International Journal of Leading Research Publication (IJLRP)

E-ISSN: 2582-8010 ● Website: www.ijlrp.com ● Email: editor@ijlrp.com

In silico identification of potential dopamine D2 receptor antagonists from *Rauwolfia serpentina* phytoconstituents

Souvik Chakraborty[1,3], Sushmita Bhowmick[1,3], Sajal Dey[2], Tarasankar Maiti[1]

[1]Department of Physiology, Bhairab Ganguly College, West Bengal, India.
[2]Department of Zoology, Sripat Singh College, West Bengal, India.
[3]Present address: University of Haifa, Haifa, Israel.
*Corresponding author: Tarasankar Maiti.

Abstract

Schizophrenia (Scz) is a complex neuropsychiatric disorder with a spectrum of symptoms that are broadly classified into two main categories, namely, the positive and negative symptoms. Positive symptoms of Scz, such as hallucinations and delusions, are associated with the excessive activation of dopamine D2 receptors, leading to dysregulated dopamine neurotransmission. D2 receptor antagonism remains one of the central therapeutic strategies for controlling positive symptoms of Scz. In the present study, 39 phytoconstituents were identified in *Rauwolfia serpentina* using Indian Medicinal Plants, Phytoconstituents and Therapeutics (IMPPAT). 39 phytoconstituents were then docked against the 3D-modeled protein structure of the dopamine D2 receptor to assess the binding affinity of the phytoconstituents with the protein structure. Molecular docking identified that 11 compounds had binding energy less than -9kcal/mol. The assessment of absorption, distribution, metabolism, excretion, and toxicity (ADMET) was done for the 11 compounds, and only 4 phytoconstituents passed the ADMET filters, namely yohimbine, 1,2-dihydrovomilenine, corynanthine, and Rauwolscine. Due to the known toxicity profiles of yohimbine, Rauwolscine, and Corynanthine, only 1,2-dihydrovomilenine is chosen for further studies. The docked complex of the D2 receptor and 1,2-dihydrovomilenine is further studied for stability using normal mode analysis, which showed that the complex remains stable. These findings suggest that 1,2-dihydrovomilenine can be used for further in vitro and in vivo-based studies for further investigation and that it possesses all the necessary requirements to act as a potential D2 receptor antagonist.

Keywords: Schizophrenia, Molecular docking, ADMET, dopamine receptor

1. Introduction

Overactivity of the D2 dopaminergic receptor is one of the main reasons for positive symptoms in Schizophrenia (Scz). About 9.8% of patients in India with mental disorders are suffering from Scz[1]. According to the dopaminergic hypothesis, the positive symptoms of Scz are a result of overactivation of dopaminergic D2 receptors; also, brain imaging of Scz patients revealed overexpression of D2 receptors

in subcortical pathways and the nucleus accumbens[2,3,4]. Targeting D2 receptors with antagonists is a well-tested pharmacological therapy used for controlling positive symptoms in Scz, and one of the drugs that is available now to target D2 receptors is haloperidol[5,6,7]. Side effects of these drugs are the motivation to identify drugs with fewer side effects. Phytoconstituents have been used for treating patients with psychosis[8].

Rauwolfia serpentina, commonly known as sarpagandha, is a dicotyledonous medicinal plant predominantly distributed across the sub-Himalayan regions and recognized for its abundance of indole alkaloids. Traditionally, R. serpentina has been employed in the management of hypertension, primarily due to the presence of reserpine, a well-established antihypertensive agent[9]. In India, reserpine extracted from R. serpentina has historically been utilized for the treatment of psychiatric disorders, fever, and snakebites[10]. The present study aimed to identify potential dopamine D2 receptor antagonists among the phytoconstituents of R. serpentina roots using the Indian Medicinal Plants, Phytochemistry, and Therapeutics (IMPPAT) database[11]. Previous investigations have also suggested that extracts of R. serpentina possess antipsychotic properties[12], highlighting their potential relevance in the management of neuropsychiatric disorders.

Molecular docking-based virtual screening identified 11 phytoconstituents with promising binding affinities toward the dopamine D2 receptor. Subsequent evaluation of their absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles resulted in the selection of four compounds that satisfied all the screening criteria: 1,2-dihydrovomilenine (−9.3 kcal/mol), corynanthine (−9.0 kcal/mol), rauwolscine (−9.6 kcal/mol), and yohimbine (−9.1 kcal/mol). Although these compounds demonstrated favorable computational profiles, previous experimental investigations have reported adverse pharmacological effects associated with yohimbine, rauwolscine, and corynanthine[13,14]. Considering these findings, 1,2-dihydrovomilenine emerged as the most promising candidate for further investigation as a potential dopamine D2 receptor antagonist. However, additional molecular dynamics simulations, receptor-binding studies, and functional in vitro assays are necessary to validate its binding stability, antagonistic activity, and pharmacological safety.

