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Bachelor thesis

5-Methoxy-N,N-dimethyltryptamine`s pharmacokinetics and viable routes of synthetization

Author:

Emil Forner

Supervisor:

Solon Oikonomopoulos

Abstract

Hallucinogenic drugs have always been a part of nature in some form or way, and new ones are frequently being discovered and classified. Among these compounds is a hallucinogenic tryptamine which is found in a wide variety of plant species as well as being secreted by the glands of at least one toad species, the *Bufo Alvarious.* The compound being 5-Methoxy-N,N-Dimethyltryptamine or 5-MeO-DMT for short, in this thesis its pharmacokinetics and possible synthesis pathways were examined. It was discovered that the most viable way of producing 5-MeO-DMT ensuring high purity of the product was through a synthetic pathway using 5-methoxytryptamine as a precursor (figure 1.1). 5-MeO-DMT showed similar toxicity traits to LSD and DOM inducing a wide variety of negative behavioural effects in animal models. In mice these included head-twitching and head-weaving responses through the activation of 5-HT1A and 5-HT2A receptors. While 5-MeO-DMT is readily inactivated through the MAO-A-mediated deamination pathway, only a small portion of the parent drug is transformed into the active metabolite bufotenine by polymorphic CYP2D6 enzymes. Co-administration with monoamine oxidase inhibitors was found to block the deamination pathway, increasing the systematic exposure of both the parent drug (5-MeO-DMT) as well as the active metabolite bufotenine.

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1 Introduction

In the history of mankind psychedelic compounds have been known to many civilizations and served many purposes such as in medicine, mood improvement, in sociocultural and ritual contexts, recreationally and as research chemicals. Over the years, various psychedelic compounds have grown in popularity and served as a tool for self-exploration or to get in contact with one`s spiritual side, while others showing promising applications in therapy against mental illnesses. For the most part, the compound groups tryptamines and phenylamines, having been proven to have psychoactive and psychedelic properties, have therefore been branded as scheduled drugs. However, there is a constant process ongoing between chemists creating new analogues and the drug administration scheduling them as illegal drugs. When a new compound is made, there is almost no way of telling exactly how it will act upon ingestion in the human body. It isn't inherently good nor bad, it simply exists as a chemical compound in its entirety. Only upon further research can one determine if the drug has any practical use in medicine or therapy, or if it is strictly toxic to the human body. Therefore, most times, test animals are utilized to give some form of indication upon how this novel compound will act in the human body. But due to the endless war on drugs, valuable information and research is often either lost or prohibited due to the stigma behind psychedelic compounds. This can potentially result in a huge loss for mankind due to the possible applications this research could have on the improvement of human lives. What is also concerning, is the stigma in the science community regarding research on phenylamines, tryptamines, and their psychoactive, psychedelic, and psychomimetic effects which for the most part stems from unauthorized uses of such compounds in psychiatric institutions and military applications in the last 50 years. There is significant evidence pointing towards many answers regarding how the human brain works lie within these groups of compounds. Being able to see different chemical shifts in human brains under the influence of various hallucinogenic compounds and looking at the change in neuronal branches and synapses, has helped towards reaching a further understanding of how the human brain works. But still, a lot about the mind and human consciousness is unknown.

An explanation and a real cure for mental illness using chemical compounds have not fully been reached yet. Therefore, there is a great deal of research to be done within the human mind to further our understanding of the life we live on earth. There is always going to be ways for technology to enhance or improve our life in some way. But one thing is well known, which is the human brain is a fragile thing, it can withstand very little physical damage before being permanently damaged. Even non-physical events can bring huge permanent changes to the brain, which can sometimes even be visible through the changes in chemical shifts. Despite psychedelics showing promising applications in medicine and the therapeutic world, some toxicological factors apply as with almost any drug administered to humans. This thesis will focus on the psychedelic compound 5-Methoxy-N,N-Dimethyltryptamine (5-MeO-DMT), which has over the years soared in popularity, especially among young people in recent years. It has a long history of use but is mostly known for its ability to dissolve one's ego. This is what has made it popular amongst not only young people, but spiritual and open-minded people who wish to reach a deeper understanding of one's self.

Promising research has also shown its applicability in the therapeutic world, proving to be a good fast-acting compound in the treatment of PTSD, anxiety, and depression. However, very few people experimenting with this very potent psychedelic compound are aware of the chemistry which lies behind it, and its possible toxicological effects. As with any drug, people respond differently due to the differences amongst humans.

Therefore, this thesis deals with the apparent risks involved with the psychedelic compound 5-MeO-DMT along with an alternate solution to produce the material, due to the fact that the ones in place

