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In silico study of dimethyltryptamine analogues against 5-HT1B receptor: Molecular docking, dynamic simulations and ADMET prediction

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ABSTRACT

Introduction: The 5-HT_{1B} receptor has a potential role in various psychiatric disorders such as depression, anxiety, and post-traumatic stress disorder. The objective of this study was to perform docking and molecular dynamics simulation to evaluate at atomic level the behavior of N,N-dimethyltryptamine (DMT) on 5-HT_{1B} receptor.
Methods: In this study, initially, a search for DMT was performed using the PubChem database. Subsequently, molecular docking was executed using AutoDock Vina based in PyRx 0.8 with a 95% analogy. Additionally, ergotamine (ERG) and serotonin were used as control. Then, it ran a total of 100 ns molecular dynamics simulations on 5-HT_{1B} bound with DMT, serotonin, 112814775, and ERG. Finally, pharmacokinetic prediction and IV acute toxicity for analogues and DMT were performed.
Results: It was possible to show that 112814775 had the lowest binding energy with the receptor. In addition, 112814775 presented great conformational stability, low mobility, and stiffness compared to the control ligands: ERG, serotonin, and DMT subsequent dynamic analysis. With respect to the free energy calculation, contributions such as Van der Waals, electrostatics, and nonpolar interactions for all systems, were highlighted.
Conclusion: 112814775 showed affinities with 5-HT_{1B} receptor and evidenced notable behavior by molecular dynamic simulation according to root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), solvent-accessible surface area (SASA), the radius of gyration, number of hydrogen bond, and free energy calculated. These results established the possible relevance of in-silico studies in search of DMT analogues against the 5-HT_{1B} receptor, which may be associated with alterations such as depression and anxiety, and may become future study molecules for the treatment of this type of disorder.

Implication for health policy/practice/research/medical education:
In this study in silico tools were employed to indicate the interaction of DMT analogues with 5-HT_{1B} receptors, which could probably become promising new structures in the treatment of disorders such as depression and anxiety.
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Introduction

The World Health Organization (WHO) has established that around 450 million individuals suffer from mental disorders such as depression, bipolar disorder, dementia, and others (1). Globally, a high number of clinical manifestations have been related to the development of mood disorders, characterized by the existence of emotional imbalances with negative and positive symptoms as expressed in depression, anxiety, and post-traumatic stress disorder (2-4). Nowadays, a high prevalence of these alterations has been increasingly observed in the world population, with a recurring threat of increasing at proportional levels.

These mood disorders are characterized by central neurobiochemical alterations, especially serotonergic dysfunction. Therefore, it is related to serotonergic neurotransmission, especially to receptors as 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2A}. Hence, one of the most widely

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studied is the 5-HT$_{1B}$ receptor, which is expressed mainly in presynaptic neurons, and which functions as an auto-receptor that reduces the serotonin release in the synaptic cleft (5). In contrast, selective 5-HT$_{1B}$ antagonists specifically increase the level of serotonin in the synaptic cleft and serve as potential antidepressant agents (5). Thus, 5-HT$_{1B}$ agonists, including ergotamine (ERG) and dihydroergotamine (DHE), have been widely clinically used for their antimigraine effects (6). The research of these highly recurrent mental disorders has been focused for years on the implicated serotonin receptors (7). However, although treatments are available, a large proportion of the diagnosed population does not adequately receive successful pharmacotherapy, not only due to a decrease in resources that cannot provide the best effective agents, but also due to the development of adverse reactions (2,8-11).

On the other hand, different molecules have been discovered in natural products with multiple therapeutic properties. One of these agents is the ayahuasca or yagé, used as a concoction by some South American tribes in rituals of divination, supra-conscience and healing, with potent psychotropic effects (12,13). A wide variety of active metabolites are isolated in decoction processes of *Banisteriopsis caapi* and *Psychotria viridis*; among them have been identified harmine and derivatives with inhibitory effect of monoamine oxidases (MAO) and serotonergic stimulants such as N,N-dimethyltryptamine (DMT), with hallucinogenic effects and improvements in mood (14,15). DMT interacts with ionotropic and metabotropic glutamate, dopamine, and sigma-1 receptors. Equally, it is able to interact with a variety of serotonin receptors, such as 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{2A}$, and 5-HT$_{2C}$, which have been related to partial agonist effect, with a variety of interaction affinity on receptors and transporters (16). However, at a molecular level, the description of the role of these receptors and their interaction with DMT is still completely unknown. Therefore, the objective of this study was to perform docking and molecular dynamics simulation to evaluate at the atomic level the behaviors of DMT on 5-HT$_{1B}$ receptors and to assess the role of these metabolites as potential treatments in disorders such as depression and anxiety.

