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Molecular Insight into the Interaction between Different Classes of Psychoplastogens and Serotonin 5-HT_{2A} Receptor

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Abstract: ***Medical treatment for behavioral disorders such as anxiety, depression, and post-traumatic stress disorder (PTSD) represent emerging challenges in the field and have been a subject of studies for a long time. Available therapeutics include selective serotonin reuptake inhibitors (SSRIs), Monoamine oxidase inhibitors (MAOIs), tricyclics, etc. Nevertheless, recent studies have identified a revolutionary new class of fast-acting antidepressants called psychoplastogens, which, unlike other conventional antidepressants, promote significant and long-lasting changes in neural plasticity during a single administration. In this study, we developed a novel classification of psychoplastogens based on their structural models. Moreover, we performed docking experiments to determine the binding energy of various classes of psychoplastogens to the serotonin 5-HT_{2A} receptor. As a result, we identified a correlation between the hallucinogenic effect of some psychoplastogens we used in our docking study and their affinity to the 5-HT_{2A} receptor. We then attempted to predict the patterns of binding affinities of newly generated psychoplastogens, which were validated using our methodology. It is expected that this study will provide insight into the future of in vitro research as well as potential clinical studies regarding psychoplastogens and provide a firm basis for the binding patterns related to these drugs in the human brain.***

Keywords: psychoplastogens, depression, plasticity, 5-HT_{2A}, docking.

1. Introduction

Mental disorders in general, and stress disorders in particular, have accompanied humans from the moment when civilization was formed [1]; as yet, the variety of mental disorders and their impact [2], as well as the importance of treating them, are often underestimated. According to the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [3], there are 22 classes of mental disorders that are clinically recognized. Together, the diseases from these classes cause substantial harm to the world economy: according to the study by [4], the global direct and indirect costs associated with this issue reached the value of $2.5 trillion, and this number is predicted to double by 2030. Several researchers give even higher estimates, stating that one in three individuals will experience a mental disorder in their lifetime, which caused the economic loss adjusting to Purchasing Power Parity to increase to a range between 4% and 8% GDP in different regions [5], [6]. In other words, the research aiming to discover new effective treatments to such conditions could significantly affect the development of the global economy, making it a priority for further research [7], [8].

Most of the treatments that are aimed at mental disorders, including the ones described in this paper, stem from the definition of this concept. The most holistic way of defining a mental disorder was introduced by Jerome C. Wakefield in the paper "*The concept of mental disorder: On the boundary between biological facts and social values.*" According to it, a condition may be considered a mental disorder only if it strictly applies to the following two criteria: (a) the condition causes some harm or deprivation of benefit to the person as judged by the standards of the person's culture, and (b) the condition results from the inability of some mental mechanism to perform its natural function, wherein a natural function is an effect that is part of the evolutionary explanation of the existence and structure of the mental mechanism [9]. Although the definition by Wakefield was further critiqued due to the criterion of mandatory malfunction and characterized by fellow researchers as reductionist [10], modern understanding of mental disorders thus far is based on the biological dysfunctions causing the behavior to be altered [11].

Out of the 22 groups listed in DSM-5, at least 11 groups of disorders contain medical treatment as a primary form of tackling these conditions. Interestingly, 7 of these 11 groups (Depressive disorders, anxiety disorders, OCD-related disorders, Trauma- and Stressor-Related Disorders, Neurocognitive disorders, Substance-related and addictive disorders, etc.) include the introduction of Selective Serotonin Reuptake Inhibitors (SSRIs) as main or case-related treatment [12]. SSRIs are a vast category of chemicals that function by selectively inhibiting the reuptake of serotonin, inducing various effects from a direct increase in prolonged concentration of serotonin in the synaptic cleft - hence enhancing serotonergic neurotransmission - to neuroplasticity through dendritic branching (Figure 1) [13], [14], [15]. Nonetheless, SSRIs are believed to have relatively low side effects and high specificity, the effectiveness of these drugs is somewhat limited [16], [17]. SSRIs, as well as other older antidepressants such as Tricyclics, often produce any measurable effect only after a long period of administration [18]. The delayed response could lead to serious consequences, especially when the treatment must be robust and quick, for example, if the risk of suicide is present. Therefore, in order to effectively tackle the issue of stress-related and depressive disorders and their implications, the new category of drugs named psychoplastogens were introduced as a potential treatment [19].

