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Molecular Modeling of the antagonist compound esketamine and its molecular docking study with non-competitive *N*-methyl-*D*-aspartate (NMDA) receptors NR1, NR2A, NR2B and NR2D

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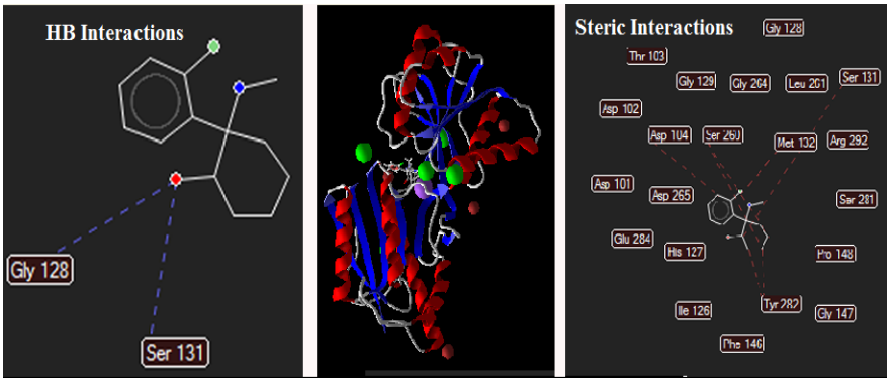
GRAPHICAL ABSTRACT



KEYWORDS

Esketamine
Major depressive disorder
Molecular docking
Molecular simulation
N-methyl-D-aspartate receptor
Treatment-resistant depression

ABSTRACT

The main purpose of the present article is reactivity and stability properties study of the antagonist compound esketamine and analyzing of its binding to the non-competitive N-methyl-D-aspartate receptor subunits (NR1, NR2A, NR2B and NR2D). In first step, the molecular structure of esketamine was optimized using density functional theory (DFT) method at B3YP/6-311++G(d,p) level of theory. The reactivity and stability properties of the title medicinal compound were studied by global reactivity indices. The computational data showed the molecule is stable and has low tendency to interact with residues of the biomolecules like receptors and proteins. Secondly, the molecule binding to the receptors were analyzed by molegro virtual docker (MVD) program. Our computations indicated that the compound asserts its pharmacological effects mainly through interactions with NR2B receptors and the NR2B residues containing Gly [A] 128, His [A] 127, Gly [A] 264, Tyr [A] 282, Ser [A] 131, Asp [A] 265, Ser [A] 260 and Met [A] 132 are the main amino acids involved in the ligand-receptor complex formation.

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1. Introduction

Major depressive disorder or MDD is a serious neurological condition that afflicts almost 300 million people around the world. Over the years, various classes of antidepressants have been developed. Although the efforts to manage MDD have been fruitful in many cases, still about 30% of patients show resistance to the available drugs. As a result, the attempt to find alternative therapies for treatment-resistant depression (TRD) has been of particular interest in the past few years [1]. Despite the prominent use of monoamine systems such as serotonin, dopamine and noradrenaline systems in modern medicine and their general efficacy in treating MDD, the glutamate system have come into focus in hopes of achieving better and more effective outcomes [2]. The glutamate system is proved to be one of the key neurological pathways contributing to depression prevalence in patients. The analysis of plasma, cerebrospinal fluid and the brain of MDD patients show elevated levels of glutamate. Furthermore, the over-expression of NMDA receptors in MDD patients have been reported in a series of studies [3]. Ketamine is an NMDA receptor antagonist commonly used as an anesthetic drug. In certain doses Ketamine has fast-acting and powerful antidepressant properties [4]. Ketamine is a racemic mixture consisting of two enantiomeric isomers R-ketamine and S-ketamine (also known as Esketamine). Esketamine has been observed to possess higher affinity towards NMDA receptors and is less likely to induce unwanted effects compared with racemic Ketamine [5]. Furthermore, Ketamine is mainly administered via infusion which greatly affects the ease of drug use in patients. On the other hand, a period of weeks to months should pass before the beneficial effects of first-line antidepressants such as SSRIs are witnessed therefore; the rapid onset of action in Esketamine is of particular importance [6]. The antidepressant effects of intranasal Esketamine take place after only 2 to 24 hours of its single dose administration [7]. The intranasal administration of Esketamine as well as efficacy and safety of this drug as a complementary therapy alongside oral antidepressants in treatment of TRD have been thoroughly evaluated [8] and in 2019, Spravato® the nasal spray of Esketamine received its FDA approval. Intranasal rout of administration not only facilitates the use of drug by patients but also remarkably increases drug bioavailability through by-passing first pass metabolism. The improved bioavailability further results in lower dose consumption and limitation of adverse effects [9]. Esketamine's comparatively low molecular weight makes it suitable in intranasal delivery due to acceptable nasal mucosa absorption [10].

Although the previous studies provide detailed information about efficacy and safety of Esketamine in treating TRD and a general outlook on the mechanism of its effect on NMDA receptors, the exact structural and molecular drug-receptor interaction and the affected NMDA subunits are still unclear. In the present study, we analyzed the exact molecular mechanisms involved in interaction of Esketamine with NMDA receptor subtypes N1, NR2A, NR2B and NR2D, using molecular docking methods and computational chemistry. Moreover, the pharmacokinetic and biological behavior of the titled drug was determined using SwissADME web tool [11-14].

