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Non-competitive *N*-methyl-*D*-aspartate (NMDA) receptor (NR2B) structure in complex with antidepressant arketamine

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Abstract: The present research study relates to investigation of the electronic properties of the novel medicinal compound arketamine as a treatment of major depressive disorder using density functional theory (DFT) method. In first step, the molecular structure of the title compound is optimized at B3LYP/6-311++G(d,p) level of theory at room temperature. Then, its stability and reactivity properties are calculated by frontier molecular orbitals (FMOs) energies. The global reactivity indices show this medicinal molecule is a more stable compound and has low reactivity.On the other hand, the docking analysis of the ligand-receptor complex shows the steric interactions play the main role in this complex formation. Also, the data shows the NR2B residues containing Gly [A] 128, His [A] 127, Tyr [A] 282, Gly [A] 264, Asp [A] 265, Met [A] 132 and Ser [A] 131 are the major amino acids participating in the arketamine-NR2B complex formation. In overall, the results of molecular docking analysis show an intermediate affinity to NR2B subunit of NMDA receptor.

Keywords: Arketamine, Major depressive disorder, Molecular docking, Molecular simulation, N-methyl-D-aspartate receptor,Treatment-resistant depression.

Introduction

Major depressive disorder (MDD) is one of the most infamous and oldest medical conditions determined by disturbances of cognition as well as neurovegetative and psychomotor functions [1]. The World Health Organization estimates the number of individuals afflicted by MDD to be well over 300 million worldwide. Despite the fact that the most commonly used antidepressants are generally effective in managing MDD, still about two out of three patients show resistance to pharmacotherapy or are at the risk of relapsing [2]. This condition is recognized as treatment-resistant depression (TRD) which is defined by inadequate response in patients following adequate therapy with antidepressants [3].

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Furthermore, the full beneficial effects of antidepressants are usually witnessed after weeks of therapy with antidepressants [4]. Consequently, targeting alternative signaling pathways to manage TRD as well as achieving more rapid responses have become areas of interest in designing new generations of antidepressants. A body of evidence associate many aspects of the glutamate system with the pathophysiological pathways involved in depression. For instance, elevated levels of glutamate was observed in plasma, cerebrospinal fluid and the brain of patients afflicted with MDD and gene expression of N-methyl-D-aspartate receptors were shown to be altered. NMDA receptors consist of two NR1 and two NR2 subunits (and NR3 less frequently expressed). NR2 subunits are categorized into NR2A–NR2D and NR2A and NR2B are recognized as the most common subunits in the central nervous system. In this regard, targeting glutamate system and NMDA receptors

seems promising in management of MDD [5]. More recently, ketamine, an NMDA receptor antagonist, has been considered as a fast acting antidepressant in treatment of TRD [6]. Ketamine is a racemic mixture of two enantiomers R-ketamine and S-ketamine [7]. Efficacy and safety of S-Ketamine has been extensively investigated in various studies [8] and the intranasal formulation was granted FDA approval in 2019. However, more recent studies have provided evidences suggesting more potent and longer-lasting antidepressant properties in R-Ketamine compared with S-Ketamine [9]. Furthermore, racemic Ketamine and S-Ketamine consumption is associated with dissociative and psychotomimetic symptoms which are absent in R-Ketamine [10]. As a result, R-Ketamine could be considered a potentially more useful antidepressant than racemic and S-Ketamine and further exploration of this drug's properties seems necessary. Previous studies have determined S-Ketamine to possess up to four times more affinity towards NMDA receptors [11]. The general consensus is that the R isomer of Ketamine mainly exerts its antidepressant effects via binding and interaction with Sigma receptors [12] which are modulatory proteins consisting of two Sigma 1 and Sigma 2 subunits and are believed to mediate antidepressant activities [13].

Results and discussion

Arketaminestructural properties study

Arketamine molecular structure is shown in Figure **1**. The title compound has a carbonyl group and an amine functional group in its structure. The chlorobenzene ring and methylamine group are bonded to one carbon center. So, this center has four different atomic groups and shows rotation in CD graph as an enantiomer structure. The right-hand image in Figure **1** indicates the optimized molecular geometry of the said compound. Arketamine molecule is optimized using density functional theory (DFT) method by B3LYP/6-311++G(d,p) basis set of theory. All computations are done at room temperature. The results of the computations show the cyclohexanone ring prefers the boat structure. It is happened due to the large groups that are attached to the alpha carbon. Figure **2** indicates the dependence between the theoretical and experimental bond lengths of the medicinal compound arketamine. This dependence is shown by the equation y=1.0122x-0.034. The higher correlation coefficient (R^2=0.9692) 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.