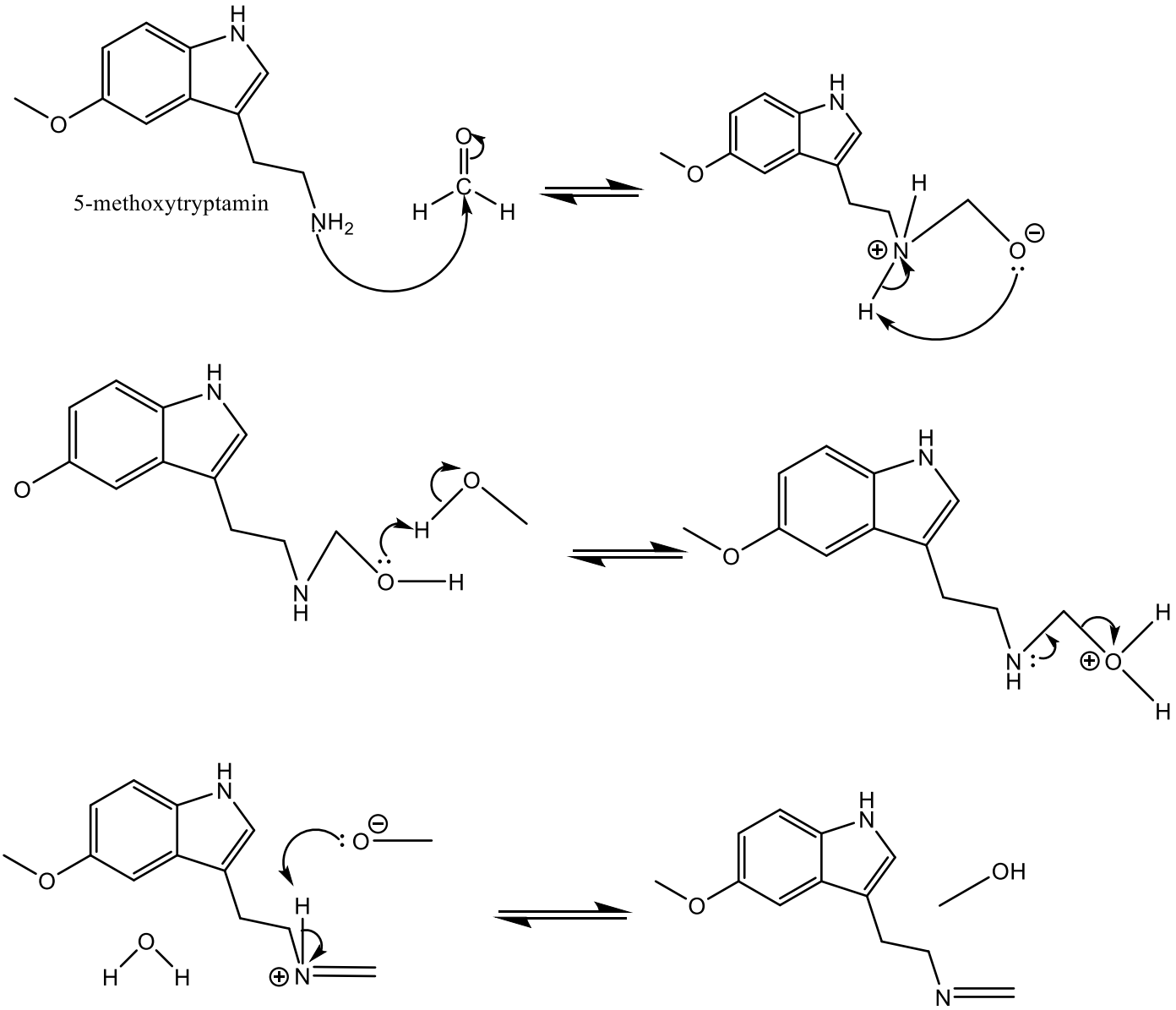
now, are not sustainable for the up-scaling of the current and possible future demand for this compound. Despite all the positive data on the treatment of PTSD, depression, and anxiety using 5-MeO-DMT, a lot is subjective or anecdotal.

Therefore, this thesis will not indulge further into this, but rather stick to the drug chemistry and toxicology of the compound using objective and well-established data mainly from animal testing, along with tests conducted with human cells.

2 Viable production routes for 5-MeO-DMT

Currently, the most common way for the extraction of 5-MeO-DMT is through the milking of the toad venom of the *Bufo Alvarius.*[26] This extraction process leaves the toads in terrible shape and in the long run, kills the toads. It has become apparent that this is not sustainable due to the increase in demand for 5-MeO-DMT, as well as the species not only faces extinction due to the increased interest in its excretion after the rise in popularity of 5-MeO-DMT, but simultaneously the species faces many other threats. Such as issues with climate change, habitat disruption, pesticide contamination, and most frequent of all being toads struck by cars due to the toads congregating towards the artificial lights on roads which attract insects on which they can feed. This has been an ongoing problem and different solutions have been presented to preserve the *Bufo Alvarious* species. This thesis will present and discuss to which degree various solutions are scalable with respect to the possible need of 5-MeO-DMT not only in therapeutic use, but also as a recreationally available compound.

Following are the reaction mechanisms for synthesizing 5-MeO-DMT from 5-methoxytryptamin which is a metabolite of melatonin that has a high frequency of occurrence in nature. The threshold dose for 5-MeO-DMT being around 1-2mg makes it possible to scale production to where anyone who would ever wish to try it or use it in therapeutic ways, has the possibility to do so. This pathway showed to be the most viable due to the possibilities of up-scaling while keeping levels of impurities low. In the reaction scheme below (figure 1.1) displaying the basic synthetic synthetization process for 5-MeO-DMT, the lone pair electrons on the basic nitrogen on 5-methoxytryptamine attack formaldehydes carbonyl-carbon, forming an iminium and water. Later the hydride ($NaBH_3$) attacks the electrophilic iminium carbon and electrons move to the nitrogen producing 5-MeO-NMT. Then the basic nitrogen (on 5-MeO-NMT) attacks a second formaldehyde carbonyl forming a tertiary iminium ion, which is reduced again (by $NaBH_3$) to create 5-methoxy-dimethyltryptamine.