Computational methods

Today, drug design and the determination of its physicochemical properties are one of the major issues of the medicinal chemistry. Calculating these properties is performed by computational chemistry. This field of chemistry is divided into two issues: quantum mechanics (QM) and molecular dynamics (MD). Optimization and computation of the molecules are done by quantum

mechanics. The main part of the quantum mechanics relates to the density functional theory (DFT) [15-17]. So, the geometry of the antagonist medicinal compound esketamine will be optimized using density functional theory method by B3LYP functional at 6-311++G(d,p) level of theory. It is necessary to say that all QM computations are done using Gaussian 03 software. After optimizing the title molecular structure, the stability and reactivity properties of the said compound will be studied using frontier molecular orbitals (FMOs) theory. Also, the physicochemical properties study is done using an online web tool www.swissadme.ca. On the other hand, the analyses of the binding interactions between esketamine and N-methyl-D-aspartate receptors are carried out using molecular virtual docker (MVD) software [11-18].

2. Results and discussion

2.1. Esketamine structural, reactivity and stability properties study

Esketamine molecular structure contains one aromatic ring (benzene) and one sextet aliphatic ring (cyclohexanone). Fig. 1 shows its molecular structure. Optimization of this active substance was done using B3LYP/6-311++G(d,p) basis set of theory at room temperature in isolated form. The optimized geometry of the title compound shows the cyclohexanone ring prefers the boat state. The electronegative chlorine element causes more electron current on the benzene ring. On the other hand, the heteroatoms oxygen, chlorine and nitrogen have changed the carbon-carbon bond lengths of the said rings. Fig. 2 indicates the dependence between the theoretical and experimental bond lengths of the antagonist compound esketamine. This dependence is shown by the equation y=1.0219x-0.0451. The higher correlation coefficient (R^2=0.9676) for this equation shows a great convergence. So, the B3LYP/6-311++G(d,p) basis set of theory is a good method to compute the electronic properties of the title compound.

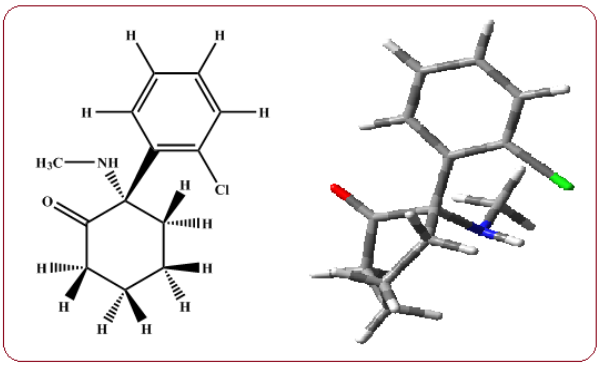

Fig. 1. The optimized molecular structure of esketamine

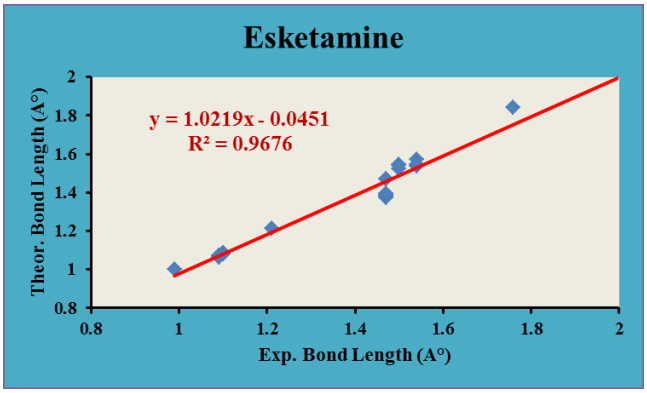

Fig. 2. The experimental and theoretical bond lengths relationship of esketamine

Stability and reactivity of organic compounds are discussed by the energies of their molecular orbitals (MOs). Each molecular orbital has a computed energy level. So, chemists sort the MOs by their energy levels. The main molecular orbitals of each organic compound relate to the frontier molecular orbitals (FMOs). HOMO and LUMO are two types of the FMOs. HOMO and LUMO stand for highest occupied molecular orbital and lowest unoccupied molecular orbital, respectively. On the other hand, chemists assume that the electrons will occupy the lowest energy level molecular orbitals first. The HOMO-LUMO gap can be used to understand the stability of the compounds. In fact, the HOMO-LUMO gap is the energy difference between the frontier molecular orbitals (HOMO and LUMO) [19-22]. Studying the reactivity and stability properties of the organic compounds are done by the global reactivity indices. The global reactivity descriptors like energy gap (Eg), ionization potential (IP), electron affinity (EA), chemical hardness (η), chemical softness (S),

electronegativity (χ), electronic chemical potential (μ) and electrophilicity index (ω) can be obtained from the energies of the frontier orbitals. These reactivity indices are achieved by following formulas [23]:

