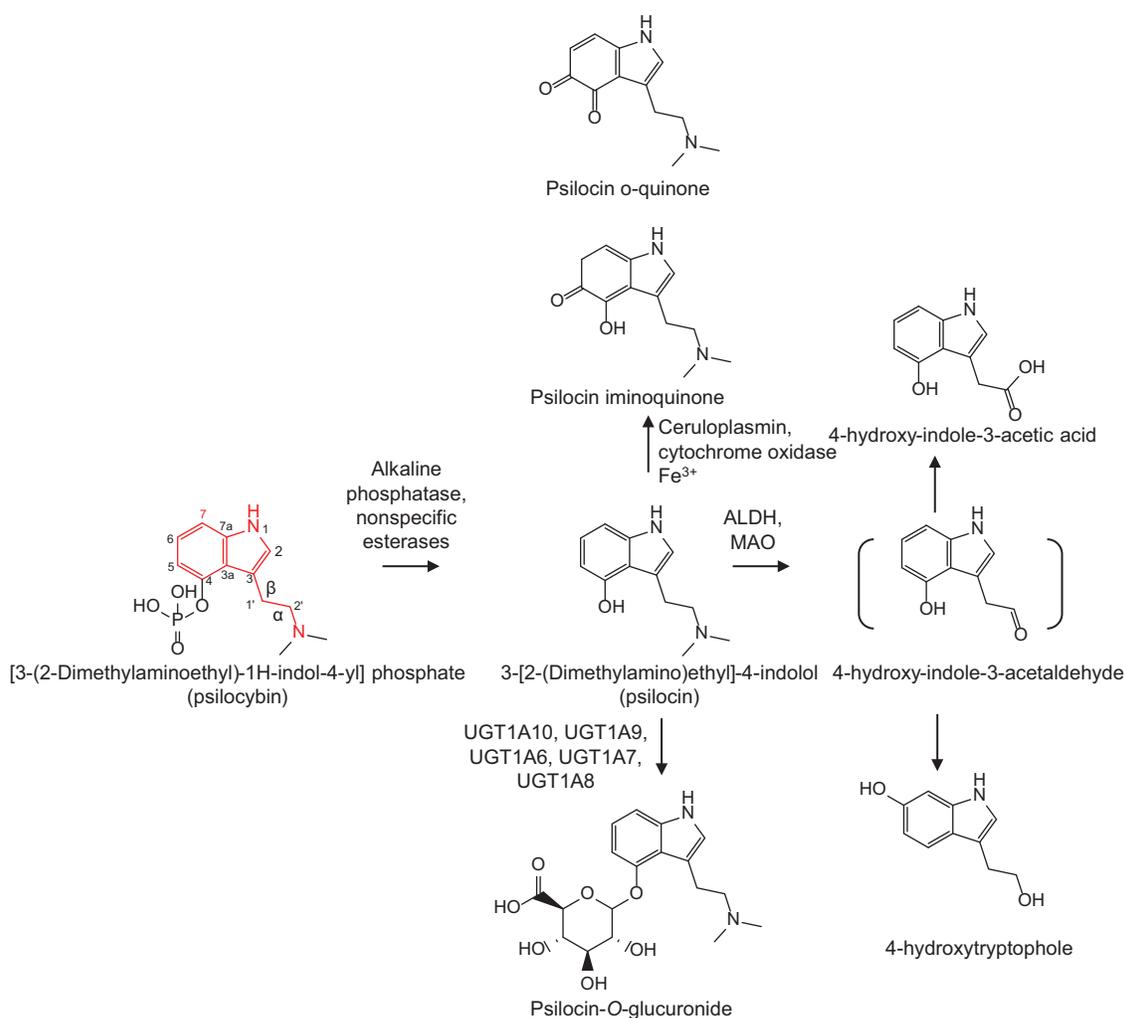


Figure 2. Metabolism of psilocybin. The structure of tryptamine is indicated in red.

Methodology

An English extensive literature search was carried out in PubMed (U.S. National Library of Medicine) without a limiting period to identify relevant articles on psilocybin, psilocin and related known metabolizing enzymes and metabolites. Electronic copies of the full papers were obtained from the retrieved journal articles as well as books on “magic mushrooms” and hallucinogens, and then further reviewed to find additional publications related to human and non-human studies.