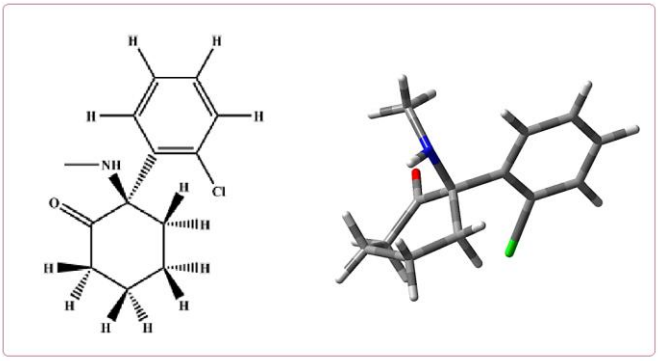

Figure 1: The theoretical geometric structure of arketamine.

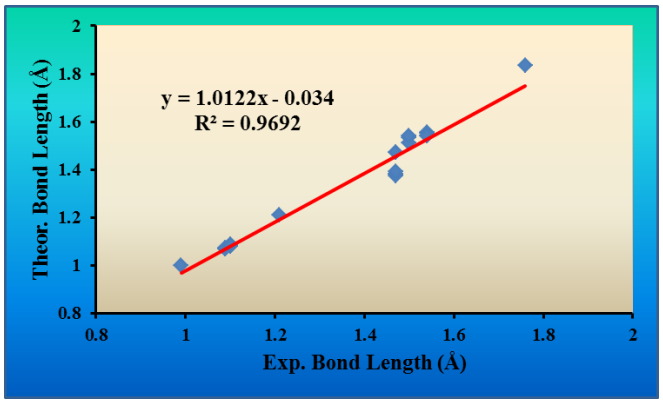

Figure 2: The experimental and theoretical bond lengths relationship of arketamine.

Stability and reactivity study of the medicinal compoundarketamine

Stability and reactivity are two important parameters to describe an organic compound. These chemical properties are gained using the frontier molecular orbitals (FMOs) calculations. The highest occupied and the lowest unoccupied molecular orbitals (HOMO and LUMO) are the frontier molecular orbitals of a chemical compound. The HOMO is filled with electrons and in contrast the LUMO is empty of electron. The title properties of a medicinal substance can be studied using the global reactivity indices [18-22].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]:

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

$$IP = -E_{HOMO}$$

$$EA = -E_{LUMO}$$
$$= \frac{(\varepsilon_{LUMO} - \varepsilon_{HOMO})}{2}$$
$$\chi = \frac{-(\varepsilon_{LUMO} + \varepsilon_{HOMO})}{2}$$
$$\mu = \frac{(\varepsilon_{LUMO} + \varepsilon_{HOMO})}{2}$$
$$\omega = \frac{\mu^2}{2}$$
$$S = \frac{1}{}$$

Figure **3** shows the graphs of the frontier molecular orbitals (HOMO and LUMO) of arketamine. The HOMO graph shows all segments of the title compound can have valence electrons. In contrast, the lowest unoccupied molecular orbital relates to the participation of the elements of the chlorobenzene ring. So, it can be predicted that the unsaturated benzene ring can play main role in arketamine binding to the NR2B receptor. From the data of the Table **1**, the HOMO and LUMO energy levels are -9.23 eV and 3.65, respectively. The big energy gap of the frontier molecular orbitals (Figure **4**) indicates high stability of the title medicinal compound. The HOMO/LUMO energy levels gap is 12.88 eV. Also, the density of states graph shows the importance of the virtual orbitals. So, it can be said the title compound prefers to interact with electrophile agents or residues. On the other hand, the high chemical hardness and the low chemical softness indices show the molecule is a stable compound against oxidant and reductant agents. The molecular electrostatic potential (MEP) graph of arketamine can be shown in Figure **5**. The red, green and blue colors in this graph show the regions of the molecules with negative, zero and positive charges, respectively. It seems the charge density of the entire of molecule equals to zero. So, it can be deduced that the molecule under study has low reactivity.