$$E_g = E_{LUMO} - E_{HOMO}$$

$$IP = -E_{HOMO}$$

$$EA = -E_{LUMO}$$

$$\eta = \frac{(\varepsilon_{LUMO} - \varepsilon_{HOMO})}{2}$$

$$\chi = \frac{-(\varepsilon_{LUMO} + \varepsilon_{HOMO})}{2}$$

$$\mu = \frac{(\varepsilon_{LUMO} + \varepsilon_{HOMO})}{2}$$

$$\omega = \frac{\mu^2}{2\eta}$$

$$S = \frac{1}{\eta}$$

The frontier molecular orbitals (filled HOMO and empty LUMO) energies and global reactivity indices of esketamine have been listed in Table 1. The HOMO energy level is -9.40 eV. So, the valence electrons of the title compound don't have tendency to excite and transfer to higher empty molecular orbitals. In contrast, the energy level of the LUMO is 3.47 eV. It means that the empty molecular orbitals of the antagonist compound esketamine can easily receive electron density from other residues or reagents in interaction with biomolecules. The difference between energy levels of the frontier molecular orbitals (HOMO-LUMO energy gap) is 12.87 eV. This high amount of HOMO-LUMO energy gap shows the high stability of the said medicinal compound. Fig. 3 indicates the density of states (DOS) graph of esketamine and the HOMO-LUMO energy gap is clearly shown on the graph. It can be deduced that the molecule will show high resistance to the electrophilic agents. The low chemical softness and high chemical softness indices indicate the molecule has low reactivity. So, it can be predicted that the molecule will hardly interact with residues of the biomolecules.

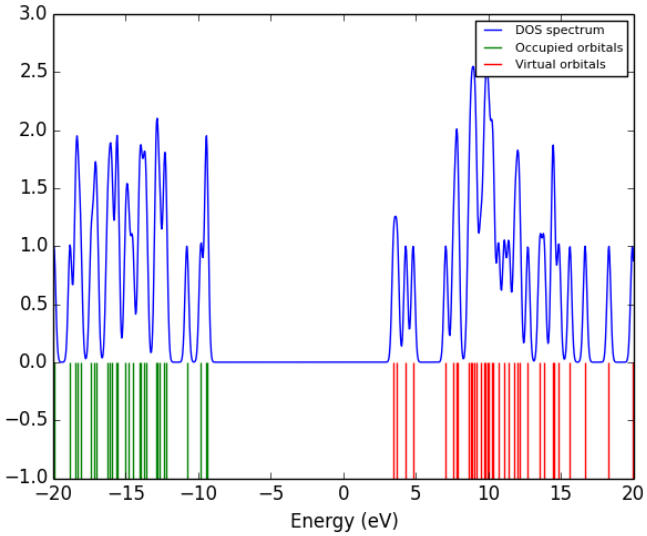

Fig. 3. The density of states (DOS) graph of esketamine

Table 1. Global reactivity indices of esketamine

Parameter	Energy value (eV)
HOMO	-9.40
LUMO	3.47
Ionization Potential (IP)	9.40
Electron Affinity (EA)	-3.47
Energy Gap (Eg)	12.87
Electronegativity (χ)	2.97
Chemical Potential (μ)	-2.97
Chemical Hardness (η)	6.44
Chemical Softness (S)	0.155
Electrophilicity index (ω)	0.685

2.2. Physicochemical descriptors and ADME parameters of the antagonist compound esketamine

In this study, SwissADME web tool was used in order to predict ADME parameters and pharmacokinetic attributes of the molecule under investigation as well as computation of physicochemical descriptors. In drug

discovery, ADME analysis of molecular structures is of particular importance in prediction of their drug likeness and relative oral bioavailability [24]. Fig. 4 indicates the predicted physicochemical graph of the title compound. The colored zone shows the suitable physicochemical space for oral bioavailability. Physiological properties of this compound is defined by a molecular weight of 237.73 g/mol, 16 heavy atoms, 6 aromatic heavy atoms, the fraction Csp3 of 0.46, 2 rotatable bonds, 2 hydrogen bond acceptors and 1 hydrogen bond donor . Moreover, topological polar surface area (TPSA) is 29.10 $Å^2$ and the molar refractivity is 66.03. Five predictive models are utilized to predict the lipophilicity and membrane permeation of the title compound. Based on calculations, iLog P of the compound is 2.36, XLog P3 is 2.18, WLog P is 2.79, MLog P is 2.46, SILICOS-IT is 3.59 and the consensus log $P_{O/W}$ is 2.68. Water solubility of the molecule significantly influences formulation and handling of the drugs and therefore is especially important in drug development and delivery. To predict water solubility three models were utilized to evaluate the molar solubility in water (log S). In this respect the compound is placed into six categories: 1) Insoluble (Log S < -10), 2) Poorly soluble (-10< Log S< -6), 3) Moderately soluble (-6< Log S< -4), 4) Soluble (-4< Log S< -2), 5) Very soluble (-4< Log S< -2) and 6) Highly soluble (Log S > 0). Based on ESOL model Log S of the compound is -2.83 (solubility: 3.49e-01 mg/ml; 1.47e-03 mol/l) and based on Ali et al., model Log S is -2.42 (solubility: 8.95e-01 mg/ml ; 3.76e-03 mol/l) determining the compound to be water soluble. On the other hand, according to SILICOS-IT model Log S is -5.00 (solubility: 2.36e-03 mg/ml ; 9.93e-06 mol/l) putting the compound in moderately soluble category. The pharmacokinetic properties estimate ADME characteristics of the drug. This compound has a high gastrointestinal (GI) absorption and permeates through blood-brain barrier (BBB). In addition, identifying CYP 450 inhibitory potential of the compound is important in predicting any drug-drug interactions and adverse effects since drug biotransformation is heavily dependent on CYP 450 isoenzyme family. The investigated compound has an inhibitory effect on CYP2D6 isoform. The skin permeation index (Log Kp) is calculated using lipophilicity and molecular weight of the compound. Lower skin permeability is associated with the more negative values. The calculated Log Kp for this molecule is -6.20 cm/s. Drug likeness is evaluated based on bioavailability score and adherence to Lipinski's rule (MW≤ 500 Daltons, NH or OH (hydrogen bond donors) ≤5, N or O (hydrogen bond acceptors) ≤10 and MLog P ≤4.15) [25]. The bioavailability score of the title compound is 0.55 and it abides Lipinski's rule.

