Designing a Novel 5-HT2A Receptor Agonist: Toward Better Antidepressants

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The following report aims to showcase the work done and the results of this drug design and is not a scientific publication.

The motivation behind my drug design project performed during the CAPU CHEM 411 course emerged from an interest in developing more effective treatments for depression. Current antidepressants, while life-changing for many, often suffer from delayed onset, adverse side effects, and inconsistent efficacy (Pigott et al., 2010). My research focused on the 5-HT2A serotonin receptor, a key player in mood regulation and a promising target for novel antidepressant therapies.

Project Overview

The primary objective of this project was to design a novel agonist for the 5-HT2A receptor with enhanced binding affinity, reduced toxicity, and favorable pharmacokinetic properties. The design process involved analyzing known synthetic and organic receptor agonists and iterating on their structural frameworks to optimize performance. Each iteration aimed to improve three core properties: binding affinity, hydrophobicity, and toxicity.

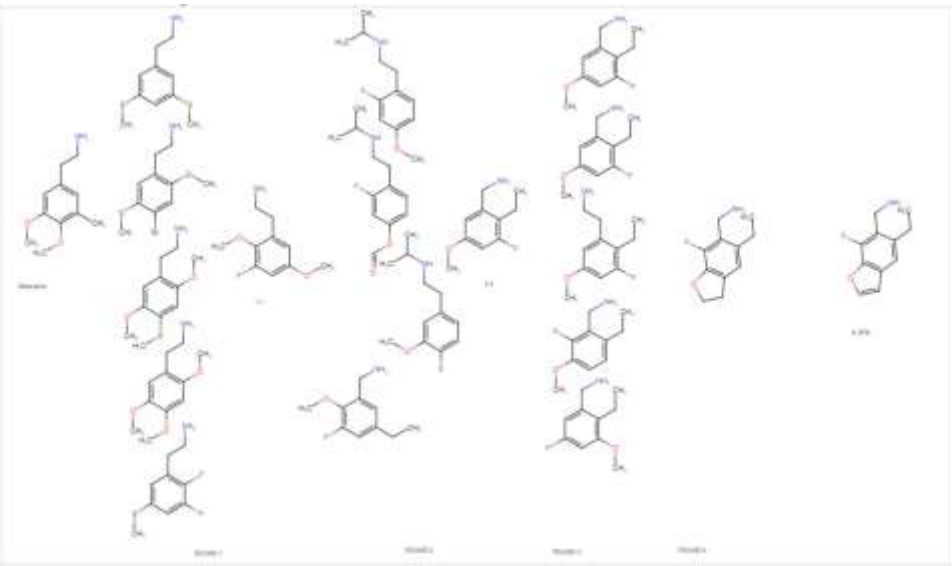

Figure 1 - Iterative process of 5-AFB design*. Starting with Mescaline, iterations were tweaked by adding rings, halogens, and different substituents to the original pharmacophore to enhance binding affinity, toxicity, and hydrophobicity.*

Working under the supervision of Dr. Vaughan from the Chemistry Department, I systematically explored molecular modifications. I selected a range of structurally diverse 5-HT2A agonists as templates and employed computational modeling to predict how changes to the molecular structure would influence receptor binding and overall drug properties. This iterative process eventually led to the synthesis of a novel compound named "5-AFB," a multicyclic substituted benzofuran.