5-methoxytryptamin

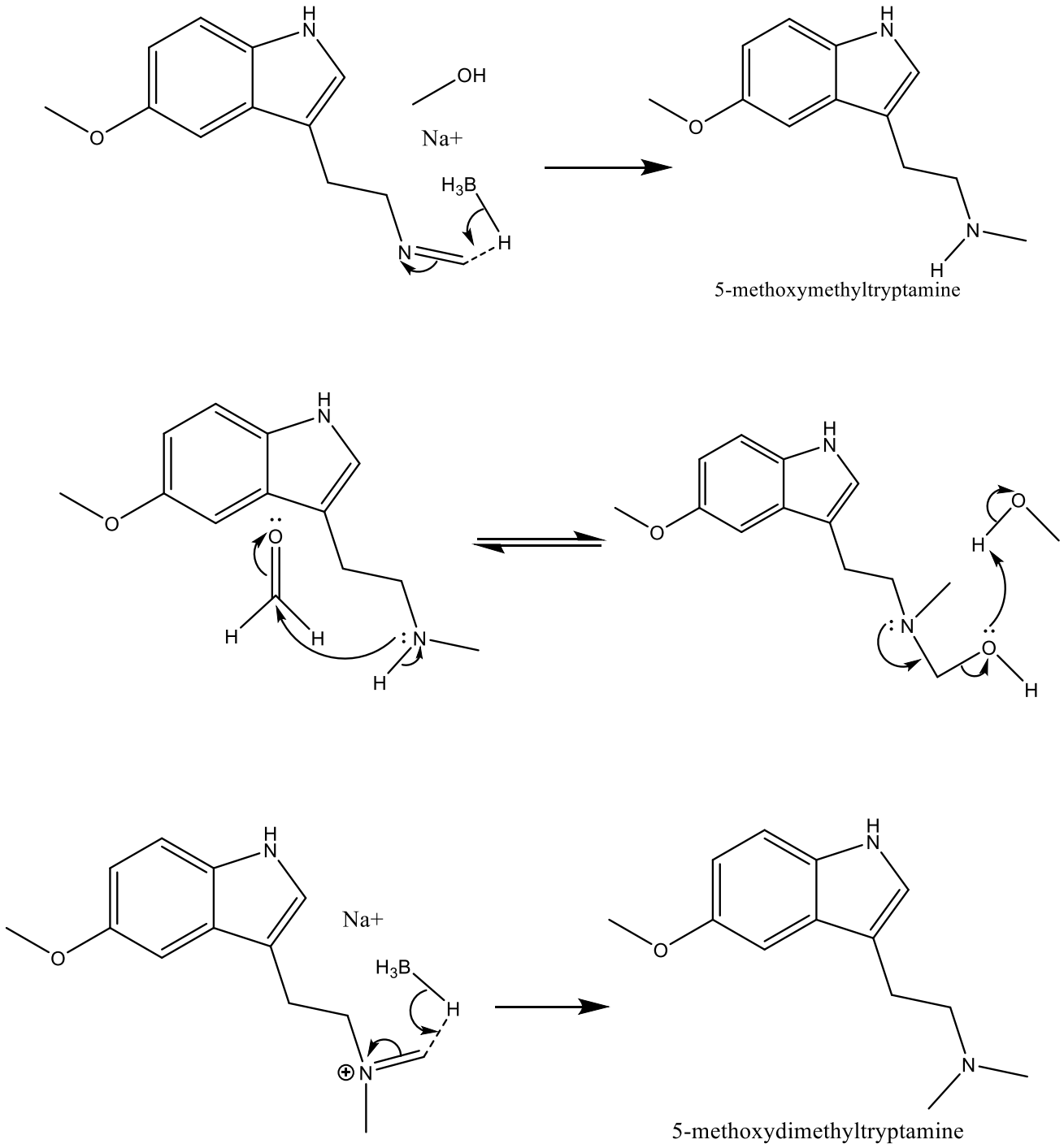


Figure 1.1: synthesis scheme of producing 5-MeO-DMT from the precursor 5-methoxytryptamine

The synthesis explained above is the most inexpensive synthetic way of producing 5-MeO-DMT (In terms of pricing). However, extraction from plants via a basic alkaloid extraction process is one of the most commonly exploited processes. There are today more than a thousand different plants, beans, grasses, and trees carrying various tryptamines such as 5-MeO-DMT in high concentrations. A full botanical appendix on all these alkaloids has yet to be produced, due to all the findings being in individual research papers and no one has really taken the time to put all these together and make a book of botanical alkaloids containing these psychotropic tryptamines. So, I will touch on the most commonly found plants and tree barks containing high concentrations of 5-MeO-DMT and their extraction of it.

First is *Virola rufula,* a tree in the family *Myristicaceae* containing alkaloids in all its components with a presence of 5-MeO-DMT in the bark, roots, and leaves at respectively 0.190%, 0.135%, and 0.092%. [17]

Second is the *Pilocarpus organensis* which is a plant belonging to the *Rutaceae* family. The plant in its entirety contains between 0.58-1.06% 5-MeO-DMT. [17]

To extract the alkaloids from the plant material, its ground into a fine powder to pulverize and rupture the cell structure. Then acidic water with pH 2 is added to the fine powder to convert the alkaloids into salts which are water-soluble. Then all that is left is to filter the solution leaving plant residue etc. and extract the alkaloid salts from the aqueous solution by defatting, basifying to pH 9, extraction via emulsions, and evaporation of the solvent. If done correctly with *Virola rufula* and *Pilocarpus organensis,* it should yield a pure product of 5-MeO-DMT. It is worth noting that a lot of these plants containing tryptamines such as 5-MeO-DMT also tend to contain other toxic alkaloids such as pilocarpine. Therefore, a purely synthetic approach will not only obtain a purer product, but also a much higher yield than that which one gets from the extraction of plants, bark, etc. Since most of these psychotropic alkaloids are controlled substances in most countries, the procedure explained above is the most common way of production of 5-MeO-DMT, along with harvesting the excretion from toad glands. Even though plant-based extraction is sustainable on the contrary to harvesting from toads, they are both inferior methods to lab production. There are many commercially available precursors through which almost all psychotropic substances can be synthesized. In the next section, a few good precursors which can be used to synthesize 5-MeO-DMT will be presented.

First, 5-methoxyindole will be presented, which is a commercially available compound whose most common use is to synthesize and analyze interactions between indole species. 5-methoxyindole is shown to display dual agonist and inverse agonist activity at the 5-HT_{3B}-receptor and partial agonism at the 5-HT_{3A}-receptor. However, it is also a good starting compound for the synthesis of 5-MeO-DMT as it shares the same backbone structure. But it has some downsides too which become important with scaling, such as the formation of unwanted intermediates (figure 1.3 and 1.4).