2. Materials and Methods

2.1.Protein structure modelling and validaton

The three-dimensional (3D) structure of the dopamine D2 receptor was generated using MODELLER (version 10.4), a computational tool that employs comparative homology modeling to predict protein structures based on experimentally determined templates[15]. The amino acid sequence of the dopamine D2 receptor was retrieved in FASTA format from the UniProt database, followed by a Basic Local Alignment Search Tool (BLAST) analysis to identify suitable structural templates. Subsequently, three experimentally resolved protein structures (PDB IDs: 7JVR, 7DFP, and 6CM4) were obtained from the Protein Data Bank (PDB) and utilized as reference templates for constructing the receptor model. Among the generated models, the most favorable structure was selected based on the lowest Discrete Optimized Protein Energy (DOPE) score, indicating a comparatively favorable predicted structural conformation. The stereochemical quality and structural reliability of the selected model were subsequently evaluated through Ramachandran plot analysis using PROCHECK, a protein structure validation tool[16]. This analysis was performed through the Structural Analysis and Verification Server

(SAVES, version 6.0), accessible at https://saves.mbi.ucla.edu/, to assess the distribution of backbone dihedral angles and identify potential stereochemical inconsistencies in the modeled receptor structure.

2.2. Virtual screening of phytoconstituents

Phytoconstituents were identified using the Indian Medicinal Plants, Phytoconstituents and Therapeutics (IMPPAT) database, and a total of 39 phytoconstituents were identified from *R. serpentina*[11]. All 39 SDF files for the corresponding compounds were then downloaded from the PubChem database (accessed on 12.08.2026). The protein and the ligands were then uploaded to PyRx software that uses AutoDock Vina as a plug-in[17]. The protein PDB structure was first converted to PDBQT format, and the SDF files of the 39 compounds were also converted to PDBQT format. A blind docking was performed, and the grid box (Center X: 23.3397, Y:11.5667, Z: -13.2207 and Dimensions (in Angstrom) of X:100.1366, Y:94.1255, Z:119.9587) was chosen in such a way that it encompasses the whole protein structure. The docked complex was further studied using BIOVIA Discovery Studio to understand the interaction of the ligand with the protein structure.

2.3. ADMET analysis of compounds

SwissADME web server was used to check the drug-likeness of the compounds that have the least binding affinity among the 39 phytoconstituents[18]. OSIRIS, a desktop-based software, was used to determine the toxicity of the compounds[19].

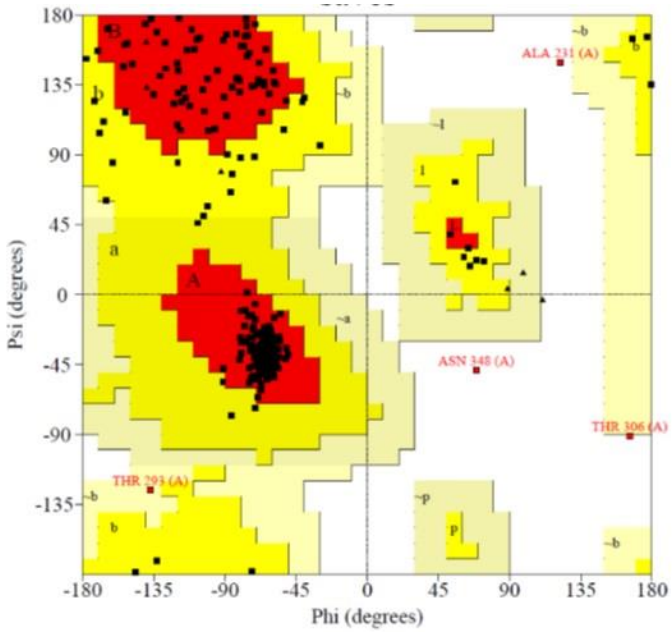
2.4. Normal mode analysis of protein structure in a docked complex

iMODS web server is used for the normal mode analysis of the protein-ligand docked complex[20].