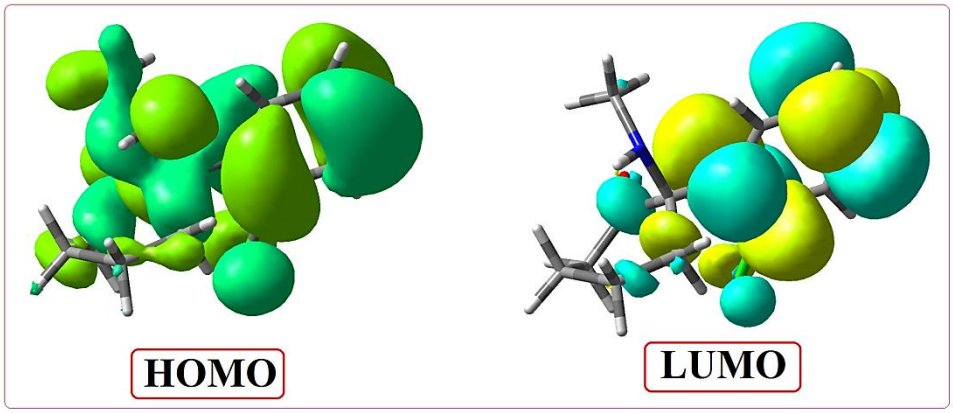

Figure 3: The frontier molecular orbitals of arketamine

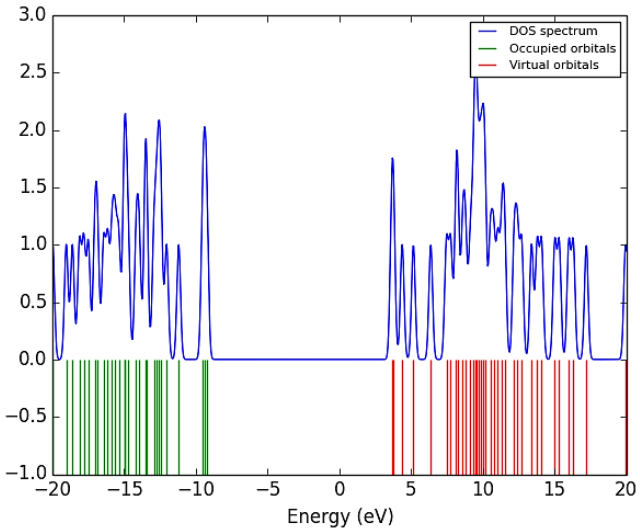

Figure 4: The density of states (DOS) graph of arketamine

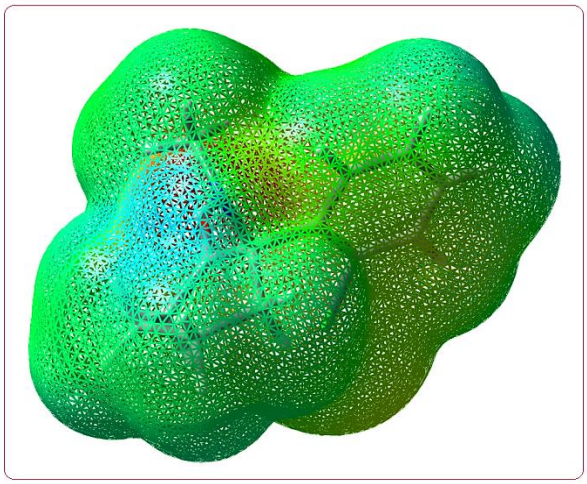

Figure 5: The molecular electrostatic potential (MEP) graph of arketamine.

Table 1: Global reactivity indices of arketamine.

Parameter	Energy value (eV)
HOMO	-9.23
LUMO	3.65
Ionization Potential (IP)	9.23
Electron Affinity (EA)	-3.65
Energy Gap (Eg)	12.88
Electronegativity (χ)	2.79
Chemical Potential (μ)	-2.79
Chemical Hardness (η)	6.44
Chemical Softness (S)	0.155
Electrophilicity index (ω)	0.604