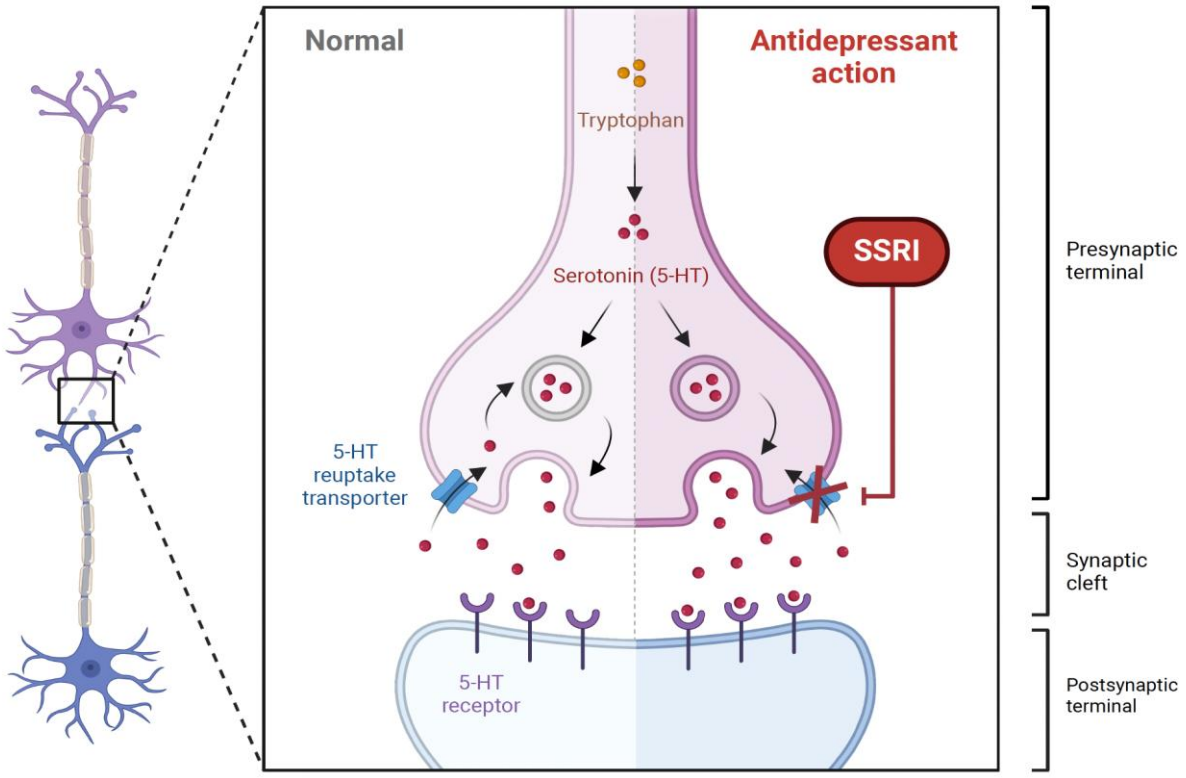

Figure 1: The graphical representation of Selective Serotonin Reuptake Inhibitors (SSRIs) mechanism of action. The 5-HT reuptake transporter (SERT) is inhibited by SSRIs, allowing it to increase the level of serotonin in the synaptic cleft [52]. Created using BioRender.

The psychoplastogens, according to the paper by David Olson (2008), are defined as compounds that are capable of producing measurable changes in brain plasticity within a short period of time during a single administration. Moreover, large compounds such as BDNF that are said to be responsible for natural neuroplasticity [20], do not fall under the category of psychoplastogens. The research data suggests that the psychoplastogens can show a very strong increase in the synaptic density of the brain compared to SSRIs [21], thus enabling the antidepressant effect [22]. However, most psychoplastogens are members of chemical groups (such as psychedelics or deliriants) that are renowned for causing serious side effects. In addition, there is no reliable evidence on specific neurochemical pathways that are followed by all psychoplastogens, making it impossible to categorize all psychoplastogens by downstream signaling [19]. With the emerging research data on psychoplastogens and increasing number of drugs classified as psychoplastogens, the classification is required to summarize and systemize all research that was previously done on the topic.

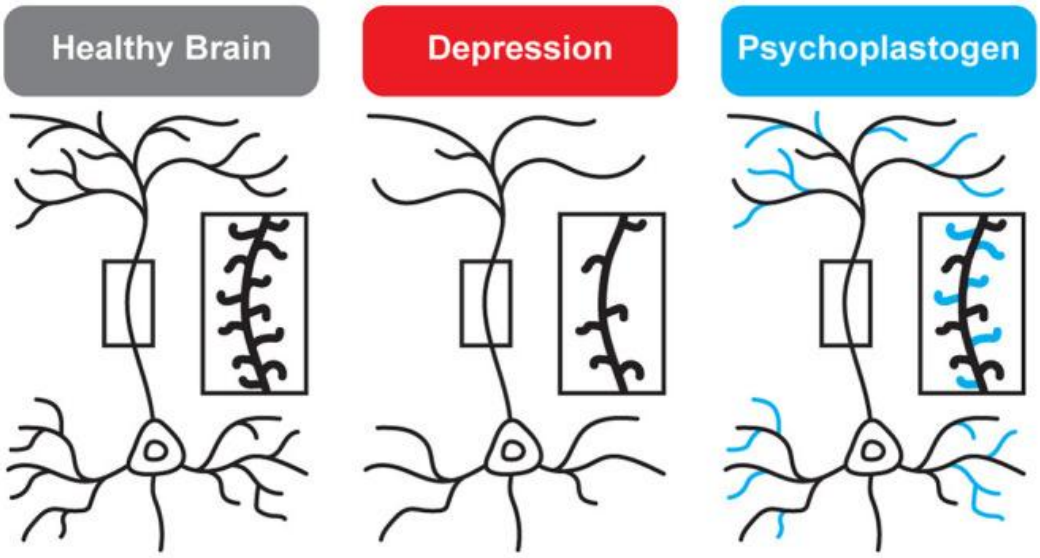

Figure 2: Depression is associated with decrease in dendritic density and active neural pruning - a process that could be reversed with the introduction of psychoplastogens. Reprinted with permission from Vargas et al. [21].

