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A Note on the Docking of some Hallucinogens to the 5-HT_{2A} Receptor.

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ABSTRACT

The activation of 5-HT_{2A} receptors by the binding of some ligands produces several altered states of consciousness in humans. The knowledge of the manner a hallucinogen interacts with this receptor should be the first step to know how these chemicals transfer information to produce the final biological effect(s). Here, we present the results of a docking study of some hallucinogens (LSD, mescaline, DMT, 25I-NBOMe and others), to a recent model of the 5-HT_{2A} receptor. The rigid and flexible residues approaches were employed. The best approach is to allow conformational flexibility to the residues of the binding site. The Val-156 residue appears to be common to all flexible docking results and all molecules interact with the transmembrane 3 helix. The other interactions are particular to each molecule.

Keywords: 5-HT_{2A} receptor, QSAR, serotonin, docking, hallucinogens, LSD, mescaline, 25I-NBOMe, DMT, MDMA, DOB, psilocybin, DON, Autodock Vina, DFT calculations.

INTRODUCTION

The use of certain plants, mushrooms, toads, etc., by some human populations to produce altered states of consciousness (ASC) has a very rich history, even rooted in the Upper Paleolithic [1-7]. The first synthetic hallucinogen, lysergic acid diethylamide (LSD), was discovered by Albert Hoffman who began to experience hallucinations after an unintentional percutaneous exposure to the drug. Today we are facing a plethora of synthetic molecules able to produce several kinds of ACSs [8, 9] (this couple of books, forgetting that these substances were and are employed mostly in traditional societies' sacred ceremonies, allowed the uncontrolled use of hallucinogens by *n'importe qui*. We know now how catastrophic the results are). Technically speaking, a hallucinogen is a chemical substance that modifies the functioning of the senses and produces hallucinations defined as perceptions or experiences departing radically from everyday reality. As men seem to need to give names to all things and processes, these substances have been named psychedelics (mind manifesters), psychotomimetics (psychosis mimickers) and/or psychotaraxics (mind disturbers). These terms, specially the last two, poorly describe the astonishing effects these chemicals have on the human mind. In the specific case of these molecules, one of the authors (J.S. G.-J.) thinks that this need to name things seems to have evolved from the ancient belief that knowing the "true" name of a thing gives one some amount of power over it. This is because none of these terms even approaches the experiences themselves. When in 1931 Lewin referred to this class of drugs as phantastica because they that can produce in our minds a world of fantasy, he also used inappropriate terms ("world of fantasy") [10]. A correct definition and classification of all these mind experiences does not exist to this date [11]. Moreover, it is well known that for some hallucinogens different doses are needed for different individuals to get a "standard" experience (considering the nature and content(s) of these experiences(s), the term "standard" has intensional vagueness) [12].

The mammalian 5-HT_{2A} receptor is a subtype of the 5-HT_2 receptor that belongs to the serotonin receptor family and is a G protein-coupled receptor. Drugs like LSD, mescaline and others act as 5-HT_{2A} receptor agonists. Their action

at this receptor is responsible for their psychedelic effects. From the theoretical point of view, one of the first steps to obtain knowledge about the nature of the ligand-5-HT_2 receptor interaction is by carrying out docking studies of some selected ligands. There have been many docking studies of different molecules to the 5-HT_{2A} receptor [13-44]. As a first effort to provide more reliable and accurate information opening the way for studies with larger molecular sets, we present here the results of a docking analysis of several hallucinogens with a very recent model of the 5-HT_{2A} receptor.

MATERIALS AND METHODS

METHODS AND CALCULATIONS

We selected the following molecules for docking: psilocybin ([3-(2-dimethylaminoethyl)-1*H*-indol-4-yl]dihydrogen phosphate), LSD ((6a*R*,9*R*)-*N*,*N*-diethyl-7-methyl-4,6,6a, 7,8,9-hexahydroindolo-[4,3-*fg*]quinoline-9-carboxamide), DMT (2-(1*H*-indol-3-yl)-*N*,*N*-dimethylethanamine), 25I-NBOMe (2-(4-iodo-2,5- dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine), (-)-MDMA ((*R*)-1-(Benzo[*d*][1,3]dioxol-5-yl)- *N*-methylpropan-2-amine), 25Nitro-NBOMe (2-(4-nitro-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine), mescaline (2-(3,4,5-trimethoxyphenyl) ethanamine), (-)-DOB ((*R*)-1-(4-bromo-2,5-dimethoxyphenyl)- 2-aminopropane) and (-)DON ((*R*)-1-(2,5-Dimethoxy-4-nitrophenyl)propan-2-amine). They are displayed in Fig. 1. No experimental information is known for 25Nitro-NBOMe.

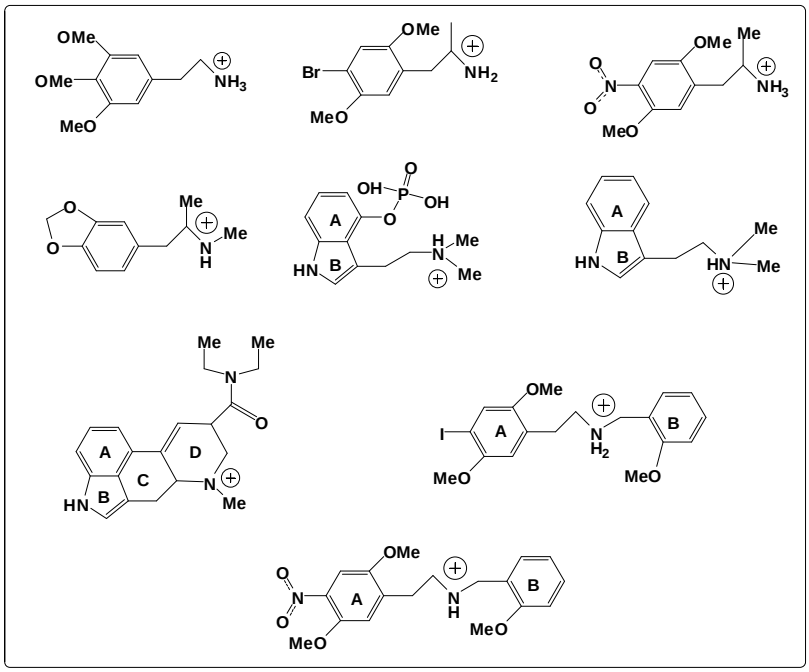

Figure 1. Mescaline, DOB, DON, MDMA, psilocybin, DMT, LSD, 25I-NBOMe and 25Nitro-NBOMe.

The geometries of all molecules in the protonated form [45-47] were fully optimized at the B3LYP/6-31G(d,p) level of theory with the Gaussian set of programs and served as the starting point for docking [48]. For the 5-HT_{2A} receptor, we employed model 2 of the P28223 (Uniprot ID) structure generated by the GPCR-I-TASSER pipeline [49, 50]. A comparison with a previous study allowed us to locate the intermembrane binding site. Fig. 2 shows the binding site.