Molecular docking analysis of arketamine-NR2B complex

The survey through previous studies determines the therapeutical effects of R-Ketamine in treatment-resistant major depressive disorder [24]. However, despite racemic and S-Ketamine, R-Ketamine is considered to convey its antidepressant properties via Sigma receptors and the drug's NMDA antagonist capacity is believed to be non-existent [25-27]. Therefore, the binding of this compound to NR2B subunit of NMDA receptor and drug-receptor interactions were investigated in this article. The three dimensional crystal structure of NR2B were obtained from protein data bank (PDB) and the docking analysis was performed using Molegro Virtual Docker (MVD) program. Figure **6** indicates R-Ketamine embedded in the active site of NR2B subunit. The data pertaining interactions of compound-NR2B complex is presented in Table **2**. It is deduced from the data that the compound-NR2B complex is mainly formed via steric interaction with moldock score of -90.239. The hydrogen bond interactions score is 0.000. Therefore, hydrogen bond interactions do not play a role in the compound-NR2B complex formation. Furthermore, the internal ligand interactions (torsional strain and steric interaction) scores are 0.399 and 18.526, respectively. With regards to both internal and external interactions of the compound-NR2B complex, the total energy score of the system is -74.395. The docking analysis determines that the steric interactionsplay the main role in the formation of compound-NR2B complex. Steric interactions of the title compound embedded in the active site of NR2B are shown in Figure **7**. The residues Tyr 282, Gly 264, Met 132, Asp 104, Arg 292 and Ser 260 are involved in steric interactions with the title compound. It can be observed from the data presented in Table **3** that the NR2B residues containing Gly [A] 128, His [A] 127, Tyr [A] 282, Gly [A] 264, Asp [A] 265, Met [A] 132 and Ser [A] 131 are the major amino acids participating in the ligand-receptor complex formation (Figure **8**). Overall, the results of R-Ketamine molecular docking suggests that as opposed to the general consensus regarding R-ketamine's lack of interaction with NMDA, based on total energy score of compound-NR2B complex (-74.395), the investigated compound shows an intermediate affinity to NR2B subunit of NMDA receptor.

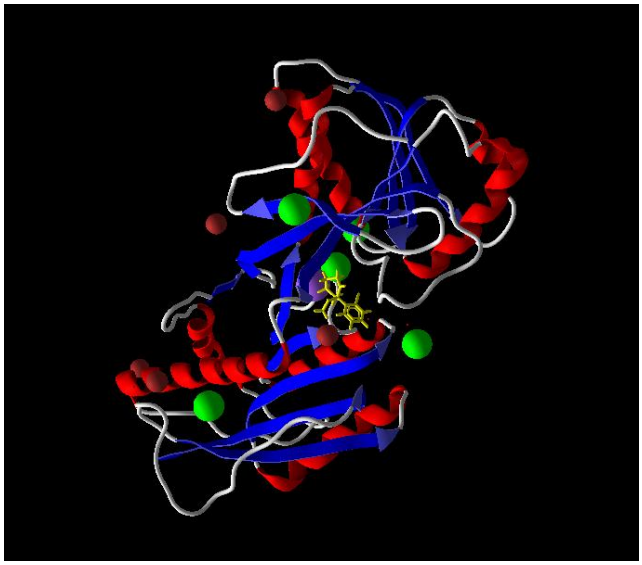

Figure 6: Ligand arketamineembedded in the active site of the NR2B receptor.

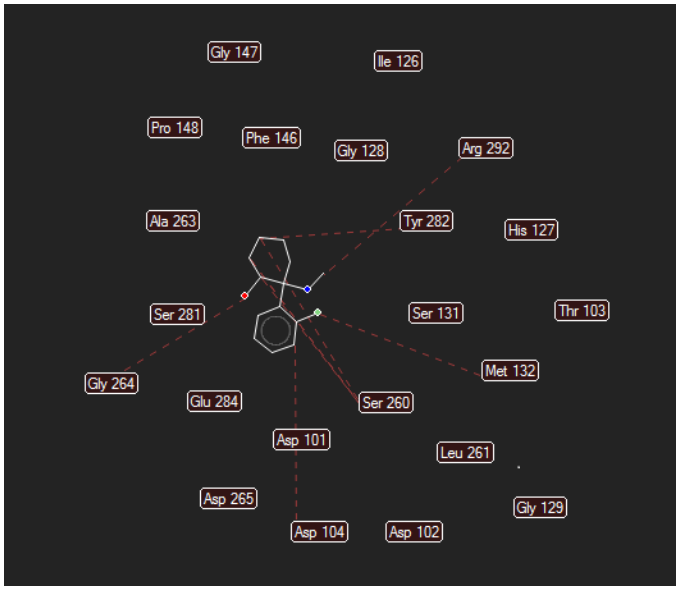

Figure 7: Steric interactions of ligandarketamineembedded in the active site of the NR2B receptor.