The history and generational classification of psychoplastogens

Before psychoplastogens were given this name, the natural compounds from this group have had a long history of use, both in medical and non-medical practices. For instance, the archaeological evidence suggests the use of psychoactive mushrooms containing psilocin dates back to at least 6000 years ago, continuing to be an important practice for several Mesoamerican cultures up to our days. After being isolated by Albert Hofmann in 1958, psilocin was often hypothesised to be effective as a mood/anxiety disorder medication [23], [24], [25]. However, this potential has not been converted into clinical purposes up to this date despite multiple attempts, leaving it in the Schedule I category according to the US Drug Enforcement Administration (DEA) due to its hallucinogenicity caused by, supposedly, binding to 5-HT_{2A} receptors [56]. The same history was repeated in the case of N, N-Dimethyltryptamine (DMT), another hallucinogenic psychoplastogen with a rich history of use and 5-HT_{2A} binding affinity. Namely, DMT was used as a spirit-enhancer in indigenous cultures of amazonian tribes as an element of the Ayahuasca brew. Later on, it was first synthesized by a Canadian chemist Richard Manske in 1931, after which its natural occurrence was demonstrated by Oswaldo Gonçalves de Lima in 1946 [26]. While DMT is often united with psilocin in terms of their potential medical use, and particular studies demonstrate their efficiency as an antidepressant [27], neither of them are excluded from Schedule I group of drugs according to the DEA [56].

In addition to psilocin and DMT, other drugs such as 5-MeO-DMT [28], LSD [29], Bufotenin, and other tryptamine derivatives, have similar properties, histories of medical use, research chronologies, chemical scaffolds, and moderate-high 5-HT_{2A} affinities, they can be united in one group: psychedelic psychoplastogens, or **Gen1 psychoplastogens.** The resemblance between the group members has made them easy to study and base the research of the new psychoplastogens. Looking ahead, new non-hallucinogenic drugs are based on the scaffolds of the chemicals from Gen1. Nevertheless, Gen1 psychoplastogens are not the only ones that are studied regarding their therapeutic potentials. Since psychoplastogens, as a phenomenon do not have the similar structures and properties besides inducting neuroplasticity, other structural groups of compounds also fall under the definition of a psychoplastogen [30]. As an example, the structural groups are: arylcyclohexylamines (ketamine) [31], deliriants and tropane alkaloids (scopolamine) [32], phenethylamines (DOI), etc. Since these compounds have various individual mechanisms and signaling of brain functioning, yet are still not ready for therapeutic use in treating depressive disorders, we decided to unite them into a second group of compounds: **Gen2 psychoplastogens**. This group, although generally less studied than Gen1, also undergoes research to determine whether compounds apart from psychedelics can induce rapid neuroplasticity during a single administration [49]. As the research on psychoplastogens was evolving, new compounds without severe side effects, which no longer fall into either Gen1 or Gen2 groups of psychoplastogens, were synthesized. These compounds include both derivatives from Gen1 and Gen2 and can be unified in one more category: **NextGen psychoplastogens.** For this research, only the NextGen derivatives of Gen1 were selected since Gen2 derivatives have less background information to base the research on, particularly regarding receptor binding. Examples of NextGen psychoplastogens include isoDMT and AAZ-A-154 [33], [34], which are proven to increase the dendritic branching rates and diminish the hallucinogenic reaction in the form of a Head Twitch Response (HTR) (Figure 2, Table 1) [35].

In this study, we aimed to analyze the binding of different psychoplastogens in 5-HT_{2A} to determine the correlation between 5-HT_{2A} affinity, hallucinogenic potential of a psychoplastogen, and its effectiveness according to previous studies. The Gen2 compounds follow a pathway not related to 5-HT_{2A} to exert their psychoplastogenic effect; thus, we focused on Gen1 and the NextGen drugs since they are based on the same chemical backbone of indole rings and are believed to follow the same signaling pathway.