3. Results

In the modeled dopamine D2 receptor structure, 91% of the residues are in the most favoured region in the Ramachandran plot, which indicates that our protein structure is a well-modeled structure that can be used for further studies (Fig 1).

Figure 1: Ramachandran plot for modelled D2 receptor protein. Glycine residues are represented by triangles, and proline is represented as 'p'.



39 phytoconstituents identified from the IMPPAT database were docked with our modeled D2 receptor. A blind docking approach was taken for this study, and after docking, only 11 phytoconstituents had a binding affinity greater than or equal to -9 kcal/mol. The control drug that we used for molecular docking is chlorpromazine (-5.8 kcal/mol) (Table 1)

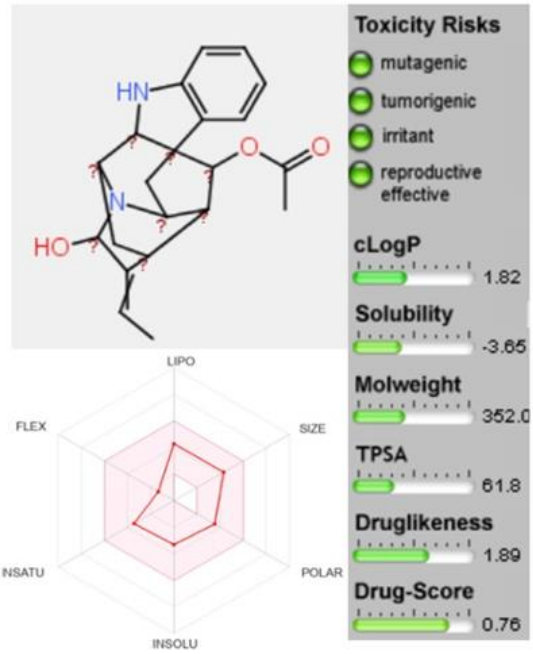
Table 1**:** Binding affinity of 11 compounds that passed the ADME filters together with the control drug chlorpromazine

Name of the Compound	**PubChem Id**	**Binding affinity score (kcal/mol)**
Chlorpromazine (Control)	2726	-5.8
Corynanthine	92766	-9.0
Raunescine	251566	-9.0
Rescinnamine	5280954	-9.1
Reserpine	5770	-9.1
Yohimbine	8969	-9.1
Swertiaside	101285202	-9.2
1,2-dihydrovomilenine	11953964	-9.3

[(1R,9R,10S,12R,13S,14R,16S,17S,18R)-13-ethyl-14-hydroxy-8-methyl-8,15-diazahexacyclo[14.2.1.01,9.02,7.010,15.012,17]nonadeca-2,4,6-trien-18-yl] 3,4,5-trimethoxybenzoate	13188743	-9.6
Rauwolscine	643606	-9.6
7-dehydrositosterol	5283634	-10.4
Beta-sitosterol	222284	-10.8