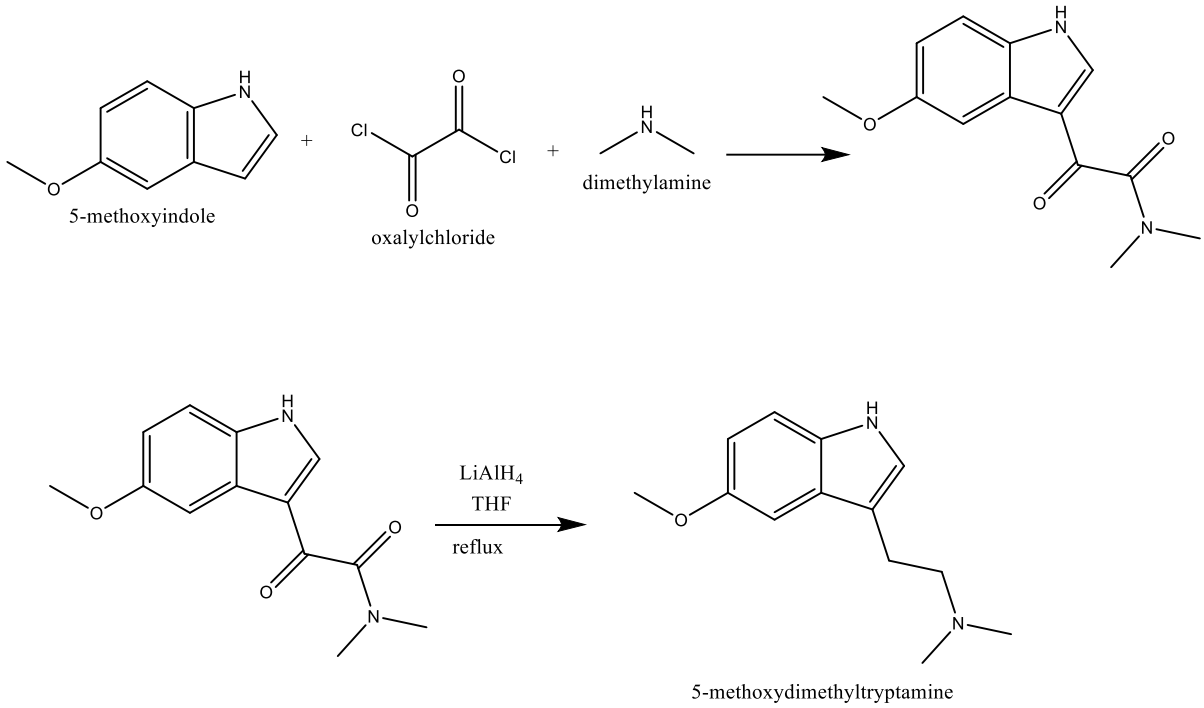


Figure 1.2: synthesis of 5-MeO-DMT using 5-methoxyindole as a precursor[18]

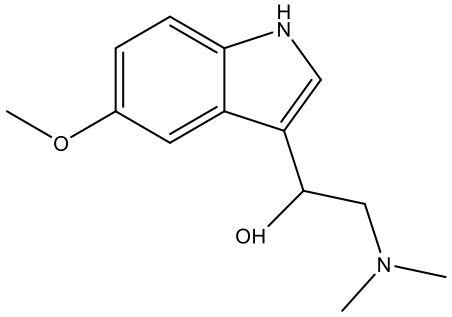


Figure 1.3: β-hydroxy intermediate impurity of synthesis using 5-methoxyindole[18]

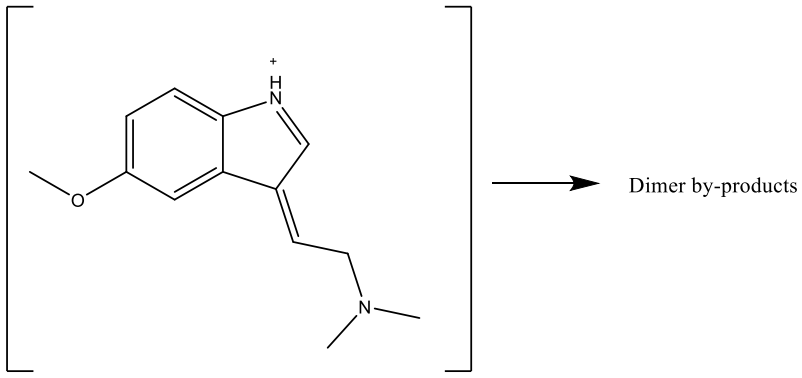


Figure 1.4: formation of reactive electrophile from the β-hydroxy intermediate[18]

The main problem arising with the upscaling of this pathway (Figure 1.2) takes place in the final reduction step on the ketoamide with pyrophoric lithium aluminum hydride (LAH), where in most cases this reduction step will stall at approximately 90% conversion with a 5-10% occurrence of an expected β-hydroxy intermediate(Figure 1.3). Also on workup, further manipulations of the crude freebase, especially in acidic conditions, conversion of the β-hydroxy impurity to a reactive electrophile (Figure 1.4) is promoted giving a mixture of isomeric dimerized impurities. Though this route of synthetization using 5-methoxyindole is viable in small quantities, the scale up would show challenges which would require additional process development to ensure that the final product (5-MeO-DMT) could reliably meet high-purity specifications, without having to rely on column chromatography. [18]

The complications involving scaling up with 5-methoxyindole as a precursor promote another synthesis route being a Fisher Indole reaction. Here the transformation occurs in a single step and does not rely on high temperatures, occurs in an aqueous solvent, and does not rely on pyrophoric or air-sensitive reactants such as seen in the previous synthesis route involving lithium aluminum hydride. For this route, the precursors are 4-methoxyphenylhydrazine and 4,4-diethoxy-*N*,*N*-dimethylbutan-1-amine (as shown in figure 1.5) which are both commercially available and inexpensive. However, when this route was explored, reaction monitoring by LCMS indicated that the 4-methoxyphenylhydrazine limiting reagent was expended within 2 hours with a crude reaction purity of around 63%, including several impurities with high molecular weight representing the remaining 37%.[27] Thus, considering this significant impurity profile, this pathway would not be viable without chromatography to isolate the product with sufficient purity.

