Supplementary Information

DFT, Docking, and Molecular Dynamics Investigation of Amazonian Alkaloids on the Dopamine D(2) Receptor Protein

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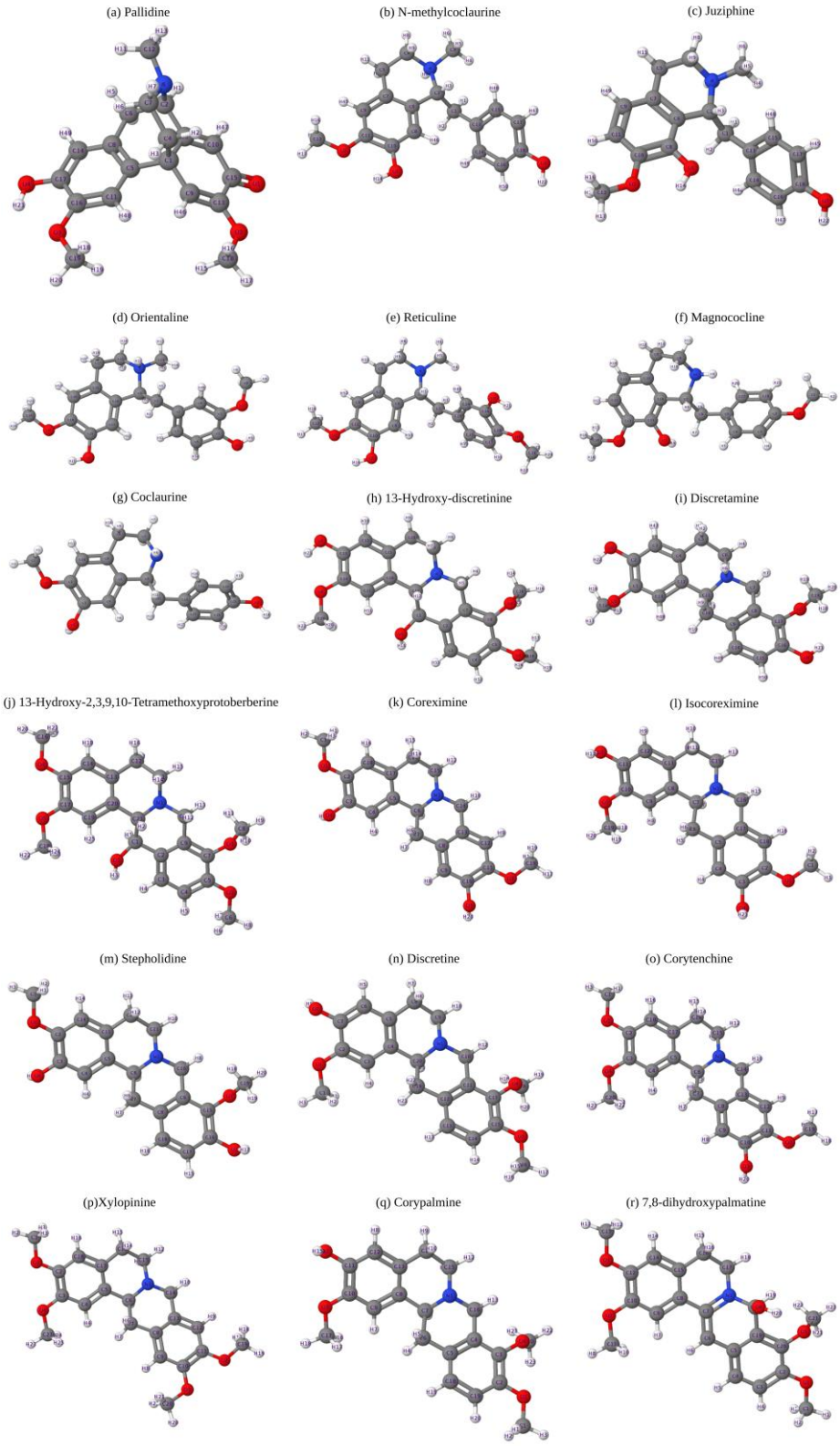


Figure 1. Structures of the investigated alkaloids with their respective atomic identification, isolated from plants of the Annonaceae family. (a) Morphinanedienone subclass, (b-g) benzyltetrahydroisoquinoline subclass, (h-r) tetrahydroprotoberbrine subclass.

