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Molecular Docking, ADMET Study and Drug Likeness Analysis for the Evaluation of Stimulating Effects of Ketamine on Dopamine D2 Receptor

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Abstract

Ketamine is an NMDA receptor antagonist that, in general, acts rapidly as an anesthetic. Due to its rapid onset of action, it is considered a preferable anesthetic agent. This study aims to evaluate the stimulating effects of Ketamine on the Dopamine D2 receptor 5AER (Chain: A). In this investigation, molecular docking of Ketamine has been performed against 5AER (Chain: A) protein associated with the stimulating effect. Several computer-based software and some online websites were used for the pharmacokinetic analysis of the ketamine. From the molecular docking, the lowest binding energy (-5.9 kcal/mol) was recorded, which ensures that ketamine shows the proper stimulating effect on the Dopamine D2 receptor. The ADMET study predicts the pharmacokinetic effects of Ketamine, whereas the Drug Likeness study confirms the possible oral bioavailability of Ketamine. That's why we hope that this study may be helpful towards the research community to think of Ketamine as an effective stimulating agent.

Keywords: NMDA; Molecular Docking; Pharmacokinetic Analysis; Non-Carcinogenic Effects; Non-Bonding Interactions; ADMET Prediction; Drug Likeness Study

Abbreviations: NMDA: N-Methyl-D-Aspartate; VGSCs: Voltage-Gated Sodium Channels; FDA: Food and Drug Administration; HCN: Hyperpolarization-Activated Cyclic Nucleotide; NO: Nitric Oxide; CGMP: Cyclic Guanosine-Mono-Phosphate; MGluR: Metabotropic Glutamate Receptors; CADD: Computer Aided Drug Design; ESP: Electrostatic Potential Analysis; HUMO: Highest Occupied Molecular Orbital; LUMO: Lowest Unoccupied Molecular Orbital; MEP: Molecular Electrostatic Potential

Introduction

Ketamine is a noncompetitive glutamatergic N-methyl-D-aspartate (NMDA) receptor antagonist, which was first synthesized in 1962 by Dr. Calvin Stevens of Wayne State University [1]. It is a well-known anesthetic agent that has been used for around 50 years for various purposes, including pain relief, treatment of neuropsychiatric disorders, depression, and schizophrenia treatment [2,3]. As a short-acting, injectable anesthetic for use in both human and veterinary purposes, ketamine has been sold in the United States since the 1970s [4]. This chemical substance, together with its salts, isomers, and salts of isomers, was added to Schedule III of the non-narcotic substances list under the Controlled Substances Act in 1999 [5]. Chemically, Ketamine is a hydro soluble aryl-cyclo-alkylamine having a molecular mass of 238 g/mol [6]. It exists as a racemic mixture of two enantiomers, (S)-ketamine and (R)-ketamine (or esketamine and arketamine), in equal amounts [7]. Both S- and R- enantiomers possess anesthetic and analgesic properties because of having binding affinity for the NMDA receptor, though (S)-ketamine is comparatively three to four-fold more potent than its R- enantiomer [8]. The United States Food and Drug Administration (FDA) approved the ketamine S-enantiomer, also known as esketamine, on March 5, 2019, recognizing its potent antidepressant properties [9].

Due to its rapid onset, short half-life (180 min), and lack of respiratory depression, ketamine is a preferable anesthetic agent that revitalized its interest in the research and development of new therapeutic agents [10]. In addition to its role in blocking NMDARs, it also has an impact on other receptors, such as dopaminergic, serotonergic, adrenergic, opioidergic, cholinergic, and sigma receptors [11,12]. Ketamine also affects a number of ion channels, including voltage-gated sodium channels (VGSCs), nicotinic acetyl-choline ion channels, delta, and mu-opioid agonists, opioid potentiation, hyperpolarization-activated cyclic nucleotide (HCN)-gated channels, nitric oxide (NO)-cyclic guanosine-mono-phosphate (cGMP) system, non-NMDA glutamate receptors, and metabotropic glutamate receptors (mGluR), as well as serotonin, noradrenaline, and dopamine reuptake transporters [13-15]. Additionally, Ketamine demonstrates a variety of diverse molecular actions, as evidenced by subsequent research [16], but it has a number of severe psychotomimetic or schizotypical side effects that impede treatment compliance [17].

In this study, we have performed molecular docking of Ketamine with the target protein of Ketamine named Dopamine D2 receptor [PDB ID: 5AER (Chain:A)] which directly interacts with the Dopamine D2 Receptor. We also performed molecular docking of Haloperidol (standard drug) with the same protein 5AER (Chain: A) for comparing the stimulating effect of Ketamine with the standard drug Haloperidol (Figures 1 & 2). Also, some other software-based study like ADMET and Drug likeness analysis was done just to guess the pharmacokinetic effects as well as the physical properties of Ketamine. We hope that our study will draw the attention of the research community to think Ketamine as the best stimulating agent [18,19].

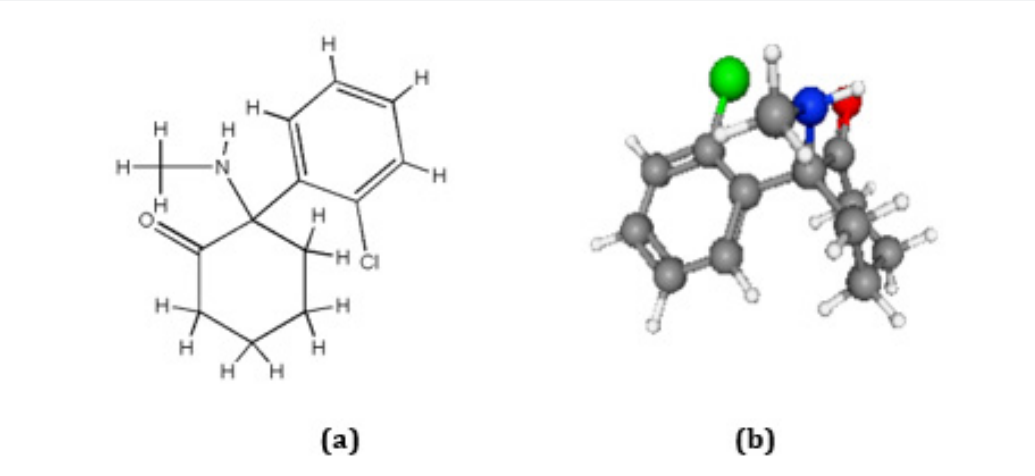

Figure 1: (a) 2D and (b) 3D structure of Ketamine.

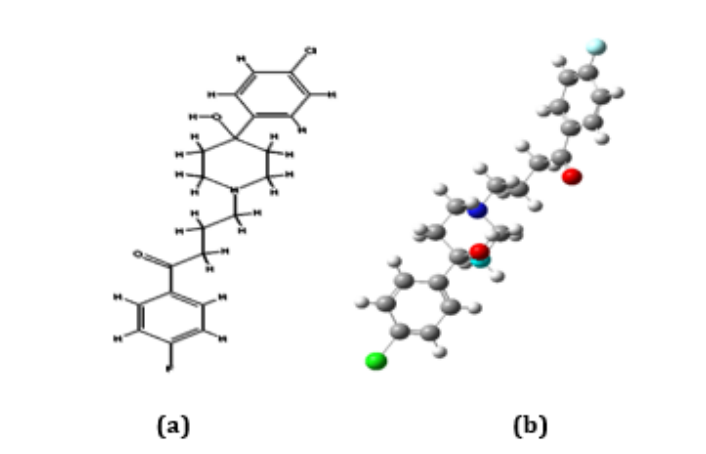

Figure 2: (a) 2D and (b) 3D structure of Haloperidol (Standard drug).