For the docking study the Autodock Vina software was employed with a 30x30x30 box [51]. Two kinds of docking were carried out for each molecule. In the first one all the residues of the binding site were considered as rigid (i.e., without conformational freedom, RRA, only the ligand has conformational flexibility). In the second study LSD was first docked with the rigid residue option. Next, all the residues inside a 4 Å region around the ligand were considered to be flexible (i.e., they can change their conformation during the docking procedure, FRA). The lowest energy conformer of each study was selected for its analysis with Autodock Vina and Discovery Studio Visualizer [52]. We carried out RRA and FRA studies to detect the differences in the results and despite the fact that an educated guess suggests that the FRA approximation should be closer to the real conditions. For the sake of simplicity we employed the following nomenclature: “weak” for interaction distances equal or greater than 5Å, “strong” for distances equal or lesser than 3Å and “intermediate” for distances lesser than 5Å and greater than 3Å.

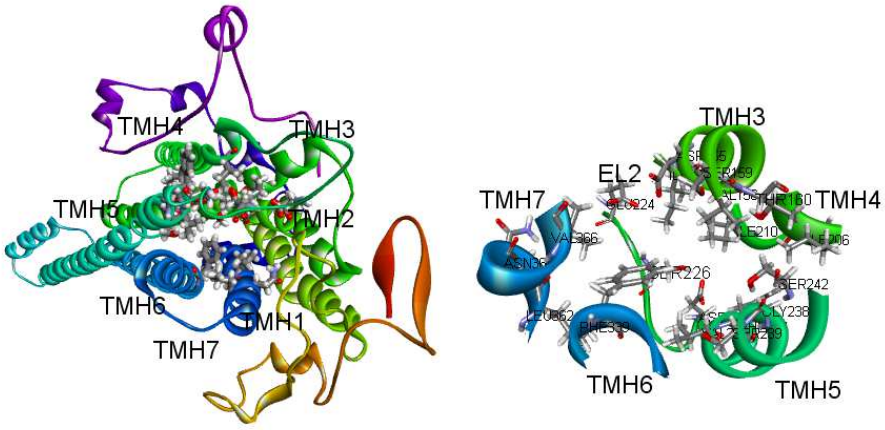

Figure 2. Left: $5HT_{2A}$ receptor (the size of the relevant residues was enlarged for a better view). Right: close view of the binding site. TMH refers to a transmembrane helix and EL to an extracellular loop.

RESULTS AND DISCUSSION

Figure 3 shows the RRA and FRA results of the docking of mescaline.

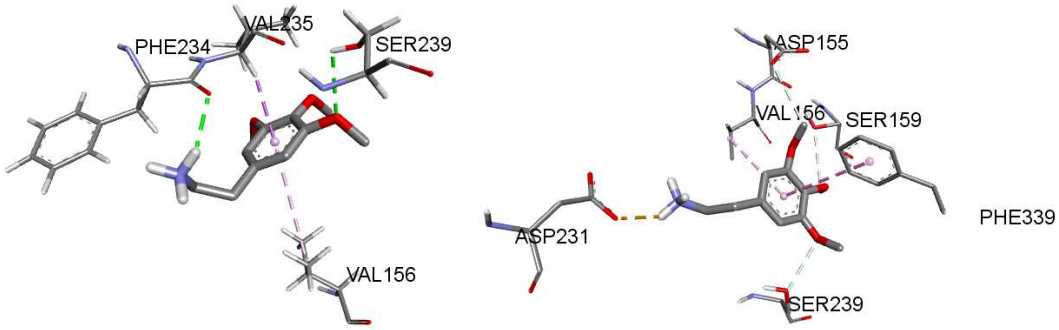

Figure 3. Mescaline docked to the 5-HT_{2A} binding site. Left: RRA results. Right: FRA results.

RRA shows a π-alkyl interaction of the aromatic ring with Val-156 (5.18Å), a π-σ interaction of the aromatic ring with Val-235 (2.77Å), a conventional H-bond between the O atom from the 5-OMe substituent and Ser-239 (2.61Å) and a conventional H-bond between one H atom from the NH_3^+ group and the backbone of Phe-234 (2.26Å). In summary: one weak interaction and three strong ones. The situation is entirely different for the FRA results. They show a π-π T-shaped interaction between the aromatic ring and Phe-339 (5.05Å), a π-alkyl interaction of the aromatic ring with Val-156 (4.83Å), a carbon H-bond between the O atom (as an acceptor) from the 5-OMe substituent and the backbone of Ser-239 (3.55Å), a carbon H-bond between the C atom (as a donor) from the 3-OMe substituent and Asp-155 (3.34Å), a carbon H-bond between the carbon atom (as a donor) of the 4-OMe substituent and Ser-159 (3.50Å) and a salt bridge interaction between one H atom from the NH_3^+ group and Asp-231 (2.41Å). In summary: One weak interaction, four intermediate interactions and one strong one. Only Ser-239 and Val-156 are common to both results. *Here and below only the FRA results will be compared with other similar works.* In a study involving the docking of mescaline, the authors noted that the 3- and 5-OMe groups adopted out-of-plane conformations [24]. In our case we observe that the three OMe groups adopted the out-of-plane position. Also, an aromatic π-π T-shaped interaction with Phe-340 was suggested while our results also show a π-π T-shaped interaction between the aromatic ring of mescaline but with Phe-339. Conventional H-bonds with Thr-160, Phe-243, Ser-159 (from the 3-, 4- and 5-OMe substituents) and Asp-155 (two H-bonds with the NH_3^+ moiety) are suggested. In our case, the three OMe substituents are involved in intermediate interactions (carbon H-bonds with Asp-155, Ser-159 and Ser-239). In our case an H atom of the NH_3^+ moiety is involved in a salt bridge interaction with Asp-231. It is interesting to note that Nichols et al. did not find any interaction with Val-156. Fig. 4 shows the FRA result including the microscopic environment.

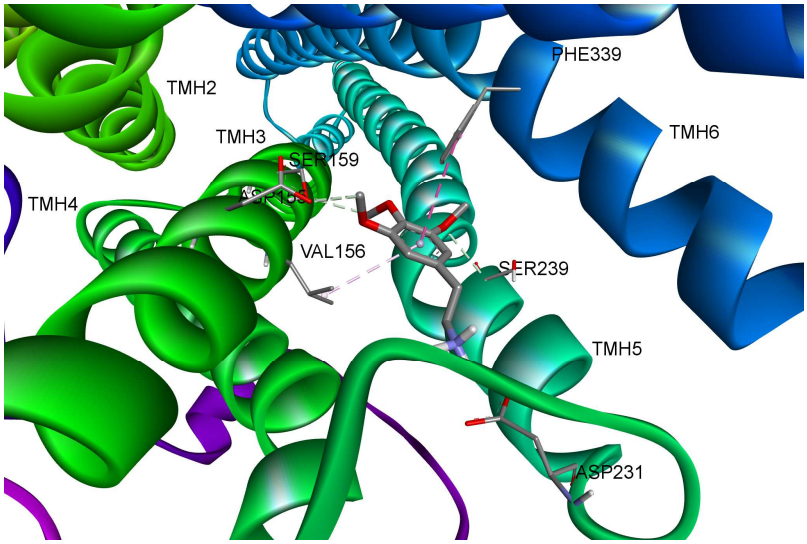

Figure 4. Mescaline docked to the 5-HT$_{2A}$ receptor.