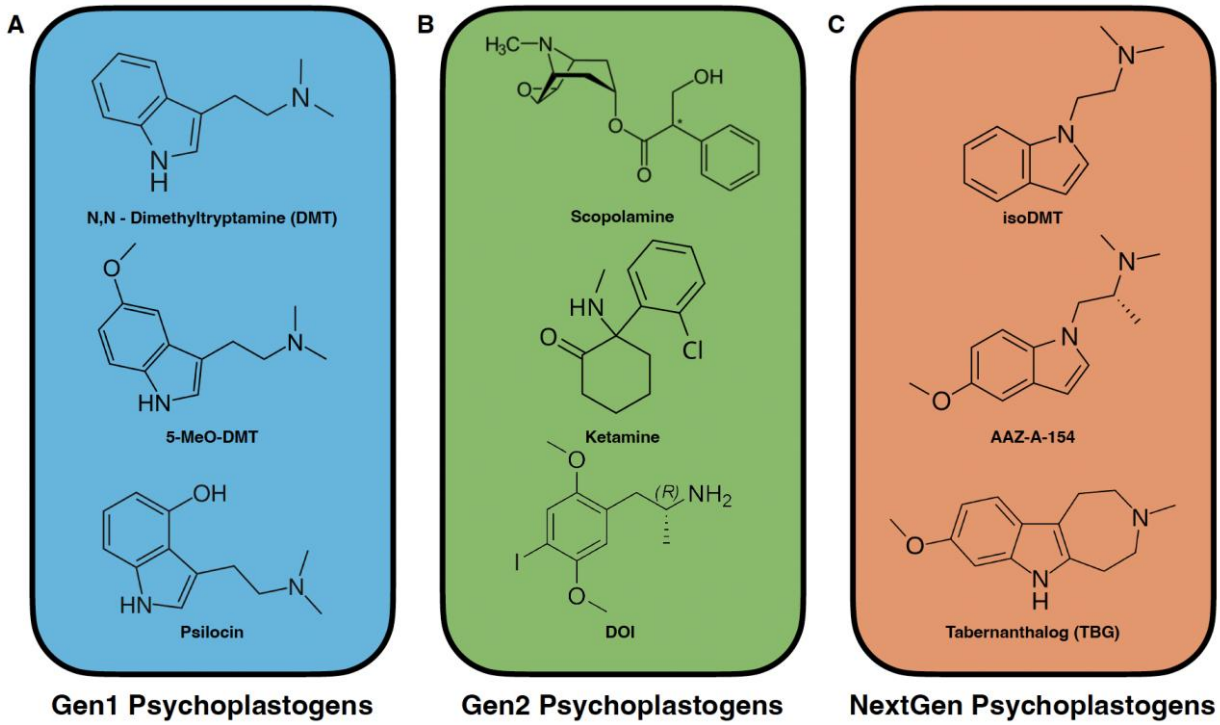

Figure 3: The structures of psychoplastogens from groups Gen1 (**A**), Gen2 (**B**), and NextGen (**C**). Gen1 psychoplastogens have a common indole group as a backbone of their structure, and NextGen psychoplastogens are mainly based on the variation of that structure. Created using Apple Keynote.

2. Method

To demonstrate the correlation between the affinity to 5-HT_{2A} receptor and hallucinogenic properties of the psychoplastogens of different generations, the chemoinformatic method was chosen, specifically, the docking of compounds to the receptor. Apart from the fact that it is highly available, it gives relatively accurate quantitative data relevant to the research. The docking itself was performed on a web-based platform SwissDock based on AutoDock Vina 1.2.0 [36], [38]. Finally, the software ChimeraX (version 1.8) [37] and PyMOL (version 3.0.0) [57] was used to visualize the results.

To perform the docking of the 5-HT_{2A} receptor with selected indole psychoplastogens, the template should have been chosen to most accurately replicate the receptor structure that was most likely to bind this type of drugs. Therefore, the 7RAN structure, obtained by cryo-electron microscopy (Cryo-EM) and taken from the GPCR Database (GPCDb) [39], was the first choice, as it had an indole-based antidepressant structure present. This compound was used as a reference for the structures obtained from docking; all ligands' positions were mapped with the compound in ChimeraX to confirm that they were in the correct position relative to the receptor.

During the docking itself, the research space was specifically defined to conserve the spatial constraints of the ligand in the structure; this is possible due to the fact that all compounds have the same scaffold structure. Hence, the docking site coordinates and size were selected according to the compound already present in the receptor from the reference 7RAN structure: the search box center coordinates were 152Å on the X-axis, 154Å on the Y-axis, and 132Å on the Z-axis, with the box size of 10Å on the X-axis, 8Å on the Y-axis, and 8Å on the Z-axis. Subsequently, the original compound was removed to avoid the docking ligand being shifted from its place. Finally, to minimize premature docking, the sampling exhaustivity was selected at 64 points.

Besides obtaining the raw data itself, the results were validated to avoid the impact of the extraneous variables. To avoid overfitting the model, the control measures were done with a mutant receptor in which the residues responsible for the binding were substituted. These residues were selected according to the results of the affinity study of the radioligand ([3H]-LSD) binding to modified 5-HT_{2A} receptor [40]. The highest affinity decrease (ΔpK_i >100) was observed when substituting D155A, S159A, W336A and F339L. In the case of this research, the Crystallographic Object-Oriented Toolkit (*Coot*) software, Version 0.9.8.95 [41], [42], was used to perform point mutation for 7RAN, which was subsequently used in SwissDock to obtain the affinity data and validate the strategy.