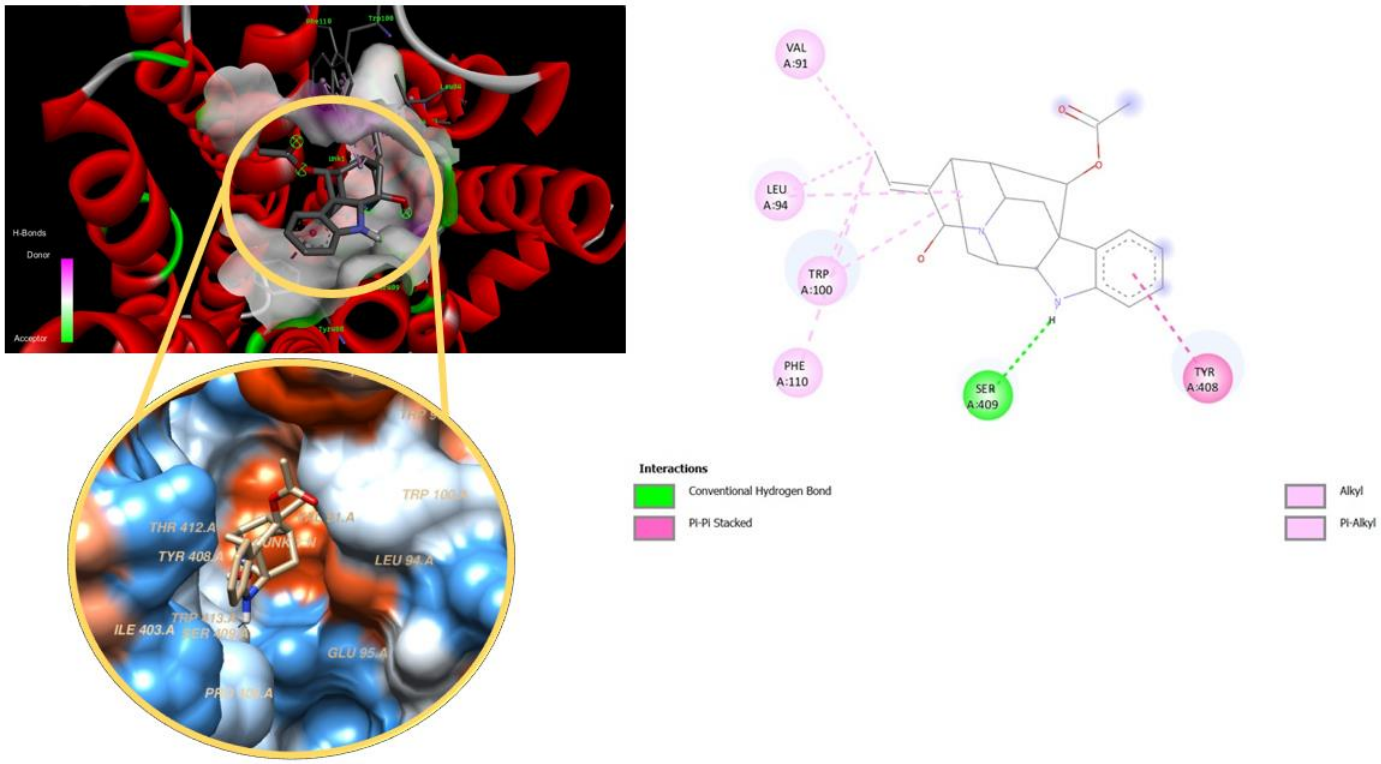
The 11 phytoconstituents undergo ADMET analysis; ADME analysis was performed using the SwissADME web server, and the toxicity profiles of these phytoconstituents were tested using OSIRIS desktop-based software. Four compounds, namely 1,2-Dihydrovomilenine (-9.3 kcal/mol), Corynanthine (-9.0 kcal/mol), Rauwolscine (-9.6 kcal/mol), and Yohimbine (-9.1 kcal/mol) passed the ADMET filters such as Lipinski's rule of five filter, polarity, and total polar surface area. 1,2-dihydrovomilenine passed all the toxicity filters (Fig. 2), other three phytoconstituents, namely corynanthine, Rauwolscine, and yohimbine, have documented evidence of toxicity. Rauwolscine is the diastereomer of yohimbine and thus, though not well documented, was not considered for further study. 1,2-dihydrovomilenine is the only phytoconstituent that is tested for its interaction with the modelled D2 receptor.

Figure 2: Bioavailability radar together with toxicity profile of 1,2-dihydrovomilenine. The pink-shaded region of the radar is the estimated physicochemical space for oral bioavailability. The exclamation marks represent carbon with unknown chirality. The safe toxicity profiles of the compound are shown as green tabs in OSIRIS software.



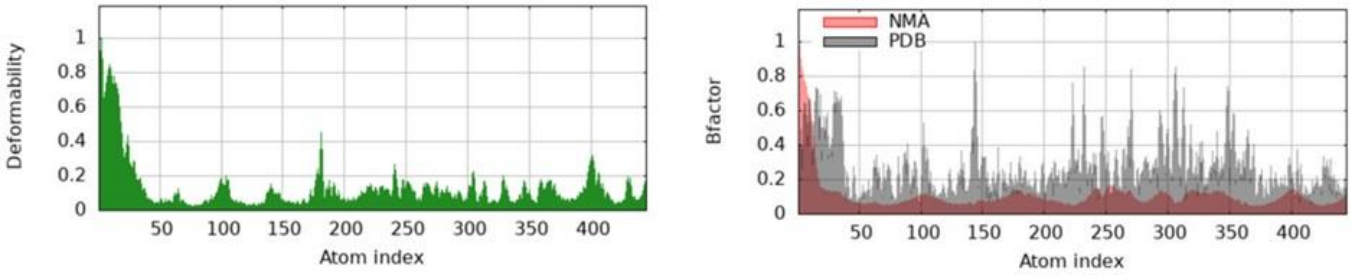
The docked complex of 1,2-Dihydrovomilenine with the D2 receptor showed that the compound interacted with residues VAL91, LEU94, TRP100, and PHE110, which were involved in alkyl and π-alkyl interactions, whereas TYR408 contributed to π–π stacking interactions. Additionally, a hydrogen bond was observed with the SER409 residue of the protein (Fig. 3).