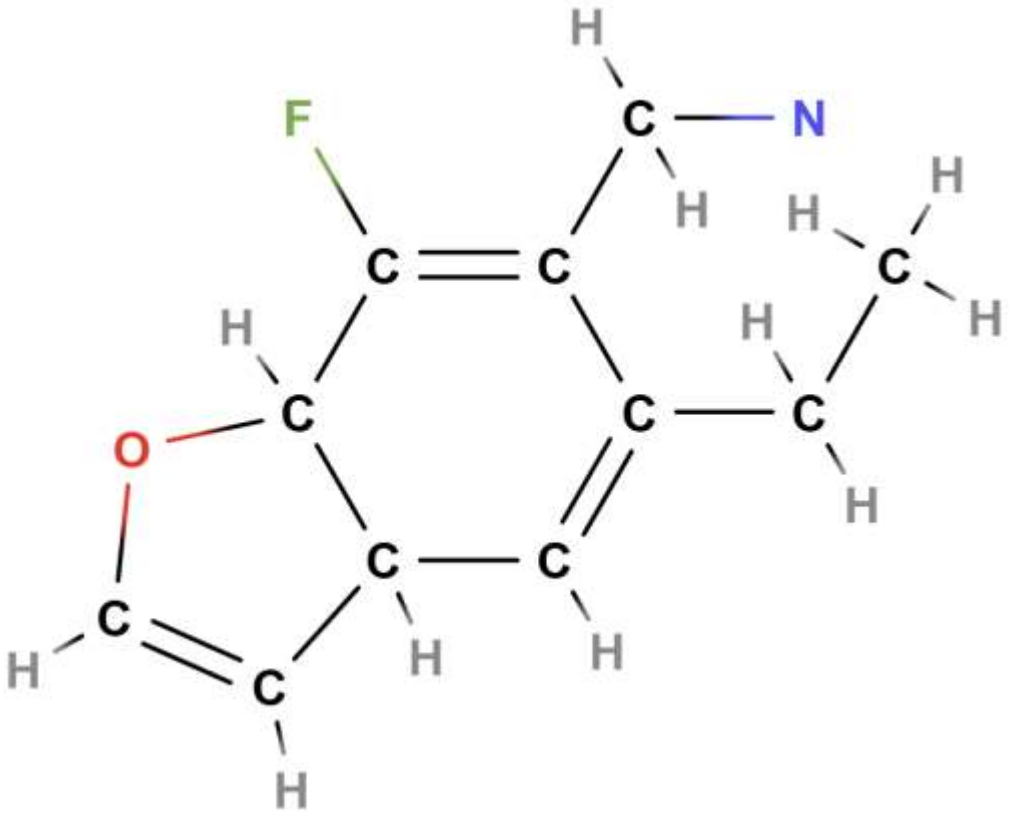

Figure 2 - 5-AFB, *1-(5-ethyl-7-fluoro-1-benzofuran-6-yl)methanamine. The result of the drug design experiment.*

The Design Process

The project unfolded across several phases:

1. Initial Molecular Selection: I began by identifying and studying the chemical structures of existing 5-HT2A receptor agonists. This literature review included analyzing both synthetic and naturally occurring compounds known for their affinity to the receptor. The chosen starting point was then determined to be

Mescaline. Mescaline is a naturally occurring 5-HT2A agonist compound found in certain cacti, such as Peyote (Dinis-Oliveira et al., 2018).

Figure 3 - The Peyote cactus *(Lophophora williamsii), native to Mexico, is rich in Mescaline.*

2. Structural iterations and Modeling: I modeled the interaction between candidate molecules and the 5-HT2A receptor by performing molecular docking simulations using Avogadro. Modifications to the molecular core included changes to functional groups and ring structures, focusing on improving receptor-ligand binding interactions. Each iteration underwent evaluation for key parameters using online machine-learning tools:
    - Binding Affinity: How effectively the molecule binds to the receptor.
    - Hydrophobicity: Influencing the compound's ability to cross biological membranes.

- Toxicity: Ensuring the structural changes did not introduce harmful properties.

ROUND 1

R1	R2	R3	R4	R5	compound	score (kcal/mol)(negati	SMILE	#	LD50 (mg/kg)
					Serotonin (Native Ligand)	6.3			2300
C-C-NH3	0	MeO	MeO	MeO	Mescaline	5.9			800
C-C-NH3	0	⁻S-C	0	⁻S-C	R3 R5 S	5.1		0.1	
C-C-NH3	⁻S-C	0	⁻Br	⁻S-C	2CB but S instead of O	5.2		0.2	
C-C-NH3	MeO	0	⁻S-C	MeO	R2R5MeOR4S	5.5		0.3	
C-C-NH3	MeO	0	MeO	MeO	R4R5MeOR2S	5.5		0.4	
C-C-NH3	⁻S-C	F	0	⁻S-C	R2R5SR3F	5.6		0.5	
C-C-NH3	MeO	F	0	MeO	R2R5MeOR3F *** md 1 wi	5.8	COc1cc(F)c(OC)c(CCN)c1	1.1	
					LSD	8.1	CCN(CC)C(=O)[C@H]1CN([C@@H]2Cc3c[nH]c4c3c(ccc4)C2=C1)C	227	