Absorption, distribution and excretion

“Magic mushrooms” are typically administered *per os* (drink or in the form of bar of chocolates due to the unpleasant flavor) or smoked. Since it is a zwitterionic alkaloid and due to the presence of a highly polar phosphate group, psilocybin is more soluble in water than psilocin (Ballesteros et al., 2006). Therefore, psilocin is more easily absorbed from the rat jejunum and colon

gastrointestinal tract, suggesting also greater central nervous system bioavailability (Eivindvik et al., 1989). Both are moderately soluble in ethanol and methanol (Ballesteros et al., 2006). Pharmacokinetic studies in animals showed that only 50% of ^{14}C -labelled psilocybin is absorbed following oral administration and is almost uniformly distributed throughout the body, including the brain, where it exerts its psychedelic properties (Hopf & Eckert, 1974). Moreover, the *in vivo* studies in rats showed that psilocybin is rapidly hydrolyzed in the intestine to psilocin, meaning that psilocybin is absorbed mostly or even all as psilocin (Eivindvik et al., 1989). In humans, psilocin is detectable in significant amounts in the plasma within 20–40 minutes after *per os* administration (Passie et al., 2002), and maximum concentrations are reached after approximately 80–100 min (Hasler et al., 1997; Lindenblatt et al., 1998). The effects completely disappear within about 4–6 h (Shulgin, 1980).

Psilocybin and psilocin have an elimination half-life in plasma of approximately 160 and 50 min, respectively

(Hasler et al., 1997; Martin et al., 2013a). *In vivo* studies in rats have shown that psilocin is excreted in urine (65%) and bile and feces (15–20%) within 8 h after oral administration (Kalberer et al., 1962). About 10–20% remained in the organism for a longer time with metabolites of psilocin being detected in urine seven days after oral administration (Hofmann, 1968; Kalberer et al., 1962). About 25% of the whole dose was shown to be excreted unaltered (Kalberer et al., 1962). A controlled study in humans showed that within 24 h, $3.4 \pm 0.9\%$ of the applied dose of psilocybin was excreted in urine as free psilocin (Hasler et al., 2002). Later pharmacokinetic and forensic studies revealed that psilocin is mostly (approximately 80%) eliminated as psilocin-*O*-glucuronide (Grieshaber et al., 2001; Sticht & Kaferstein, 2000). The enzymatic hydrolysis of this conjugate during analysis extends the time of detectability for psilocin in urine samples, namely due to the higher stability of this metabolite compared to psilocin, especially at room temperature (Hasler et al., 2002; Martin et al., 2014).

Metabolism

The metabolism of psilocybin and psilocin is presented in Figure 2. After oral administration, psilocybin is rapidly dephosphorylated under acidic environment of the stomach or by alkaline phosphatase (and other nonspecific esterases) in intestine, kidney and perhaps in the blood to generate the phenol compound psilocin, which easily crosses the blood-brain barrier (Hasler et al., 1997; Horita & Weber, 1961b, 1962). Other rodent tissue studies presented more evidence for complete conversion of psilocybin to psilocin before entering the systemic circulation (Eivindvik et al., 1989). This assumption is also supported by the observation that equimolar amounts of psilocybin and psilocin evoke qualitatively and quantitatively similar psychotropic effects in humans (Passie et al., 2002). Psilocybin could therefore be referred to as a prodrug and whenever a reference is made to the *in vivo* effects of psilocybin, it should be understood that it is psilocin the responsible for the effects. Noteworthy is the relative potency of psilocin to psilocybin (1.48); almost identical to the molecular weight ratio between the two compounds (Wolbach et al., 1962). Moreover, blockage of alkaline phosphatase by means of competitive substrates (β -glycerophosphate) prevents the symptoms of intoxication (Horita, 1963). Since psilocin is structurally related to the neurotransmitter serotonin (Figures 1 and 2), it undergoes comparable human metabolism (Helsley et al., 1998). Indeed, psilocin is then further metabolized by a demethylation and oxidative deamination catalyzed by liver monoamine oxidase (MAO) or aldehyde