Figure 5 shows the RRA and FRA results of the docking of LSD.

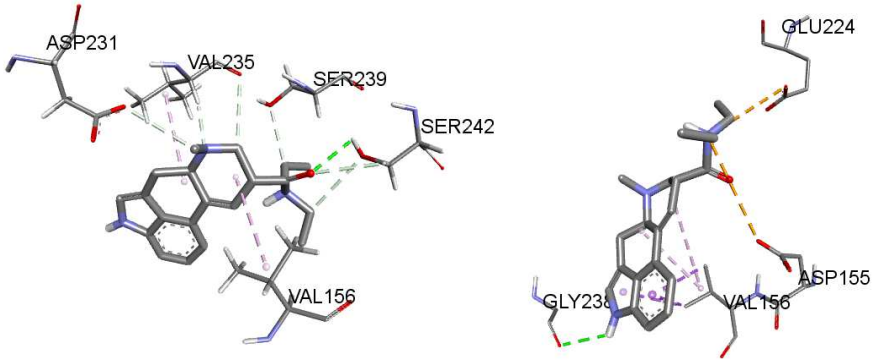

Figure 5. LSD docked to the 5-HT$_{2A}$ binding site. Left: RRA results. Right: FRA results.

The RRA results show an alkyl interaction of ring C with Val-235 (4.56Å), a carbon H-bond between a C atom of ring D and the backbone of Val-235 (3.76Å), a carbon H-bond between the N atom of ring D and the backbone of Val-235 (2.31Å), a carbon H-bond between the C atom from the Me substituent in ring D and Asp-231 (3.43Å), a carbon H-bond between a C atom from the diethylamide moiety and Ser-239 (3.2Å), a conventional H-bond between the oxygen atom of the amide moiety and Ser-242 (2.68Å), a carbon H-bond between the O atom of the amide moiety and Ser-242 (3.01Å), a carbon H-bond between a carbon atom from the diethylamide moiety and Ser-242 (3.45Å) and an alkyl interaction of ring D with Val-156 (4.42Å). It is interesting to note that there are no interactions of rings A and B with any residue. These rings seem to be very important in structurally simpler hallucinogens such as mescaline, DMT, DON, etc. In summary: No weak interactions, seven intermediate interactions and two strong ones. The FRA results show two π-σ interactions of ring A with Val-156 (3.94Å and 3.97Å), a π-σ interaction of ring B with Val-156 (3.70Å), alkyl interactions of rings C and D with Val-156 (4.46Å and 5.41Å respectively), a conventional H-bond between the indole H(N) and Gly-238 (2.63Å) and attractive charge interactions of the N atom from the diethylamide moiety with Asp-155 (5.23Å) and Glu-224 (5.36Å). In summary: Three weak interactions, four intermediate interactions and one strong one. In a docking study of LSD the authors find three hydrogen bonds: one between the H(N) atom of the indole ring with an OH group of Ser-242, another between the LSD proton and a carboxylate group of Asp-155 and a third one between the oxygen atom of the diethylamide group with Asn-343 [18]. In our case, the H(N) atom of the indole ring forms an H-bond with Gly-238 and the nitrogen atom of the diethylamide group interacts via an attractive charge interaction with the carboxylate group of Asp-155. In another study of LSD docking, an interaction between the indole nitrogen and Ser-242 is proposed [26]. We did not found that interaction. Other interactions of LSD with Ser-239, Phe-340, Phe-339 and Asp-155 are found. Our FRA results found only the aforementioned interaction with Asp-155. Fig. 6 shows the FRA result including the microscopic environment.

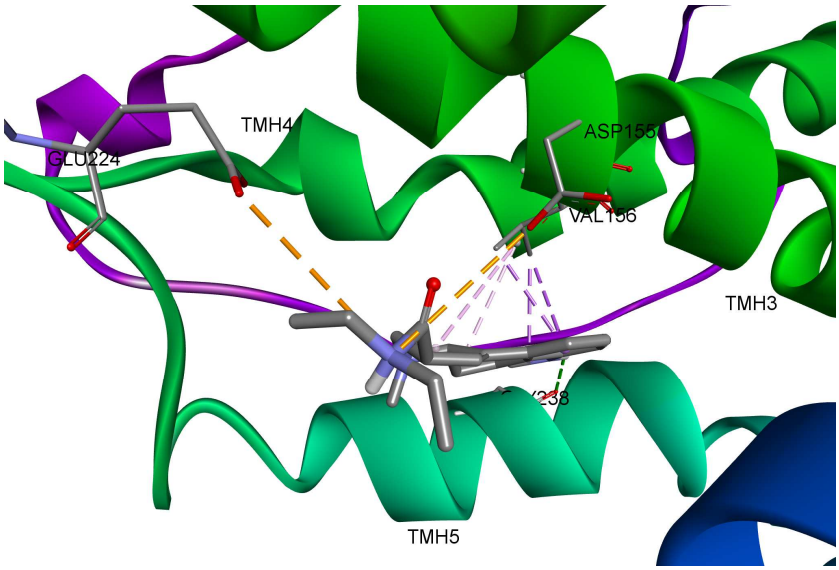

Figure 6. LSD docked to the 5-HT_{2A} receptor.

Figure 7 shows the RRA and FRA results of the docking of (-)-DOB.

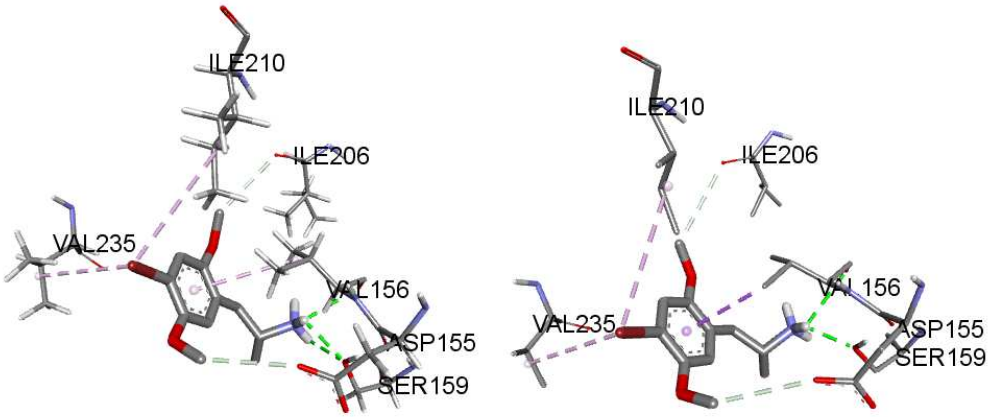

Figure 7. (-)-DOB docked to the 5-HT_{2A} binding site. Left: RRA results. Right: FRA results.