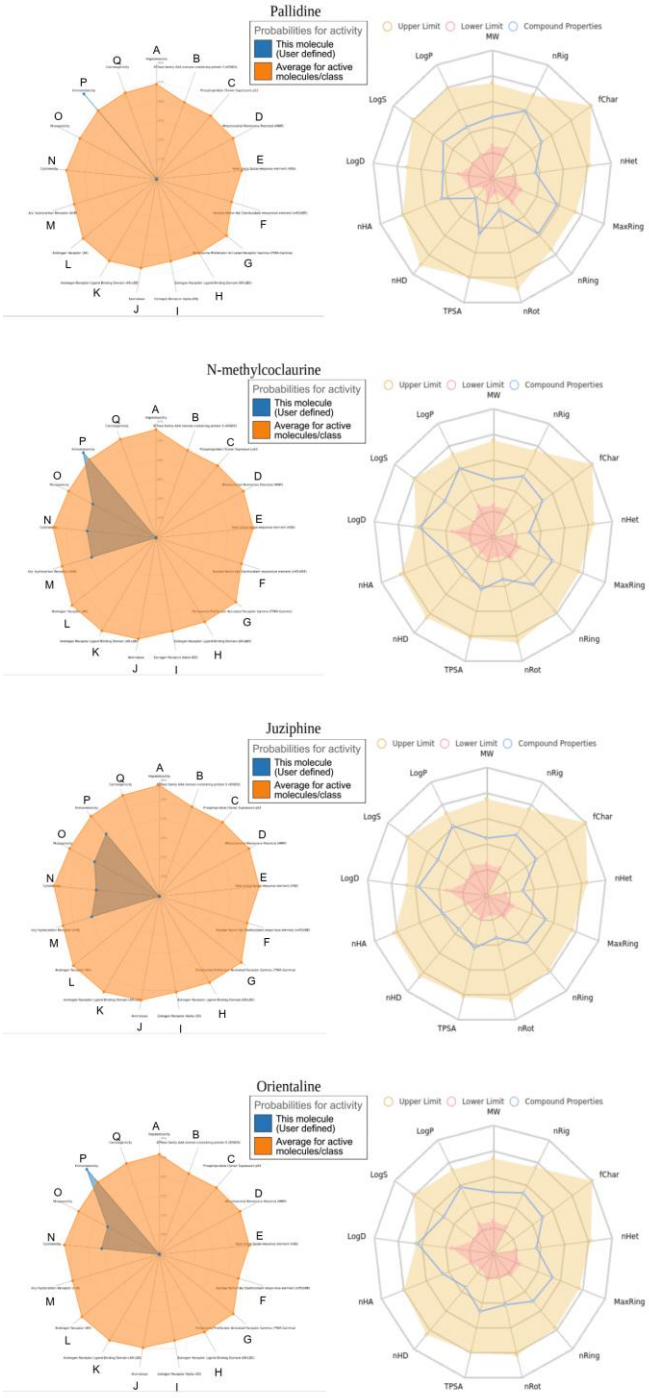


Figure S2. Toxicity radar (left side) and bioavailability radar (right side) based on theoretical prediction of the physicochemical properties of pallidine, *N*-methylcoclaurine, juziphine and orientaline. (A) Hepatotoxicity; (B) ATPase family AAA domain-containing protein 5 (ATAD5); (C) phosphoprotein (tumor supressor) p53; (D) mitochondrial membrane potential (MMP); (E) heat shock factor response element (HSE); (F) nuclear factor like 2/antioxidant responsive element (nrf2/ARE); (G) peroxisome proliferator activated receptor gamma (PPAR-Gamma); (H) estrogen receptor ligand binding domain (ER-LBD); (I) estrogen receptor alpha (ER); (J) aromatase; (K) androgen receptor ligand binding domain (AR-LBD); (L) androgen receptor (AR); (M) aryl hydrocarbon receptor (AhR); (N) citotoxity; (O) mutagenicity; (P) immunotocity; (Q) carcinogenicity.

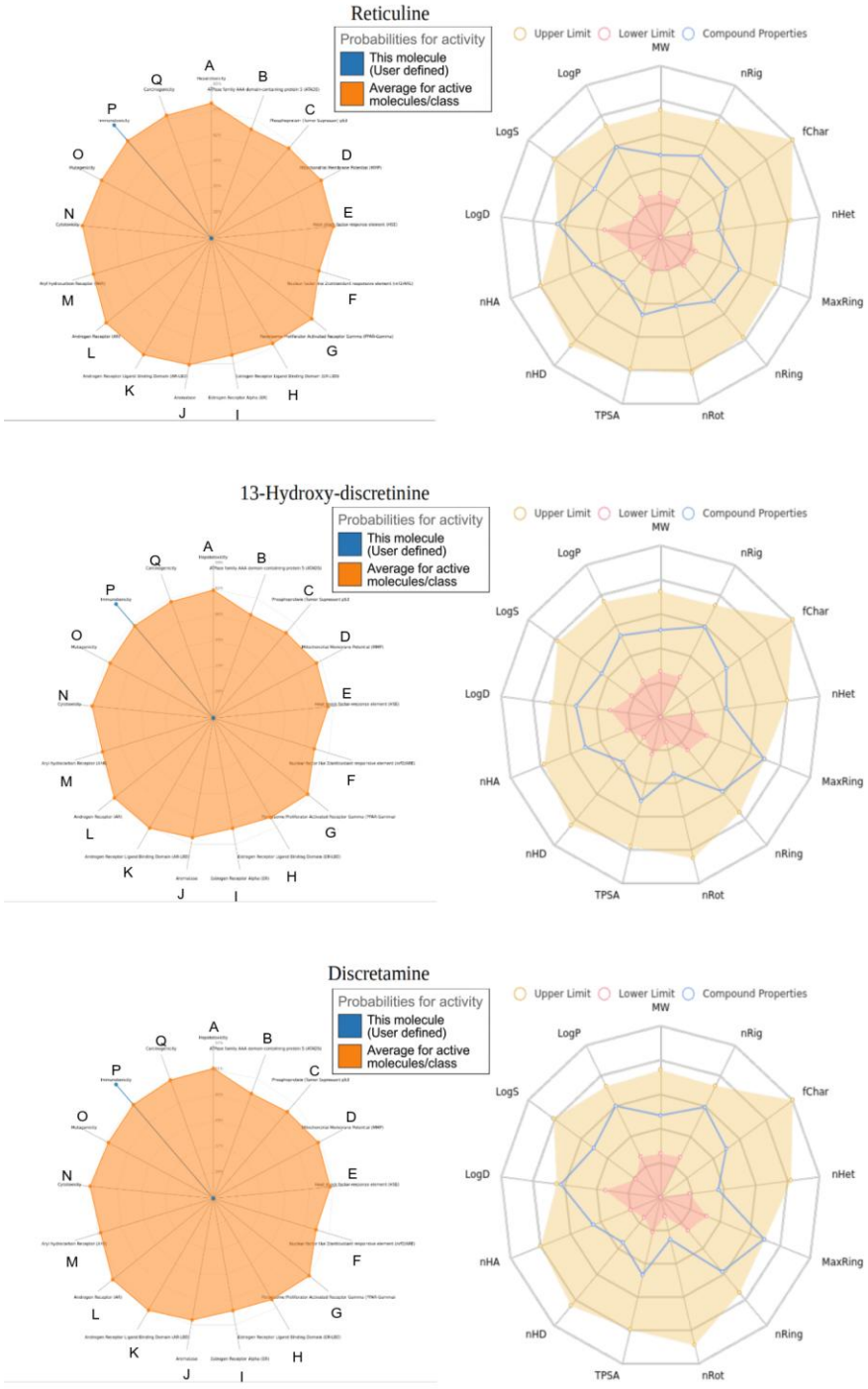


Figure S3. Toxicity radar (left side) and bioavailability radar (right side) based on theoretical prediction of the physicochemical properties of reticuline, 13-hydroxy-discretine and discretamine. (A) Hepatotoxicity; (B) ATPase family AAA domain-containing protein 5 (ATAD5); (C) phosphoprotein (tumor supressor) p53; (D) mitochondrial membrane potential (MMP); (E) heat shock factor response element (HSE); (F) nuclear factor like 2/antioxidant responsive element (nrf2/ARE); (G) peroxisome proliferator activated receptor gamma (PPAR-Gamma); (H) estrogen receptor ligand binding domain (ER-LBD); (I) estrogen receptor alpha (ER); (J) aromatase; (K) androgen receptor ligand binding domain (AR-LBD); (L) androgen receptor (AR); (M) aryl hydrocarbon receptor (AhR); (N) citotoxity; (O) mutagenicity; (P) immunotocity; (Q) carcinogenicity.