To make a prediction about the hallucinogenic properties of oxygen-containing NextGen psychoplastogens, 8 different variations of isoDMT with substitution of OH- and MeO-groups were created. This was done using the ChemInfo SMILES generator, where chemical structures from the sketcher were converted into SMILES codes, which were then used in SwissDock for further docking.

In Figure 1, the BioRender software was used to demonstrate the model of SSRI functioning in the synaptic cleft of a neuron [52]. In Figure 4, the software PyMOL (version 3.0.0) was used [57]. In Figure 5, the formula $\frac{\Delta G_{compound} - \Delta G_{serotonin}}{\Delta G_{serotonin}} \cdot 100\%$, in which ΔG is Gibbs Free

Energy in kcal/mol, was used in order to calculate the percentage difference between the affinities of serotonin and the selected compound to the 5-HT_{2A} receptor.

3. Results and Discussion

The drugs and their association with various disorders

Compounds used in the docking with 5-HT_{2A} are described in Table 1.

Table 1: The Psychoplastogenic drugs used in the docking to the 5-HT_{2A} receptor, including their chemical class, receptor, phenotype, and common effect association

Drug	Class	Receptor	Phenotype	Common effects and function	Reference
Serotonin	Tryptamines	5-HTR group	Agonist, activates Gq/11 protein [43]	Neurotransmitter, no association with certain effects when introduced	[53]
Psilocin	Tryptamines	5-HT_{2A}	Agonist, activates Gq/11 protein [43]	Proven G1 psychoplastogen. Introduces psychedelic effects, including hallucinations and increased brain entropy. Used as a drug synthesized from psychedelic mushrooms	[53]
DMT	Tryptamines	5-HT_{2A}	Agonist, activates Gq/11 protein [43]	Proven G1 [58] psychoplastogen. Introduces psychedelic effects, including hallucinations and increased brain entropy. Also used as a psychedelic drug	[54]
isoDMT	Indole alkaloids	5-HT_{2A}	No data	Potential psychoplastogen, has decreased hallucinogenic potential compared to psilocin and DMT. Discovered using SAR and investigated using in vitro experiments	[55]
AAZ-A-154	Indole alkaloids	5-HT_{2A}	No data	Experimental drug, potential NextGen psychoplastogen, has decreased hallucinogenic potential. Investigated using PsychLight biosensor	[34]

As stated in the previous sections, the psychoplastogens are defined not by the typical structure, mechanism of action, or a cascade of properties but rather by one single feature that is implied by their definition, which is the stimulation of dendritic branching within a short period of time during a single administration. Therefore, to narrow down the research scope, indole alkaloids were selected as a group of compounds that will be used in docking. The indole alkaloids, in general, and tryptamines, in particular, are the most abundant and studied group of potent psychoplastogens. Currently, the NextGen psychoplastogens from this group, such as AAZ-A-154 and isoDMT, undergo clinical trials to determine their effectiveness in therapy, which makes this group most relevant to predict side effects, such as hallucinations, by using simulations.

The most likely hypothesis that explains why Gen1 psychoplastogens induce intense hallucinations lies in the 5-HT_{2A} receptor: in multiple studies, the correlation was found between the activation of 5-HT_{2A} receptors and the presence of powerful hallucinations, which was most evident when the group of tryptamines called psychedelics was introduced [44], [50], [51]. Therefore, according to this hypothesis, it was decided to find the correlation between the generation of the indole psychoplastogens and affinity towards the 5-HT_{2A} receptor. For the study, it was selected to include at least three indole hallucinogens from group Gen1 and two different psychoplastogens from the NextGen group. As stated above, compounds from Gen2 were not selected, as they have a different mechanism of action compared to Gen1 psychoplastogens which varies between different chemical groups of compounds. To provide more scientific context about the chemicals, the most well-known and investigated compounds with the same indole backbone were chosen: namely, DMT, LSD, and Psilocin from Gen1, as well as isoDMT and AAZ-A-154 from NextGen (Table 1).

Establishment of a docking model for the representative psychoplastogens in 5-HT_{2A} serotonin receptor

From the beginning of the research, the appropriate 5-HT_{2A} model for the docking was sought. Although there are various agonist/antagonist-bound 5-HT_{2A} models present in different databases, the existing models did not fully represent the binding mode we expected to see when bound to the selected molecules, primarily due to the difference in molecular scaffolds. As a result, it was decided to select the 5-HT_{2A} model with the PDB code of 7RAN synthesized by Kaplan et al. [45], which is 5-HT_{2A} receptor with a ***(R)-69*** compound bound, which is a tetrahydropyrimidine with an indole-like structure attached. Thus, the structure of the receptor was captured in a fully active G protein-bound state that would enable us to perform docking using a variety of agonists described before.