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Materials and Methods

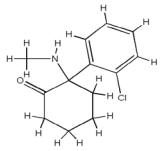
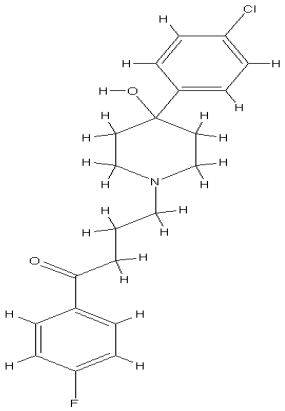
Software and online tools for computational study

In this study, we have used several kinds of required softwires and online websites for evaluating the stimulating effects of Ketamine. Several kinds of softwires like Gauss View 6.0, Gabedit, Swiss-PDB, Pymol, PyRx (Version 0.8), Discover Studio (2021) etc. are used for computer based analytical study. On the other hand, several online servers like Drug bank online, PubChem, RCSB:PDB, Webmo server, Online smile convertor, ADMET prediction, PASS prediction, Drug likeness etc. are used for developing the pharmacokinetic profile of the drug. From PubChem the 3D structure of Ketamine has been downloaded and through Gauss View 6.0 the drug is first cleaned and then symmetrized. Gabedit software is used for energy minimization of the ligand (Ketamine), whereas, Swiss-PDB (Version: 4.1.0) is used for the energy minimization of protein molecules. Discover Studio (2021) is used for protein visualization whereas, Pymol is used for docking visualization. Finally, PyRx is used for the docking analysis between ligand and protein molecules. On the other hand, several kinds of online websites like Pub Chem are used for downloading ligand's 3D structure, RCSB:PDB is used for downloading protein 3D structures in PDB format, Webmo server is used for deriving gaussian calculation results, Online smile convertor is used for creating smile number required for ADMET, PASS and Drug likeness prediction.

Ligand Preparation

For ligand preparation initially the Ketamine and the standard drug Haloperidol were searched in PubChem website and from there the drug were saved as mol file. Subsequently, the stored files were undergone through the Gabedit software for energy minimization. The ligands used for the docking against proteins are shown in the table below (Table 1).

Table 1: Molecular formula, weight and 2D structure of ligand molecules.

Ligand	Molecular Formula	Molecular Weight	2-D Structure
Ketamine	$C_{13}H_{16}ClNO$	237.72 g/mol	
Haloperidol	$C_{21}H_{23}ClFNO_2$	375.9 g/mol	

Protein Preparation

For protein selection initially the drug was searched through Drug bank and from its target sites a target protein named neuronal calcium sensor-1 (NCS-1) protein was selected which directly interacts with the Dopamine D2 Receptor and whose molecular weight is 50618.91 Da and uniprot ID is P14416. Then from RCSB PDB (protein data bank) the 3D structure of the selected protein [PDB ID: 5AER (Chain: A)] was collected at 2.19 Å resolution in PDB format. Then protein chain is prepared through Discover Studio (2016) by removing hetero atoms and water molecules. The selected protein with its PDB ID, molecular weight, sequence length, chain and crystal structure are presented in the (Table 2) below.

Molecular docking and visualization

In computer aided drug design (CADD), molecular docking simulation helps to predict the binding affinity of a ligand molecule with a protein molecule [20]. Molecular docking analysis was done by using PyRx software (0.8) considering the drug (both Ketamine and Haloperidol) as ligand and protein [5AER (Chain:A)] as macromolecules. Here, we performed rigid docking analysis where the rotatable bonds were transformed into non rotatable bonds. The grid box size recorded both for

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Ketamine and Haloperidol were respectively 41.0471, 39.3765 and 56.5965 Å along with x, y and z directions. After, performing docking the lowest binding affinity for each docking was recorded. Then the drug protein complex preparation was done by utilizing Pymol software and saved in PDB format which was further opened by Discovery Studio (2016) for non-bonding calculation and visualization. The non-bonding interactions were done for analyzing, visualizing and finally for the explanation of the docking results and different kinds of interactions between ligand and amino acid residues of target protein. The schematic representation of the entire molecular docking process is shown below (Figure 3).

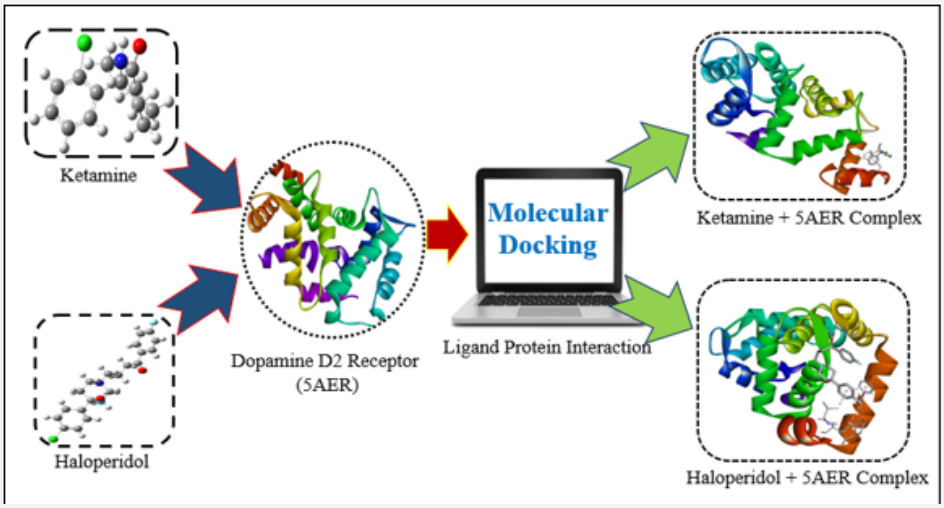

Figure 3: Schematic representation of molecular docking.

Geometry optimization details of Ketamine

In geometrical optimization generally the bond distance, bond angle and dihedral angles of ketamine drug were being calculated. To perform geometrical optimization initially the 3D structure of ketamine drug was collected in PDB format from PubChem an online source of structural database. Then the PDB format of Ketamine drug was run through Gabedit software for energy minimization and saved in mol format. Then Gaussian calculation was executed for optimization and frequency calculation simultaneously by using DFT (Density functional theory) along with B3LYP method and 6-31G basis set which results in check file (also known as standard or command file) and log file (also known as output file). From the log file geometric data (e.g. bond distance, bond angle and dihedral angles calculation), thermodynamic data (e.g. molecular form, molecular weight, internal energy, enthalpy, Gibb's free energy and dipole moment) and molecular orbital analysis (e.g. HUMO, LUMO, energy gap. hardness, softness, chemical potential) were being performed, whereas electrostatic potential analysis (ESP) was performed from check file. Webmo server was also used for thermodynamic data calculation. However, the following equations were used for molecular orbital analysis [21].

ADMET, PASS and drug likeness prediction

Different computational methods are used in computer aided drug design (CADD) for the pharmacokinetic analysis of a drug compound. For pharmacokinetic analysis first of all a smile number was created from online website named online smile convertor (https://cactus.nci.nih.gov/translate/). Usually, the pharmacological parameters of a drug consist of absorption, distribution, metabolism, excretion and its toxicity study which were predicted by utilizing available online web site named pkCSM (http://biosig.unimelb.edu.au/pkcsm/prediction) [22]. On the other hand, drug likeness predictions were explored from the available online website named SwissADME (http://www.swissadme.ch/). These sites actually assist a researcher to lessen the number of empirical experimentations and to promote the success of research outcomes [23].

Results and Discussion

Pre-molecular docking analysis

Before going through thermodynamic calculation, we first performed energy minimization of Ketamine drug by using Gabedit software where the lowest energy minimized structure found at 14.963954 Kcal/mol (Figures 4 & 5). After energy minimization the file is saved as mol file. On the other hand, the minimum energy found for several selected protein (5AER) was -11433.567 Kjmol-1.