Material and Methods

Selection and preparation of ligands and receptors

A search for DMT analogues was performed using the PubChem (17) database. The structure name was inserted and the registration code was identified. Likewise, information about the physical representation, activity, and solubility of each analogue was established. Subsequently, a search filter was performed with 98% identity. Three hundred thirty-one structures were randomly chosen to carry out the molecular docking. The addition of hydrogen atoms, neutralization of charges, and geometric optimization was developed by MMFF94 force fields, using conjugate gradients, including 2000 steps with Open Babel algorithm tools. Additionally, the protein structure of 5-HT$_{1B}$ linked with ERG (code: 4AIR, resolution of 2.70 Å) was selected using Protein Data Bank (18). Previously, the proteins obtained in PDB format were prepared using the free software package UCSF Chimera(19), in which the removal of solvent molecules (water) and the assignment of partial charges (using the AMBER force field) were carried out.

Molecular docking

The molecular docking by duplicate was executed by AutoDock Vina based in PyRx 0.8 software (20). These were generated in a center grid space of x = -11.310 Å, y = -17.015 Å, z = 20.723 Å with offset values of x = 17.584 Å, y = 11.493 Å and z = 11.719 Å. Additionality, each molecular docking was developed with exhaustiveness of 8 and simulated individually, determining nine conformations based on effectiveness value, free energy, and RMSD between conformations. The results of the best conformations were registered at pdbqt format and visualized by PyMOL software version 2.3.2 (21) and then converted in PDB format. Finally, BIOVIA Discovery Studio visualizer version 4.5 (22) was used to obtain interaction forces and binding types of each complex.

Molecular dynamics simulation (MD)

Unrestrained all-atom molecular dynamics simulations were performed using PMEMD of AMBER16 software (23). MD minimization, equilibration, production protocols, and analyses were done according to Alviz-Amador et al (24). This was done for all systems of 5-HT$_{1B}$ bound with DMT, serotonin, 112814775, and ERG.

Solvated structures with the TIP3P water model were minimized using 1000 steps of steepest descent, followed by 1000 steps of the conjugate gradient minimization, applying a restraint force constant of 25 kcal/mol-Å2 to the entire solute molecule. The heating was done over 5000 steps of MD from 100 to 300 K with a time step of 2 fs, employing a weak coupling thermostat at constant pressure and constraining bonds involving hydrogen using SHAKE with the tolerance set to 0.00001. A non-bonded cutoff of 8 Å was used. Long-range electrostatics were handled using Particle Mesh Ewald (PME) with the default PME parameters for Amber with automated pair list updating. After heating, the restraints applied to the peptides and proteins were slowly decreased from 5 to 0.5 kcal/mol-A^2 in 5 intervals, each step first minimizing using 1000 steps of steepest descent followed by 500 steps of conjugated gradient minimization and a time step of 2 fs, followed by 50 ps of MD at 300 K, constant pressure and temperature, both with Berendsen coupling constants of 0.2 ps.

Total production time was 100 ns for each system. A summary of all simulations is described in Table 1.

Then, the root-mean-square deviation (RMSD) analyzes were performed using the average structures as

Table 1. Summary of molecular dynamics simulation performed in this study

Starting structure Protein	Source	Simulation times
5-HT$_{1B}$-DMT	PDB: 4IAR	100 ns
5-HT$_{1B}$-ergotamine	PDB: 4IAR	100 ns
5-HT$_{1B}$-serotonin	PDB: 4IAR	100 ns
5-HT$_{1B}$-ligand (112814775)	PDB: 4IAR	100 ns

DMT: N,N-dimethyltryptamine; Er, ergotamine.

references to study the stability of native receptor and ligand-receptor complex. Similarly, a mobility analysis was performed using the root-mean-square fluctuation (RMSF) calculations. Likewise, the solvent-accessible surface area (SASA), the radius of gyration (Rg), and hydrogen bond (H-bond) analyses were done.