dehydrogenase, via a presumed intermediate metabolite, 4-hydroxyindole-3-acetaldehyde, to yield 4-hydroxyindole-3-acetic acid, 4-hydroxyindole-3-acetaldehyde and 4-hydroxytryptophole (Kalberer et al., 1962; Lindenblatt et al., 1998). Therefore, MAO inhibitors are also co-consumed by psilocin abusers to intensify its hallucinogenic effects (Halpern, 2004). Indeed, ethanol may enhance the trip since its primary metabolite acetaldehyde reacts *in vivo* with endogenous biogenic amines producing the MAO-inhibitors tetrahydroisoquinolines and β -carbolines. Tobacco use is also associated with lowered levels of MAO in the brain and peripheral tissues and therefore extended effects of “magic mushrooms” are likely (Fowler et al., 1996). Moreover, since psilocin may cause competitive inhibition of MAO and this enzyme also metabolizes serotonin, brain levels of serotonin may be elevated and simultaneously 5-HIAA may decrease (Freedman et al., 1970). It was also described a minor oxidation metabolic pathway of psilocin to a deep blue color product with an *o*-quinone or iminoquinone structure. This pathway was claimed to be catalyzed by hydroxyindol oxidases (e.g., ceruloplasmin, the copper containing oxidase of mammalian plasma and cytochrome oxidase) or non-enzymatically by Fe^{3+} (Blaschko & Levine, 1960; Horita & Weber, 1961a; Kovacic, 2009). Although these metabolites may present physiological activity related to production of reactive oxygen species during catalytic cycling, data are yet limited (Kovacic & Cooksy, 2005). Additionally, the oxidation to the bluish products also appears when mushrooms are handled or damaged.

The analysis of serum samples collected 5 h after “magic mushrooms” intoxication showed that up to 80% of the psilocin was present as the *O*-glucuronide conjugate and is eliminated by urine in this form (Kamata et al., 2006). Glucuronidation of hydroxyl group to psilocin *O*-glucuronide seems to be an important detoxification step. Indeed, the same occurs in the formation of 5-hydroxytryptamine *O*-glucuronide during serotonin metabolism (Eivindvik et al., 1989; Sticht & Kaferstein, 2000). Therefore, enzymatic hydrolysis extends the detection time for psilocin in urine samples (Hasler et al., 2002). Whereas psilocin may be subjected to extensive glucuronidation by UDP-glucuronosyltransferases (UGT)1A10 in the small intestine, UGT1A9 is likely the main contributor to its glucuronidation once it has been absorbed into the circulation (Manevski et al., 2010). *N*-glucuronidation was not observed (Manevski et al., 2010).

The analysis of psilocybin and psilocin in body fluids is challenging since the analytes are rapidly metabolized and are unstable under the influence of light and air, especially when in solution (Hasler et al., 1997).

Blood samples stored at room temperature evidenced a continuous decrease of about 90% of the analyte within one week (Martin et al., 2012). Storage at 4 °C improved stability to almost seven days if fluoride was added. Surprisingly, freezing blood samples led to an unreproducible and uncontrollable loss of psilocin. The authors suggested that enzymes involved in psilocin metabolism are released from hemolysis that occurs during freezing (Martin et al., 2012). Therefore, if psilocin needs to be analyzed, whole blood samples should not be stored at room temperature or frozen. It is preferable that blood samples be cooled until they reach the laboratory and then centrifuged to freeze the serum (Martin et al., 2012).

Conclusion and future perspectives

Use of hallucinogens remains a significant problem for a population of drug abusers. These drugs have a long history and their popularity comes and goes with time, but they remain a constant presence in the drug community, mainly by young people seeking psychedelic experiences. Although pure synthetic psilocybin (Indocybin[®]) was marketed for experimental and psychiatric therapy in the 1960s, only limited pharmacokinetic and pharmacodynamic data are available.

In this work, the metabolism of psilocybin and psilocin was fully reviewed. Psilocybin is predominately dephosphorylated in the intestine and liver by alkaline phosphatase to psilocin, which is the main psychoactive compound. More studies are needed to identify additional metabolites, and the influence of drug interactions and polymorphisms in pharmacokinetics and pharmacodynamics. Indeed, Lindenblatt et al. (1998) revealed a large interindividual variation as regards psilocin plasma concentrations in healthy volunteers after oral administration of psilocybin. The identification of additional metabolites is also important for qualitative and quantitative toxicological analysis (Dinis-Oliveira, 2016b). Particularly, further sensitive analytical methods will prove consumption in a wider detection window, especially if hydrolysis of glucuronide conjugates is performed.