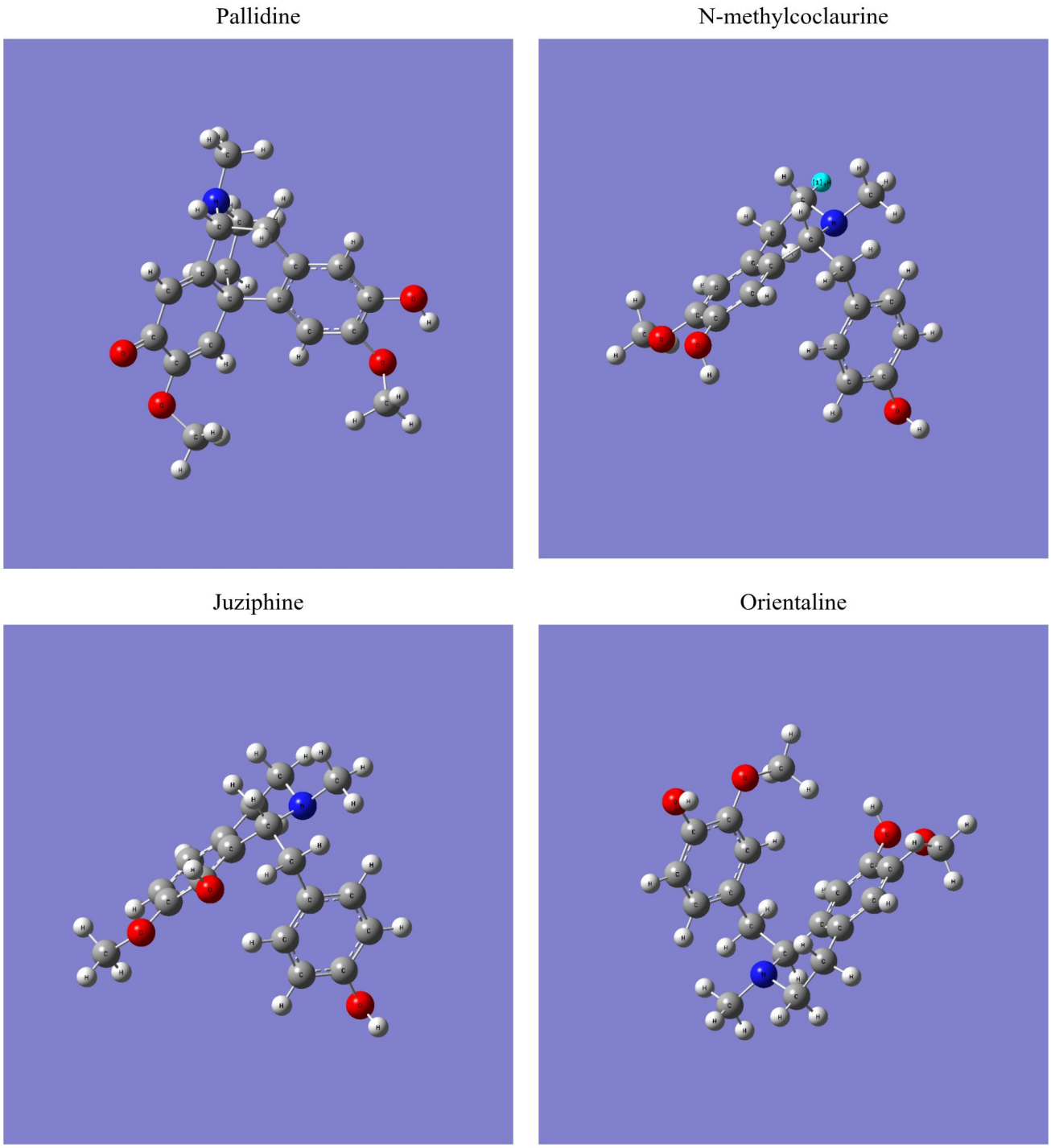


Figure S4. DFT optimized structures for the pallidine, *N*-methylcoclaurine, juziphine and orientaline.

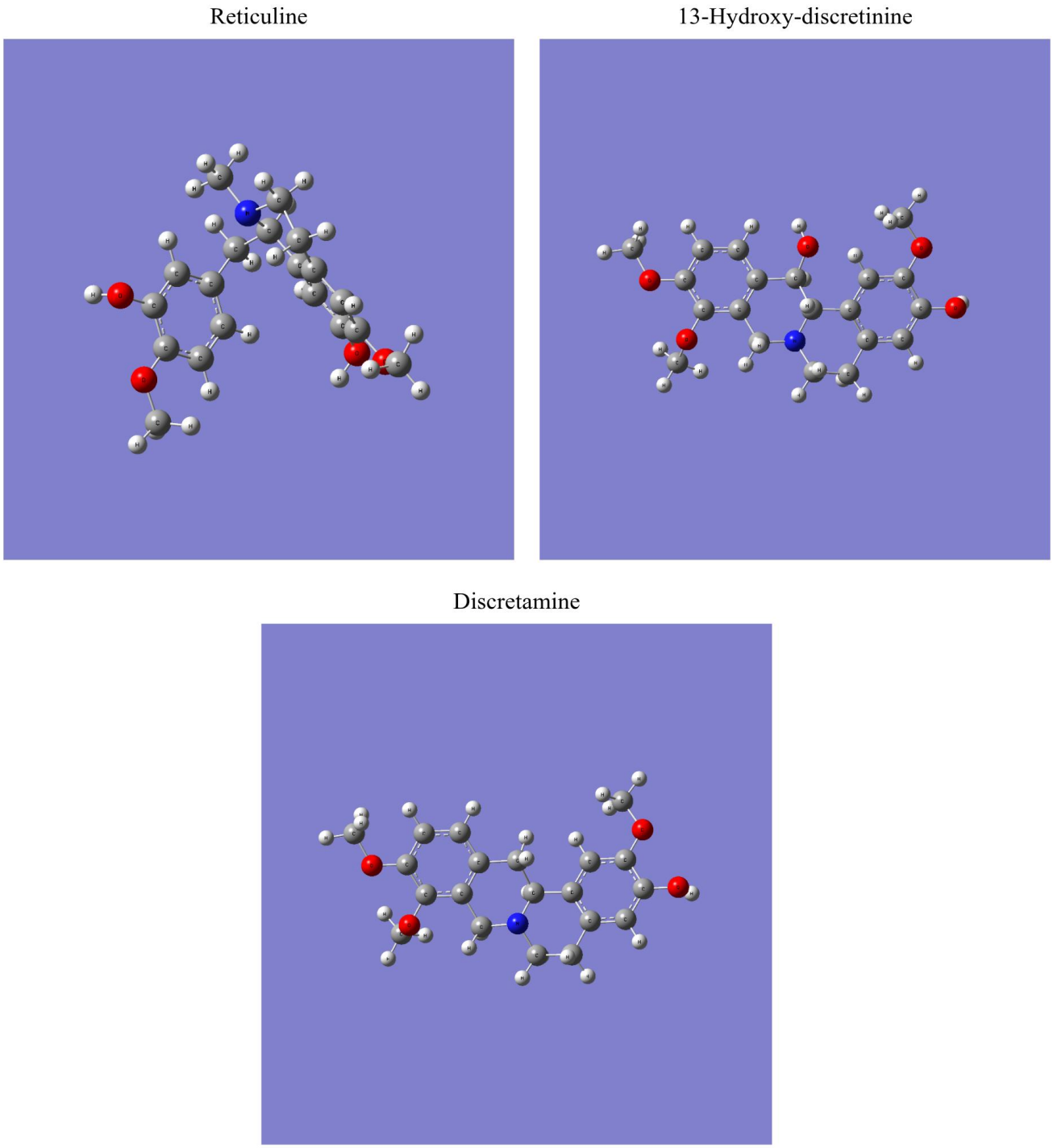


Figure S5. DFT optimized structures for the reticuline, 13-hydroxy-discretine and discretamine.