Calculation of binding free energy of 5-HT$_{1B}$ ligand-receptors.

In order to calculate the binding free energy of each ligand bound to 5-HT$_{1B}$ receptors, the molecular mechanics/generalized born surface area (MM-GBSA) method was carried out using the MMPBSA.py tool (25). In total, 50 snapshots were extracted from the trajectory (100 ns) of MD simulations. The binding free energy of each complex was computed by the following equation:

$$\Delta G_{bind} = G_{complex} - (G_{receptor} + G_{ligand})$$

Where $G_{complex}$ indicates the free energy of the ligand-receptor complex, and $G_{receptor}$ (5-HT$_{1B}$) and G_{ligand} (DMT, serotonin, 112814775, and ERG) are the free energies of isolated protein and ligand in the solvent, respectively following the methodology proposed by Alviz-Amador et al (26). When calculating the Gibbs free energy (ΔG), the entropy contribution of the protein was ignored because the binding energy was used here to determine the relative binding strength of each complex.

Prediction of pharmacokinetic, drug-likeness, and toxicity

Pharmacokinetic and drug-likeness prediction for the higher affinity analogue and DMT was performed using the SwissADME online tool from the Swiss Institute of Bioinformatics (http://www.sib.swiss) (27) and PreADMET (https://preadmet.bmdrc.kr), a web server from Yonsei University, Republic of Korea (28,29). For this, the canonical SMILES chain and the structure file generator found in the SwissADME online tool were incorporated. These parameters were molecular weight, XlogP3, inhibitory cytochrome P450 (CYP450) family, blood-brain barrier permeability (BBB), binding to P-glycoproteins (P-gp), and Caco2. On the other hand, pharmacological similarity prediction parameters were Lipinski's rules and bioavailability. Additionality, the *in silico* toxicity of the molecules of the DMT analogues using the GUSAR-Online server was evaluated (30), inserting the canonical SMILE molecular representation followed by predictions of lethal dose 50 (LD_{50}) values for rats IV administration, and finally, showing the acute toxicity classification in rodents based on the OECD project.

Results

Molecular docking

Three hundred thirty-one molecules were evaluated by molecular docking studies between the serotonin 5-HT$_{1B}$ receptor with the structural DMT analogues (Supplementary file 1 – Table S1), which showed the interactions of the active site residues of the highest affinity DMT analogue, as well as the binding between DMT, serotonin, and ERG as comparative elements (Figure 1 AD). In Table 2, binding energies -9.05±0.07, -6.65 ± 0.07, -6.50 ± 0.14, and -13.95 ± 0.07 kcal/mol are shown for 112814775, DMT, serotonin, and ERG bound to the receptor, respectively. In our study, 112814775 showed one hydrogen bond between D129 positions. Additionally, several other hydrophobic interactions were also found at C133, I130, Y109, W125, A216, F330, and F331. On the other hand, in the ERG complex, one hydrogen bond with V201 and eight hydrophobic interactions with I130, C133, A216, F330, F331, M337, L348, and F351 were evidenced. Likewise, DMT and serotonin showed common hydrogen bonds with D129; like pi-sulfur related to C133, π-alkyl with A216, and aromatic interactions linked to F331.

Molecular dynamic analysis

In Figure 2 the different trajectory analyses are shown: RMSD to evaluate stability, RMSF to verify fluctuations, SASA analysis to identify the area of solvent accessibility, and finally, the radius of gyration to evaluate compaction of ligands with 5-HT$_{1B}$ receptor.