Fig. 4. The physicochemical properties graph of esketamine

2.3. Molecular docking analysis of esketamine binding to the NMDA receptors

The survey through previous studies determines the therapeutical effects of Esketamine in treatment-resistant major depressive disorder through glutamate systems [26]. Therefore, the binding of this compound to four NMDA receptor subtypes namely, NR1, NR2A, NR2B and NR2D and their interactions were analyzed in this article. The three dimensional crystal structures of the said receptors were obtained from protein data bank (PDB) and the docking analysis was performed using Molegro Virtual Docker (MVD) program. Fig. 5 shows the esketamine binding to the NR1 residues. -53.112 is the MolDock score for the ligand-receptor complex formation. It can be seen from the data of the Table 2, the scores of the steric and hydrogen bond interactions between esketamine and NR1 residues are -48.153 and -0.004,

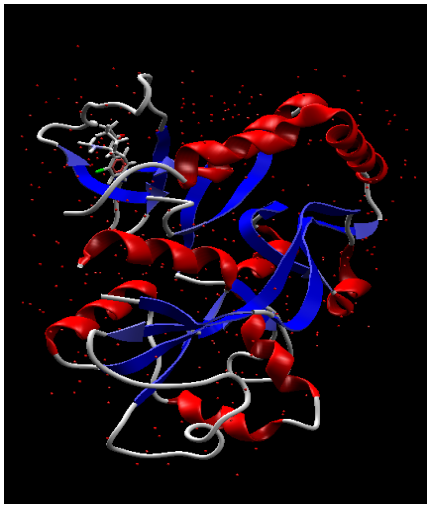

Fig. 5. Ligand esketamine embedded in the active site of the NR1

respectively. So, the steric interactions play main role in binding of the said antagonist compound to the active site of the receptor. On the other hand, -25.858 is MolDock score of the water-ligand interactions. Esketamine makes hydrogen bonds with Val 34 and three water molecules. The residues Asp 291, Tyr 287, Gln 288, Val 34, Thr 33, Val 39, Thr 283, Phe 32, Tyr 18, Trp 284 and Tyr 64 interact with esketamine by steric interactions. In overall, the main interactions between the said medicinal compound and the NR1 receptor relate to the residues Tyr 287, Val 34, Gln 288, Tyr 18 and Thr 33 (Table 3).

Fig. 6 indicates Esketamine embedded in the active site of NMDA receptor. From the data of the Table 4, the compound-NR2A complex is mainly formed via steric interactions with MolDock score of -82.487. The hydrogen bond interactions score is 0.000. So, the hydrogen bond interactions do not have a role in the formation of the compound-NR2A complex. Moreover, the scores of internal ligand interactions (torsional strain and steric interaction) are 0.380 and 18.137, respectively. Considering both internal and external interactions of the compound-NR2A complex, the total energy score of the system is -70.031.

Table 2. The esketamine-NR1 interactions

Interactions		MolDock Score
Protein-Ligand Interactions	Steric (by PLP)	-48.153
	Steric (by LJ12-6)	-8.872
	Hydrogen bonds	-0.004
	Hydrogen bonds (no directionality)	-0.810
Water-Ligand Interactions		-25.858
Internal Ligand Interactions	Torsional strain	0.549
	Steric (by PLP)	20.355
	Steric (by LJ12-6)	69.794
External and Internal Ligand Interactions	Total Energy	-53.112

Our docking analysis indicates that steric interactions play the main role in the formation of compound-NR2A complex formation. The residues Trp 255, Phe 76, Gln 258, Ile 259 participate in steric interactions with the compound. It can be observed from the data presented in Table 5 that the NR2A residues containing Trp [A] 255, Phe [A] 76, Val [A] 74, Gln [A] 258, Asn [A] 7 are the main amino acids involved in the ligand-receptor complex formation.