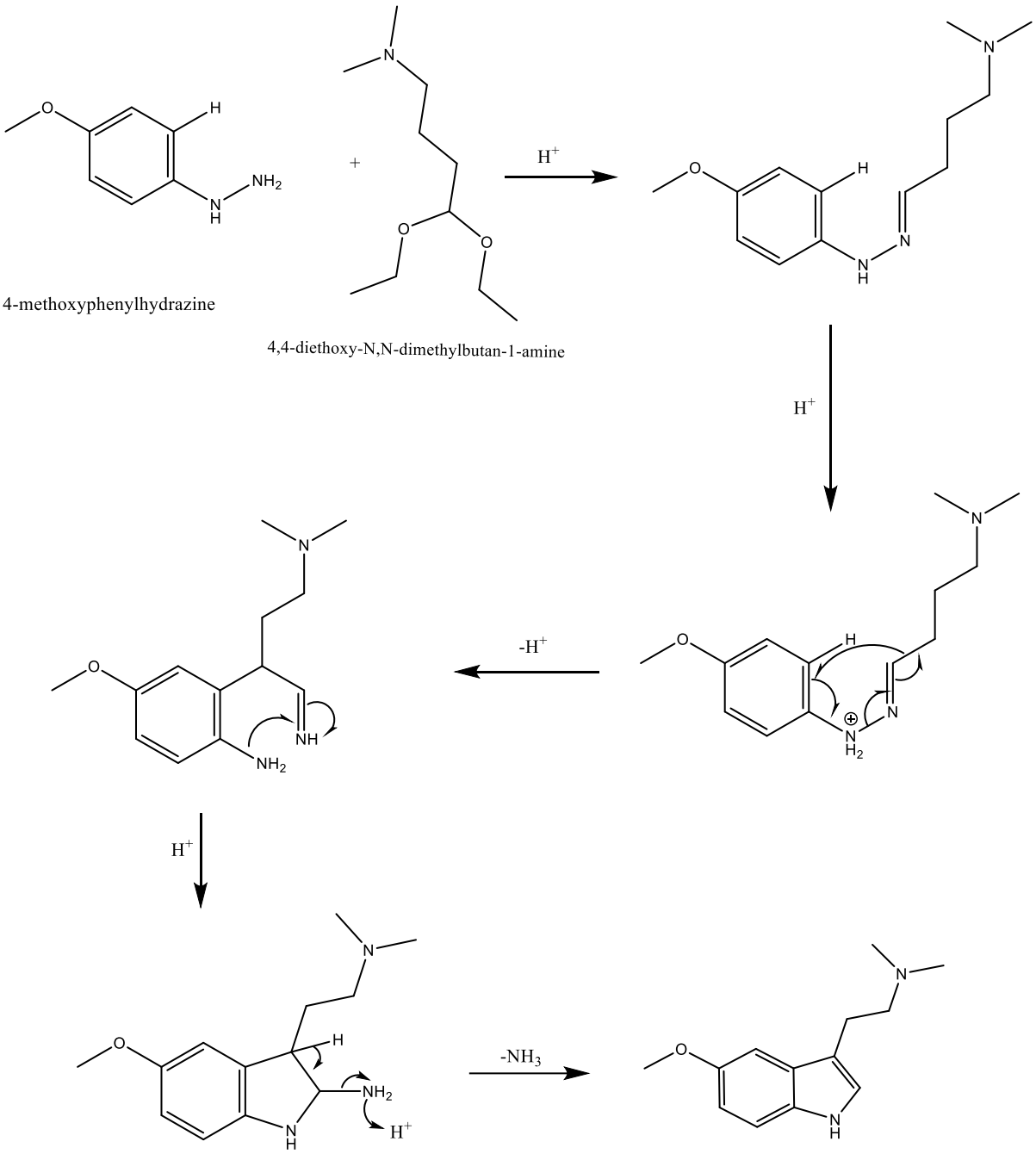


Figure: 1.5: synthetization of 5-MeO-DMT via Fisher Indole reaction[18]

3 Pharmacokinetics of 5-MeO-DMT

5-Methoxy-N,N-Dimethyltryptamine acts as a nonselective serotonin agonist which causes the physiological and psychological changes upon ingestion of the material. The serotonin receptors 5-hydroxytryptamine (5-HT) are a group of G protein-coupled receptors and ligand-gated ions channels which are located in the central and peripheral nervous system and mediate both excitatory and inhibitory neurotransmission. But very few molecules reach these receptors due to it in a large degree being inactivated through the deamination pathway which is mediated by monoamine oxidase A (MAO-A). This prevents 5-MeO-DMT from being *O*-demethylated by the enzyme cytochrome P4502D6 (CYP2D6) into its active metabolite, bufotenine.[4] Therefore, a MAO-A-inhibitor such as harmine or harmaline is usually ingested alongside the 5-MeO-DMT to ensure better oral activity. Both these compounds reduce deamination metabolism and therefore gives a prolonged exposure to the parent molecule 5-MeO-DMT, as well as the active metabolite bufotenine. Both 5-MeO-DMT and bufotenine are hallucinogenic compounds, but meanwhile bufotenine exhibits about a 5- to 10-fold higher affinity to the 5-HT-receptors and around a 3-fold higher potency than 5-MeO-DMT at similar levels in the brain. [8]