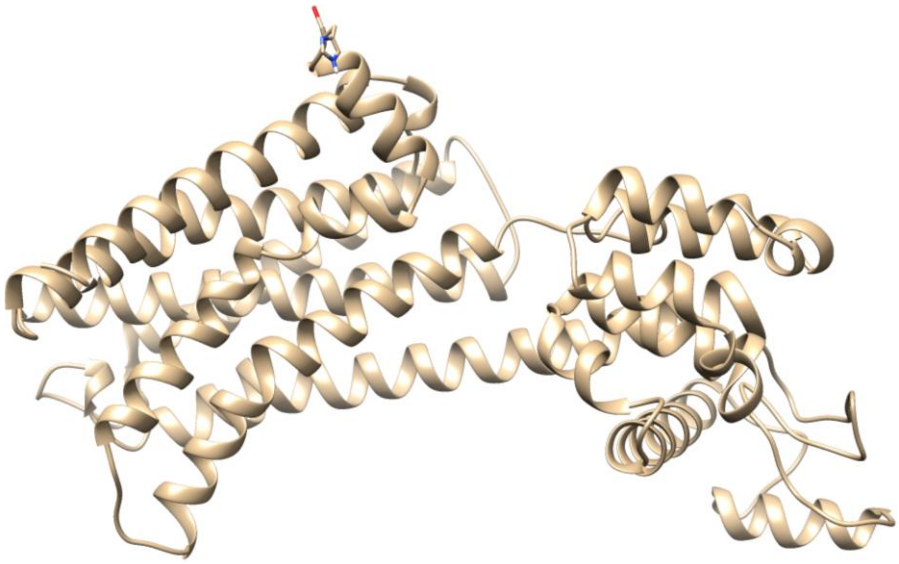


Figure 2. Structure of dopamine D(2) receptor protein (6CM4).

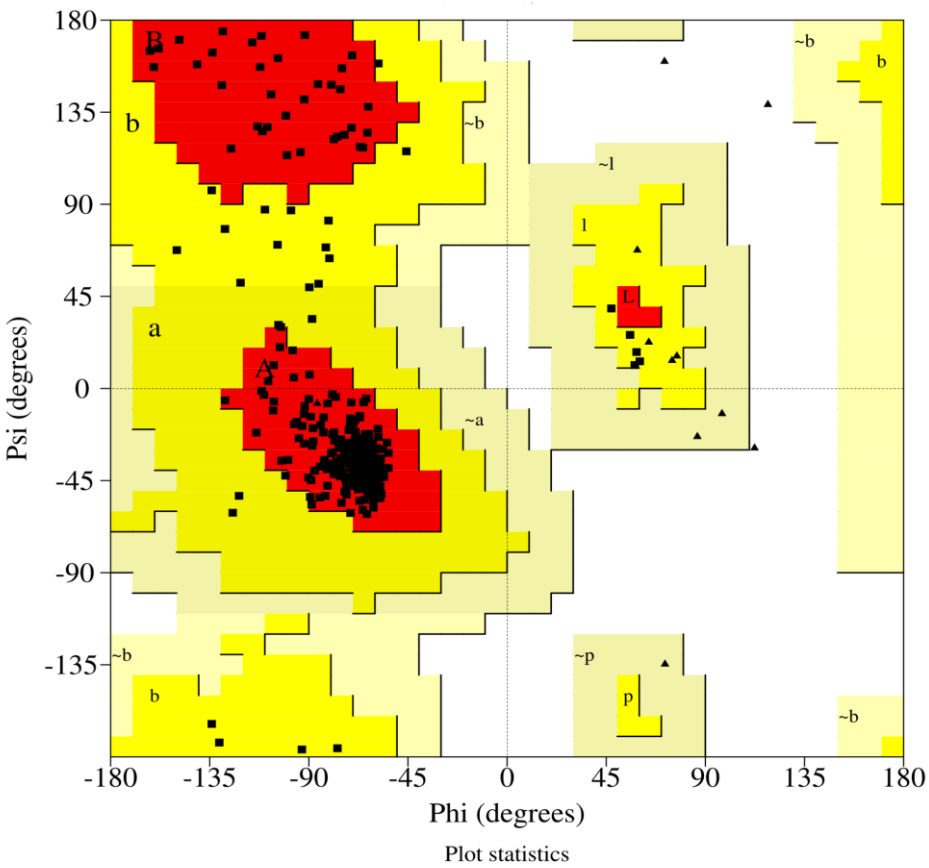
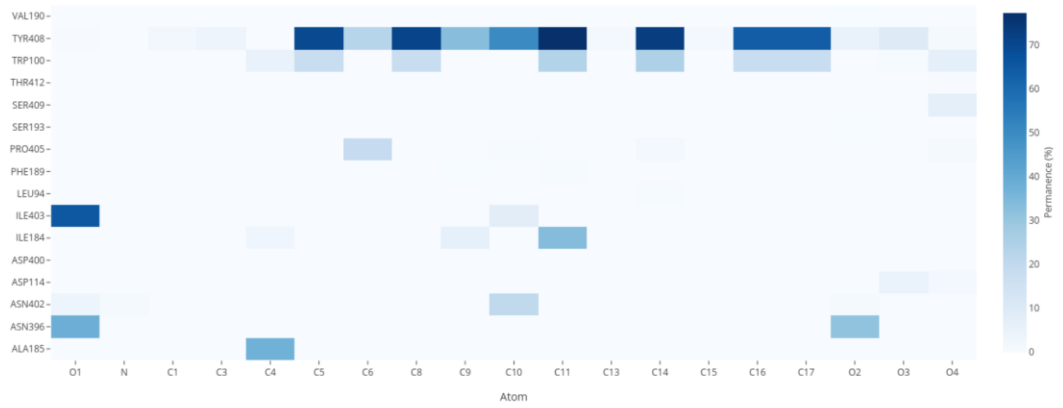
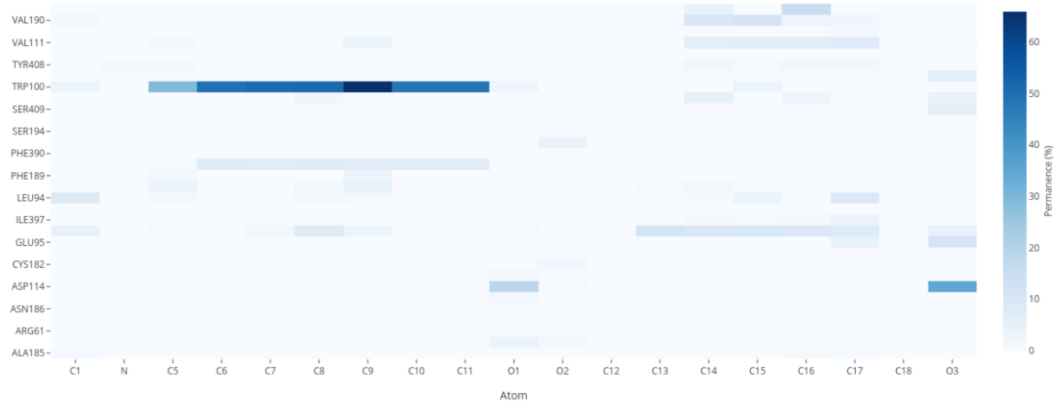


Figure 3. Ramachandran plot depicting distinct regions (most favored, additionally allowed, and generously allowed regions) of the target receptor.