The selected model was found to perfectly fit the initial hypothesis; therefore, the docking with it was performed with the box center coordinates of 152Å on the X-axis, 154Å on the Y-axis, and 132Å on the Z-axis, as well as the box size of 30Å on the X-axis, 30Å on the Y-axis, and 30Å on the Z-axis. The sampling exhaustivity in the docking was selected as a maximum of 64. Nevertheless, when the first control docking with a serotonin molecule was performed and compared to the initial structure from the paper, it was found that the docking software tried to maximize the Gibbs Free Energy output, hence the initial model was far from the experimental data. Therefore, it was selected to reduce the research space to 10Å on the X-axis, 8Å on the Y-axis, and 8Å on the Z-axis: these coordinates were selected as they resemble the scaffold of the original 7RAN ligand, increasing the probability of the docking compound to be placed correctly. After it was confirmed that the compound affinities, specifically, the serotonin affinity, towards the receptor were accurate, the full

docking study, involving Gen1 and NextGen groups of psychoplastogens, was conducted.

Finally, it was decided to include several derivatives of isoDMT, each given the number from C3 to C10, in the docking model, to make a prediction about the possible chemical groups that could influence the 5-HT_{2A} binding. All artificial compounds have an isoDMT backbone, except for additional hydroxyl (OH) groups in compounds C3 to C6 and additional methoxy (MeO) groups in compounds C7 to C10 added to the 4th, 5th, 6th, and 7th atoms, respectively. Some of these compounds (C8 and C9) were already tested in the Structure-Activity Relationship (SAR) study by Dunlap et al. [33] It is assumed that the potential further synthesis and tests of these compounds would reveal new insights about the correlation between the psychoplastogenic effect of certain drugs, their hallucinogenicity, and 5-HT_{2A} affinity.

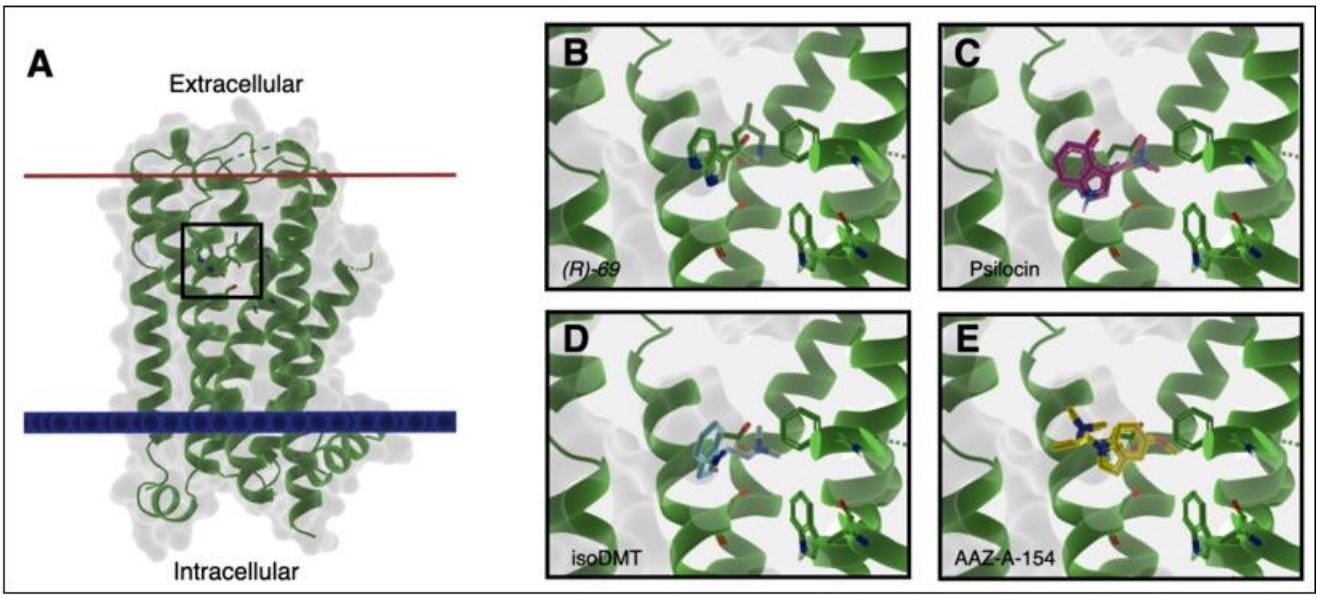

Figure 4: the graphical representation of the 5-HT_{2A} receptor located in the phospholipid bilayer (**A**), with the specific demonstrations of binding of several compounds: *(R)-69* (**B**) taken from the paper by Kaplan et al., (2023), as well as Psilocin (**C**), isoDMT (**D**), and AAZ-A-154 (**E**) bound through docking using the SwissDock web service (see Method). Created using PyMOL (version 3.0.0).