Drug optimization and frequency analysis

The energy minimized structure was run for Gaussian calculation (optimization & frequency calculation) which provides

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two results respectively check file (input file) and log file (output file) (Figure 6). From, the log file geometric data, thermodynamic calculation and molecular orbital analysis were being performed, whereas from the check file only electrostatic potential analysis (ESP) were performed

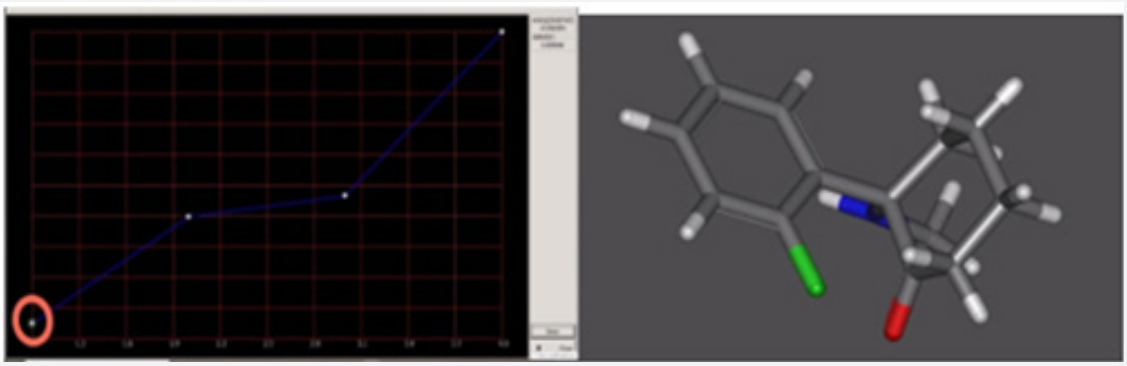

Figure 4: Energy minimization of Ketamine Drug.

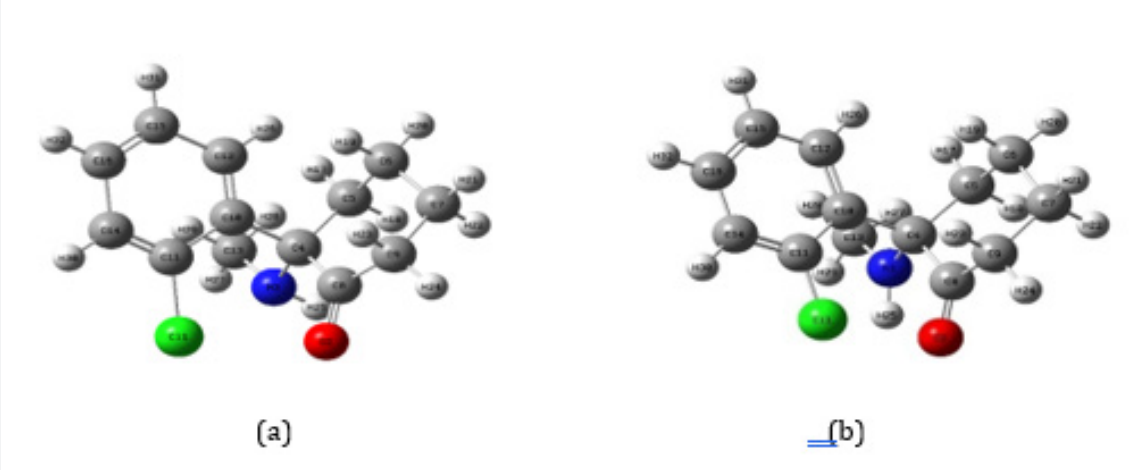

Figure 5: a) 3D structures of Ketamine before energy minimization, b) 3D structures of Ketamine after energy minimization.

Thermodynamic properties analysis

Thermodynamic analysis helps one to guess the stability of a chemical reaction as well as its kinetic reactions. Generally, in thermochemistry we try to analyze the enthalpy, gives free energy, dipole moment, internal energy, molecular form and its weight of a particular drug. Among these the enthalpy, gives free energy, dipole moment and internal energy are influenced by the chemical stability of a molecule and it also influence how much energy they absorb or release while a chemical reaction take place [24,25]. For thermodynamic calculation the log file is inputted into Webmo server for thermodynamic calculation (Table 3).

The spontaneous binding of a drug molecule with protein has been identified from the negative sign of energy. The more negative will be the energy value, the closer bond formation with available bindings site will be possible [26,27]. Here electronic energy, enthalpy, Gibb's free energy are respectively-1094.703327 Hartree, -1094.702383 Hartree, -1094.759831 Hartree which possess highly negative value. This alludes that Ketamine has available binding sites where close bond formation will be possible. On the other hand, dipole moment also bears high significance value which depicts the electronic property of a molecule. If the dipole moment becomes high then a molecule will be more polar and more intermolecular interactions will take place [28,29]. Here ketamine drug possesses high dipole moment (4.6399 Debye) which is a sign of proof for the drug having high non-bonding interactions with high molecular bond affinity and H-bond formation in a drug protein complex [30,31].

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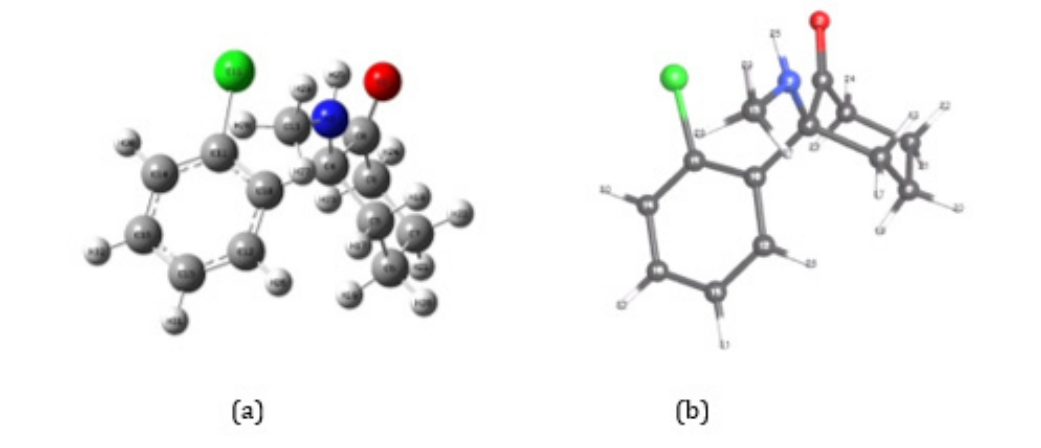


Figure 6: 3D structure of Ketamine after Optimization and Frequency Calculation (a) figure from gaussian software, (b) figure from Webmo server.

Table 2: Crystal structure of targeted protein.

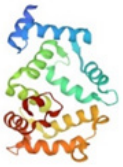
Protein Name	PDB ID	Molecular Weight	Sequence Length	Chain	Crystal Structure of Protein Targets
Neuronal calcium sensor-1 (NCS-1)	5AER	50618.91 Da	190	A	

Table 3: Stoichiometry, molecular weight, electronic energy, enthalpy, Gibb's free energy in Hartree, and dipole moment (Debye) of Ketamine.

Stoichiometry	Molecular weight	Electronic energy (Hartree)	Enthalpy (Hartree)	Gibb's free energy (Hartree)	Dipole moment (Debye)
$C_{13}H_{16}ClNO$	237.72	-1094.7	-1094.7	-1094.76	4.6399

Molecular orbital analysis

HUMO and LUMO stands for Highest Occupied Molecular Orbital and Lowest Unoccupied Molecular Orbital respectively which are essential for different types of chemical reactions [32]. The gap between the energy of HUMO and LUMO plays a significant role in determining the nature of chemical reactions of a molecule [33]. Small gap between HOMO and LUMO describes the high chemical reactivity and low kinetic stability, alternatively large gap between HOMO and LUMO represents high kinetic stability and low chemical reactivity resulting in chemically harder than the previous molecules [34,35]. The electronic absorption is associated with a shift from the ground state to the first excited state and is mostly explained by one electron excitation from HOMO to LUMO [36].