The RRA results show a carbon H-bond between the Me moiety of the 5-OMe substituent and Asp-155 (3.49Å), a conventional H-bond between two hydrogen atoms from the NH_3^+ group and Ser-159 (2.40Å and 2.34Å), a conventional H-bond between an H atom from the NH_3^+ group and the backbone of Val-156 (2.63Å), a π-alkyl interaction of the aromatic ring with Val-156 (4.07Å), alkyl interactions of the bromine atom with Ile-210 (5.22Å) and Val-135 (4.81Å), and a carbon H-bond between the Me moiety of the 2-OMe substituent with the backbone of Ile-206 (3.55Å). In summary: One weak interaction, four intermediate interactions and three strong ones. The FRA results are almost the same: a carbon H-bond between the Me moiety from the 5-OMe substituent and Asp-155 (3.56Å), a conventional H-bond between an H atom from the NH_3^+ group and Ser-159 (2.14Å), a conventional H-bond between an H atom from the NH_3^+ group and the backbone of Val-156 (2.79Å), a π-σ interaction of the aromatic ring with Val-156 (3.72Å), alkyl interactions of Br with Ile-210 (5.20Å) and Val-135 (4.92Å) and a carbon H-bond between the Me moiety of the 2-OMe substituent with the backbone of Ile-206 (3.79Å). In summary: One weak interaction, four intermediate interactions and two strong ones. Two interesting studies are found in the docking literature. In the first one, Phe-340 associates with the aromatic ring of the ligand through a T-shaped interaction and the α-methyl group of the ligand appears to undergo Van der Waals interactions with Phe-340 [22]. Our FRA results do not find any interaction with Phe-340. In a more detailed study, it is found that the aromatic ring is associated closely with Trp-336, Phe-339 and Phe-340 [29]. None of these interactions are found in this study. The 2-OMe group of DOB accepts a hydrogen bond from Asn-343. Our results show that this substituent is engaged in a carbon hydrogen interaction with Ile-206. The 5-OMe group is near Ser-159, Thr-160 and Ser-242 and can potentially form hydrogen bonds with these residues. Our results do not show these interactions. It is suggested that a lipophilic interaction occurs between the methyl of the 5-OMe group and Trp-336 but our results do not show it. Other aromatic residues that can potentially interact with the aromatic ring of DOB include Phe-243 and Phe-340.

Phe-339 is in a position to further stabilize the ammonium-Asp-155-Ser-159 complex via a π-cation interaction (there is more information about other possible interactions in the Suppl. Mat. of this reference). In summary, our results are entirely different. Fig. 8 shows the FRA result including the microscopic environment.

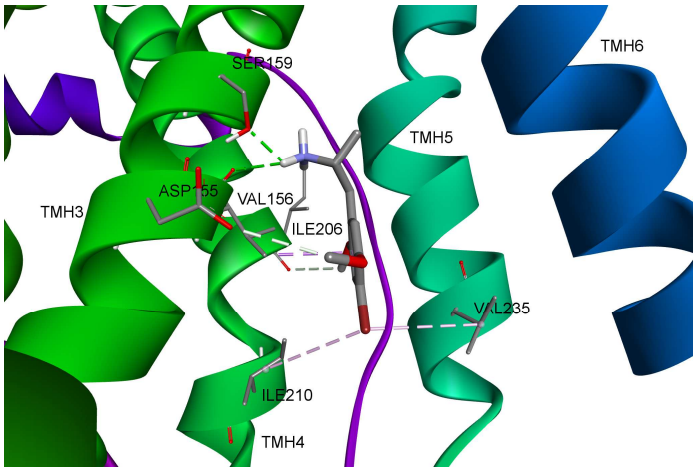

Figure 8. (-)-DOB docked to the 5-HT_{2A} receptor.

Figure 9 shows the RRA and FRA results of the docking of (-)-DON.

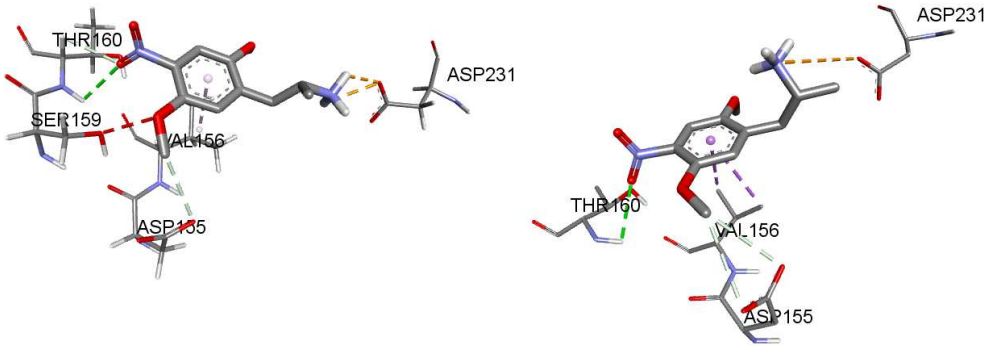

Figure 9. (-)-DON docked to the 5-HT_{2A} binding site. Left: RRA results. Right: FRA results.

We can see that the RRA results show a carbon H-bond between the Me moiety of the 5-OMe substituent and Asp-155 (3.32Å), an unfavorable acceptor-acceptor interaction of the O atom of the 5-OMe substituent with Ser-159 (2.95Å), a π-alkyl interaction of the aromatic ring with Val-156 (3.74Å), a conventional H-bond between one oxygen atom of the 4-NO_2 substituent and the backbone of Thr-160 (2.85Å), a carbon H-bond between one oxygen atom from the 4-NO_2 substituent and the backbone of Thr-160 (3.09Å) and salt-bridge interactions between two hydrogen atoms from the NH_3^+ group and Asp-231 (2.62Å and 3.00Å). In summary: No weak interactions, four intermediate interactions and three strong ones. The FRA shows a carbon H-bond of the Me moiety of the 5-OMe substituent with Asp-155 (3.61Å and 3.58Å), π-σ interactions of the aromatic ring with Val-156 (3.90Å and 3.84Å), a conventional H-bond between one oxygen atom from the 4-NO_2 substituent and the backbone of Thr-160 (2.85Å) and an attractive charge interaction between the N atom from the amine group and Asp-231 (5.53Å). In summary: One weak interaction, four intermediate interactions and one strong one. Fig. 10 shows the FRA result including the microscopic environment.

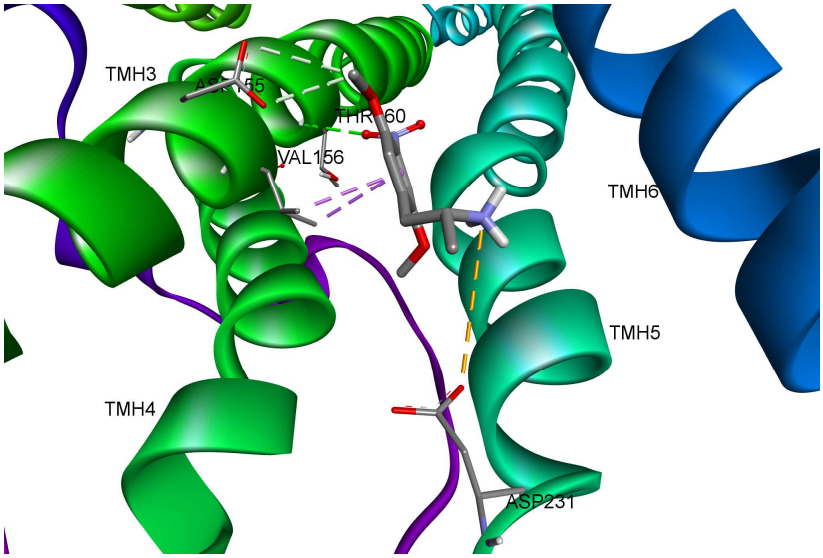

Figure 10. (-)-DON docked to the 5-HT$_{2A}$ receptor.