Panel A of Figure 2 shows backbone RMSD analysis of the different 5-HT$_{1B}$ receptor-ligand complexes

Table 2. Docking result of N,N-dimethyltryptamine (DMT) analogue, serotonin, DMT and ergotamine against 5-HT$_{1B}$ receptor

Protein	Ligands	Docking score (kcal/mol)	Interacting residues	
			Hydrogen bond ligand atom amino acid	Other non-bonding interactions
5-HT$_{1B}$	112814775	-9.05 ± 0.07	D129	Y109, I130, C133, W125, A216, F330, F331
	Serotonin	-6.50 ± 0.14	D129, S212	C133, I130 A216, F331
	DMT	-6.65 ± 0.07	D129, I130, T134, T355	C133, A216, F330, F331
	Ergotamine	-13.95 ± 0.07	V201	I130, C133, A216, F330, F331, L348, M337, F351

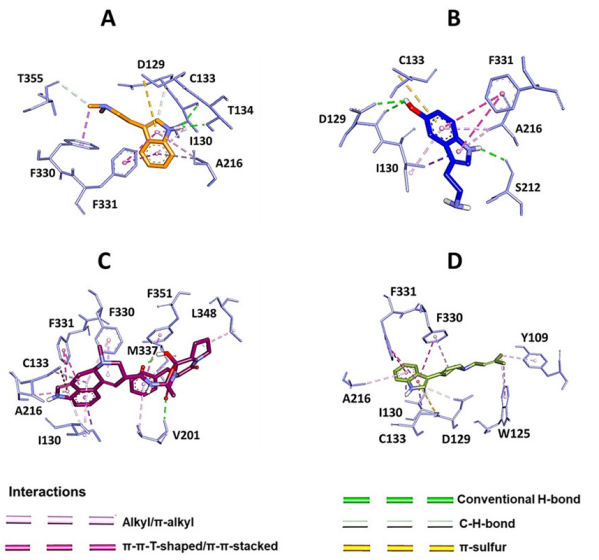

Figure 1. Molecular interaction of N,N-dimethyltryptamine (DMT), serotonin, and ergotamine against 5-HT1B receptor. (A) DMT. (B) Serotonin. (C) Ergotamine. (D) 112814775 (DMT analogue). DMT: N,N-dimethyltryptamine.

evaluated during the trajectory with average structure as a reference, which explores in detail the interaction between ligands and 5-HT$_{1B}$ receptor and the most important conformational changes that determine the stability of the studied complexes. In Figure 2 (Panel A), it was observed that the serotonin-receptor (5-HT$_{1B}$-serotonin), DMT-receptor (5-HT$_{1B}$-DMT), and -ligand analogue- receptor (5-HT$_{1B}$-112814775) were more stable with RMSD values below 2.5 Å in comparison with the ergotamine-receptor complex (5-HT$_{1B}$-ERG). which reached values above 2.5 Å. This may demonstrate the important conformational changes that the drug ERG causes on this receptor, and how the role of DMT is similar to serotonin, while 112814775 is the one that causes less conformational changes in the receptor.

RMSF values were calculated to understand the mobility profile of residues in the 4 complexes; the highest values represent the residues with the highest flexibility. Figure 2 (Panel B) shows that 5-HT$_{1B}$-ERG presented the highest overall flexibility profile (blue colored line). However, 5-HT$_{1B}$-serotonin and 5-HT$_{1B}$-DMT complexes evidenced flexibility profiles between residues 140 and 160 of the sequence (SISISLPPFFWRQASEXVVNT) with RMSF values of 8 and 5 Å, respectively. Similarly, the 5-HT$_{1B}$-DMT complex indicated flexibility with RMSF values of 4 Å between residues 330 and 350 of the sequence (ISLVMPIWFXLAIFDFFTWLGY). Conversely, 5-HT$_{1B}$-112814775 presented the lowest mobility profile of all the complexes during the trajectory.

Figure 2 (Panel C) illustrates the solvent accessible area (SASA) for all the complexes formed between the 5-HT$_{1B}$-serotonin receptor and different ligands. It should be noted that the 5-HT$_{1B}$-serotonin, 5-HT$_{1B}$-DMT, and 5-HT$_{1B}$-ERG complexes stretched a SASA value around 22 000 Å^2 during the entire 100ns trajectory. However, the 5-HT$_{1B}$-112814775 complex, which refers to a new ligand studied in the present work, presented SASA values lower