In Figure 7 and Table 4, the HUMO and LUMO energies, gap, hardness, softness, and chemical potential, of Ketamine are presented. The energies of HOMO and LUMO and gap between them directly influence on molecules hardness, softness, and chemical potential. For example, smaller value of a molecule's HUMO-LUMO gap indicates its higher chemical reactivity [37,38].

For Ketamine, the values for HOMO and LUMO are -0.5.40eV and -0.82eV, and the gap between HOMO and LUMO is 4.58eV (Figure 6) which is not so much high. On the other hand, we know that the lower the hardness and higher the softness value, the more chemically a molecule will be reactive. In case of ketamine the hardness and softness values are respectively 2.29ev and 0.44ev where the hardness value is not so high and the softness value is not so much small which indicates that Ketamine is chemically reactive (Table 4).

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Table 4: HUMO-LUMO Calculation.

Drug	HUMO	LUMO	Gap	Hardness (η)	Softness (S)	Chemical Potential (μ)
Ketamine	-0.5.40	-0.82	4.58	2.29	0.44	-3.11

Table 5: Bond Distance Calculation.

Drug Name	Atom Number	Bond Distance (Å) Calculation
Ketamine	C (11)-Cl (1)	1.83416
	N (3)-C (4)	1.45648
	N (3)-C (13)	1.45416
	N (3)-H (25)	1.01276
	C (8)-O (2)	1.23994

Table 6: Bond Angle Calculation.

Drug Name	Atom Number	Bond Angle (º)Calculation
Ketamine	Cl (1)-C (11)-C (10)	121.5026
	Cl (1)-C (11)-C (14)	115.2035
	H (25)-N (3)-C (4)	113.112
	H (25)-N (3)-C (13)	117.49136
	C (4)-N (3)-C (13)	121.54093
	O (2)-C (8)-C (4)	121.05423
	O (2)-C (8)-C (9)	122.3034

Table 7: Vibrational frequencies (cm^{-1}) of IR and Raman spectra.

Drug's Name	Spectra	Molecular vibration	Vibrational frequencies (cm^{-1})
Ketamine	IR	(C_4-N_3), Stretching	1163
		(C_8=O_2), Symmetric Stretching	1775
		(C_{13}-H_{28}), Symmetric Stretching	2855
		(N_3-H_{25}), Symmetric Stretching	3452
	Raman	(H_{21}-C_7-H_{22}), Bending	1536
		(C_8=O_2), Stretching	1720
		(H_{18}-C_5-H_{17}), Stretching	3048
		(C_{12}-H_{26}), Stretching	3248
		(N_3-H_{25}), Stretching	3592

Table 8: Binding score of Ketamine and Haloperidol.

Ligand	Protein	Binding Score (Kcal/mol)
Ketamine	Dopamine D2 receptor protein [5AER (Chain:A)]	-6
Haloperidol (Standard)		-6.3

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Molecular Bond Analysis

For the purpose of structural optimization of any chemical species, equilibrium geometry is a crucial factor that considers the bond distances and bond angles between the atoms in molecules. The objective of structural or geometrical optimization is to find an atomic arrangement that makes a chemically low-energy molecule as well as significantly stable [39]. This optimization is done by changing the system's geometry to minimize the total energy of that system [40]. The bond analysis must be done before starting a geometrical optimization. Changes in geometry and vibrational frequencies can result from structural changes and solvent action [39].

In the chemical structure of Ketamine (C13H16ClNO), all bond distances and bond angles are listed with their respective atom numbers (Tables 5 & 6). From Table 5, all calculated bond distances are approximately same with each other with an exceptionally reduction in distance (Å=1.01276) between N (3)-H (25). Similarly in Table 6, it has been found that all calculated bond angles are almost similar which indicates its optimized state

Electrostatic potential map analysis

The molecular electrostatic potential (MEP) map shows the entire charge distribution of the nuclei and electrons, and provides some insight into the molecule's partial charge, dipole moment, electronegativity, and chemical reactivity [41]. It also shows regions of positive, negative, and neutral electrostatic potential as well as molecule shape, size and color gradation. Concurrently, MEP indicates the reactive sites for electrophilic and nucleophilic attack of all optimized structures and provides recognition biologically. MEP utilizes the colors blue and red to depict potential electrophilic and nucleophilic attacks, respectively, where red indicates the maximum negative area, blue indicates the maximum positive area and green area indicates zero potential areas [42]. in Figure 8, the maximum negative potential value is – 6.021a.u. indicating by red, where the blue color indicates the highest positive potentiality (+6.021a.u.) in the structure of Ketamine. Green portion around the molecule indicates zero potential areas.

Vibrational frequency analysis (IR and Raman)

Vibrational frequency is completely an energy sensitive method that uses periodic changes of dipole moments and polarizabilities for IR and Raman analysis respectively [43]. Using a combination of IR and Raman, vibrational frequency analysis demonstrates the distinctive fingerprint spectra of a molecule via the interaction of electromagnetic radiations with the test samples [44]. This combination of method is providing an effective tool in the vibrational analysis of drug or protein molecules. The findings of the investigation would aid in the precise identification of vibrational modes as well as the bonding and structural characteristics of complicated organic molecule systems [45].

The vibrational spectroscopy which is also known as fingerprint spectroscopic technique is the combination of IR and Raman spectra and depicted in (Figures 9 & 10) and also in (Table 7) respectively. Here, the vibrational spectra both for IR and Raman has been demonstrated for ketamine drug where the wavelength was measured in the range of (400-4000) cm^{-1}. Both of these vibrational spectra are helpful for the identification and structural explanation of the functional groups in the drug molecule [46]. From IR, we can see the band found for (C_8=O_2), symmetric stretching at the wavelength of 1775 cm^{-1}, whereas in case of Raman spectra the same functional group (C_8=O_2) was found at the wavelength of 1720 cm^{-1} which is quite close to the IR spectra. Here the range is (1720 to 1775) cm^{-1}. The same kind of similarity was also found for (N_3-H_{25}) functional group. In case of IR the wavelength for (N_3-H_{25}) symmetric stretching was 3452 cm^{-1}, whereas for Raman the wavelength was 3592 and these two values are also near to each other where the range is (3452 to 3592) cm^{-1}. In this way, the (C=O) same functional group was found both in IR and Raman at the same range of wavelength within a high intensity. Another band (N-H) symmetric stretching was also found at the same range of wavelength and frequency both in IR and Raman. From the vibrational frequency analysis both for IR and Raman we can say that the results possessed the same identity of the functional group for Ketamine drug.

Drug-Protein Interactions and Visualization

In order to induce the stimulating effect both the Ketamine and Haloperidol (Standard) drugs were docked with Dopamine D2 receptor protein [5AER (Chain:A)`]. This experimental conformer is obtained by molecular docking analysis that assists in the prediction of compounds binding affinities and ligand protein interactions [47]. The purpose of this docking procedure is to determine the binding affinity of Ketamine and Haloperidol (Standard) drug at the target binding site of Dopamine D2 receptor protein and finally make a comparison of the stimulating effects of the Ketamine with the standard drug Haloperidol. The best docking results were analyzed based on different binding energy. The negative value of binding affinity indicates the strongest bonding within the ligand molecule and receptor protein. However, the docking simulation was accomplished by using PyRx software where the lowest binding affinity for the docking of Ketamine and Haloperidol were recorded respectively -6.0 and -6.3 Kcal/mol (Table 8). This indicates that Ketamine possesses very close stimulating effects as the standard drug Haloperidol. Therefore, this docking analysis indicates that the binding energy is effective and suitable for further investigation of drug protein complex interaction analysis (Figures 11 & 12).