The data regarding the compound's interaction with NR2B is presented in Table 6. It is deduced from the data that the compound-NR2B complex (Fig. 7) is majorly formed via steric interaction with moldock score of -105.410.

Table 3. The participated NR1 residues in ligand-receptor interactions

Residue/HOH	Total energy score
Tyr [A] 287	-11.5947
Val [A] 34	-10.0262
Gln [A] 288	-6.41797
Tyr [A] 18	-5.87959
Water HOH [A] 296	-5.84583
Thr [A] 33	-5.38938
Water HOH [A] 178	-4.47778
Water HOH [A] 193	-4.41068
Trp [A] 284	-2.80150
Water HOH [A] 237	-2.16946
Water HOH [A] 18	-1.90884
Phe [A] 32	-1.56969
Water HOH [A] 15	-1.52534
Water HOH [A] 88	-1.16120
Water HOH [A] 226	-1.15213
Water HOH [A] 222	-1.12227
Tyr [A] 64	-0.691924
Water HOH [A] 95	-0.461427
Thr [A] 283	-0.456408
Water HOH [A] 149	-0.426421
Water HOH [A] 161	-0.400000
Val [A] 39	-0.362442
Asp [A] 291	-0.343794
Water HOH [A] 291	-0.322266

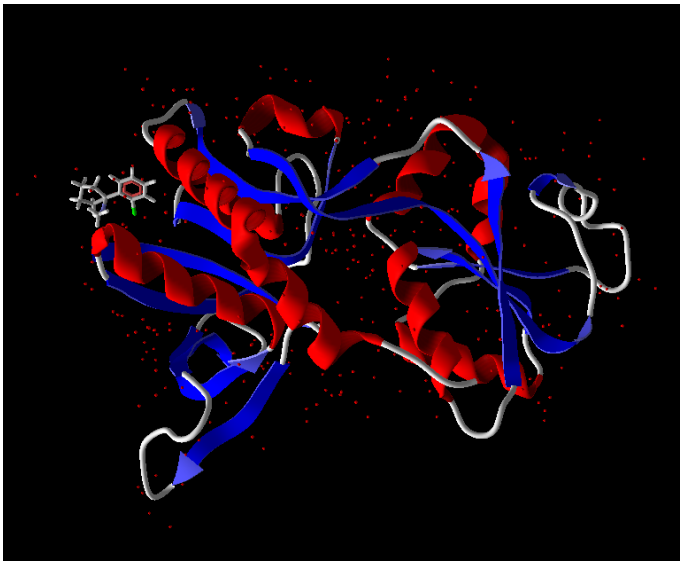

Fig. 6. Ligand esketamine embedded in the active site of the NR2A

Table 4. The esketamine-NR2A interactions

Interactions		MolDock Score
Protein-Ligand Interactions	Steric (by PLP)	-82.487
	Steric (by LJ12-6)	-14.005
	Hydrogen bonds	0.000
	Hydrogen bonds (no directionality)	-2.500
Water-Ligand Interactions		-6.063
Internal Ligand Interactions	Torsional strain	0.380
	Steric (by PLP)	18.137
	Steric (by LJ12-6)	70.322
External and Internal Ligand Interactions	Total Energy	-70.031

Table 5. The participated NR2A residues in ligand-receptor interactions

Residue/HOH	Total energy score
Trp [A] 255	-37.9078
Phe [A] 76	-11.2410
Val [A] 74	-9.03873
Gln [A] 258	-8.51370
Asn [A] 7	-5.99272
Ile [A] 259	-4.66848
Water HOH [A] 161	-1.91010
Lys [A] 75	-1.85910
Water HOH [A] 96	-1.52176
Water HOH [A] 216	-1.35770
Met [A] 110	-0.999572
Water HOH [A] 67	-0.973154
Val [A] 109	-0.438062
Pro [A] 254	-0.355752

The score of hydrogen bond interactions is -3.635. Therefore, the hydrogen bond interactions do not have an important role in the formation of the compound-NR2B complex. Furthermore, the scores for internal ligand interactions (torsional strain and steric interaction) are 0.138 and 50.784, respectively. With regards to both internal and external interactions of the compound-NR2B complex, the total energy score of the system is -91.562. Our docking analysis indicates that steric interactions play the main role in the formation of compound-NR2B complex formation. The residues Gly 128 and Ser 131 are involved in hydrogen interactions of compound-NR2B complex and Tyr 282, Ser 131, Ser 260, Met 132 and Asp 104 participate in steric interactions with the compound.