Figure 11 shows the RRA and FRA results of the docking of (-)-MDMA.

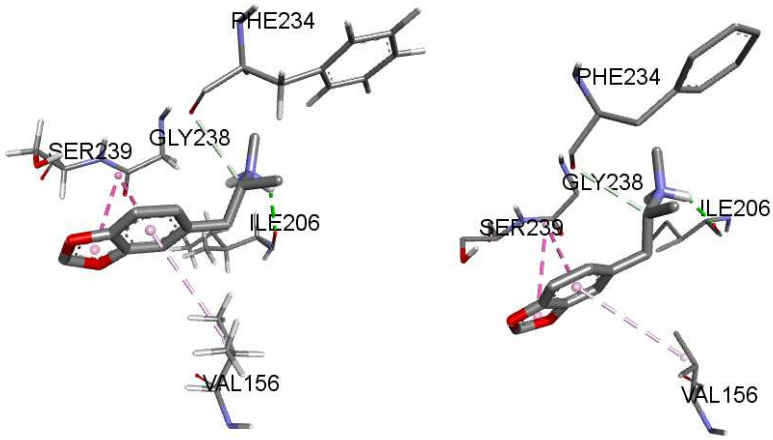

Figure 11. (-)-MDMA docked to the 5-HT$_{2A}$ binding site. Left: RRA results. Right: FRA results.

The RRA results show an amide-π stacking interaction of ring A with the backbone of Gly-238 (3.84Å), an amide-π stacking interaction of ring B with the backbone of Gly-238 (3.85Å), a π-alkyl interaction of ring A with Val-156 (4.84Å), a conventional H-bond between an hydrogen atom of the amine group and the backbone of Ile-206 (2.25Å) and a carbon H-bond between a carbon atom of the alkyl chain of ring B and the backbone of Phe-234 (3.27Å). In summary: No weak interactions, four intermediate interactions and one strong one. The FRA shows an amide-π stacking interaction of ring A with the backbone of Gly-238 (3.83Å), an amide-π stacking interaction of ring B with the backbone of Gly-238 (3.97Å), a π-alkyl interaction of ring A with Val-156 (4.87Å), a conventional H-bond between one hydrogen atom from the amine group and the backbone of Ile-206 (2.09Å) and a carbon H-bond between a C atom of the alkyl chain of ring B and the backbone of Phe-234 (3.28Å). Note that both studies produce almost identical results. In summary: No weak interactions, four intermediate interactions and one strong one. Fig. 12 shows the FRA result including the microscopic environment.

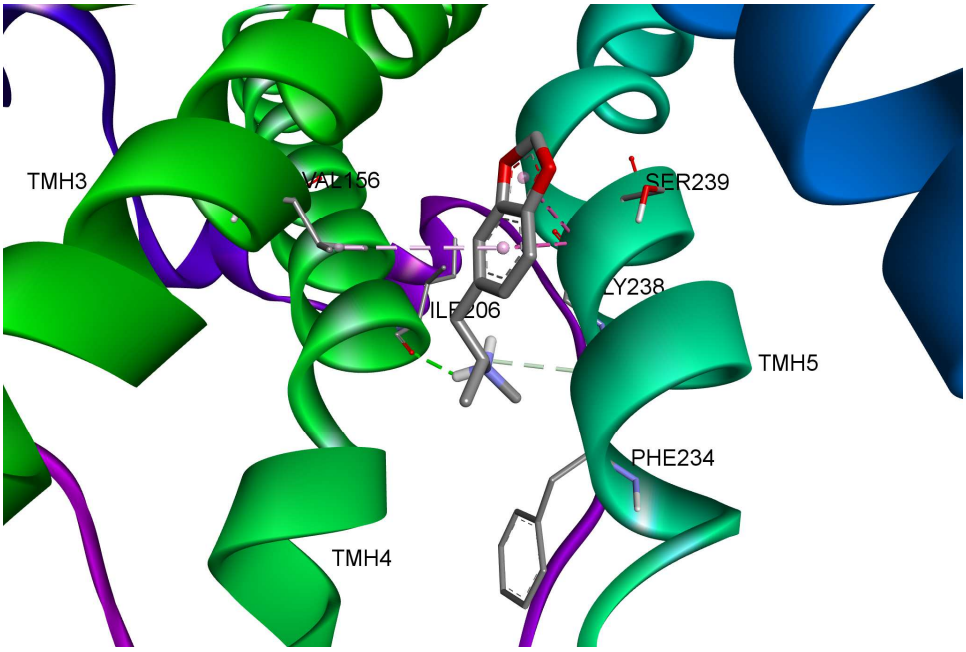

Figure 12. (-)-MDMA docked to the 5-HT_{2A} receptor.

Figure 13 shows the RRA and FRA results of the docking of 25I-NBOMe.

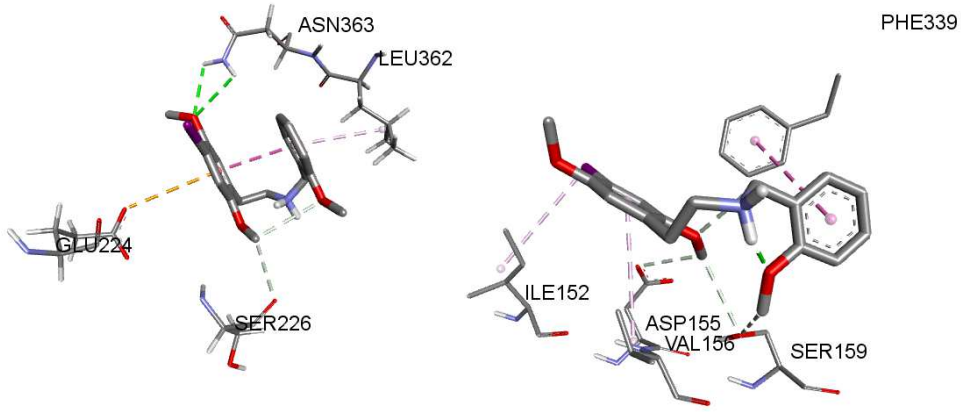

Figure 13. 25I-NBOMe docked to the 5-HT_{2A} binding site. Left: RRA results. Right: FRA results.

