Study molecular of interaction between N, N-dimethyltryptamine analogs (DMT) with 5-HT_{1A} and 5-HT_{1B} receptors, associated in neuronal alterations

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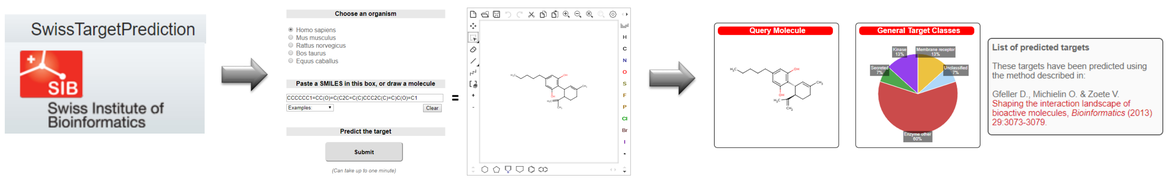
1. Introduction

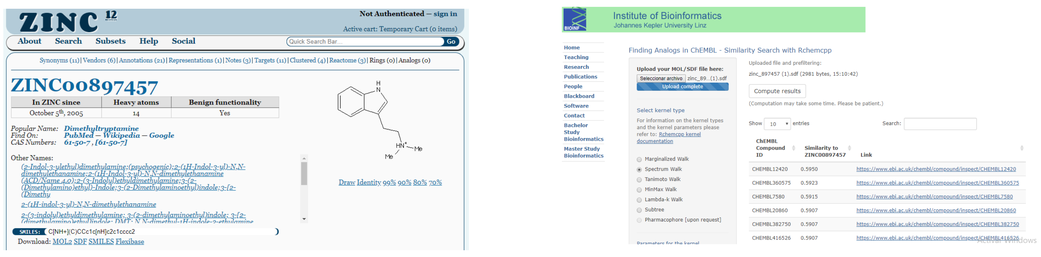
Ayahuasca is considered a mixture of plants used in traditional medicine, consisting of the ayahuasca vine (*Banisteriopsis caapi*) and the chacruna shrub (*Psychotria viridis*). Active metabolites, such as harmine and N, N-dimethyltriptamine (DMT) with MAOI properties and activity on serotonergic (5-HT) receptors, respectively, have been isolated from these plants. In addition, responsible for hallucinogenic effects in the body [1]. However, the molecular mechanisms of biological activity on these receptors have not been fully elucidated. Therefore, the *in silico* activity of DMT analogs has been evaluated by docking molecular studies of the ligand-receptor interaction type in order to identify promising molecules for the treatment of neuronal disorders such as post-traumatic stress disorders and anxiety [2].

2. Methods

1. Selection of receptors by bioinformatic analysis with SwissTargetPrediction



2. Search and selection of DMT analogs



3. Search for 5-HT_{1B} receptor in PDB Construction by homology of the 5-HT_{1A} receptor

Fasta sequence obtained by UniProtKB

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>sp|P34972|CNR2_HUMAN Cannabinoid receptor 2 OS=Homo sapiens
OX=9606 GN=CNR2 PE=1 SV=1
>sp|P34972|CNR2_HUMAN Cannabinoid receptor 2 OS=Homo sapiens
MEECWVTEIANGSKDGLDSNPMKDYMILSGPQKTAVAVLCTLLGLLSALENVAVLYLILS
SHQLRRKPSYLFIGSLAGADFLASVVFACSFVNFHVFHGVDSKAVFLLKIGSVTMTFTAS
VGSLLLTAIDRYLCLRYPPSYKALLTRGRALVTLGIMWVLSALVSYLPLMGWTCCPRPCS
ELFPLIPNDYLLSWLLFIAFLFSGIIYTYGHVLWKAHQHVASLSGHQDRQVPGMARMRLD
VRLAKTLGLVLAVLLICWFPVLALMAHSLATTLSDQVKKAFAFCSMLCLINSMVNPVIYA
LRSGEIRSSAHHCLAHWKKCVRGLGSEAKEEAPRSSVTETEADGKITPWPDSRDLDLSDC
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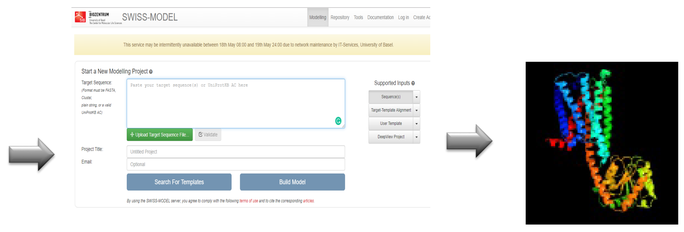
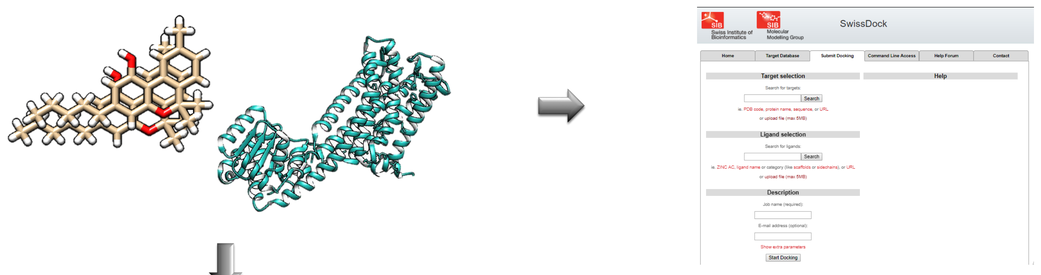