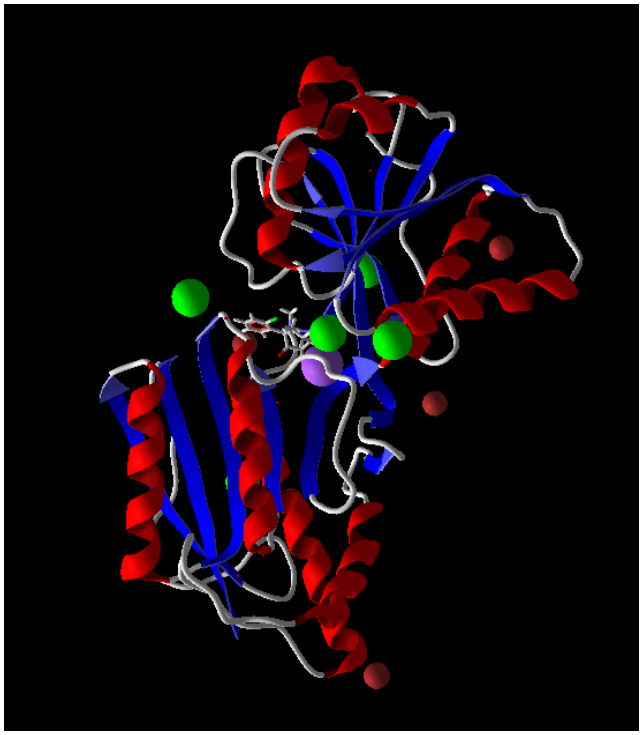

Fig. 7. Ligand esketamine embedded in the active site of the NR2B

Table 6. The esketamine-NR2B interactions

Interactions		MolDock Score
Protein-Ligand Interactions	Steric (by PLP)	-105.410
	Steric (by LJ12-6)	-33.495
	Hydrogen bonds	-3.635
	Hydrogen bonds (no directionality)	-5.000
Cofactor-Ligand Interactions		-3.440
Internal Ligand Interactions	Torsional strain	0.138
	Steric (by PLP)	50.784
	Steric (by LJ12-6)	70.492
External and Internal Ligand Interactions	Total Energy	-91.562

It can be observed from the data presented in Table 7 that the NR2B residues containing Gly [A] 128, His [A] 127, Gly [A] 264, Tyr [A] 282, Ser [A] 131, Asp [A] 265, Ser [A] 260 and Met [A] 132 are the main amino acids involved in the ligand-receptor complex formation.

On the other hand, the Cofactor [A] 601 and Cofactor [A] 901 of NR2B interact with the molecule with the energy scores of -1.20322 and -0.469178, respectively.

The data pertaining interactions of compound-NR2D complex (Fig. 8) is presented in Table 8. It is concluded that the compound-NR2D complex is majorly formed via steric interaction with moldock score of -71.414. The score for hydrogen bond interactions is -0.579 thus, the hydrogen bond interactions do not play an important role in the formation of the compound-NR2D complex. Furthermore, the scores for internal ligand interactions (torsional strain and steric interaction) are 0.826 and 17.189, respectively. With respect to both internal and external interactions of the compound-NR2D complex, the total energy score of the system is -55.261. Our docking analysis indicates that steric interactions play the main role in the formation of compound-NR2D complex formation. The residues Ser 173, Water HOH 301, Water HOH 305 and Water HOH 319 are involved in hydrogen interactions of compound-NR2D complex and Ser 173, His 88, Asp 215, Gly 172, Thr 174, Tyr 214, Thr 116, Ser 114 and Arg 121 participate in steric interactions with the compound. It can be observed from the data presented in Table 9 that the NR2D residues containing Ser [A] 173, His [A] 88, Asp [A] 215, Leu [A] 115 and Gly [A] 172 are the main amino acids involved in the ligand-receptor complex formation.

Overall, the result extracted from molecular docking of esketamine suggests that the compound asserts its pharmacological effects mainly through interactions with NR2B receptors.

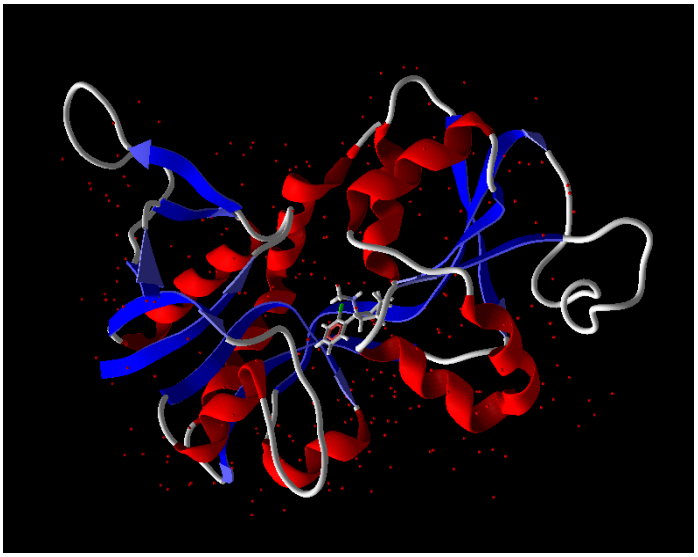

Fig. 8. Ligand esketamine embedded in the active site of the NR2D

Table 7. The participated NR2B residues in ligand-receptor interactions

Residue/HOH	Total energy score
Gly [A] 128	-18.8082
His [A] 127	-12.8141
Gly [A] 264	-11.2802
Tyr [A] 282	-10.7315
Ser [A] 131	-8.45072
Asp [A] 265	-7.68446
Ser [A] 260	-6.81750
Met [A] 132	-5.22460
Leu [A] 261	-3.35935
Asp [A] 104	-3.01595
Thr [A] 103	-2.82693
Glu [A] 284	-2.81744
Gly [A] 129	-2.62726
Ser [A] 281	-1.82832
Cofactor [A] 701	-1.76759
Asp [A] 102	-1.74925
Phe [A] 146	-1.51536
Arg [A] 292	-1.36775
Cofactor [A] 601	-1.20322
Asp [A] 101	-0.907844
Pro [A] 148	-0.650140
Gly [A] 147	-0.530951
Cofactor [A] 901	-0.469178
Ile [A] 126	-0.433673