(a)



(b)



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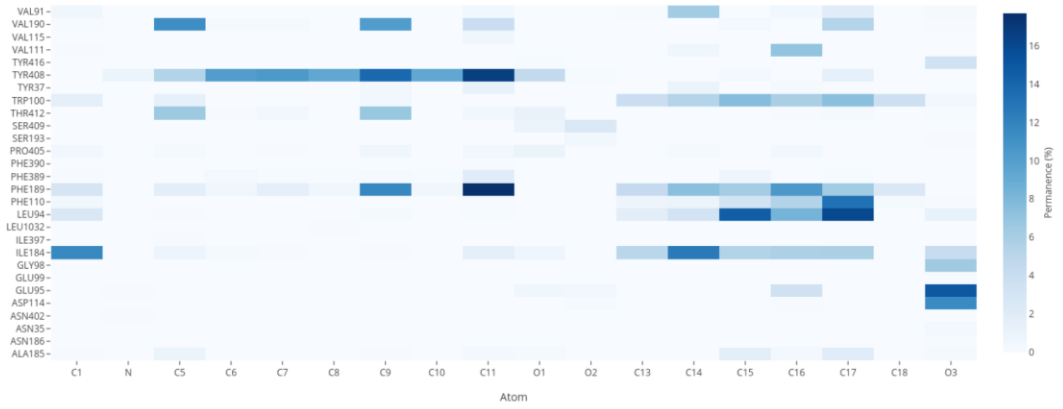
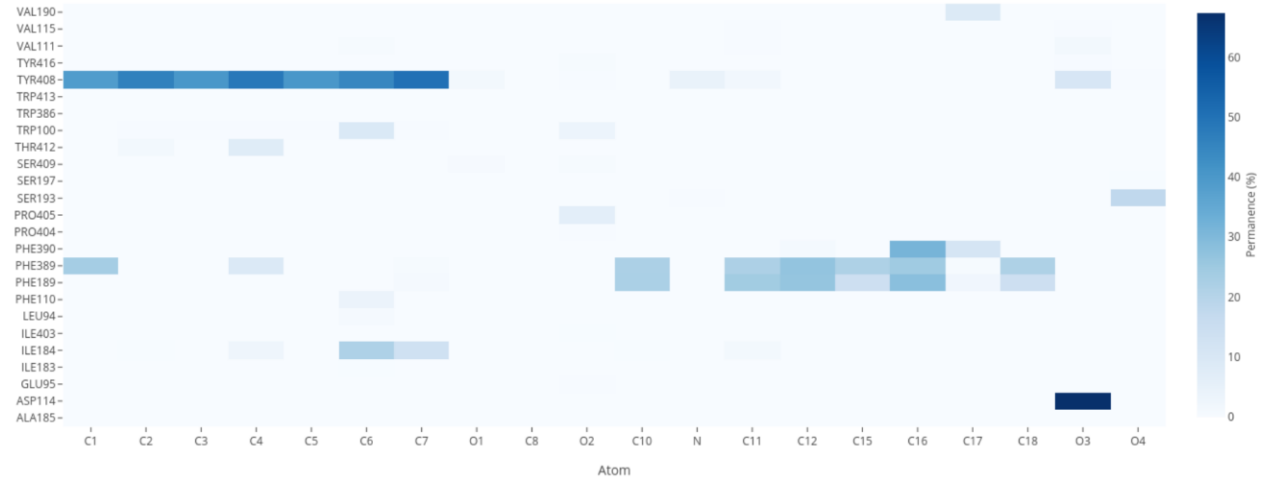


Figure S8. Percentage of persistence of the most significant non-covalent interactions between the atoms of the lead compounds and the amino acid residues of the 6CM4 receptor. The sequence is as follows: (a) pallidine, (b) *N*-methylcoclaurine, (c) juziphine, (d) orientaline.

(a)



(b)

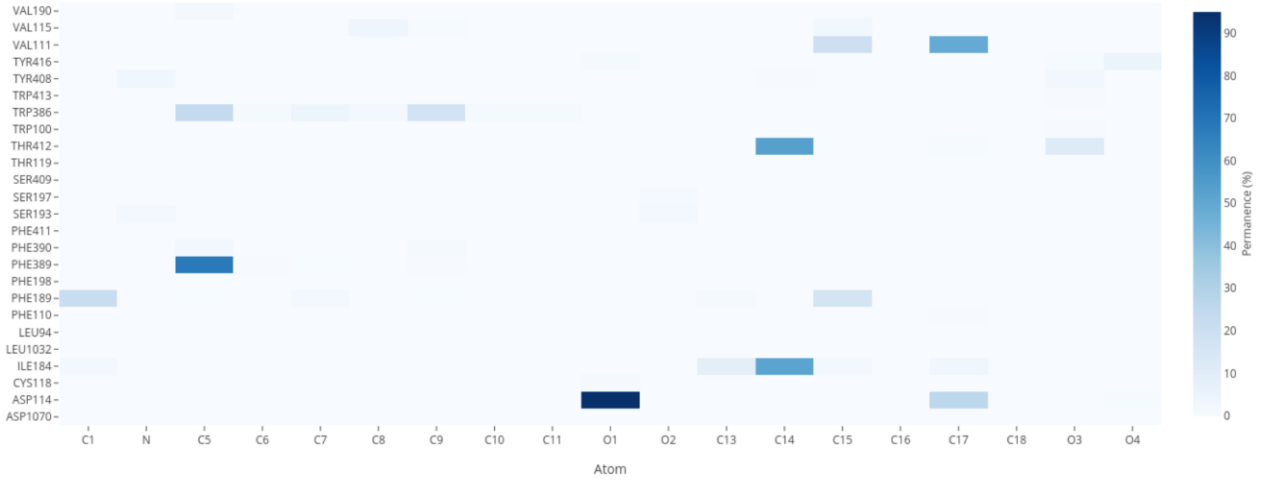
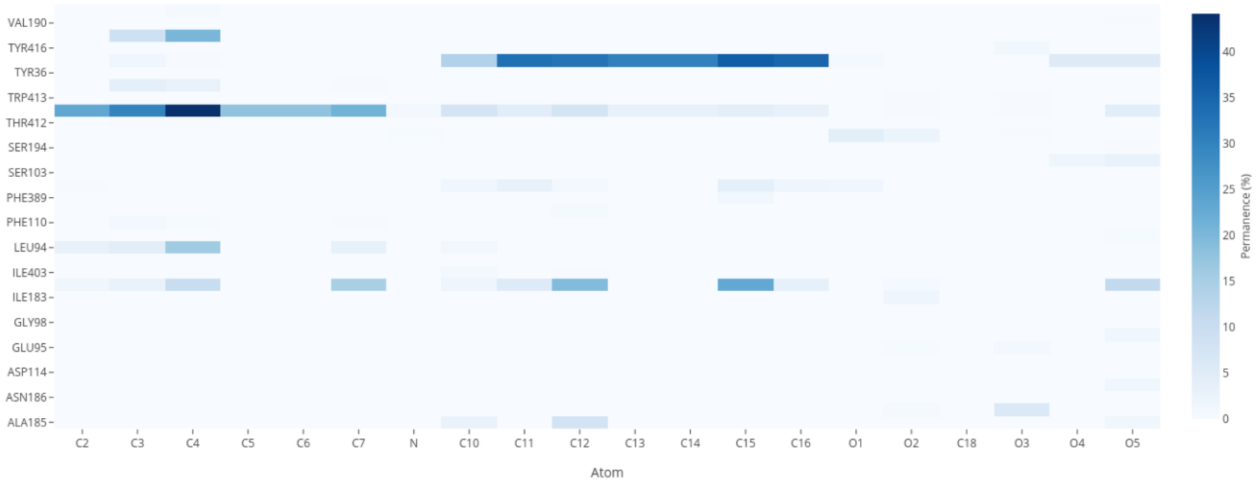