Server for the development of modeling

4. Docking Molecular of DMT analogues with 5-HT_{1A} y 5-H5HT_{1B} receptor [3]



Preparation at Discovery Studios

- Neutralize charged groups,
- Generate ionization states
- Generate tautomers
- Identify alternative chiralities,
- Optimize geometries
- Conversion of the output file

Addition of hydrogens to the protein

Use of CHARMM force fields

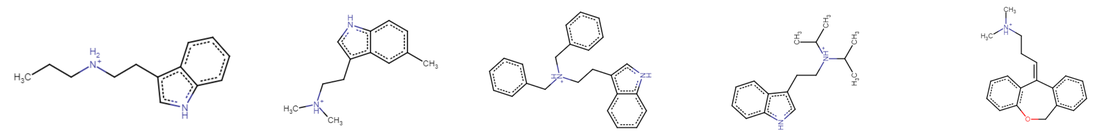
Favorable bind mode with FACTS, minimum energy set in cluster

3. Results

1. Serotoninergic receptors found with high affinity

Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability*	Known actives (3D/2D)
Serotonin 2b (5-HT2b) receptor	HTR2B	P41595	CHEMBL1833	Family A G protein-coupled receptor		68 / 29
Serotonin 1a (5-HT1a) receptor	HTR1A	P08908	CHEMBL214	Family A G protein-coupled receptor		59 / 54
Serotonin 2a (5-HT2a) receptor	HTR2A	P28223	CHEMBL224	Family A G protein-coupled receptor		218 / 89
Serotonin 2c (5-HT2c) receptor	HTR2C	P28335	CHEMBL225	Family A G protein-coupled receptor		160 / 60
Serotonin transporter	SLC6A4	P31645	CHEMBL228	Electrochemical transporter		477 / 47
Dopamine transporter *(by homology)*	SLC6A3	Q01959	CHEMBL238	Electrochemical transporter		337 / 29
Serotonin 6 (5-HT6) receptor	HTR6	P50406	CHEMBL3371	Family A G protein-coupled receptor		68 / 51
Serotonin 1b (5-HT1b) receptor	HTR1B	P28222	CHEMBL1898	Family A G protein-coupled receptor		59 / 69
Serotonin 1d (5-HT1d) receptor	HTR1D	P28221	CHEMBL1983	Family A G protein-coupled receptor		47 / 66
Alpha-1a adrenergic receptor	ADRA1A	P35348	CHEMBL229	Family A G protein-coupled receptor		21 / 17