Non-bonding Interactions Analysis

Non-bonding interactions analysis is thought an important consideration while a particular ligand compound makes a complex formation with a particular protein molecule [31]. In

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case of docked structure both for Ketamine and Haloperidol with 5AER, several types of non-bonded interactions were visualized (Figure 13). Mainly, two types of non-bonding interactions were found such as hydrogen bond and hydrophobic bond interaction (Table 9). The Higher binding affinity in a compound indicates strong hydrogen bond that expresses compounds increased binding property with receptor molecules [48]. In this study, binding affinity obtained both for Ketamine and Haloperidol are respectively -6.0 and -6.3 kcal/mol which is supposed to be moderately low indicating weak hydrogen bond in interactions [49]. In case of Ketamine several non-bonding interactions such as conventional hydrogen bond, hydrophobic bond such as Pi-Pi Stacked bond, Alkyl bond, Pi-Alkyl bonds are related to the structure of examined compound (Figure 13). On the other hand, in case of Haloperidol several non-bonding interactions like conventional hydrogen bond, Pi-Sigma bond, Pi-Pi Stacked bond and Alkyl bonds are identified (Figure 14). Bond distances also play an important role in determining the binding affinity [50]. In case of Ketamine the conventional hydrogen bond distance is 2.15Å whereas in case of Haloperidon it is 3.01Å (Table 7). However, from the research study, it has been found that the binding affinity can be increased by several orders of magnitude with a hydrogen bond length of less than 2.3Å [41,51].

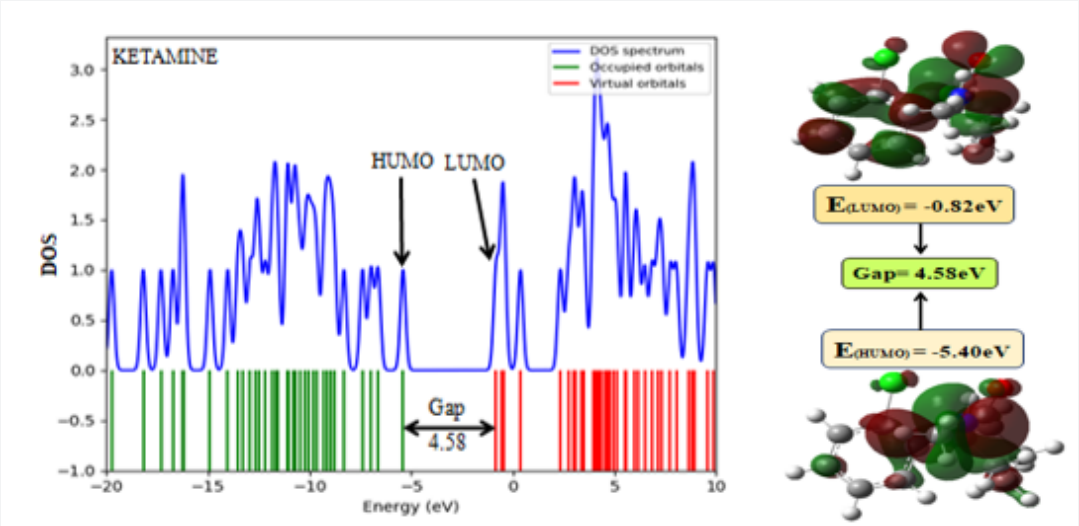

Figure 7: DOS plot and HUMO-LUMO energy gap for Ketamine.

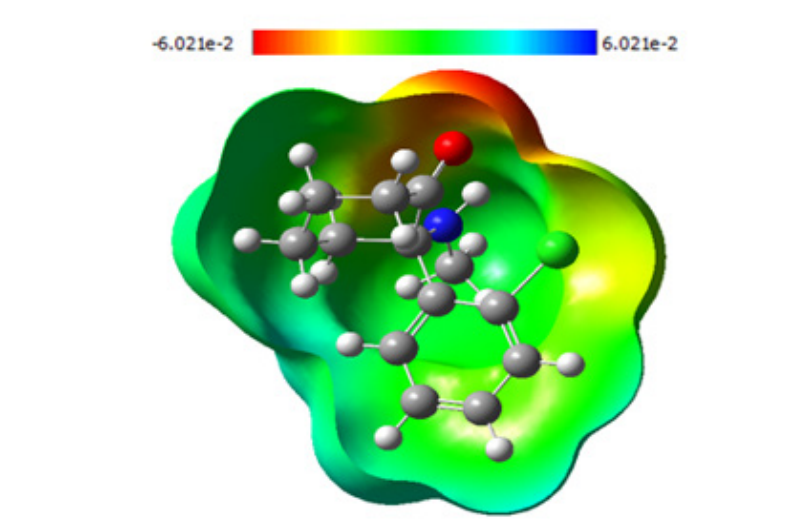

Figure 8: Molecular electrostatic potential map of Ketamine.

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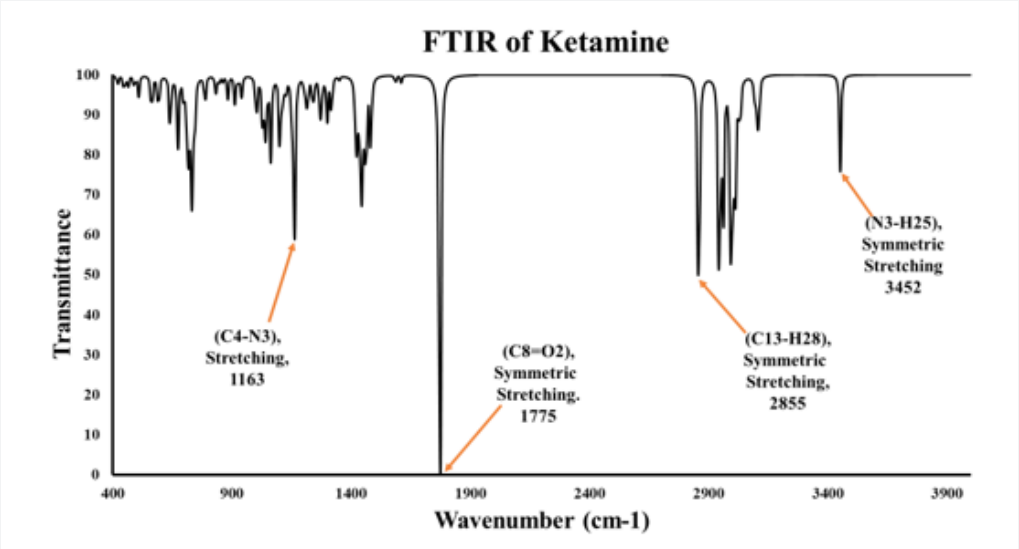

Figure 9: FT-IR spectra of Ketamine.

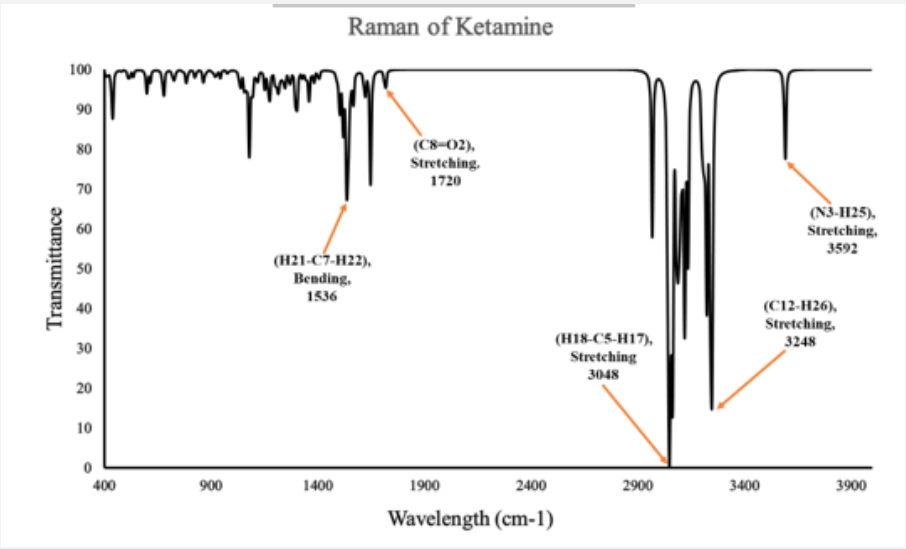

Figure 10: Raman spectra of Ketamine.