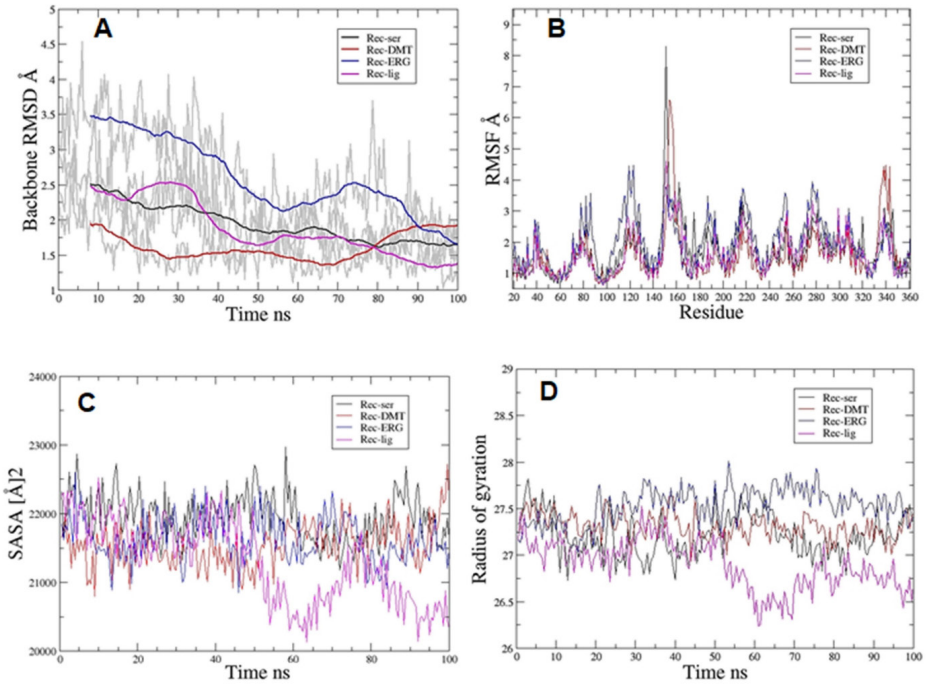

Figure 2. Molecular dynamic analysis of ligand against 5-HT$_{1B}$ receptor. (A) RMSD, (B) SASA, (C) RMSF, and (D) Rg analysis of all trajectories. Rec-ser: 5-HT$_{1B}$-serotonin, Rec-DMT: 5-HT$_{1B}$-DMT, Rec-ERG: 5-HT$_{1B}$-Ergotamine, Rec-lig (5-HT$_{1B}$-112814775).

than 21000 Å^2 after 40 ns of trajectory until 100 ns.

On the other hand, Figure 2 (Panel D) shows that the radius of gyration of the 5-HT$_{1B}$-serotonin, 5-HT$_{1B}$-DMT, and 5-HT$_{1B}$-ERG complexes are higher compared to the 5-HT$_{1B}$-112814775 complex, which means that the latter one is more compact.

Figure 3 and Table 3 show the total number of hydrogen bonds of the four complexes during the simulation. Consequently, the 5-HT$_{1B}$-DMT complex presented a higher average number of hydrogen bonds, followed by 5-HT$_{1B}$-112814775, 5-HT$_{1B}$-serotonin, and 5-HT$_{1B}$-ERG with average values of 116.49, 114.42, 114.29, and 110.53, respectively.

Additionally, Table 4 describes the analysis results of binding free energy interaction. The complex with the best interaction energy is 5-HT$_{1B}$-ERG followed by 5-HT$_{1B}$-112814775, 5-HT$_{1B}$-DMT, and finally 5-HT$_{1B}$-serotonin with values of -55.61 ± 0.23, -36.83 ± 0.28, -26.93 ± 0.25, and -16.68 ± 0.18 Kcal/mol respectively obtained by the MM-GBSA method. Table 4 highlights the electrostatic and Van der Waals interactions in addition to the ones reported in the docking analysis.

Table 5 presents the pharmacokinetic properties predicted using SwissADME and PreADMET and acute oral toxicity in rats obtained with GUSAR predictor. According to OECD, both studied structures, DMT and 112814775, show compliance with Lipinski's rules, a variable inhibitory prediction on CYP and class IV acute toxicity.