Figure S9. Percentage of persistence of the most significant non-covalent interactions between the atoms of the lead compounds and the amino acid residues of the 6CM4 receptor. The sequence is as follows: (a) orientaline, (b) reticuline.

(a)



(b)

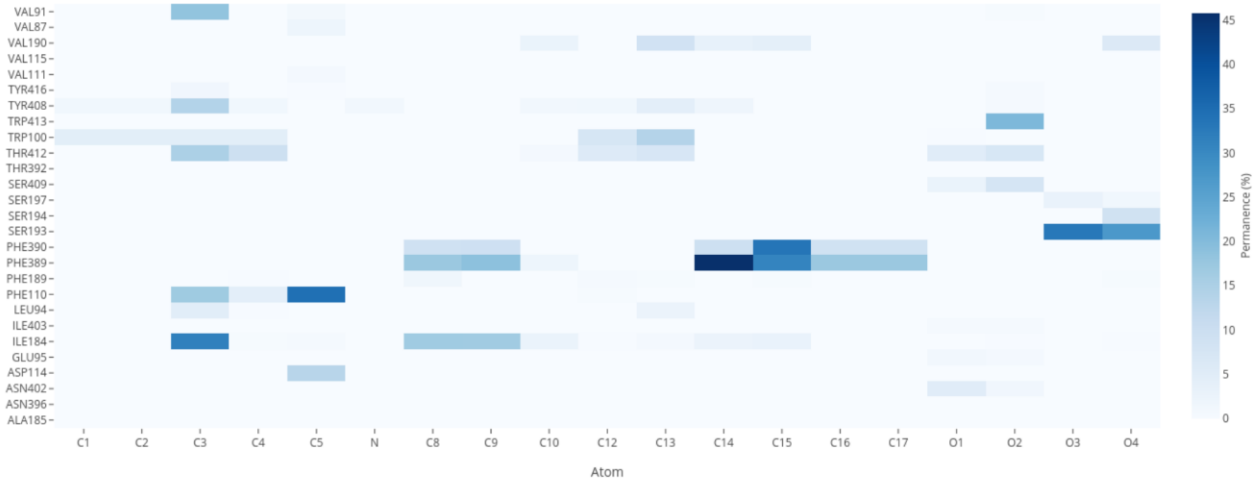


Figure S10. Percentage of persistence of the most significant non-covalent interactions between the atoms of the lead compounds and the amino acid residues of the 6CM4 receptor. The sequence is as follows: (a) 13-hydroxy-discretine, (b) discretamine.