Round1 Notes: no Br,

ROUND 2

R1	R2	R3	R4	R5	compound	score (kcal/mol)(negati	SMILE	#	
					Serotonin (Native Ligand)	6.3			
C-C-NH3	MeO	F	0	MeO	R2R5MeOR3F *** md 1 wi	5.8	COc1cc(F)c(OC)c(CCN)c1	1.1	
CCNC[C]2	F	0	MeO	0		6	CC[C]NCCc1ccc(OC)cc1F	2.1	
CCNC[C]2	F	0	MeO = 0			6.6	CC[C]NCCc1ccc(OC(=O)[cc1F	2.2	
CCNC[C]2	0	MeO	F	0		6.7	CC[C]NCCc1ccc(F)c(OC)c1	2.3	
C-C-NH3	methyl	F	0	MeO = O		6.7	CCC1=C(F)C=C(OC)C=C1CN	2.4	
C-C-NH3	MeO	F	0	methyl		6.5	CCC1=CC(F)=C(OC)C(CN)=C1	2.5	

ROUND 3

R1	R2	R3	R4	R5	compound	score (kcal/mol)(negati	SMILE	#	
					Serotonin (Native Ligand)	6.3			
C-C-NH3	methyl	F	0	MeO = O		6.7	CCC1=C(F)C=C(OC)C=C1CN	2.4	
						6.7	CCC1=C(F)C=C(OC)C=C1CN	3.1	
						6.9	CCC1=C(F)C=C(OC)C=C1CCN	3.2	135
						6.9	CCC1=CC=C(OC)C(F)=C1CN	3.3	450
						6.5	CCC1=C(OC)C=C(F)C=C1CN	3.4	

ROUND 4

R1	R2	R3	R4	R5	compound	score (kcal/mol)(negati	SMILE	#	
					Serotonin (Native Ligand)	6.3			
						7.2	CCC1=CC2=C(OCC2)C(F)=C1CN	4.1	510

ROUND 5

R1	R2	R3	R4	R5	compound	score (kcal/mol)(negati	SMILE	#
					Serotonin (Native Ligand)	6.3		

Figure 4 - Sample data of the iterative process. *More than 7 rounds of iteration were performed, each round making corrections and changes to the previous iterations to improve the desired metrics.*

3. Evaluation of 5-AFB: The final molecule, 5-AFB, exhibited improved binding affinity and hydrophobicity without significant increases in predicted toxicity. This outcome suggests it holds potential as a candidate for further preclinical testing.

Personal Connection and Broader Implications

My interest in this project extends beyond my academic curiosity. Depression is a pervasive condition affecting millions worldwide, and I have personally witnessed its

profound impact on friends and family members. This personal connection drives my commitment to exploring better pharmacological solutions that offer faster, more reliable relief.

In choosing Mescaline as the starting point for my research project, I've selected a compound inseparable from the Peyote cactus, a plant that the indigenous tribes of the Rio Grande Valley region of Mexico have held sacred for centuries (Shonle, Ruth. 1925). This decision hopefully pays a deep respect to the traditions of these indigenous cultures, whose pre-colonization practices wove Peyote into their spiritual and communal lives. Honoring the profound wisdom these communities cultivated long before modern science turned its gaze their way, hopefully recognizes their enduring legacy.

Moreover, this project aligns with my broader organic and medicinal chemistry research focus. Designing molecules that interact with complex biological targets involves both creativity and scientific rigor, and this work represents a simulated yet meaningful step toward my goal of contributing to therapeutic innovation.

Reflection and Future Directions

This project underscored the complexity and promise of rational drug design. While 5-AFB represents a successful proof of concept, future work may focus on in vitro testing to validate its pharmacological properties. Further structural refinements and in-depth toxicity studies will also be essential to determine its viability as a clinical candidate.

In retrospect, the iterative design process mirrored the trial-and-error nature of scientific inquiry. Each failure and adjustment deepened my understanding of both the receptor's nuances and the subtleties of molecular interactions. This project not only sharpened my technical skills but also reinforced the importance of persistence and creativity in the pursuit of meaningful scientific advancements.