The results of the docking have shown several trends in the 5-HT_{2A} affinity of indole-based compounds. To begin with, the natural hallucinogens, including LSD, DMT, and Psilocin, which were first found to have psychoplastogenic properties, demonstrated a significant increase in the affinity towards the receptor in comparison with endogenous ligand serotonin (Figure 1). With the values of -8.281 kcal/mol, -6.120 kcal/mol, and -6.244 kcal/mol, the ΔG for LSD, DMT, and Psilocin, respectively, were the highest affinity numbers in the dataset. Interestingly, the high affinity of the 5-HT_{2A} binding in LSD correlates with the data on its incredible potency of the hallucinogenic effect [46], which also applies to DMT and psilocin [26], [47], although both their affinity and hallucinogenic effect are less significant compared to LSD.

On the contrary, docking of NextGen compounds based on the reversed indole structure - isoDMT and AAZ - showed noticeably lower affinities towards the receptor when compared to serotonin (Figure 1). Nevertheless, there was a distinction between the compounds: isoDMT showed the ΔG of -5.594 kcal/mol, which is significantly lower than the -5.948 kcal/mol value of serotonin, while AAZ-A-154 demonstrated a value of -5.907 kcal/mol, being quite similar to serotonin. Finally, dependent on the placement of the -OMe and -OH groups, the compounds C3-C10 demonstrated a decreased affinity compared to serotonin, with only C5 and C6 showing a similar ΔG to the endogenous ligand.

Validation by mutant protein docking

After performing the initial docking of all compounds, the validation of the docking strategy was performed by substituting amino acids in the 5-HT_{2A} protein structure, which are critical in the binding of psychoplastogens to 5-HT_{2A} [53]. This validation was done as a necessary step to escape the overfitting of the docking model, which could potentially reduce the validity of the results of the study. In order to do so, we followed two strategies. To begin with, we limited the size of the research space to 10Å on the X-axis, 8Å on the Y-axis, and 8Å on the Z-axis, as already discussed in the *method* section. In that case, the ligands will have additional constraints, making them bind in the same way as the ligands in *In vitro* conditions (see the Pymol figure). It is important to note that the ligands used for validation and prediction have similar scaffolds to the ligands used in the initial model, allowing to exploit this method of validation.

Then, we performed a mutational study to confirm the effect of the key residues responsible for ligand recognition. These residues were selected from a study published by Kim et al. [40], where radioligand binding assay of [3H]-LSD was performed on a mutated 5-HT_{2A} receptor with quantitative results in ΔpK_i. In Figure 3d of the study, it is indicated that amino acids D155, S159, W336, and F339 are key residues in ligand recognition, and mutating them will significantly decrease the LSD affinity. As a result, the mutation of these residues through *Coot* (see Method section) decreased the

affinity of all compounds in docking, confirming its validity (see Table 2).

Prediction of the influence of OH and MeO groups on the binding of NextGen compounds

As shown in Figure 3, there is a noticeable difference in the affinity of isoDMT and AAZ-A-154, although the structures of these compounds have similar inverse indole structures. Therefore, it was decided to test whether other oxygen-containing compounds, which are based on isoDMT structures with additional OH and MeO groups, would have an affinity closer to isoDMT or AAZ (See *Establishing of the Docking Model*). After docking these compounds to the 5-HT_{2A} receptor through the same method as for other psychoplastogens, it was discovered that the affinities of all compounds except for C5 and C6 were placed on a spectrum between the value of isoDMT and AAZ. Nevertheless, compounds C5 and C6, which contain the OH groups at the 6th and 7th C atoms of the indole ring, experienced a similar affinity as the serotonin molecule. Further *in vitro* and clinical studies are required to determine the behavioral implications of these affinity patterns.

Table 2: The results of docking, in kcal/mol, of compounds from Gen1, Gen2, and NextGen to 5-HT_{2A} receptor, its versions with D155A, S159A, W336A, and F339L substituted, and mutated version with all four listed amino acids substituted

	5-HT2A	5-HT2A$_{D155A}$	5-HT2A$_{S159A}$	5-HT2A$_{W336L}$	5-HT2A$_{F339L}$	5-HT2Aq
Serotonin	-5.948	-5.71	-5.71	-5.823	-5.782	-5.178
LSD	-8.281	-8.32	-8.369	-7.924	-7.888	-7.377
Psilocin	-6.244	-6.203	-6.196	-6.008	-6.025	-5.666
DMT	-6.12	-6.126	-6.186	-6.019	-5.975	-5.646
isoDMT (C1)	-5.594	-5.539	-5.466	-5.257	-5.838	-5.214
AAZ (C2)	-5.907	-5.696	-5.921	-5.7	-6.098	-5.587
C3	-5.8	-5.772	-5.442	-5.339	-5.897	-5.102
C4	-5.666	-5.563	-5.59	-5.567	-5.721	-5.216
C5	-5.942	-5.714	-5.839	-5.524	-5.752	-5.124
C6	-5.958	-5.825	-5.899	-5.665	-5.712	-5.274
C7	-5.638	-5.638	-5.609	-5.526	-5.728	-5.409
C8	-5.672	-5.571	-5.686	-5.601	-5.796	-5.332
C9	-5.723	-5.665	-5.447	-5.757	-5.796	-5.191
C10	-5.842	-5.639	-5.723	-5.554	-5.837	-5.236