Figure 3**:** Interaction of 1,2-Dihydrovomilinine with D2 receptor. The left side represents he pocket of the D2 receptor where the 1,2-Dihydrovomilenine is bound; the right image represents the 2D interaction map of the same.



Normal Mode Analysis (NMA) was performed to investigate the flexibility and dynamic behavior of the docked protein–ligand complex. The deformability plot showed relatively low fluctuations across most regions, suggesting limited structural flexibility. However, a few prominent peaks indicated localized regions with greater mobility. Similarly, the B-factor analysis revealed generally low predicted atomic fluctuations, with occasional peaks representing more flexible regions of the protein. The NMA-derived B-factors were comparatively lower than the PDB-derived values across most regions. Overall, these findings suggest that the docked complex exhibits relatively restricted motions in several regions, alongside localized flexibility that may contribute to conformational changes (Fig. 4).

Fig 4: Deformability and beta factor of the docked complex.



4.Discussion

In this study, we tried to explore the potential of *R. serpentina* phytoconstituents as a dopamine D2 receptor antagonist for alleviating positive symptoms of Scz. Dysregulation of dopamine receptors is strongly associated with psychotic episodes, making D2 receptors one of the main targets in patients associated with positive symptoms in Scz[21]. Here we investigated 39 phytoconstituents from *R. serpentina* and screened these compounds using in silico molecular docking methods. 11 compounds with favourable binding affinity scores (≤ −9 kcal/mol) were screened using ADMET filters, which resulted in the identification of 4 compounds, namely 1,2-dihydrovomilenine, corynanthine, rauwolscine, and yohimbine. In a study it was stated that yohimbine ingestion by bodybuilders caused severe neurotoxicity among athletes who took them[22]. Rauwolscine which is also known as α yohimbine and Corynanthine are diastereomers of yohimbine, so their toxicity profile has to be checked before they are considered for any study both in mice and human models[23]. Thus, among these 4 compounds, 1,2-dihydrovomilenine emerged as one of the most favourable lead compounds exhibiting favourable receptor binding interactions and pharmacokinetic properties. The findings presented here in this article strongly suggest the importance of naturally occurring alkaloids in identifying new D2 receptor inhibitors. Further investigation is required to validate the inhibitory potential and the actual binding stability of 1,2-dihydrovomilenine with the dopamine D2 receptor.

Conflict of Interest

Authors declare no conflict of interest.

REFERENCES:

1. D. Lalit et.al. The burden of mental disorders across the states of India: the global burden of disease study 1990-2017. Lancet Psychiatry 2019; p. 148. DOI: 10.1016/S2215-0366(19)30475-4
2. D. Im, A. Inoue, T. Fujiwara, *et al.* Structure of the dopamine D_2 receptor in complex with the antipsychotic drug spiperone. Nature Communication. 2020; 11, 6442. DOI: 10.1038/s41467-020-20221-0
3. S. Phillip. Schizophrenia and dopamine receptors. European Neuropsychopharmacology. 2013; 23: 999-1009. DOI:10.1016/j.euroneuro.2013.06.005
4. Thompson, Ilse A, de Vries, Erik F.J, Sommer, Iris E.C. Dopamine D2 up-regulation in psychosis patients after antipsychotic drug treatment. Current Opinion in Psychiatry. 2020; 33(3): 200-205. DOI: 10.1097/YCO.0000000000000598