Hydrophobic bond also exists in Ketamine. But among all the interactions conventional hydrogen bond (TYR31) [bond distance 2.15073 Å] is readily important for the binding affinity (Figure 15).

ADMET study and drug likeliness prediction analysis of Ketamine

The ADMET study is generally determined by the pharmacokinetic properties of a drug where absorption, distribution, metabolism, excretion, and toxicity are calculated. The fate as well as the effects of a drug inside the body is being predicted by this study. For example, if a drug is administered orally, then how much it's absorption will be in the gastrointestinal tract is being predicted by ADMET study. Because if there is poor absorption of a drug, then ultimately its distribution and metabolism will be affected which may cause neurotoxicity or nephrotoxicity. Finally, this study assists oneself to understand how a drug deposits within a particular organ. Thus, ADMET study plays a significant role in drug discovery as well as in computer aided drug design [52]. As a result, the rate of failing a particular drug compound in clinical trial become reduced and ultimately its efficacy is improved [53].

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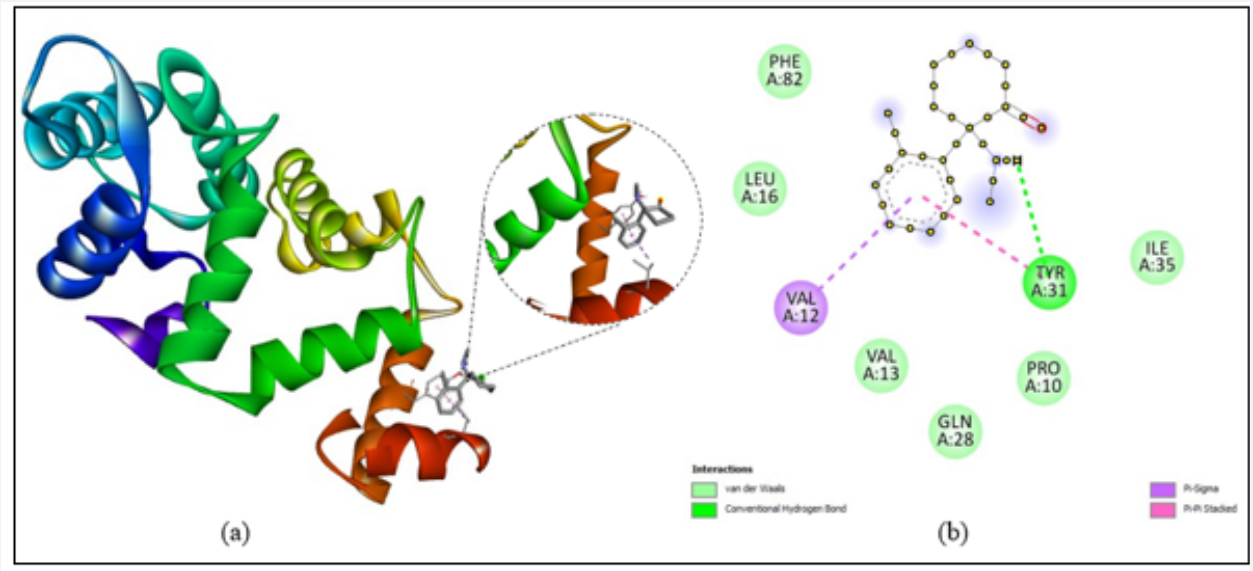

Figure 11: (a) 3D and (b) 2D interaction of Ketamine drug at the inhibition binding site of 5AER protein.

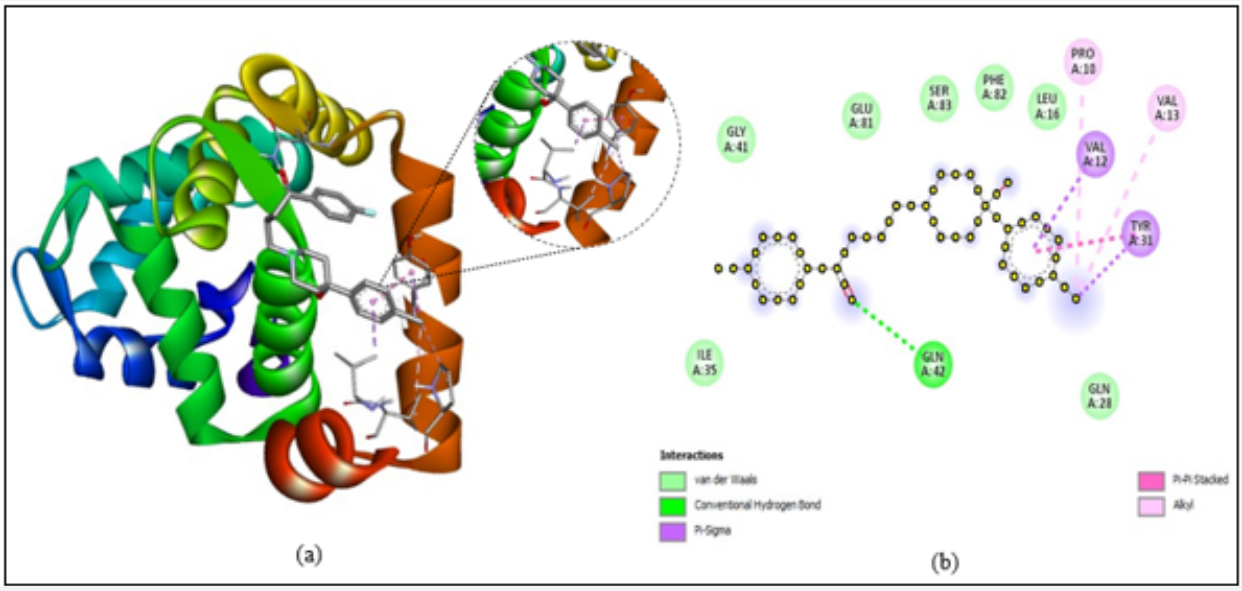

Figure 12: (a) 3D and (b) 2D interaction of Haloperidol (Standard) drug at the inhibition binding site of 5AER protein.

However, for ADMET analysis first of all from online smile convertor website a smile number CNC1(CCCCC1=O)C2=CC=CC=C2Cl was created. Then from pkCSM website by using smile number the ADMET prediction results were being documented. All the computed results for ADMET study of Ketamine drug are tabulated in Table 10. The predicted results showed that the analysis of pure water solubility is-2.764log mol/L which indicates that the Ketamine drug is poorly water soluble. The Caco-2 permeability assay is done basically to investigate intestinal permeability [54]. According to binning criteria if the Caco-2 permeability range is 0.500 < Papp < 2.50 (x10-6 cm/s), then it is moderately permeable [55]. In case of KetaminetheCaco-2 permeability is 1.474log Papp in 10-6 cm/s which indicates that Ketamine drug is moderately permeable. The predicted value for intestinal absorption of Ketamine is 93.125which estimates that the high absorption of Ketamine takes place in small intestine.

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According to research study, it has been estimated that if the log kp of a compound becomes greater than -2.5, then it is said that it will have low skin permeability [56]. The skin permeability for Ketamine was recorded as -2.771log kp which indicates that Ketamine drug has very low skin permeability. The others parameters for drug absorption like P-glycoprotein substrate, P-glycoprotein I inhibitor and P-glycoprotein II inhibitor are absent for Ketamine drug.