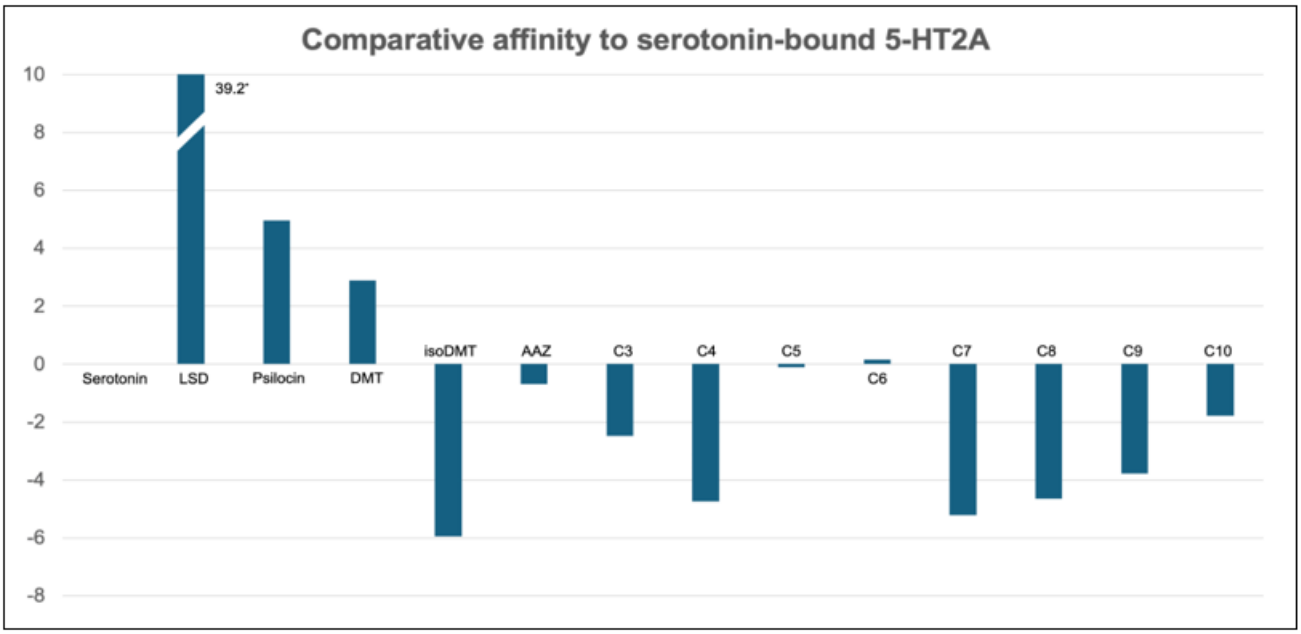

Figure 5: Comparative affinity of compounds towards the 5-HT_{2A} receptor, showing the relative difference between the compound affinity and serotonin affinity. To calculate the data for the graph, the formula was used: $\frac{\Delta G_{compound} - \Delta G_{serotonin}}{\Delta G_{serotonin}}$. *100%* (see Method section).

4. Conclusion

As a possible solution to the depression issue, the topic of psychoplastogens has an incredible potential in research. With the development of first fast-acting non-hallucinogenic antidepressants based on Gen1 psychoplastogen backbones, it is possible that in several years the economic burdens caused by mood and stress disorders will be alleviated, if not eliminated whatsoever. That being said, it is impossible to reliably predict how the future design of NextGen psychoplastogens will proceed; currently, the clinical trials are conducted for isoDMT, AAZ-A-154, and other drugs, so conclusions about psychoplastogens may be made after their completion. Therefore, it might occur that the development of safe psychoplastogens will happen through a long trial-and-error process. The results of this study suggest a potential correlation between the hallucinogenic potential of a

psychoplastogen and its affinity to the 5-HT_{2A} receptor, which can be refined using cross-validation via multiple docking tools in the future. At the same time, it is impossible to make conclusions about the impact of 5-HT2A affinity on psychoplastogen effectiveness from the gathered data. Although this study can provide a deeper understanding of the NextGen Psychoplastogens' chemical features that either increase or decrease the ability to induce hallucinations, extensive *in vitro* or *in vivo* assays should be conducted in order to confirm or refute these findings and apply them to the future drug development. Moreover, the long-term effects of psychoplastogens are yet to be discovered. Since Gen1 and Gen2 psychoplastogens are not applied in long-term therapeutic use due to their addictive and hallucinogenic properties, it is impossible to draw conclusions about the side effects that will appear after extensive treatment. Finally, psychoplastogens showed great promise in the development of drugs for the treatment of various neurological disorders; further research can provide insight into their function and the development of the future generation of drugs.

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