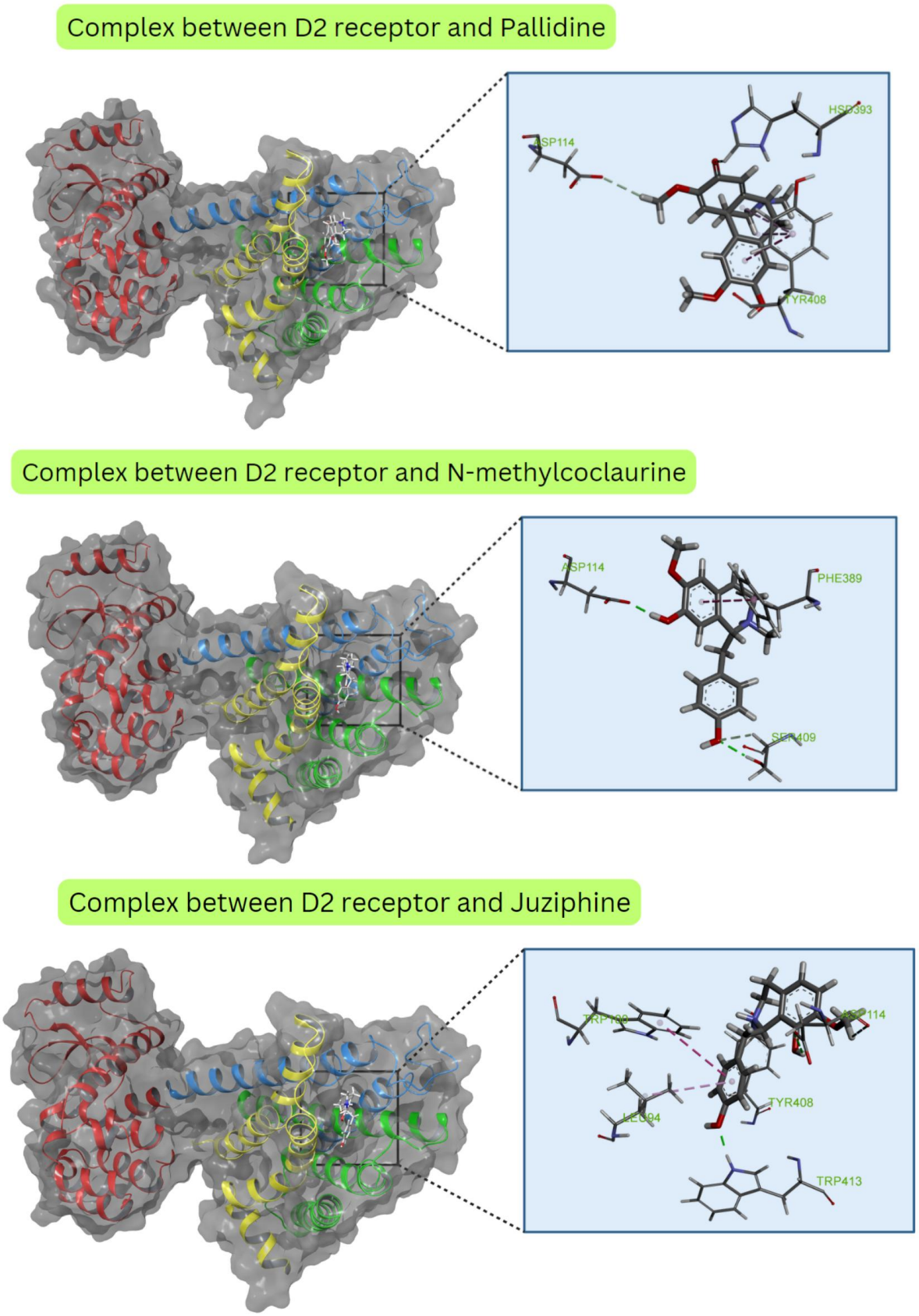


Figure S11. 3D structures of the pallidine, *N*-methylcoclaurine, juziphine and orientaline docked in the receptor pocket. The residues most involved in the formation of interactions with the amino acids of the 6CM4 receptor are highlighted.

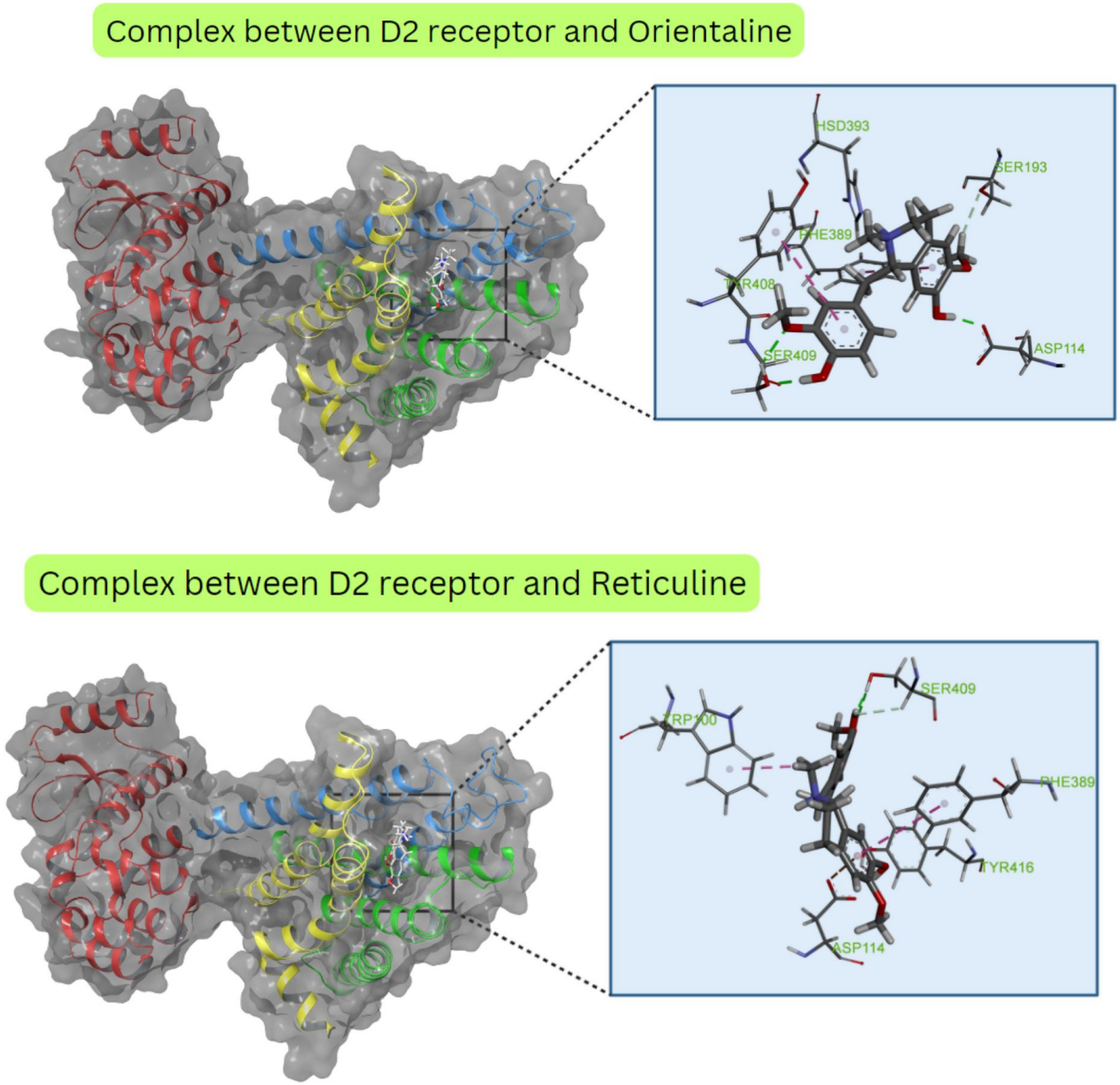


Figure S12. 3D structures of the orientaline and reticuline docked in the receptor pocket. The residues most involved in the formation of interactions with the amino acids of the 6CM4 receptor are highlighted.