5-MeO-DMT does however have some toxicity traits. Studies with monkeys, mice, sheep and rats revealed remarkable ataxia, tremor, mydriasis, shivering and convulsion after being administered 5-MeO-DMT. Especially susceptible were sheep, exhibiting tachycardia, stringy salivation and respiratory failure when exposed to 1mg/kg of 5-MeO-DMT. [5,6] Apart from the drug-induced discriminative stimulus control, 5-MeO-DMT also provokes a variety of other behavioral effect in animal models, these include head shaking, forepaw treading, straub tail, flat-body posture and hindlimb abduction. All of which are commonly shared with other hallucinogens such as lysergic acid diethylamide (LSD) and 2,5- Dimethoxy-4-methylamphetamine (DOM). 5-MeO-DMT in mice induce head-twitching and head-weaving responses through the activation of 5-HT_{1A} and 5-HT_{2A} receptors. While in rats, low doses (0.5-1.0 mg/kg) of 5-MeO-DMT cause hypothermia and high doses (3-10 mg/kg) cause hyperthermia.[9] But in the presence of the 5-HT_{2A} antagonist, ketanserin, the hyperthermic effect is completely attenuated or even converted into hypothermia.

After administering an intraperitoneal injection, 5-MeO-DMT reaches the maximum drug concentration at around 5-7 minutes. After having reached its maximum concentration it is eliminated with a terminal half-life of 12-19 minutes in mice.[28] The fast absorption of the parent drug and short half-life is also present in rats.[29] As for the parent drug, it is predominantly eliminated through MAO-A-mediated metabolism, supported by biliary excretion and low urinary recovery. 5-MeO-DMT also has a relatively high water/oil partition coefficient (3.30), suggesting that the compound may easily penetrate various lipoprotein barriers including the blood-brain barrier. Although 5-MeO-DMT significantly accumulates in many organs such as the liver, kidney and brain in different animal models, The brain concentration 45 minutes after an intraperitoneal injection is around 1.7-fold higher than that in the blood. 5-MeO-DMT also shows a wide range of distribution in different rat brain regions including, thalamus, hippocampus, medulla, pons, cortex, cerebellum and basal ganglia. For the metabolite of 5-Meo-DMT, Bufotenine, the elimination from the body happens rapidly. In a study where healthy volunteers receive an intravenous infusion of ^{14}C-labeled bufotenine, nearly all the radioactivity was recovered within the first 12-hour time-period. [10] While only 1-6% of the total recovered radioactivity was identified as unchanged bufotenine, the deaminated metabolite 5-HIAA accounted for 68-74% of the radioactivity.

Also, compared to 5-MeO-DMT, bufotenine has a poor partition coefficient whilst also showing a low penetration across the blood-brain barrier, but has a high accumulation in rat`s lungs after subcutaneous injection. [11]

Another factor inducing possible toxic or even fatal effects are the drug-drug interactions (DDI), where subjects are exposed to polypharmacy. When a perpetrator drug is introduced, altercations can take place in the disposition, absorption, metabolism or excretion of the victim drug (5-MeO-DMT), which can translate into a significant change in the drugs toxicity and/or efficacy. Concomitant use of 5-MeO-DMT and for example harmaline or any other MAOI can leads to both drugs acting on a common target, which can lead to antagonistic or synergistic responses potentially triggering severe or even fatal levels of toxicity. When inhibiting the MAO-A-mediated 5-HT degradation, MAOI itself will promote serotonergic transmission as shown in figure 1.2. Harmaline is in addition a 5-HT agonist which can potentiate serotonergic actions of 5-MeO-DMT while also reducing the 5-MeO-DMT deamination metabolism. This leads to a prolonged and increased exposure to both the parent drug 5-MeO-DMT as well as the more potent psychoactive metabolite bufotenine which depends upon the CYP2D6 status. [12, 13]