Works Cited

Dinis-Oliveira, R. J., Pereira, C. L., & Da Silva, D. D. (2018). Pharmacokinetic and pharmacodynamic aspects of peyote and mescaline: clinical and forensic repercussions. *Current Molecular Pharmacology*, *12*(3), 184–194. https://doi.org/10.2174/1874467211666181010154139

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ProTox-3.0 - Prediction of TOXicity of chemicals. (n.d.). https://tox.charite.de/

Shonle, Ruth. “Peyote, the Giver of Visions.” *American Anthropologist*, vol. 27, no. 1, 1925, pp. 53–75. *JSTOR*, http://www.jstor.org/stable/661497. Accessed 5 Mar. 2025.

Appendix 1 – Molecular Properties

Property	Value
Molecular Formula	C11H12FNO
Empirical Formula	C11H12FNO
Molecular Mass	193.21698 amu
Monoisotopic Mass	193.0903 amu
Degree of Unsaturation	6
Hydrogen Bond Acceptors	3
Hydrogen Bond Donors	1
Rotatable Bonds	2
Total Electrons	102
Molecular Polarizability	21.098347 A^3
Molar Refractivity	53.660984 cm^3/mol
Polar Surface Area	39.16 A^2
vdW Volume	147.65268 A^3
logP	2.0140002
Complexity	277.8147

miLogP	2.36
TPSA	39.16
natoms	14
MW	193.22
nON	2
nOHNH	2
nviolations	0
nrotb	2
volume	175.99

Appendix 2 – Predicted Toxicity Reports

Appendix 2.1 – General Toxicity Reports

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Inactive	0.71
Organ toxicity	Neurotoxicity	neuro	Active	0.62
Organ toxicity	Nephrotoxicity	nephro	Inactive	0.77
Organ toxicity	Respiratory toxicity	respi	Active	0.66
Organ toxicity	Cardiotoxicity	cardio	Inactive	0.67
Toxicity end points	Carcinogenicity	carcino	Active	0.57
Toxicity end points	Immunotoxicity	immuno	Inactive	0.88
Toxicity end points	Mutagenicity	mutagen	Inactive	0.62
Toxicity end points	Cytotoxicity	cyto	Inactive	0.62
Toxicity end points	BBB-barrier	bbb	Active	0.92
Toxicity end points	Ecotoxicity	eco	Active	0.65
Toxicity end points	Clinical toxicity	clinical	Inactive	0.63
Toxicity end points	Nutritional toxicity	nutri	Active	0.52
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.71
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.94
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.96
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_aromatase	Inactive	0.79
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Inactive	0.78
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Inactive	0.93
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.96
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/ antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.90
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.90
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.74
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.82
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.94
Molecular Initiating Events	Thyroid hormone receptor alpha (THRα)	mie_thr_alpha	Inactive	0.84

Classification	Target	Shorthand	Prediction	Probability
Events	isoxazolepropionate receptor (AMPAR)			
Molecular Initiating Events	Kainate receptor (KAR)	mie_kar	Inactive	0.99
Molecular Initiating Events	Achetylcholinesterase (AChE)	mie_ache	Inactive	0.67
Molecular Initiating Events	Constitutive androstane receptor (CAR)	mie_car	Inactive	0.99
Molecular Initiating Events	Pregnane X receptor (PXR)	mie_pxr	Inactive	0.70
Molecular Initiating Events	NADH-quinone oxidoreductase (NADHOX)	mie_nadhox	Inactive	0.81
Molecular Initiating Events	Voltage gated sodium channel (VGSC)	mie_vgsc	Inactive	0.79
Molecular Initiating Events	Na+/I- symporter (NIS)	mie_nis	Inactive	0.81
Metabolism	Cytochrome CYP1A2	CYP1A2	Active	0.56
Metabolism	Cytochrome CYP2C19	CYP2C19	Inactive	0.53
Metabolism	Cytochrome CYP2C9	CYP2C9	Active	0.60
Metabolism	Cytochrome CYP2D6	CYP2D6	Active	0.65
Metabolism	Cytochrome CYP3A4	CYP3A4	Inactive	0.66
Metabolism	Cytochrome CYP2E1	CYP2E1	Inactive	0.82
Molecular Initiating Events	Thyroid hormone receptor alpha (THRα)	mie_thr_alpha	Inactive	0.84
Molecular Initiating Events	Thyroid hormone receptor beta (THRβ)	mie_thr_beta	Inactive	0.71
Molecular Initiating Events	Transtyretrin (TTR)	mie_ttr	Inactive	0.57
Molecular Initiating Events	Ryanodine receptor (RYR)	mie_ryr	Inactive	0.92
Molecular Initiating Events	GABA receptor (GABAR)	mie_gabar	Inactive	0.67
Molecular Initiating Events	Glutamate N-methyl-D-aspartate receptor (NMDAR)	mie_nmdar	Inactive	0.90
Molecular Initiating	alpha-amino-3-hydroxy-5-methyl-4-	mie_ampar	Inactive	1.0