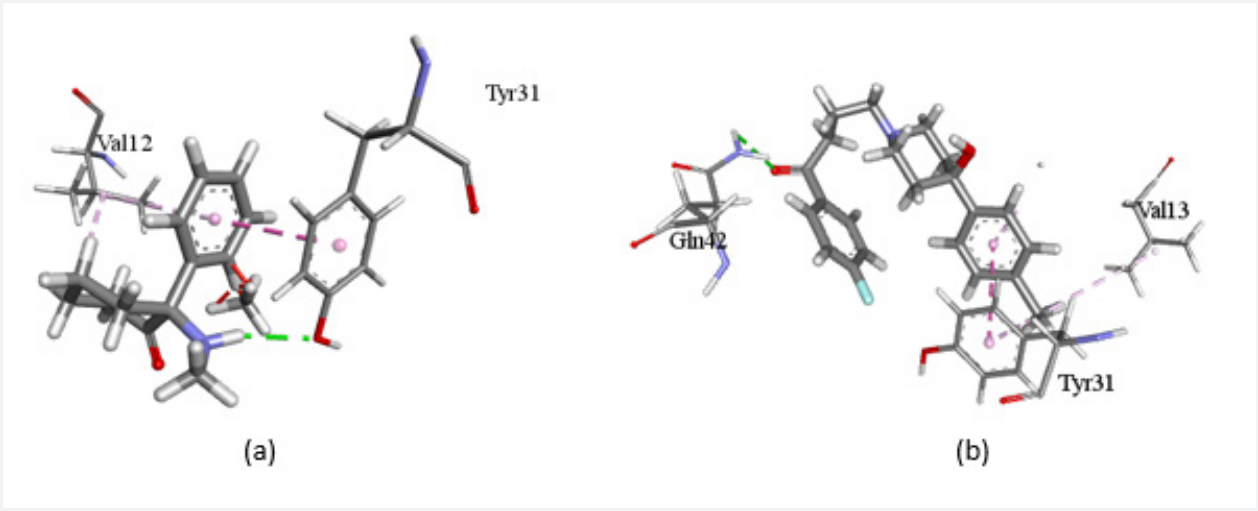

Figure 13: Nonbonding interactions of (a) Ketamine and (b) Haloperidol (Standard) drug with 5AER protein generated by Discover Studio.

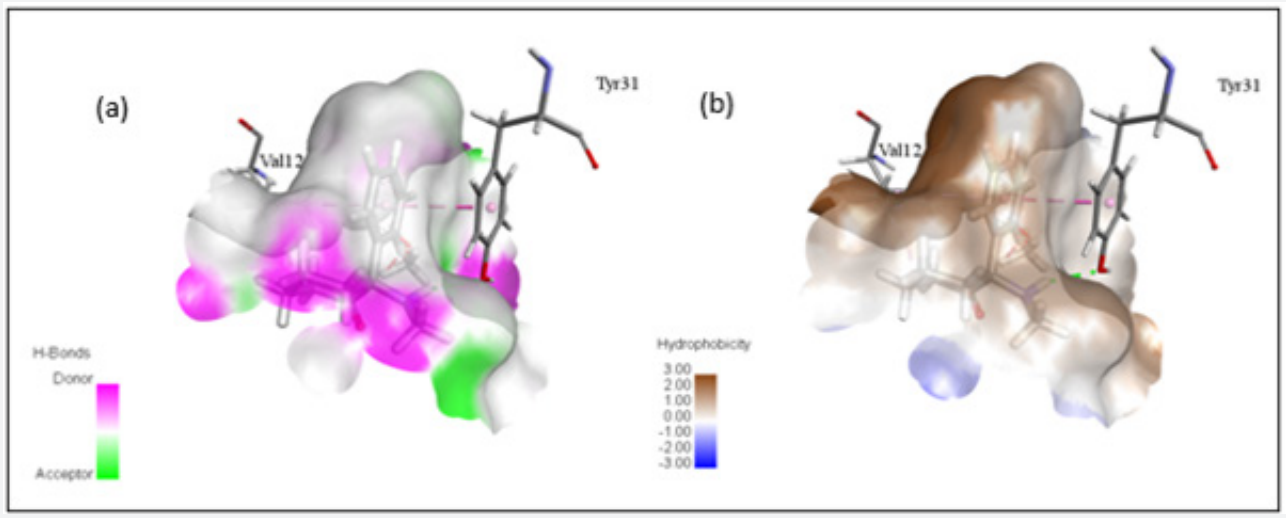

Figure 14: (a) Hydrogen and (b) Hydrophobic bond surface of 5AER (Chain: A) with ketamine drug.

The total doses of a drug substance need a uniform volume of drug distribution in the blood plasma which is denoted as VDss. If the VDss become high, then the distribution of a drug will be high in tissue rather than plasma. VDss will become low when log VDss<-0.15 and high when VDss>-0.45 [52]. Here, the VDss value for Ketamine is0.743log L/kg which indicates that Ketamine drug possess high volume of distribution. The fraction unbound disclose the fraction which will be unbound in blood plasma as predicted in Table 6. Blood brain barrier (BBB) is an important aspect to test the ability of a medicine to penetrate into blood brain. If the logBB>0.3, it indicates that a drug can very easily cross the BBB whereas, drug with a logBB<-1 can poorly distributed to

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the brain. For Ketamine the logBB value is 0.143 which indicates that Ketamine cannot very easily penetrate into the blood brain. Another measurement for CNS Permeability study is that if a compound having logPS>-2 is considered to penetrate into the CNS whereas, in case of Ketamine the logPS value for Ketamine is -2.105which indicates that the drug will be unable to penetrate into the CNS [56]. The presence or absence of different metabolic substrates or inhibitors were predicted in Table 10 where all the substrates and inhibitor possessed negative results. The total clearance for Ketamine drug is 0.874log ml/min/kg which will be helpful in dose rate setting. On the other hand, OCT2 is a renal uptake transporter which possess a significant role in renal drug clearance. It is predicted that Ketamine will not act as a OCT2 substrate facilitating the clearance of drug.

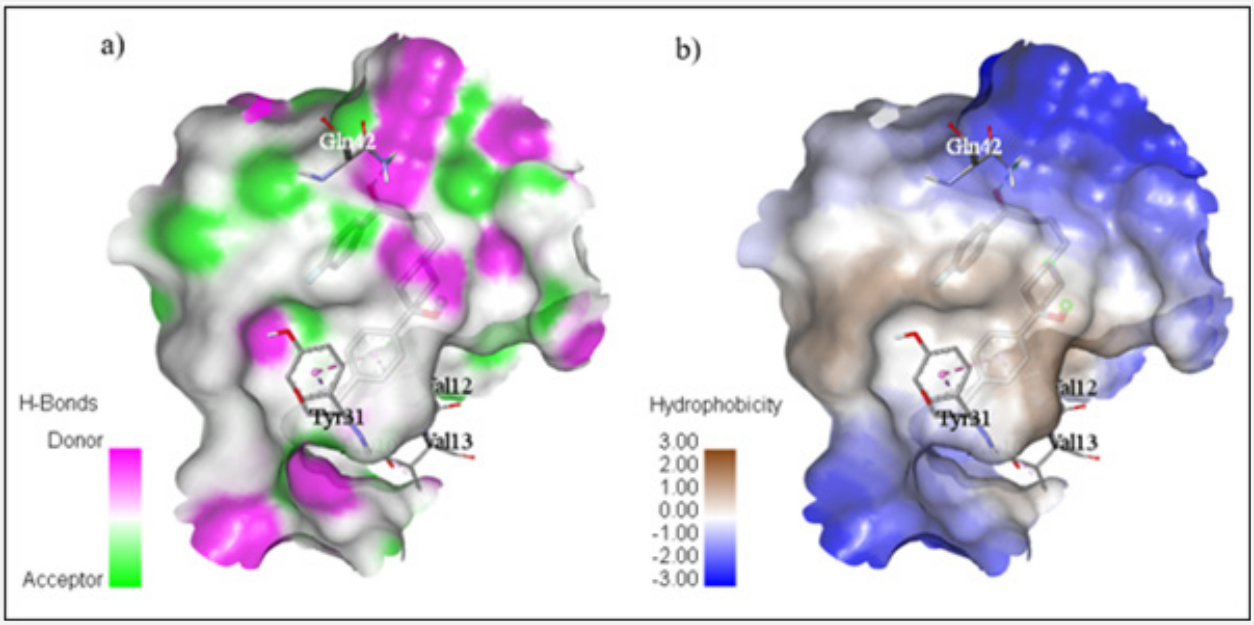

Figure 15: (a) Hydrogen and (b) Hydrophobic bond surface of 5AER (Chain: A) with Haloperidol (Standard) drug.