Literature data suggests that psilocybin and psilocin exhibit low toxicity and may be seen as physiologically well tolerated. However, most studies are old and do not meet contemporary standards for safety assessment and therefore more controlled studies are needed to ascertain the therapeutic role in certain diseases, especially those psychiatry-related (Passie et al., 2002). Although exhibiting different potencies and time course, it is known that psilocybin and psilocin produce mainly pharmacological effects similar to those of LSD

and mescaline; stimulation of central serotonin receptors and blockade of peripheral serotonin receptors (Wolbach et al., 1962). They bind with high affinity at 5-hydroxytryptamine (5-HT)_{2A} and to a lesser extent at 5-HT_{1A}, 5-HT_{1D} and 5-HT_{2C} subtype receptors (McKenna et al., 1990). In contrast, they exhibit no apparent affinity for dopamine D₂ receptors (Creese et al., 1975). However, results are contradictory since the administration of haloperidol (i.e., D₂ receptor antagonist) also reduces psilocybin-induced psychotomimesis, raising the possibility of a dopaminergic neuronal transmission involvement. Indeed, the administration of psilocybin to healthy human volunteers, decreased the binding of the dopamine D₂ antagonist [¹¹C] raclopride in both caudate nucleus and putamen (Vollenweider et al., 1999). This effect is compatible with an increase in extracellular dopamine that competitively displaces the antagonist. Therefore, the probability that the interaction of indolylalkylamines with non-5-HT₂ receptors with psychopharmacological and behavioral consequences should not be excluded (Halberstadt & Geyer, 2011). Although psilocybin does not show any affinity to dopamine receptor of D₂ subtype, interactions between serotonergic and dopaminergic neuronal systems are known to exist (Vollenweider et al., 1999). Since the pharmacodynamics and the mechanisms underlying the emergence of psychedelic alterations are not fully understood, metabolomic studies may provide additional insights to help clinical and forensic toxicologists in the interpretation of toxicological results. Noteworthy is the recent renewed interest of psilocin in the treatment of resistant depression, obsessive compulsive disorder, cancer anxiety, and alcohol and tobacco addiction (de Veen et al., 2016; Hendrie & Pickles, 2016; Nichols, 2016). In these pathologies, clinical trials with adequate control of metabolic profile and metabolome (e.g., stress hormones such as cortisol) can help to predict if psilocybin outweighs its adverse effects.

Finally, scarce data is available regarding other active hallucinogen compounds found in mushrooms. Indeed, besides psilocybin and psilocin, magic mushrooms also contain baeocystin (4-phosphoryloxy-*N*-methyltryptamine) and norbaeocystin (4-phosphoryloxytryptamine), which are mono- and di-*N*-demethylated equivalents of psilocybin, respectively (Figure 3) (Franke et al., 2002; Mahmood et al., 2010). It is also known that there are further psychoactive compounds found in other mushrooms species such as aeruginascin (*N,N,N*-trimethyl-4-phosphoryloxytryptamine), a trimethyl analog of psilocybin, and bufotenine (*N,N*-dimethyl-5-hydroxytryptamine), a positional isomer of psilocin (Figure 3) (Jensen et al., 2006; Franke et al., 2002;

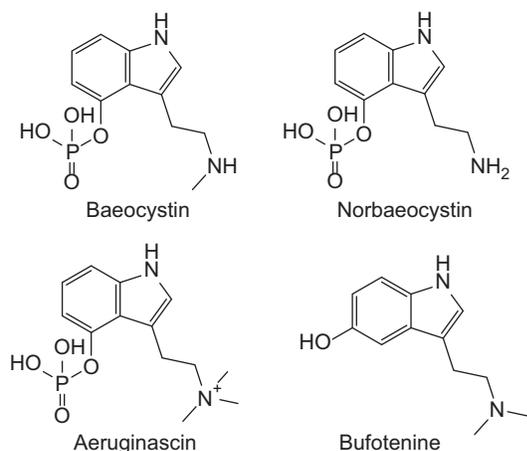


Figure 3. Chemical structures of other hallucinogens present in “magic mushrooms”.

Martin et al., 2013b). Together these compounds are less explored than psilocybin and psilocin and dephosphorization is also expected for psilocybin analogs to produce psychoactive metabolites.

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