2. Were selected 24 analogues of DMT and 1 Drug (Referent)

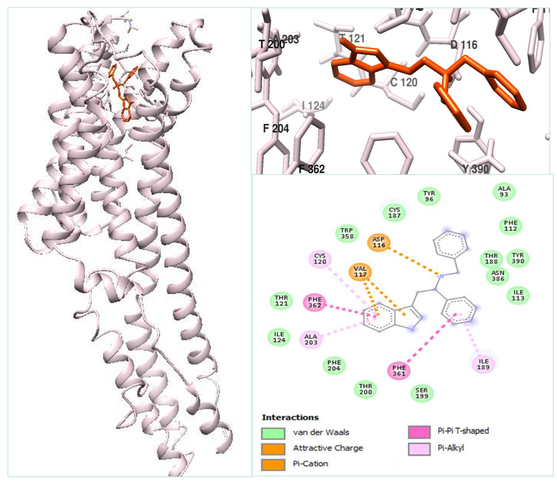


Zinc01999154 | Zinc057395 | Zinco1279899 | Zinco1996369 | Doxepine

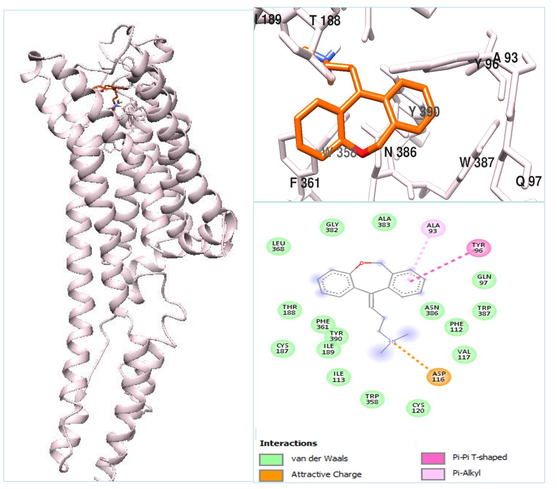
3. Docking Molecular with 5-HT_{1BA} y 5-HT_{1B} receptors

LIGANDO (5-HT_{1A})	E. ENLACE	LIGANDO (5-HT_{1B})	E. ENLACE
zinc_1279899_5-HT_{1A}	-8,7	zinc_71772919_5-HT_{1B}	-8,8
zinc_220398_5-HT_{1A}	-8,6	zinc_1279899_5-HT_{1B}	-8,7
zinc_71772919_5-HT_{1A}	-8,3	zinc_57395_5-HT_{1B}	-8,6
zinc_1999154_5-HT_{1A}	-8,2	zinc_1604295_5-HT_{1B}	-8,6
Doxepina_5-HT_{1A}	-8,8	Doxepina_5-HT_{1B}	-8,7

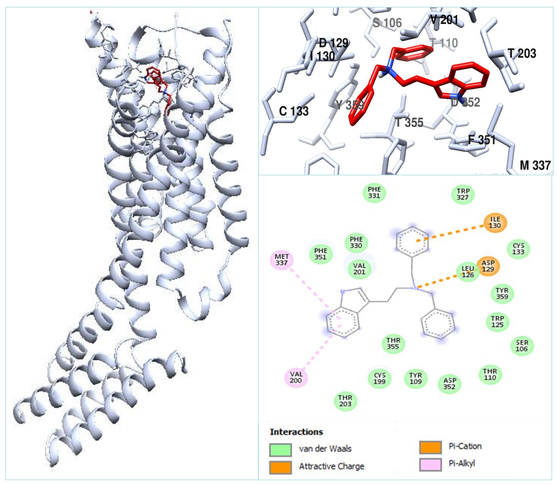
Binding Energy: Kcal/mol



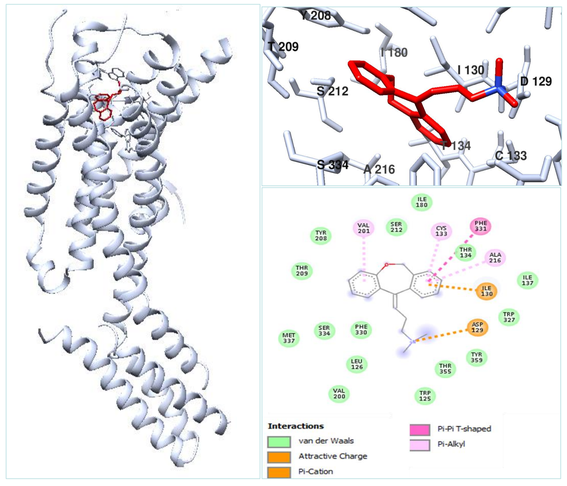
zinc_1279899_5-HT_{1A}



Doxepine_5-HT_{1A}



zinc_1279899_5-HT_{1B}



Doxepine_5-HT_{1B}

4. Conclusion

New analogs of DMT with activity in the serotoninergic receptors with high structural and energetic affinity were identified. Finally, the complexes of receptors and ligands were refined by means of molecular modeling showing that the considered interactions propose new tools of agents for the treatment of alterations related to pathologies of neuronal order such as post-traumatic stress disorders and anxiety.

5. References

[1] Riba J, Romero S, Grasa E, Mena E, Carrió I, Barbanoj MJ (2006) Increased frontal and paralimbic activation following ayahuasca, the pan-amazonian inebriant. Psychopharmacology (Berl) 186:93–98

[2] Wang Y qiang, Lin W wei, Wu N, Wang S yi, Chen M zi, Lin Z hua, Xie XQ, Feng Z wei (2019) Structural insight into the serotonin (5-HT) receptor family by molecular docking, molecular dynamics simulation and systems pharmacology analysis. Acta Pharmacol Sin 1–19.

[3] Grosdidier A, Zoete V, Michielin O (2011) SwissDock, a protein-small molecule docking web service based on EADock DSS. Nucleic Acids Res 39:270–277