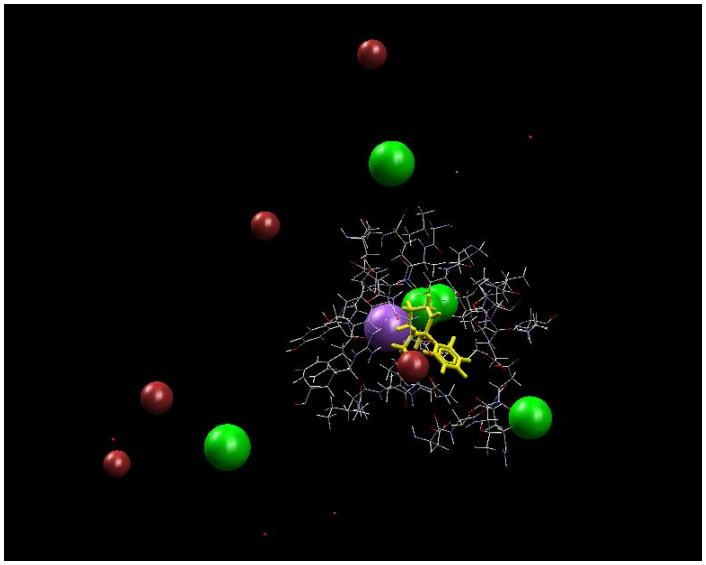

Figure 8: The interacted NR2B residues in ligand-receptor complex.

Table 2: The ligand-NR2B interactions.

Interactions		MolDock Score
Protein-Ligand Interactions	Steric (by PLP)	-90.239
	Steric (by LJ12-6)	85.009
	Hydrogen bonds	0.000
	Hydrogen bonds (no directionality)	0.000
Cofactor-Ligand Interactions		-3.082
Internal Ligand Interactions	Torsional strain	0.399
	Steric (by PLP)	18.526
	Steric (by LJ12-6)	66.461
External and Internal Ligand Interactions	Total Energy	-74.395

Table 3: The participated NR2Bresidues in ligand-receptor interactions.

Residue/HOH	Total energy score
Gly [A] 128	-14.4974
His [A] 127	-13.5641
Tyr [A] 282	-12.3596
Gly [A] 264	-10.6982
Asp [A] 265	-6.69139
Met [A] 132	-5.40466
Ser [A] 131	-5.20469
Ser [A] 281	-3.76899
Glu [A] 284	-3.37651
Asp [A] 104	-3.00483
Leu [A] 261	-2.84912
Thr [A] 103	-2.49656
Gly [A] 129	-2.46786
Asp [A] 102	-1.55446
Cofactor [A] 601	-1.54345
Arg [A] 292	-1.40142
Cofactor [A] 701	-0.978704
Asp [A] 101	-0.926834
Pro [A] 148	-0.608684
Cofactor [A] 901	-0.559497
Phe [A] 146	-0.549037
Ala [A] 263	-0.366255
Gly [A] 147	-0.354645
Ile [A] 126	-0.341174
Ser [A] 260	6.24767

Conclusions

The present research article relates to the molecular simulation and studying the stability and reactivity properties of the antidepressant molecule arketamine and its binding modes to the N-methyl-D-aspartate receptor (NR2B). The quantum mechanical (QM) computations show the molecule is a high stable compound and it has low reactivity against the oxidant and reductant agents. On the other hand, the molecular docking analysis shows the NR2B residues containing Gly [A] 128, His [A] 127, Tyr [A] 282, Gly [A] 264, Asp [A] 265, Met [A] 132 and Ser [A] 131 are the major amino acids participating in the arketamine-NR2B complex formation. In overall, the results of molecular docking analysis show an intermediate affinity to NR2B subunit of NMDA receptor.

Computational methods

Molecular simulation of the organic compounds and analysis of their binding to the macromolecules like proteins, receptors and enzymes are a new concept in drug discovery [14-16]. Molecular simulation is carried out by quantum mechanical (QM) studies [17]. So, the arketamine molecular structure will be optimized using density functional theory (DFT) in this study. In first step, arketamine molecular structure is optimized at B3LYP/6-311++G(d,p) level of theory in isolated form at room temperature using Gaussian 03 software. After molecular geometry optimization, the stability and reactivity properties of the title medicinal compound will be discussed using global reactivity indices. These parameters are calculated using the energy levels of the frontier molecular orbitals (FMOs). Finally, the complex formation between arketamine and NR2B receptor will be analyzed by molecular docking analysis. Our docking analysis is performed by Molegro Virtual Docker (MVD) program.

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