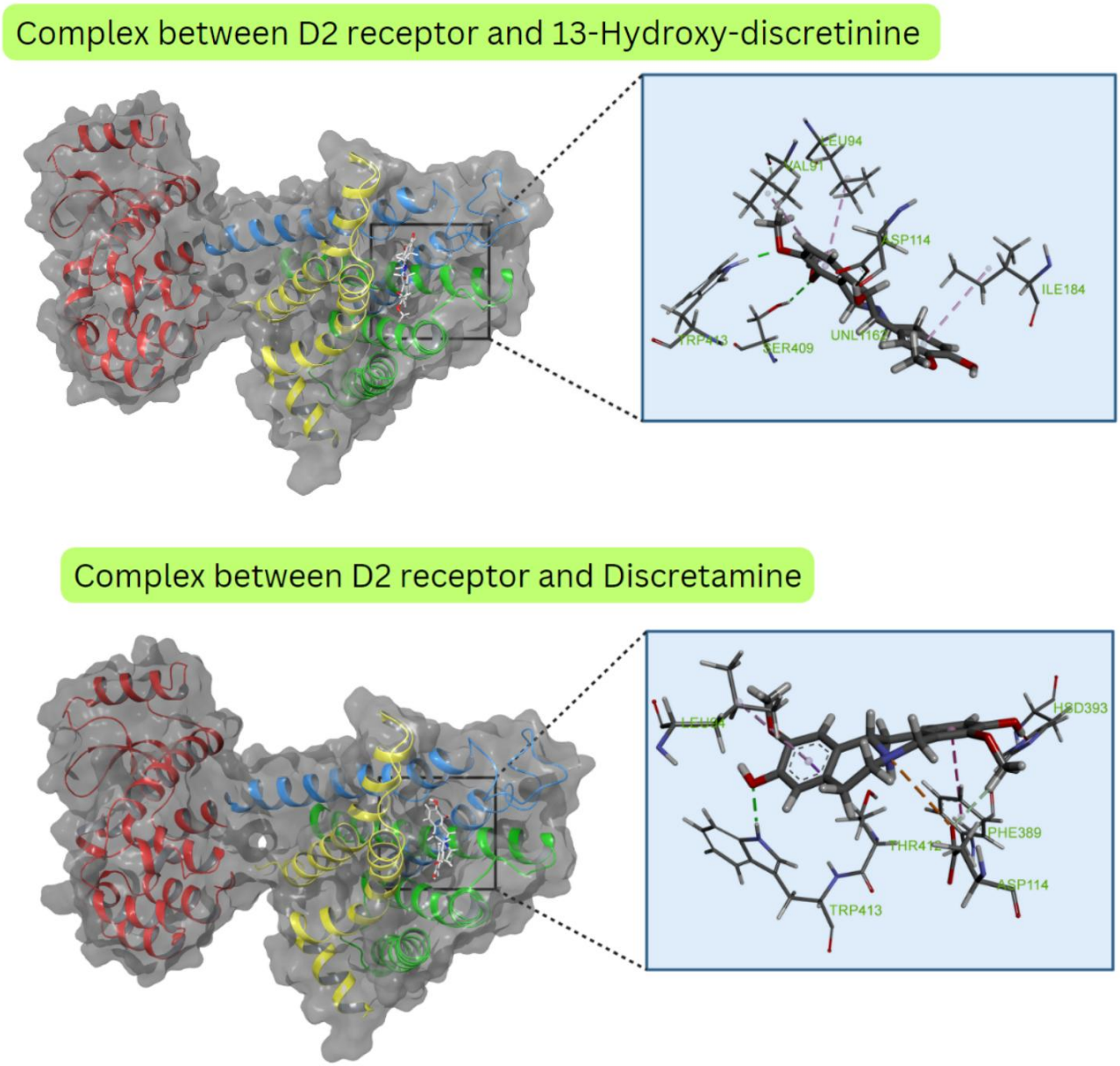


Figure S13. 3D structures of the 13-hydroxy-discretine and discretamine docked in the receptor pocket. The residues most involved in the formation of interactions with the amino acids of the 6CM4 receptor are highlighted.

Table S1. Key ADMET characteristics of lead compounds

Property	Model name	Predicted value						
		Pallidine	*N*-Methylcoclaurine	Juziphine	Orientaline	Reticuline	13-Hydroxy-discretinine	Discretamine
Absorption	water solubility / (log mol L^{-1})	–2.985	–3.717	–3.675	–2.97	–3.856	–3.188	–3.483
	$CaCO_2$ permeability / (log Papp in 10^{-6} cm s^{-1})	1.247	1.218	1.22	0.994	0.919	1.013	1.01
	human intestinal absorption / (% absorbed)	95.594	92.936	91.827	91.684	91.276	95.897	94.142
	skin permeability / (log Kp)	–3.66	–2.794	–2.885	–2.791	–2.897	–2.732	–3.052
	P-glycoprotein substrate	yes	yes	yes	yes	yes	yes	yes
	P-glycoprotein I inhibitor	no	no	no	no	no	no	no
	P-glycoprotein II inhibitor	no	no	no	no	yes	no	no
Distribution	human VDss / (log L Kg^{-1})	0.758	0.973	0.919	1.536	0.778	1.24	1.072
	human fraction unbound / Fu	0.33	0.202	0.172	0.32	0.134	0.306	0.202
	BBB permeability / log BB	–0.495	0.144	–0.176	0.168	–0.502	–0.777	0.283
	CNS permeability / log PS	–2.354	–2.102	–2.098	–2.369	–2.244	–2.896	–2.17
Metabolism	CYP2D6 substrate	no	yes	yes	no	yes	no	yes
	CYP3A4 substrate	yes	yes	yes	yes	yes	no	yes
	CYP1A2 inhibitior	no	yes	yes	yes	yes	no	yes
	CYP2C19 inhibitior	no	no	no	no	no	no	no
	CYP2C9 inhibitior	no	no	no	no	no	no	no
	CYP2D6 inhibitior	no	yes	yes	yes	no	no	yes
	CYP3A4 inhibitior	no	no	no	no	no	no	no
Excretion	total clearance / (log ml min^{-1} kg^{-1})	1.053	1.009	0.987	1.026	1.04	1.168	1.12
	renal OCT2 substrate	yes	no	no	no	yes	no	no
Toxicity	AMES toxicity	yes	no	no	no	no	no	no
	human max. tolerated dose / (log mg^{-1} kg^{-1} day^{-1})	–0.632	0.038	–0.084	–0.349	0.232	–0.163	–0.059
	hERG I inhibitor	no	no	no	no	no	no	no
	hERG II inhibitor	yes	yes	yes	yes	yes	no	yes

oral rat acute toxicity (LD50) / (mol kg^{-1})	2.814	2.483	2.481	3.093	2.296	2.313	2.531
oral rat chronic toxicity (LOAEL) / (log mg kg^{-1}_bw day^{-1})	0.178	1.076	0.924	1.827	1.542	2.023	1.435
hepatotoxicity	no	no	no	no	no	no	no
skin sensitization	no	no	no	no	no	no	no
T. pyriformis toxicity / (log ug L^{-1})	0.792	0.944	1.126	0.313	0.895	0.285	0.519
minnow toxicity (log mM)	1.837	1.012	1.262	0.312	1.26	0.336	0.36

ADMET: absorption, distribution, metabolism, excretion, and toxicity; VDss: volume of distribution at steady state; BBB: blood-brain barrier; CNS: central nervous system; LOAEL: lowest observed adverse effect level; LD50: median lethal dose; AMES: mutagenicity test.

Table S2. Penalty scores in the ligand topologies obtained using the CGenFF

Compound	Penalty					
	Charge / e	Bond / Å	Angle / °	Dihedral / °	Mean	Interpretation
Pallidine	9.56	4.00	4.62	16.72	8.73	Reliable
N-Methylcoclaurine	7.38	2.50	1.02	4.47	3.84	Reliable
Juziphine	7.66	2.50	1.02	5.08	4.07	Reliable
Orientaline	6.83	2.50	1.02	4.47	3.71	Reliable
Reticuline	6.83	2.50	1.02	4.47	3.71	Reliable
13-Hydroxy-discretinine	2.57	4.00	1.63	6.65	3.71	Reliable
Discretamine	8.20	2.50	1.07	4.98	4.19	Reliable