Table 8. The esketamine-NR2D interactions

Interactions		MolDock Score
Protein-Ligand Interactions	Steric (by PLP)	-71.414
	Steric (by LJ12-6)	111.577
	Hydrogen bonds	-0.579
	Hydrogen bonds (no directionality)	-7.070
Water-Ligand Interactions		-1.283
Internal Ligand Interactions	Torsional strain	0.826
	Steric (by PLP)	17.189
	Steric (by LJ12-6)	70.178
External and Internal Ligand Interactions	Total Energy	-55.261

Conclusions

Studying the reactivity and stability properties of the antagonist compound esketamine and its docking with NMDA receptor subunits are the main purposes of the present investigation. To attain these chemical and biochemical properties, the molecular structure of the title medicinal molecular structure was optimized at B3LYP/ 6-311++G(d,p) basis set of theory and then its binding with NMDA receptor subunits was analyzed using MVD software. The ligand-receptor complex docking analysis shows the said compound asserts its pharmacological effects mainly through interactions with NR2B receptors and the NR2B residues containing Gly [A] 128, His [A] 127, Gly [A] 264, Tyr [A] 282, Ser [A] 131, Asp [A] 265, Ser [A] 260 and Met [A] 132 are the main amino acids involved in the ligand-receptor complex formation.

Table 9. The participated NR2D residues in ligand-receptor interactions

Residue/HOH	Total energy score
Ser [A] 173	-15.8784
His [A] 88	-10.3355
Asp [A] 215	-8.72199
Leu [A] 115	-7.85957
Gly [A] 172	-7.31085
Water HOH [A] 13	-4.98390
Thr [A] 174	-4.92955
Water HOH [A] 31	-4.61998
Tyr [A] 214	-3.92886
Thr [A] 116	-3.87822
Glu [A] 14	-3.25040
Tyr [A] 245	-2.73742
Val [A] 169	-2.54650
Water HOH [A] 119	-2.32104
Thr [A] 168	-1.07218
Ser [A] 114	-0.896528
Glu [A] 175	-0.766534
Gly [A] 135	-0.569837
Gly [A] 89	-0.567024
Water HOH [A] 19	-0.541538
Asn [A] 171	-0.455907
Ile [A] 213	-0.372001
Water HOH [A] 24	0.365572
Water HOH [A] 12	2.98629
Water HOH [A] 6	3.69525
Water HOH [A] 17	4.63107
Arg [A] 121	7.16538

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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References:

[1] F.S. Correia-Melo, G.C. Leal, M.S. Carvalho, A.P. Jesus-Nunes, C.B. Ferreira, F. Vieira, G. Magnavita, L.A. Vale, R.P. Mello and C. Nakahira, Comparative study of esketamine and racemic ketamine in treatment-resistant depression: Protocol for a non-inferiority clinical trial. *Medicine*, 97 (2018) e12414.

[2] J.W. Murrough, C.G. Abdallah and S.J. Mathew, Targeting glutamate signalling in depression: progress and prospects. *Nature Reviews Drug Discovery*, 16 (2017) 472.

[3] C. Pittenger, G. Sanacora and J.H. Krystal, The NMDA receptor as a therapeutic target in major depressive disorder. *CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders)*, 6 (2007) 101-115.

[4] J.W. Murrough, Ketamine for depression: an update. *Biological psychiatry*, 80 (2016) 416-418.

[5] C. Andrade, Ketamine for depression, 3: does chirality matter? *The Journal of clinical psychiatry*, 78 (2017) e674-e677.

[6] R. Machado-Vieira, G. Salvadore, N. DiazGranados and C.A. Zarate Jr, Ketamine and the next generation of antidepressants with a rapid onset of action. *Pharmacology & therapeutics*, 123 (2009) 143-150.

[7] J.B. Singh, M. Fedgchin, E. Daly, L. Xi, C. Melman, G. De Bruecker, A. Tadic, P. Sienaert, F. Wiegand and H. Manji, Intravenous esketamine in adult treatment-resistant depression: a double-blind, double-randomization, placebo-controlled study. *Biological psychiatry*, 80 (2016) 424-431.

[8] E.J. Daly, J.B. Singh, M. Fedgchin, K. Cooper, P. Lim, R.C. Shelton, M.E. Thase, A. Winokur, L. Van Nueten and H. Manji, Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. *JAMA psychiatry*, 75 (2018) 139-148.

[9] T.K. Vyas, A. Shahiwala, S. Marathe and A. Misra, Intranasal drug delivery for brain targeting. *Current drug delivery*, 2 (2005) 165-175.