5. P. Li, G.L. Snyder, K.E. Vanover. Dopamine targeting drugs for the treatment of Schizophrenia: Past Present Future. Current Topics in Medicinal Chemistry. 2016; 16(29): 3385-3403. DOI: 10.2174/1568026616666160608084834
6. H.j. Moller, M Riedel, M. Jager, F. Wickelmaier, et al. Short-term treatment with risperidone or haloperidol in first-episode Schizophrenia: 8-week results of a randomized controlled trial within the German research network on Schizophrenia. International Journal of Neuropsychopharmacology. 2008; 11(7): 985-997. DOI: 10.1017/S1461145708008791
7. Pham, J.Y. Lee, C.W.T. Miller. Acute extrapyramidal side effects from smoked haloperidol. Case Reports in Psychiatry. 2021; 4177263. DOI: 10.1155/2021/4177263
8. T.W. Tang, W.H. Tang. Opportunities in novel psychotropic drug design from natural compounds. International Journal of Neuropsychopharmacology. 2019; 22(9): 601-607. DOI: 10.1093/ijnp/pyz042
9. M. R. Weir. Reserpine: A new consideration of an old drug for refractory hypertension. American Journal of Hypertension. 2020; 33(8): 708-710. DOI: 10.1093/ajh/hpaa069
10. P. Roy. Global pharma and local science the untold tale of Reserpine. Indian Journal of Psychiatry. 2018; 60: S277-S283. PMID 29527061
11. K. Mohanraj, B. Shanmugam Karthikeyan, R.P. Vivek-Ananth, R.P. Bharath Chand, S.R. Aparna, P. Mangalapandi, A. Samal. *IMPPAT:* A curated database of Indian Medicinal Plants, Phytochemistry and Therapeutics. Scientific Reports. 2018*;* 8:4329. DOI: 10.1038/s41598-018-22631-z
12. W. B. Ali, E. Shireen, M. Masroor, S. Kiran, N. Memon, N. Junaid, D.J. Haleem. Oral administration of Rauwolfia serpentina plant extract mitigated immobilization stress induced behavioural and biochemic and deficits in rats. Biology and life sciences forum. 2022; 12(1): 32. DOI: 10.3390/IECN2022-12393
13. F. Saverio Bersani, Marialuce Coviello, Claudio Imperatori, Marta Francesconi, Christina M. Hough, Giuseppe Valeriani, Gianfranco De Stefano, Flaminia Bolzan Mariotti Posocco, Rita Santacroce, Amedeo Minichino, Ornella Corazza. Adverse Psychiatric Effects Associated with Herbal Weight-Loss Products. BioMed Research International. 2015; Article ID 120679. DOI: 10.1155/2015/120679
14. S. Bisong, R. Brown, E. Osim. Comparative effects of Rauwolfia vomitoria and chlorpromazine on social behavior and pain. North American Journal of Medical Sciences. 2011; 3(1): 48-54. DOI: 10.4297/najms.2011.348
15. N. Eswar, B. Webb, M.A. Marti-Renom, M.S. Madhusudhan, D. Erimian, M. yi-Shen, U. Pieper, A. Sali. Comparative protein structure modelling using Modeller. Current protocols in Bioinformatics. 2014. DOI: 10.1002/cpbi.3
16. R.A. Laskowski, M.W. MacArthur, D.S Moss, J. N. Thornton. PROCHECK: A program to check the stereochemical quality of protein structure. Journal of Applied Crystallography. 1993; 26: 283-291. DOI: 10.1107/S0021889892009944
17. O. Trott, A.J. Olson. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading. Journal of Computational Chemistry. 2009; 31: 455-461. DOI: 10.1002/jcc.21334

18. Daina, A., Michielin, O. & Zoete, V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific Reports. 2017; **7**, 42717. DOI: https://doi.org/10.1038/srep42717
19. Thomas Sander, Joel Freyss, Modest von Korff, Jacqueline Renée Reich, and Christian Rufener. OSIRIS- An entirely in-house developed drug discovery informatics system. Journal of Chemical Information and Modelling. 2009; 49(2): 232-246. DOI: 10.1021/ci800305f.
20. José Ramón López-Blanco, José I. Aliaga, Enrique S. Quintana-Ortí, Pablo Chacón. iMODS: internal coordinates normal mode analysis server. Nucleic Acids Research. 2014; 42 :W271–W276, https://doi.org/10.1093/nar/gku339
21. Oda Y, Kanahara N, Iyo M. Alterations of Dopamine D2 Receptors and Related Receptor-Interacting Proteins in Schizophrenia: The Pivotal Position of Dopamine Supersensitivity Psychosis in Treatment-Resistant Schizophrenia. International Journal of Molecular Sciences. 2015; 16(12):30144-30163. https://doi.org/10.3390/ijms161226228
22. Giempreti, D. Lonati, C. Locatelli, L. Rocchi, M. T. Campailla. Acute neurotoxicity after yohimbine ingestion by a body builder. 2009; 47(8): 827-829. DOI: 10.1080/15563650903081601
23. N. R. Jabir, C.K. Firoz, T. K. Zughaibi, et al. A literature perspective on the pharmacological applications of yohimbine. 2022; 54(1): 2849-2863. DOI: 10.1080/07853890.2022.2131330