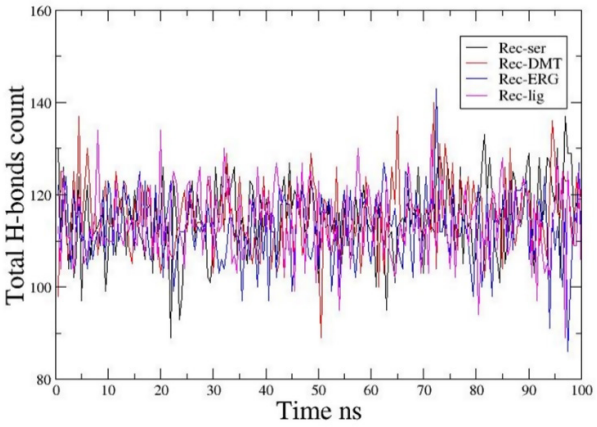

Figure 3. Total count of hydrogen bonds within protein during the simulation.

Discussion

The molecular study of serotonin receptors has characterized its binding sites composed of TM3, TM5, TM6, and TM7 domains (5). In the studies proposed by Wang et al, the role of inverse agonists, such as SB-236057, in the functioning of 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors have been studied, where residues such as D129, I130, C133, Y208, T209, S212, A216, W327, F330, F331, S334, D352, T355, and Y390 were identified (5,31). Therefore, the tryptamine pharmacophoric group plays a fundamental role in binding to the active site of the receptor (32). The structural arrangement of DMT analogues in regard to the binding site of 5-HT$_{1B}$ receptor show voluminous groups formed by aromatic groups substituted at the C3 position of the tryptamine structure as evidenced in 112814775. The receptor shows a varied effect of chemical interactions with DMT analogues, with the predominance of aromatic interactions within residues A216 and F331 coinciding with ERG and serotonin, which have been linked as

Table 3. Average of total count of hydrogen bonds within protein during the simulation

	5-HT$_{1B}$-serotonin	5-HT$_{1B}$-DMT	5-HT$_{1B}$-ERG	5-HT$_{1B}$-112814775
Average	114.29	116.49	110.53	114.42
DESVEST	8.16	7.87	7.70	8.00
ESM	0.29	0.46	0.28	0.35

Table 4. Binding free energy (kcal/mol ± standard error of mean) components for the complexes receptor 5-HT$_{1B}$ and ligands determined by using the MM-GBSA method

Energy component	5-HT$_{1B}$-serotonin	5-HT$_{1B}$-DMT	5-HT$_{1B}$-ERG	5-HT$_{1B}$-112814775
VDW	-23.35 ± 0.13	-69.37 ± 0.21	-27.15 ± 0.13	-38.33 ± 0.16
EEL	-15.36 ± 0.22	-8.28 ± 0.15	-12.65 ± 0.19	-11.88 ± 0.22
EGB	25.46 ± 0.17	29.98 ± 0.16	16.64 ± 0.16	18.44 ± 0.14
ESURF	-3.42 ± 0.01	-7.93 ± 0.02	-3.77 ± 0.01	-5.04 ± 0.01
ΔG gas	-38.71 ± 0.24	-77.66 ± 0.31	-39.80 ± 0.24	-50.22 ± 0.32
ΔG Sol	22.03 ± 0.17	22.04 ± 0.15	12.87 ± 0.16	13.39 ± 0.13
ΔG Total	-16.68 ± 0.18	-55.61 ± 0.23	-26.93 ± 025	-36.83 ± 0.28

EEL: Electrostatic energy, EGB: Summation of electrostatic, ESURF: Surface energy, ΔG gas: Gibb's energy in the gas phase ΔG sol: Gibb´s energy in aqueous phase, ΔG Total: Total Gibb´s energy, VDW: Van der Waals.