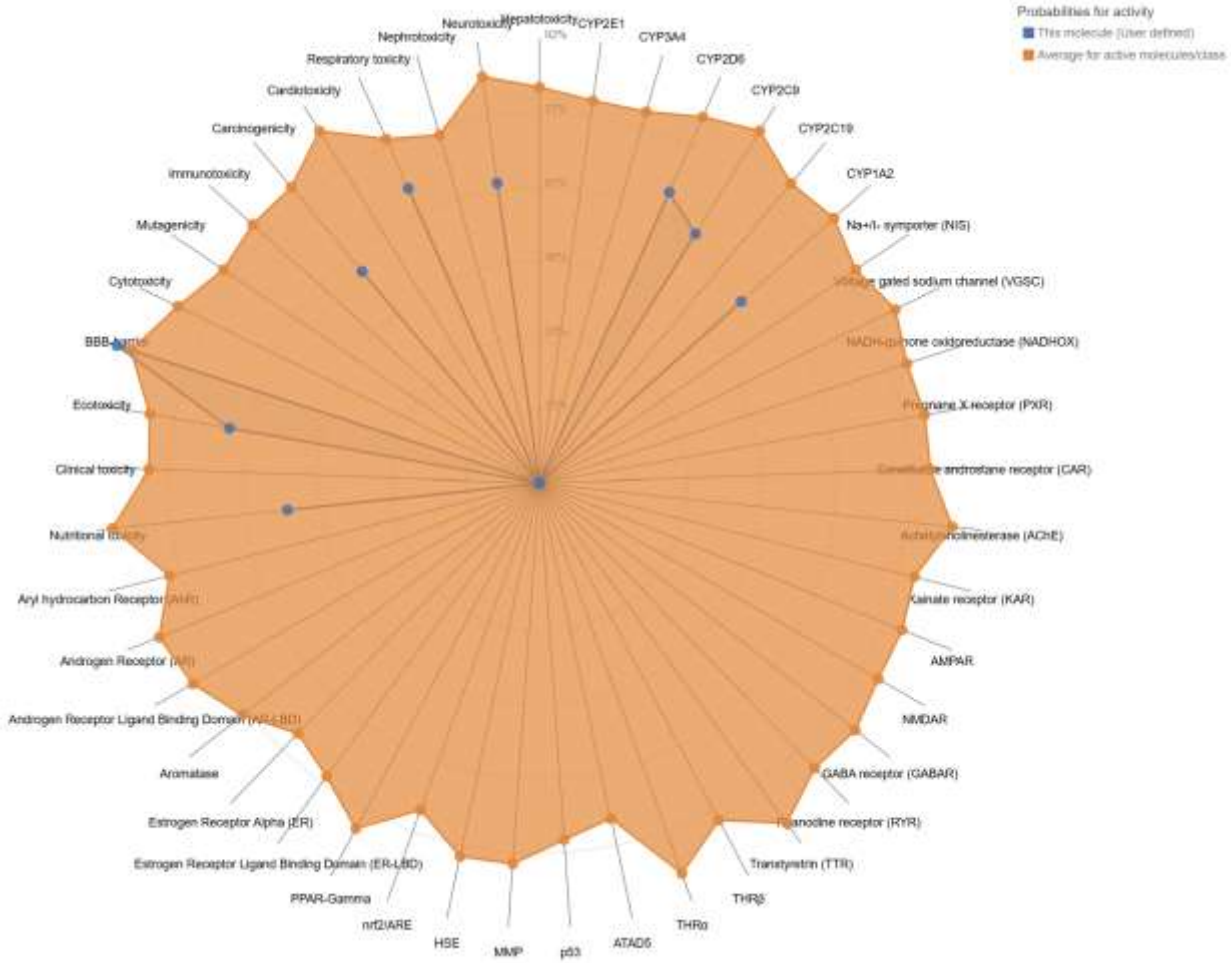
Predicted LD50: 700mg/kg

Predicted Toxicity Class: 4

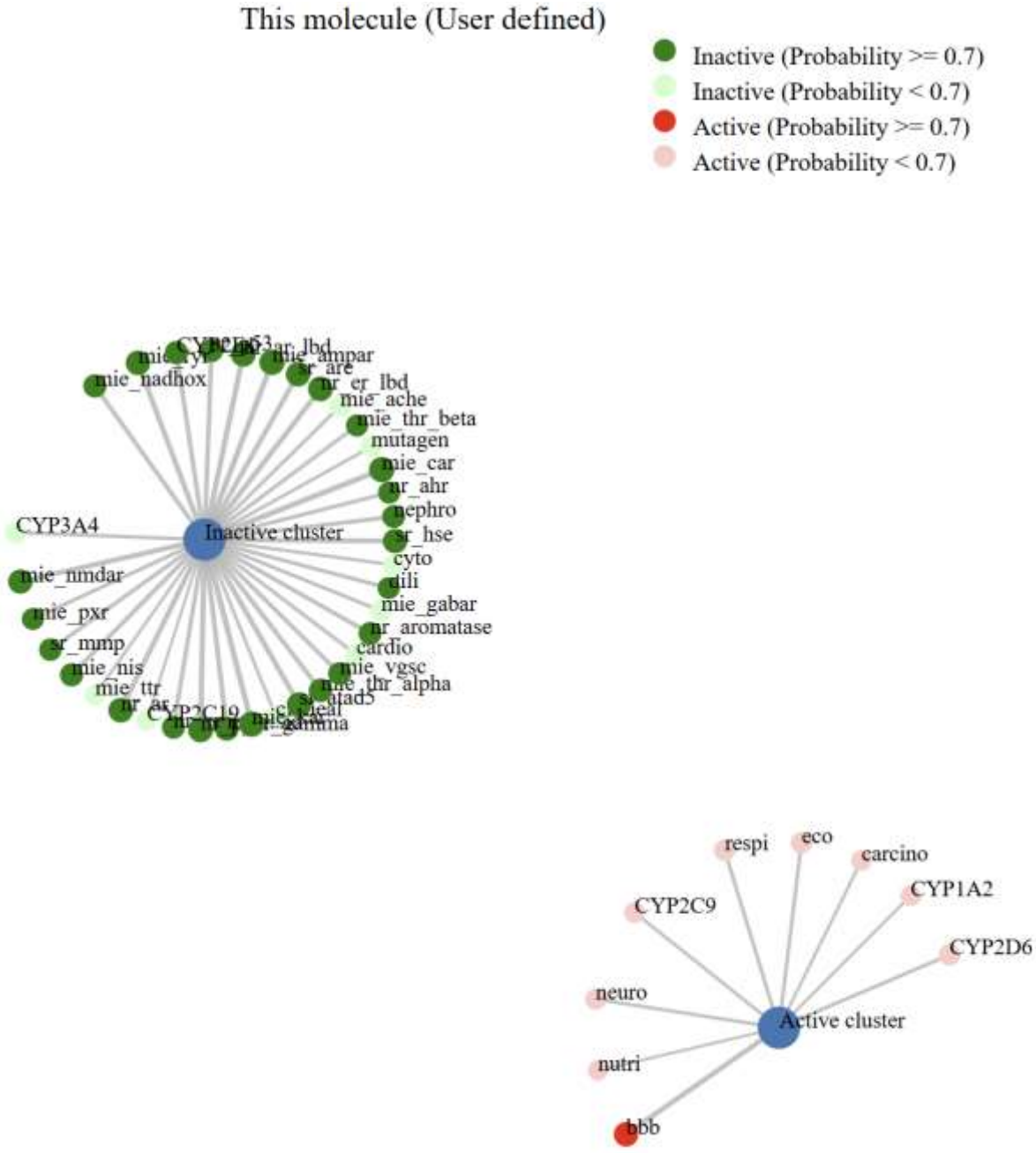
Average similarity: 46.01%

Prediction accuracy: 54.26%

Appendix 2.2 - The confidence of positive toxicity results compared to the average of its class



Appendix 2.3 – connection between 5-AFB and predicted activities



Appendix 2.4 – Distributions of molweight and Dose Value