We can see that in this case the RRA and the FRA produced very different docked structures. The RRA results show a π-anion interaction of ring A with Glu-224 (4.51Å), two conventional H-bonds of the oxygen atom of the 5-OMe substituent with Asn-363 (2.56Å and 2.83Å), a carbon H-bond between the O atom of the 2-OMe substituent and the backbone of Ser-226, a π-alkyl interaction of ring B with Leu-362 (4.21Å). Also, there is an intramolecular π-π stacking interaction of ring A with ring B (3.83Å), and another intramolecular carbon H-bond between the carbon atom of the 2-OMe substituent in ring A with the O atom of the 2-OMe substituent in ring B (3.42Å). In summary: No weak interactions, four intermediate interactions and two strong ones. The FRA results show a π-alkyl interaction of ring A with Val-156 (4.85Å), two carbon H-bonds between the C atom from the 2-OMe substituent in ring A and Asp-155 (3.46Å) and Ser-159 (3.53Å), an alkyl interaction of iodine with Ile-152 (5.23Å), a π-π stacking interaction of ring B with Phe-339 (4.96Å), a carbon H-bond between the C atom of the 2-OMe substituent in ring B and Ser-159 (3.50Å). There is an intramolecular carbon H-bond between the O atom from the 2-OMe substituent of ring A and the C atom linking the NH_2^+ group with ring B (3.34Å) and other intramolecular H-bond between the H atom from the NH_2^+ group and the O atom from the 2-OMe substituent of ring B (1.94Å). In summary: One weak interaction, six intermediate interactions and one strong one. Fig. 14 shows the FRA result including the microscopic environment.

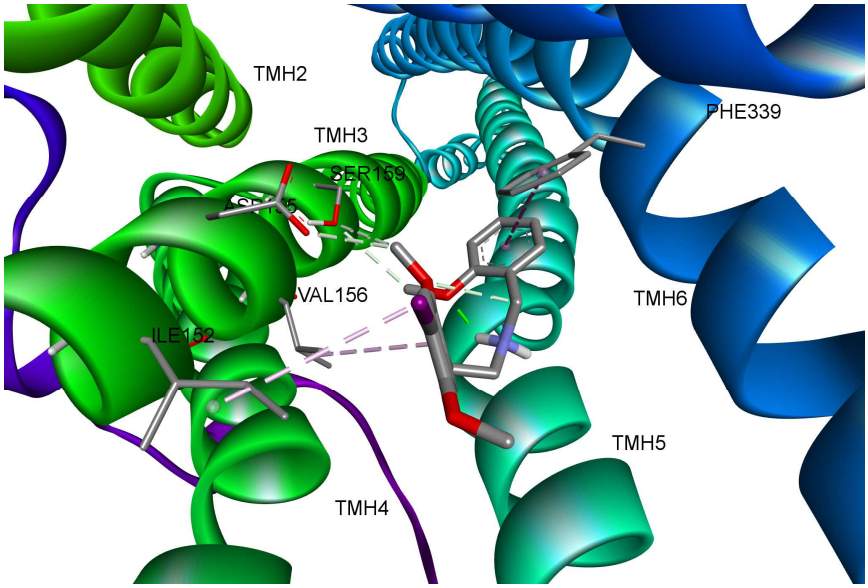

Figure 14. 25I-NBOMe docked to the 5-HT$_{2A}$ receptor.

Figure 15 shows the RRA and FRA results of the docking of 25NITRO-NBOMe.

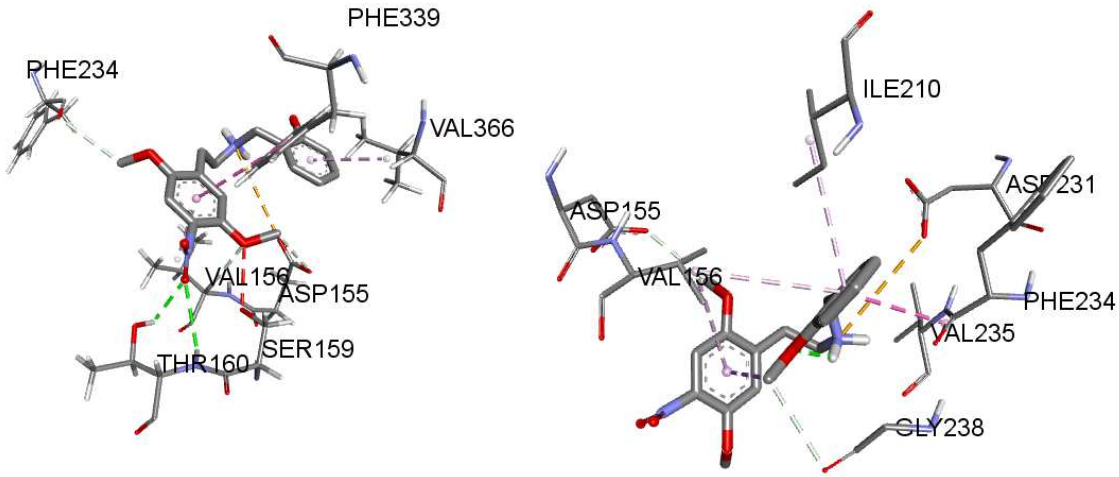

Figure 15. 25NITRO-NBOMe docked to the 5-HT$_{2A}$ binding site. Left: RRA results. Right: FRA results.

We can see that the RRA shows the following interactions with the 5-HT$_{2A}$ receptor: two conventional H-bonds between one oxygen atom from the 4-NO$_2$ substituent with HN and HO groups of Thr-160 (2.36Å and 2.92Å), an unfavorable acceptor-acceptor interaction of the oxygen atom from 5-OMe substituent in ring A with an oxygen atom of Ser-159 (2.72Å), a carbon H-bond between this same oxygen atom with the backbone of Val-156 (2.74Å), two carbon H-bonds between the Me moiety of the 5-OMe substituent and both carboxylate oxygen atoms of Asp-155 (3.50Å and 3.53Å), a π-alkyl interaction of ring A with Val-156 (3.90Å), a π-π T-shaped interaction of ring A with the aromatic ring of Phe-339 (4.97Å), a carbon H-bond between the carbon atom of the 2-OMe substituent and Phe-234 (3.50Å), a π-alkyl interaction of ring B with Val-366 (4.29Å) and an attractive charge interaction of the nitrogen atom from the amine group with a carboxylate oxygen atom of Asp-155 (4.99Å). In summary: No weak interactions, seven intermediate interactions and four strong ones. The FRA shows a carbon H-bond between the C atom of the 2-OMe substituent and Asp-155 (3.04Å), a π-alkyl interaction of ring A with Val-156 (5.11Å), a π-alkyl interaction of ring B with Ile-210 (5.01Å) and Val-156 (4.85Å), an amide-π stacking interaction of ring B with the backbone of Phe-234 (4.05Å), an attractive charge interaction of the N atom from the amine group and Asp-231 (4.93Å). There is an intermolecular H-bond between one H atom from the amine group and the O atom from the 2-OMe substituent of ring B (2.08Å) and another intramolecular π-σ interaction of ring A with the C atom from 2-OMe in ring B (3.65Å). In summary: two weak interactions, five intermediate interactions and one strong one. Fig. 16 shows the FRA result including the microscopic environment.