Table 5. ADME parameter and acute oral toxicity properties of 112814775 and DMT by SwissADME, PreADMET, and GUSAR online prediction

Parameters	112814775	DMT
Lipinski	Yes	Yes
Bioavailability	0.55	0.55
Molecular weight	266.38	188.27
XlogP3	3.76	1.68
TPSA	19.03	19.03
BBB permeant	Yes	Yes
P-gp substrate	No	No
Log Kp (skin permeation)	-5.26	-6.26
CYP2D6 inhibitor	Yes	No
CYP3A4 inhibitor	No	No
CYP1A2 inhibitor	Yes	Yes
Caco2	24.96	56,97
hERG inhibition	Medium risk	Medium risk
Rat IV LD_{50} (mg/kg)	29.00 (IV)	32.04 (IV)

TPSA, Topological Polar Surface Area; P-gp, P-Glycoprotein; Log Kp, Human skin permeability coefficients; CYP, Cytochrome; IV, Intravenous; LD_{50}, Lethal dose 50.

important residues in the affinity of the receptor with co-crystalized molecules, which are key to strong molecular bonding and correlated with hydrophobic interactions (6). Similarly, the relevance of F330 has been distinguished, which interacts with the highest affinity analogues through substituents of tetrahydropyridine, establishing attractive forces of non-covalent nature between the rings and responsible for stabilizing effect, whose interaction is similar with this same residue in the structural portion or ergoline. Likewise, it has been reported π-σ bonds with I130 and electrostatic effect between the thiol group of residues C133 and the aromatic ring (33,34). On the other hand, D129 residues may allow the formation of hydrogen bonds preferably with N-indole atoms, which are key in the stabilization and recognition between ligands-proteins (5,35), which is confirmed by Sullivan et al, where it states that this residue is involved in the cleavage with ergoline through the formation of saline bonds, further stabilized by the hydrogen bonds with Y359 (6).

With regard to the RMSD analysis of trajectories after simulation by molecular dynamics of the four complexes, it is important to note that these 4 proteins interacting with these ligands do not deploy and present similar results to the ones reported by Wang et al for serotonin 5-HT$_{1B}$ inhibitor and receptor complexes with RMSD values between 1.4 and 3 Å (31). On the other hand, due to the fact that ERG is a reference drug with aromatic groups, it provides greater conformational changes to the serotonin 5-HT$_{1B}$ receptor according to the results shown.

In the dynamic analysis of RMSF, the 5-HT$_{1B}$-ERG complex presented the best global mobility profile. However, during the trajectory, it maintained around 2 to 3 Å approximately, similar to those reported by Sullivan et al for ERG and DHE complex with 5-HT$_{1B}$ (6). With respect to the 5-HT$_{1B}$ with serotonin and DMT complexes, both presented increased mobility profiles between residues 140 and 160 of the sequence (SISISLPPFFWRQASEXVVNT). In contrast, the 5-HT$_{1B}$-DMT complex increased mobility profile was between residues 330 and 350 of the sequences (ISLVMPIWFXLAIFDFFTWLGY), which are close to the interaction sites reported in the molecular docking analysis of the present study in Table 2. Also, it is evidenced that these areas were slightly more mobile for the ERG and DHE complex with 5-HT$_{1B}$ (6).

In relation to SASA analysis, the result suggests that 5-HT$_{1B}$ receptor complexes with serotonin, DMT, and ERG are fairly widespread, which matches with the fluctuation analysis, where the greater the fluctuation, the greater the accessibility to solvent, as described by Junaid et al (36). On the contrary, the complex with 112814775 shrinks the protein from 40 ns, which could explain its low mobility profile and great stability. Likewise, the analysis of radius of gyration of the 5-HT$_{1B}$-112814775 complex indicated a lower value, conditioning greater compactness of the system, which would indicate that it is the most rigid system of the four complexes analyzed according to the scientific literature (37,38). This means that the more compact a system is, the greater its stiffness (38), which follows the trend shown of greater stability, less mobility, less solvent accessibility, and more compaction or stiffness in all analyses.