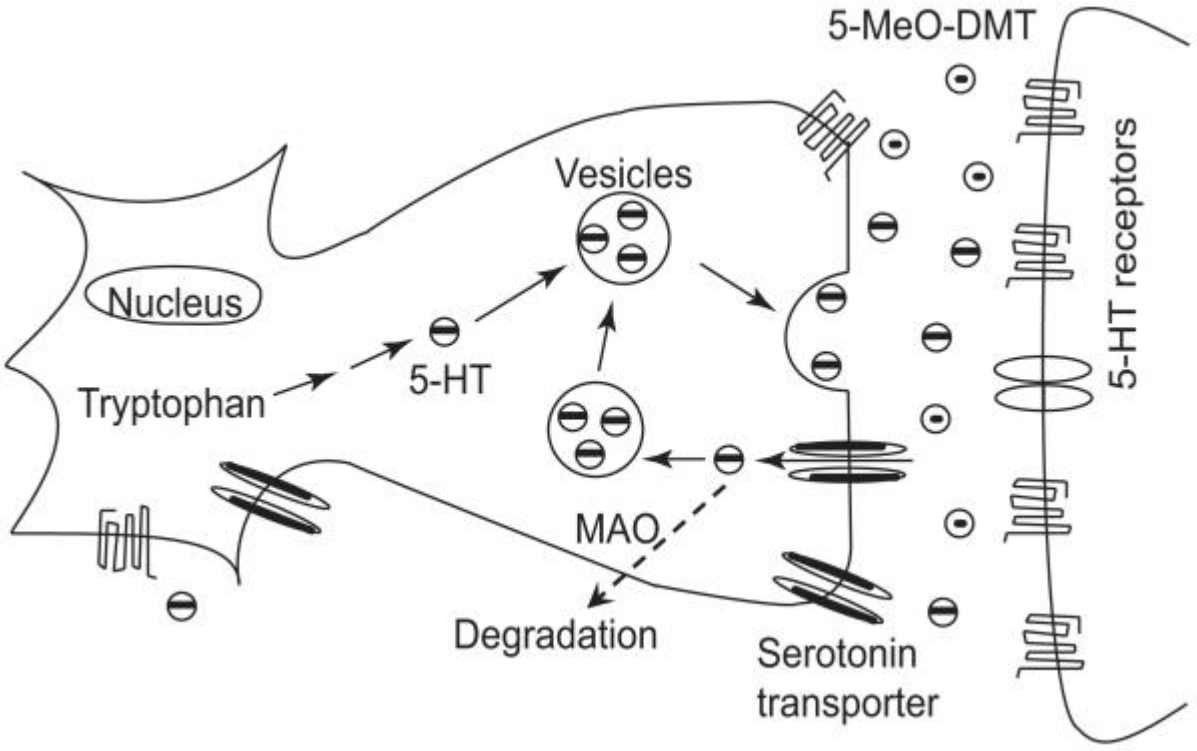


Figure 1.2: MAO blocking 5-HT degradation possibly inducing hyper-serotonergic effects from 5-MeO-DMT activating 5-HT receptors within the synaptic cleft.[4]

When 5-MeO-DMT is co-administered with MAOI, the pharmacokinetics can be significantly altered. As an example, co-incubation of 5-MeO-DMT with harmaline in human hepatocytes completely blocks the depletion of the parent drug, and in addition reduces the in vitro intrinsic clearance by over 24-fold. While in rats, pretreatment with iproniazid significantly increased the 5-MeO-DMT levels in blood, urine and other tissues.[14]

In mice pretreated with harmaline, the clearance of 5-MeO-DMT was decreased by a 4.4-fold higher systematic exposure to 5-MeO-DMT as shown in figure 1.3. While the concomitant administration of harmaline affects the pharmacokinetics of 5-MeO-DMT, it also influences formation of bufotenine as also shown in figure 1.3. When the deamination metabolism is inhibited, a larger amount of 5-MeO-DMT is diverted to other metabolic pathways, such as O-methylation with an increased production of bufotenine. In human CYP2D6 extensive metabolizer hepatocytes, the bufotenine formation significantly increases when 5-MeO-DMT is co-incubated with harmaline. And due to bufotenine being for the most part inactivated through the MAO-A-mediated deamination pathway, MAOI will not only increase the production of bufotenine, but in addition, reduce its elimination.[15] As a result of this, the maximum concentration and of bufotenine increase to 2.6- and 6-fold respectively in mice after harmaline pretreatment.

Along with impact on 5-MeO-DMT pharmacokinetics, harmaline also acts on serotonergic systems and exhibits a high variety of neuropharmacological activities. This is due to harmaline being one of the most potent inhibitors of MAO-A, and having the possibility to interact with 5-HT, dopamine, N-methyl-d-aspartate (NMDA) and gamma-amino-butyric acid (GABA) receptors. Due to the limits of scientific data on human testing, there is only anecdotal reports by human self-experimenters which suggest that enhancement of the psychedelic effect of 5-MeO-DMT when combined with harmine or harmaline. [16] For instance, intranasally or sublingually administration of 10mg 5-MeO-DMT causes significant visionary responses, whereas the same dosage (10mg) orally administered does not show to have any effect in humans. This is probably due to the extensive first-pass metabolism by MAO-A. Meanwhile, 10 mg 5-MeO-DMT administered orally together with harmaline showed nearly equal intensity of psychedelic effect as the same dosage administered sublingually or intranasally. [16] This indicates that 5-MeO-DMT`s toxicological and pharmacological effects are in general potentiated by a concurrent MAOI due to the pharmacokinetic and dynamic interactions due to the DDI.

While the first pass metabolism can detoxify 5-MeO-DMT in most humans, there are always variables between subjects which must be taken into consideration. One thing that could have a big impact is CYP2D6 genetic polymorphism, which can vary from subject to subject. 5-MeO-DMT O-methylation is as previously mentioned dependent on the cytochrome P450 2D6 (CYP2D6) gene in humans to produce the active metabolite bufotenine. Enzyme kinetic studies with the use of recombinant CYP2D6 allelic isozymes display that CYP2D6.2 and CYP2D6.10 show a 2.6- and 40-fold lower catalytic efficiency respectively in producing bufotenine than the wild-type CYP2D6. While the genetics of subjects may influence the metabolic pathway of 5-MeO-DMT, the effects on gene expression have also been shown on proteins in human brain organoids. [19] In the study, around 6700 proteins were sampled, out of which more than 900 were differentially expressed after treatment with 5-MeO-DMT using mass spectrometry and shotgun proteomics. The proteins which differentiated, impacted long-term potentiation, anti-inflammatory effects, the formation of dendritic spines, cytoskeletal reorganization, and microtubule dynamics. [21] Another important factor to take into consideration, is the existence of more than 100 allelic variants of the P450 enzyme CYP2D6. Many of which do not exist in rats, opening the possibility of several new metabolic pathways, all of which could give altered drug responses. This leaves room for personalization of 5-MeO-DMT as a medicine, adjusting dosage levels according to phenotype and genotype or prescription of different medication.[23]