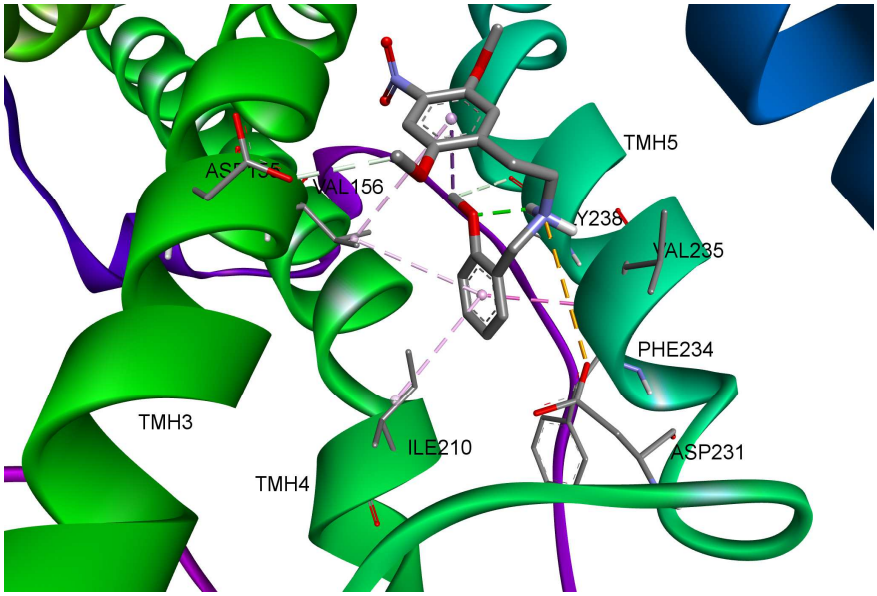

Figure 16. 25NITRO-NBOMe docked to the 5-HT$_{2A}$ receptor.

Figure 17 shows the RRA and FRA results of the docking of DMT.

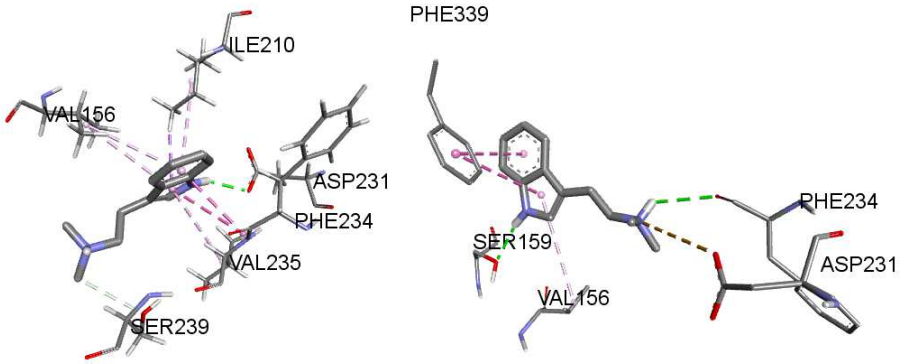

Figure 17. DMT docked to the 5-HT$_{2A}$ binding site. Left: RRA results. Right: FRA results.

The RRA shows a carbon H-bond between Me from $NHMe_2$ and Ser-159 (3.43Å), a conventional H-bond between the H(N) atom of the indole moiety and Asp-231 (2.17Å), a π-alkyl interaction between ring A with Ile-210 (5.00Å) and Val-156 (4.95Å), an amide-π stacking interaction between ring A and the backbone of Phe-234 (3.98Å), an amide-π stacking interaction between ring B and the backbone of Phe-234 (4.12Å), a π-alkyl interaction between ring B and Val-235 (4.95Å) and Val-156 (5.01Å) and a π-σ interaction of ring B with Ile-210 (2.83Å). In summary: two weak interactions, five intermediate interactions and two strong ones. FRA shows a conventional H-bond of the H(N) from the indole moiety with Ser-159 (2.30Å), an attractive charge interaction of the N atom from $NHMe_2$ with Asp-231 (5.46Å), a conventional H-bond between the H(N) from $NHMe_2$ with an oxygen atom of Phe-234 (2.90Å), a π-alkyl interaction of ring B with Val-156 (5.27Å), a π-π T-shaped interaction of ring A with Phe-339 (5.32Å) and a π-π T-shaped interaction of ring B with Phe-339 (4.84Å). In summary: three weak interactions, one intermediate interactions and two strong ones. For DMT, a study suggested that the protonated amine group of the agonist forms a strong salt bridge with Asp-155 [15]. Our FRA results show that the $NHMe_2$ group is engaged in interactions with Asp-231 and Phe-234. Fig. 18 shows the FRA result including the microscopic environment.

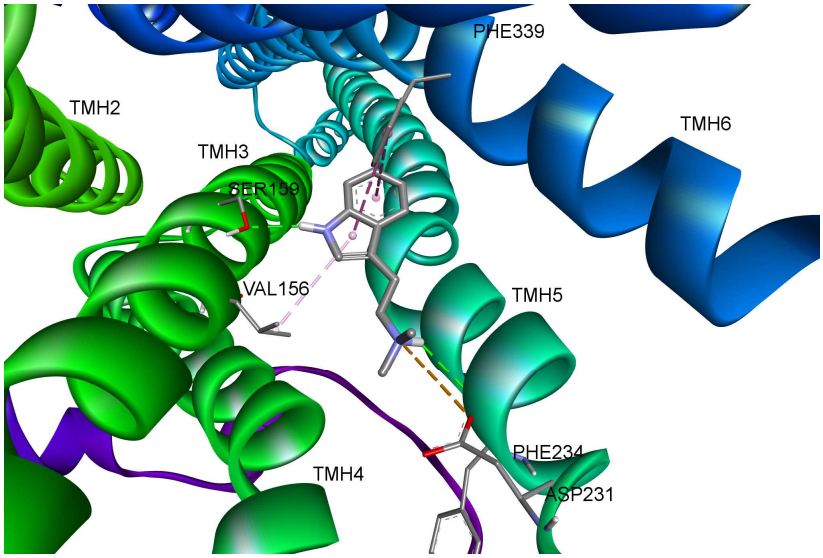

Figure 18. DMT docked to the 5-HT$_{2A}$ receptor.

Figure 19 shows the RRA and FRA results of the docking of psilocybin.

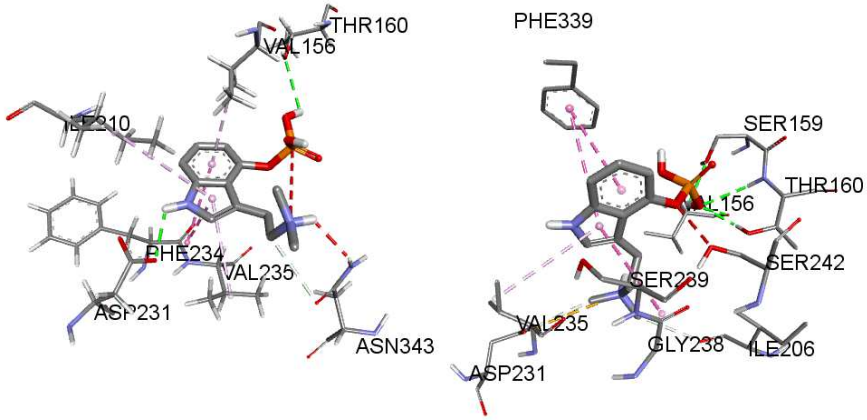

Figure 19. Psilocybin docked to the 5-HT$_{2A}$ binding site. Left: RRA results. Right: FRA results.