[10] D.S. Quintana, N.E. Steen and O.A. Andreassen, The promise of intranasal esketamine as a novel and effective antidepressant. *JAMA psychiatry*, 75 (2018) 123-124.

[11] M. Nabati, M.-a. Kermanian, H. Mohammadnejad-Mehrabani, H. Rahbar Kafshboran, M. Mehmannavaz and S. Sarshar, Theoretical Investigation on the Antitumor Drug: ThioTEPA and its Interaction with S-donor Biomolecules and DNA Purine Bases. *Chemical Methodologies*, 2 (2018) 128-140.

[12] M. Nabati and M. Mahkam, DFT Study of the Six-Membered Heterocyclic SinN6-nHn (n= 0-6): Stability and Aromaticity. *Organic Chemistry Research*, 2 (2016) 70-80.

[13] M. Nabati, Reactivity and aromaticity of hexasiline derivatives Si6XH5 (X= H, F, Cl, Br, COOH, NO2, NH2, CH3 and tBu). *Journal of Physical & Theoretical Chemistry*, 14 (2018) 283-293.

[14] M. Nabati, Prediction of the Structural and Spectral Properties and Reactivity of the Silicon Analogs of Cyclobutadiene C4-nSinH4 (n=0-4) by Density Functional Theory Computations. *Chemical Methodologies*, 1 (2017) 121-135.

[15] M. Nabati, Prediction of the structural and spectral properties for L, L-ethylenedicysteine diethylester (EC) and its complex with Technetium-99m radionuclide. *Journal of Physical & Theoretical Chemistry*, 14 (2017) 49-61.

[16] M. Nabati and H. Sabahnoo, Spectroscopic (FT-IR and UV-Vis), electronic and docking studies on the red clover isoflavone irilone as a progesterone receptor (PR) effect supporter in endometrial and ovarian cancer cell lines. *Journal of Medicinal and Chemical Sciences*, 2 (2019) 118-125.

[17] M. Nabati, Modeling and interactions analysis of the novel antagonist agent flibanserin with 5-hydroxytryptamine 2A (5-HT2A) serotonin receptor as a HSDD treatment in premenopausal women. *Iranian Chemical Communication*, 7 (2019) 324-334.

[18] M. Nabati, H. Sabahnoo, E. Lohrasbi and M. Mazidi, Structural Properties Study and Spectroscopic (FT-IR and UV-Vis) Profiling of the Novel Antagonist LY2157299 as a Transforming Growth Factor-β (TGF-β) Receptor I Kinase Inhibitor by Quantum-mechanical (QM) and Molecular Docking Techniques. *Chemical Methodologies*, 3 (2019) 377-391.

[19] M. Nabati, Insight into the Stability, Reactivity, Structural and Spectral Properties of the Anti, Syn-endo and Syn-exo Isomers of Bis(N-ethoxy-N-ethyl-dithiocarbamato)Nitrido Technetium-99m [99mTc-N(NOEt)2] Radiopharmaceutical. *Chemical Methodologies*, 2 (2018) 223-238.

[20] M. Nabati, Structural and spectral (IR, UV-Vis, CD and DOS) properties of active substance d,l-HMPAO and its complex with technetium-99m radionuclide 99mTc-exametazime. *Iranian Journal of Organic Chemistry*, 10 (2018) 2457-2465.

[21] M. Nabati, Insight into the structural and spectral (IR and UV-Vis) properties of the salts of alkali (Li, Na and K) and alkaline earth (Be, Mg and Ca) metals with pertechnetate oxoanion (99mTcO4-) as the convenient water-soluble sources of the radioactive element technetium. *Asian Journal of Green Chemistry*, 3 (2019) 258-270.

[22] A. Kumer, N. Sarker, S. Paul and A. Zannat, The Theoretical Prediction of Thermophysical properties, HOMO, LUMO, QSAR and Biological Indics of Cannabinoids (CBD) and Tetrahhdrocannabinol (THC) by Computational Chemistry. *Advanced Journal of Chemistry, Section A: Theoretical, Engineering and Applied Chemistry*, 2 (2019) 190-202.

[23] M. Rahimi, S. Jamehbozorgi, H. Chermette, R. Ghiasi and M. Poor Kalhor, Computational study of substituent effect on the electronic properties of ferrocylidene acetophenones complexes. *Iranian Chemical Communication*, 7 (2019) 472-479.

[24] M. Nabati and M. Mahkam, pH-sensitive nano carriers for oral-curcumin delivery. *Iran. J. Org. Chem*, 5 (2013) 1157-1161.

[25] K.K. Alisher, T.S. Khamza and Y.S. Ikbol, Quantum-chemical study of geometric and energy characteristics of some bases of shiff gossipol. *Progress in Chemical and Biochemical Research*, 2 (2019) 1-5.

[26] F. Abdollahi, A. Taheri and M. Shahmari, Application of selective solid-phase extraction using a new core-shell-shell magnetic ion-imprinted polymer for the analysis of ultra-trace mercury in serum of gallstone patients. *Separation Science and Technology*, (2019) 1-14.