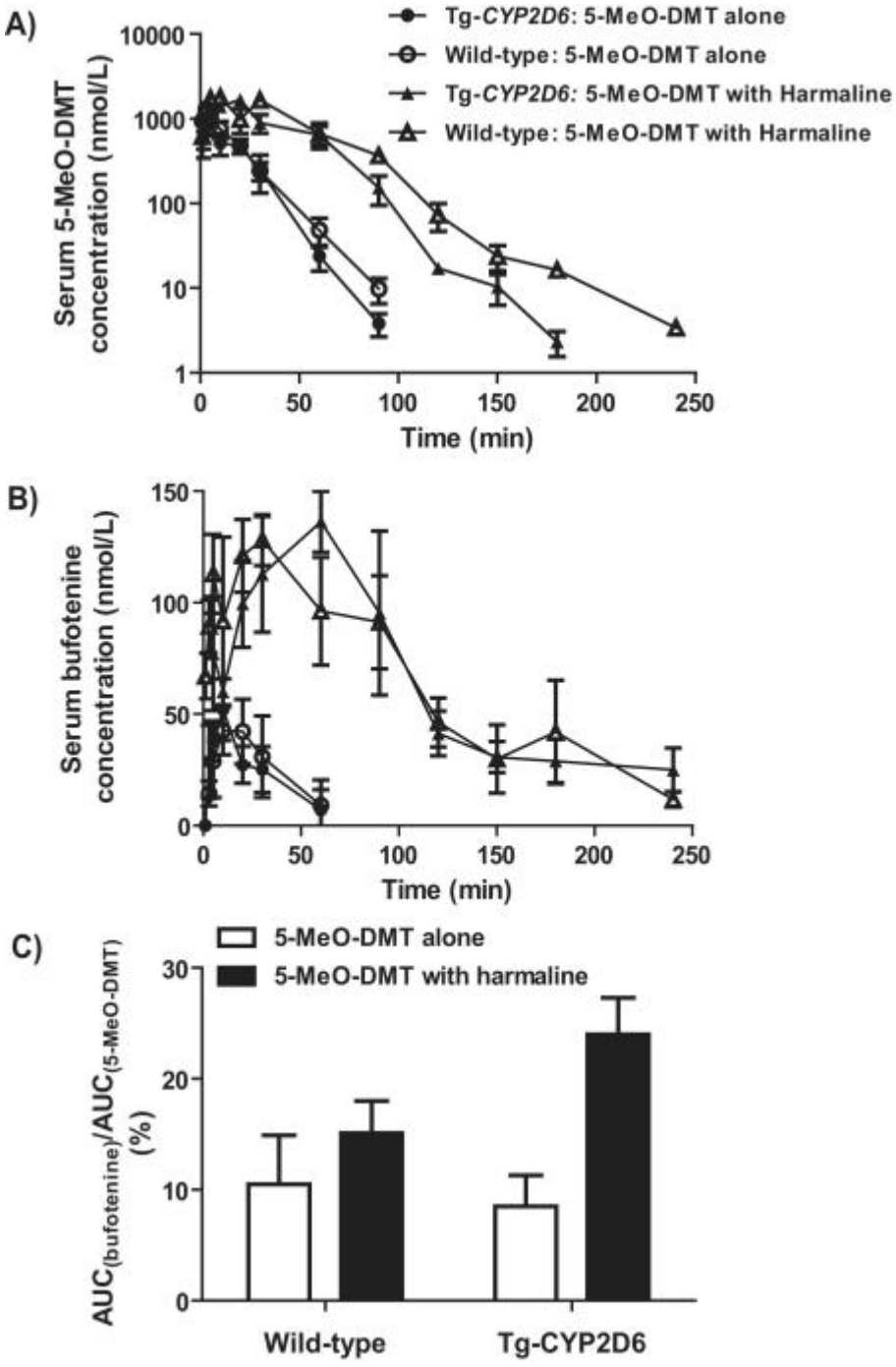


Figure 1.3: Harmaline co-administered with 5-MeO-DMT, altering the blood concentrations of the parent drug (A) and the active metabolite bufotenine (B), and the ratio of their systematic exposures (C) in both wild-type and Tg-CYP2D6 mouse models. [14]

4 Conclusion

5-MeO-DMT represents a natural psychoactive tryptamine drug of abuse. It is a fast-acting drug that induces many physiological and behavioral alternations in both human and animal models, such as auditory and visionary distortion, head-twitch, hypothermia, and stimulus control, revolving around the actions of 5-HT receptors. Conducted receptor binding studies show that 5-MeO-DMT is more selective towards the 5-HT_{1A} receptor while bufotenine for the most part acts as a 5-HT_{2A} agonist. 5-MeO-DMT is readily inactivated through the MAO-A-mediated deamination pathway, while only a small portion of the parent drug is transformed into the active metabolite bufotenine by polymorphic CYP2D6 enzymes. Therefore 5-MeO-DMT is often co-administered with an MAOI such as harmine or harmaline to enhance hallucinogenic effects. The MAOI showed to inhibit deamination metabolism, increasing both the amount and duration of the systematic exposure to 5-MeO-DMT as well as bufotenine. The studies conducted with harmaline showed that both harmaline and the parent drug 5-MeO-DMT act agonistically on the serotonergic systems, potentiating drug responses, sometimes leading to severe or fatal serotonin toxicity in animal models. Anecdotal data show, that intoxication and death due to abuse of 5-MeO-DMT reported in humans has been, for the most part, in coadministration with harmaline. The rise in popularity of 5-MeO-DMT has increased the need for the compound leading to excessive milking of the toad *bufo alvarius* which now faces extinction. Therefore, this thesis presents other means of producing 5-MeO-DMT to cover the increasing demand for it. The synthesis of 5-MeO-DMT from commercially available precursors produces improved results in terms of purity of the product as well as yield, compared to the extraction of plants, bark or beans, etc. Among the methods of synthesis explored till today, using 5-methoxytryptamine as a precursor produced the highest purity and yield in the synthesis of 5-MeO-DMT. While positive results of using 5-MeO-DMT as a rapid-acting treatment for people suffering from PTSD have been obtained, it is still a novel compound that shows a lot of promising practical uses in therapy. Further research will help us understand more about mental health and the treatment of mental health problems.

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