RRA results show a π-alkyl interaction of ring A with Val-156 (4.43Å), an amide-π interaction of ring A with the backbone of Phe-234 (4.37Å), π-alkyl interactions of ring B with Ile-210 (5.44Å) and Val-235 (4.63Å), an amide-π interaction of ring B with the backbone of Phe-234 (3.87Å), a conventional H-bond between H(N) from the indole ring and Asp-231 (2.36Å), a conventional H-bond between H from the H_2PO_3 substituent and Thr-160 (2.90Å), an unfavorable donor-donor interaction of H from $NHMe_2$ moiety and Asn-343 (2.31Å), and a carbon H bond between a C atom of the alkyl chain of ring B and the backbone of Asn-343 (3.44Å). In summary: one weak interaction, five intermediate interactions and three strong ones. FRA results show a π-π stacking interaction between ring A and Phe-339 (4.68Å), a π-π stacking interaction of ring B with Phe-339 (5.45Å), an amide-π stacking interaction of ring B with the backbone of Gly-238 (4.85Å), a π-alkyl interaction of ring B with Val-235 (5.50Å), a carbon H-bond between Me from the $NHMe_2$ group and the backbone of Ile-206 (3.57Å), an attractive charge interaction of the Me moiety of $NHMe_2$ with Asp-231 (5.11Å), a carbon H-bond between the Me moiety of $NHMe_2$ and Asp-231 (3.63Å), conventional H-bonds of an hydrogen atom of the H_2PO_3 substituent with Ser-159 (2.46Å) and with the backbone of Val-156 (2.69Å) and conventional H-bonds of an oxygen atom of the H_2PO_3 substituent with Thr-160 (2.24Å) and with the backbone of Ser-159 (2.98Å). In summary: three weak interactions, four intermediate interactions and four strong ones. Fig. 20 shows the FRA result including the microscopic environment.

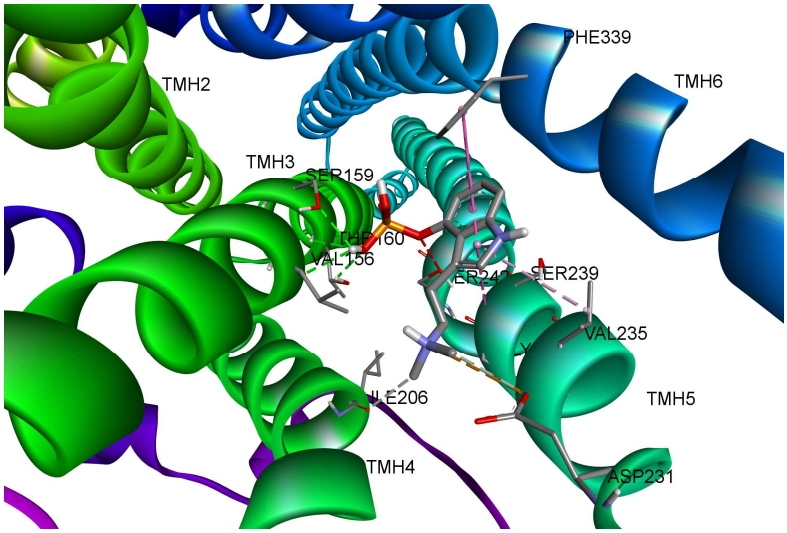

Figure 20. Psilocybin docked to the 5-HT$_{2A}$ receptor.

The difference between our results and the ones discussed above can be explained by the use of different software and 5-HT$_{2A}$ receptor models. Table 1 shows the 5-HT$_{2A}$ residues involved in interactions with the different ligands.

Table 1. Amino acids of the 5-HT$_{2A}$ binding site participating in interactions with the ligands.

Mol.	Flexible residues results
Mescaline	Phe-339 (TMH6, 5.05Å), Val-156 (TMH3, 4.83Å), Ser-239 (TMH5, 3.55Å), Asp-155 (TMH3, 3.34Å), Ser-159 (TMH3, 3.50Å), Asp-231 (EL2, 2.41Å).
LSD	Val-156 (TMH3, 3.94Å, 3.97Å, 3.70Å, 4.46Å, 5.41Å), Gly-238 (TMH5, 2.63Å), Asp-155 (TMH3, 5.23Å), Glu-224 (EL2, 5.36Å).
(-)-DOB	Asp-155 (TMH3, 3.56Å), Ser-159 (TMH3, 2.14Å), Val-156 (TMH3, 2.79Å, 3.72Å), Ile-210 (TMH4, 5.20Å), Val-235 (TMH5, 4.92Å), Ile-206 (TMH4, 3.79Å).
(-)-DON	Asp-155 (TMH3, 3.61Å, 3.58Å), Val-156 (TMH3, 3.90Å, 3.84Å), Thr-160 (TMH3, 2.85Å), Asp-231 (EL2, 5.53Å).
DMT	Ser-159 (TMH3, 2.30Å), Asp-231 (EL2, 5.46Å), Phe-234 (TMH5, 2.90Å), Val-156 (TMH3, 5.27Å), Phe-339 (TMH6, 5.32Å, 4.84Å).
Psilocybin	Phe-339 (TMH6, 4.68Å, 5.45Å), Gly-238 (TMH5, 4.85Å), Val-235 (TMH5, 5.50Å), Ile-206 (TMH4, 3.57Å), Asp-231 (EL2, 5.11Å, 3.63Å), Ser-159 (TMH3, 2.46Å, 2.98Å), Val-156 (TMH3, 2.69Å), Thr-160 (TMH3, 2.24Å).
(-)-MDMA	Gly-238 (TMH5, 3.83Å, 3.97Å), Val-156 (TMH3, 4.87Å), Ile-206 (TMH4, 2.09Å), Phe-234 (TMH5, 3.28Å).
25I-NBOMe	Val-156 (TMH3, 4.85Å), Asp-155 (TMH3, 3.46Å), Ser-159 (TMH3, 3.53Å, 3.50Å), Ile-152 (TMH3, 5.23Å), Phe-339 (TMH6, 4.96Å).
25NITRO-NBOMe	Asp-155 (TMH3, 3.04Å), Val-156 (TMH3, 5.11Å, 4.85Å), Ile-210 (TMH4, 5.01Å), Phe-234 (TMH5, 4.05Å), Asp-231 (EL2, 4.93Å).

We can see that only the interaction with Val-156 is common to all the set of ligands. With the exception of psilocybin and (-)-DOB, Val-156 seems to participate only in intermediate and weak interactions. Another common feature is the interaction of all the molecules analyzed with residues belonging to TMH3. Mescaline, LSD, (-)-DON, DMT, psilocybin and 25NITRO-NBOMe interact also with the extracellular loop 2 (EL2, Fig. 2). 25I-NBOMe seems to interact with only two TMHs. The remaining interactions do not seem to follow a common pattern. In summary, we have studied the docking of several molecules endowed with (different) psychoactive activities to the 5-HT$_{2A}$ receptor, finding several common elements. The most reasonable approximation for these kinds of studies is by giving full conformational flexibility to the residues composing the binding site.

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