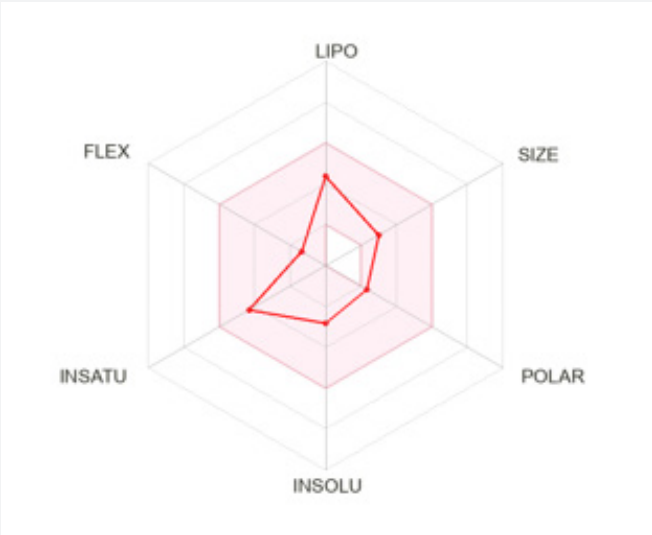

Figure 16: The bioavailability radar plot image for Ketamine.

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Table 9: Non-bonding Calculation.

Name	Binding Affinity (Kcal/mol)	Residues in Contact	Bond Type	Interactions Type	Bond Distance (Å)
Ketamine	-6	TYR31	Hydrogen Bond	Conventional Hydrogen Bond	2.15073
		TYR31	Hydrophobic	Pi-Pi Stacked	3.83297
		VAL12	Hydrophobic	Alkyl	4.19832
		VAL12	Hydrophobic	Pi-Alkyl	4.38892
Haloperidol	-6.3	GLN42	Hydrogen Bond	Conventional Hydrogen Bond	3.01335
		VAL12	Hydrophobic	Pi-Sigma	3.9971
		TYR31	Hydrophobic	Pi-Pi Stacked	4.2245
		PRO10	Hydrophobic	Alkyl	5.47166
		VAL13	Hydrophobic	Alkyl	5.39674

Table 10: Pharmacokinetic Properties of Ketamine.

Pharmacokinetic Properties	Ketamine Drug	
	Parameters	Predicted Value
Absorption	Water Absorption (log mol/L)	-2.764
	Caco-2 (log Papp in 10-6 cm/s)	1.474
	Intestinal Absorption (% Absorbed)	93.125
	Skin Permeability (log Kp)	-2.771
	P-glycoprotein substrate	No
	P-glycoprotein I inhibitor	No
	P-glycoprotein II inhibitor	No
Distribution	VDss (human, log L/kg)	0.743
	Fraction unbound (human, FU)	0.373
	BBB permeability (log BB)	0.143
	CNS permeability (log PS)	-2.105
Metabolism	CYP2D6 substrate	No
	CYP3A4 substrate	No
	CYP1A2 inhibitior	No
	CYP2C19 inhibitior	No
	CYP2C9 inhibitior	No
	CYP2D6 inhibitior	No
	CYP3A4 inhibitior	No
Excretion	Total Clearance (log ml/min/kg)	0.874
	Renal OCT2 substrate	No
Toxicity	AMES Toixicity	No
	Max. Tolerated Dose in (human, log mg/kg/day)	0.249
	HERG I Inhibitor	No
	HERG II Inhibitor	No
	Oral Rat Acute Toxicity (LD50, mol/kg)	2.763
	Oral Rat Chronic Toxicity (LOAEL, log mg/kg bw/day)	1.121
	Hepatotoxicity	No
	Skin sensation	Yes

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Table 11: Different parameters of Ketamine.

Physicochemical Properties		
Parameters	Values	Lipinski rules
MW (g/mol)	237.73g/mol	<500
ROTB (n)	2	<10
HBA (n)	2	<10
HBD (n)	1	<5
Log S (ESOL)	-2.83 (MS)	-
Lipophilicity		
TPSA (Å2)	29.1	<140
CLog Po/w	2.67	<5
Drug-likeness		
Bioavailability Score	0.55	-
Lipinski filter	Yes (0 violation)	-
Pharmacokinetics		
GIA	High	-
BBB permeant	Yes	-
P-gp substrate	No	-
CYP3A4 inhibitor	No	-
LogKp (Skin Permeation)	-6.20 cm/s	<5

The AMES test is used to determine the mutagenic effect of a compound where the positive test conforms that the compound is mutagenic. The AMES test predicts that Ketamine is non-mutagenic. The maximum tolerated dose for Ketamine is 0.249log mg/kg/day which indicates that Ketamine is effective at lower dose. The potassium channels inhibition is depicted by HERG which is considered as the primary reason for the development of long QT syndrome. The predictions indicate that Ketamine is unlikely to be HERG I or II inhibitor. The standard measurement of acute toxicity is determined by LD50 which refers to the amount drug substances which causes 50% death of a group of test animals. The predicted LD50 value (2.763) is given in mol/kg. Chronic toxicity studies are designed to assess the minimum dose of a drug which may cause a negative impact and maximum dose at which there will be no adverse effects. Here, the predicted values for chronic toxicity (1.121) are given in log (mg/kg bw/day). The predicted values also show that Ketamine will not possess any hepatotoxicity whereas skin sensation is present.

Drug Likeness Prediction Analysis

The concept of drug-likeness prediction analysis is essential for the virtual screening of a drug compound. It helps to detect qualitatively the possibility for a compound to become an oral drug with its respective bioavailability. It was analyzed to test whether a bioactive component meets favorable ADMET properties or not. However, the drug likeness of Ketamine was listed in Table 11 with different parameters. Drug likeness analysis is based on Lipinski five rules which is associated with drug's solubility and permeability. The more a drug compound deviates from the Lipinski five rule, the more the absorption and permeation of that drug will be poor [57]. From, the data analysis of drug likeness for Ketamine, we can see that the drug met all the required parameters according to the Lipinski rule.

We can also get the prediction of drug-likeness analysis from the bioavailability radar plot image for Ketamine (Figure 16). Basically, emphasis had been given on two important parameters used in the prediction of oral drug bioavailability respectively flexibility (determined by the number of rotatable bonds) and polarity (determined by topological polar surface area). It had been estimated that any drug compound having more than 10 rotatable bonds will be considered to have poor oral bioavailability [58]. On the other hand, having lower topological polar surface area is the indication of high oral bioavailability [59]. From this image we can see that the flexibility value of Ketamine is far away from its standard value. On the other hand, the polar value is somehow close to the standard value. The unsaturated and lipopholicity value is also close to the standards. This indicates that Ketamine will possess a good oral bioavailability.

Conclusion

In this study, Ketamine has been studied for the evaluation of its stimulating effects by comparing it with the standard drug Haloperidol on Dopamine D2 receptor 5AER (Chain:A) by

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molecular docking interaction where the results showed that Ketamine possessed stimulating effects as like as the standard drug Haloperidol. Several non-bonding calculations had also been done for the analysis of ligand-protein complex formation. Moreover, some software-based study like ADMET and Drug likeness analysis had been done just to guess the pharmacokinetic effects of Ketamine. The ADMET study predicts that Ketamine is non-carcinogenic and safe for oral administration. On the other hand, drug likeness study analysis predicts that Ketamine is suitable for good oral bioavailability. Considering the present investigation, we can say that Ketamine drug can be used for inducing the stimulating effects of Dopamine D2 receptor. Also, it's our hope that this investigation will draw the attention of scientific community to think about Ketamine as an effective stimulating agent.

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