This result contrasts with the 5-HT$_{1B}$-ERG complex, which turned out to have the largest conformational change (RMSD), the highest global fluctuations (RMSF), and the highest solvent accessibility surface area (SASA), which suggests that ERG ensures an extension of the complex. On the contrary, a higher radius of gyration than the rest of the complex, making it the least compact or rigid, proves its high mobility and large conformational changes. It should be noted that ERG is a drug that already has an intrinsic pharmacological activity demonstrated. These conformational changes would explain the pharmacological effects at the already demonstrated atomic level, similar to the complex with serotonin and DMT. However, these compounds also revealed a large number of hydrogen bonds during molecular dynamics simulation, which is a good indicator of the stability of the complex and its ligands, as shown in Figure 3. Nevertheless, the analysis of molecular interaction with 5-HT$_{1B}$ receptor showed a low number of hydrogen bonds for DMT, serotonin, ERG, and poor hydrogen bonds for 112814775, suggesting that the binding mechanism does not depend on this type of interaction. Therefore, these results may propose that the amino acids that interact by hydrogen bonds slightly contribute to the activity, but condition conformational changes.

In addition to the results of the MM-GBSA free energy calculation, it is important to note that ERG presented the strongest binding free energy value compared to the other ligands studied (112814775, DMT and serotonin), which is similar to the one reported by Sullivan et al, who

compared the binding energy of ERG with other analogues demonstrating better interaction with the 5-HT_{1B} receptor (6). The most important energy contributions that determined the relative binding free energy (ΔGTotal) for all complexes were related to Van Der Waals interactions (ΔEvdw), electrostatic interactions (ΔEEel), and the non-polar solvation component (ΔEsurf), additional to those reported in the docking analysis in the present study. These Van Der Waals, electrostatic and non-polar interactions were also reported by Wang et al (31).

Finally, in the pharmacokinetic parameters and toxicity predictions for 112814775 and DMT, most of the predicted parameters showed a similar profile. In this way, it is interesting to note that these types of molecules could influence the central level, the aspect that is supported in some experimental investigations in which the intravenous administration of DMT by means of marked probes showed permeable and stimulating effects in less than 1 minute, as it has been ensured the ability to remain for 2-7 days at central nervous system level (16). Regarding metabolism, DMT-like compounds such as 5-MeO-DMT have shown biotransformation processes associated with isoforms such as CYP2D6, evidenced by the metabolic capacity of this type of metabolites and the importance of using MAO inhibitors as an adjuvant (39-41). Similarly, studies carried out in tryptamine derivatives on the CYP2D6 system showed the low inhibitory capacity of DMT in regard to the other molecules at values of 100 mM, which could be in accordance with the suggested predictions (42). On the other hand, it has been reported that the prediction values of LD_{50} IV in rats were between 29 and 32 mg/kg, similarly described in the literature (43,44), while the ingestion of ayahuasca preparations has been shown to have estimated LD_{50} values at 8 mg/kg (45). However, these parameters are relevant in the determination with greater precision for DMT analogues, including each pharmacokinetic aspect in an exhaustive way, looking for promising candidates for the treatment of pathologies related to neuronal activity.

Conclusion

In this study, a docking-based virtual screening was performed with the aim of studying DMT analogues, DMT, serotonin, ERG, and their interaction with the 5-HT_{1B} receptor. These analogues are promising for the search for new pharmacological treatments for psychiatric disorders such as depression and anxiety, taking into account the ethno-pharmacological and pharmacological history with ayahuasca. Likewise, it was evidenced that 112814775 has the best affinity with the 5-HT_{1B} receptor through molecular docking. Also, 112814775 in the dynamic analysis showed great conformational stability, low mobility, and rigidity compared to the control ligands: ERG, serotonin, and DMT. After the free energy calculation, contributions such as Van Der Waals, electrostatics, and non-polar interactions are highlighted for all systems. Finally, the predictions of some pharmacokinetic properties and acute toxicity of the compound with the highest affinity analogue and DMT were performed. However, additional studies are needed to clarify the molecular mechanism of this important group of molecules, especially the ligand 112814775 on the 5-HT_{1B} receptor.

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Authors' contributions

NC and AA conceived the research idea and designed the work, NC and AA carried out the *in silico* simulations, NC, AA, and IM wrote the first draft of the manuscript, IM carried out the literature search, NC, AA, and IM carried out the graphical design, AA supervised the study. All authors read and approved the final manuscript for publication.

Conflict of interests

Authors declare no conflict of interest

Ethical considerations

The authors have carefully observed all ethical issues. Authors fullfilled ethical issues related to the manuscript.

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Supplementary files

Supplementary file 1 contains Table S1.

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