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Comparative assessment of some benzodiazepine drugs based on Density Functional Theory, molecular docking, and ADMET studies

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RESEARCH ARTICLE

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ABSTRACT

Benzodiazepines are widely used to treat anxiety, insomnia, agitation, seizures, and muscle spasms. It works through the $GABA_A$ receptors to promote sleep by inhibiting brainstem monoaminergic arousal pathways. It is safe and effective for short-term use, and arises some crucial side effects based on dose and physical condition. In this investigation, physicochemical properties, molecular docking, and ADMET properties have been studied. Density functional theory with B3LYP/6-311G+(d,p) level of theory was set for geometry optimization and elucidate their thermodynamic, orbital, dipole moment, and electrostatic potential properties. Molecular docking and interaction calculations have performed against human $GABA_A$ receptor protein (PDB ID: 4COF) to search the binding affinity and effective interactions of drugs with the receptor protein. ADMET prediction has performed to investigate their absorption, metabolism, and toxic properties. Thermochemical data suggest the thermal stability; the docking result predicts effecting bindings and ADMET calculation disclose non-carcinogenic and relatively harmless phenomena for oral administration of all drugs.

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1. Introduction

Benzodiazepines (BZs) are widely used in the treatment of anxiety, insomnia, agitation, seizures, and muscle spasms. They enhance the effect of the neurotransmitter gamma-amino-butyric acid (GABA) at the $GABA_A$ receptor [1-3]. $GABA_A$ receptors are the major inhibitory neurotransmitter receptors in mammalian brain. To investigate the mechanism of drug action at $GABA_A$ receptors, it is valuable to understand the precise location of the ligand and identify the amino acid residues involved in GABA/BZ binding. $GABA_A$ receptors are the targets of a wide range of drugs including benzodiazepines [4]. $GABA_A$ receptors also mediate alcohol inebriation and are targets for endogenous modulators such as eurysternids [5]. An overdose of benzodiazepines may also cause anterograde amnesia and dissociation [2,6].

In this study, some selected benzodiazepine drugs (Figure 1) were optimized to investigate their biochemical behavior based on the quantum mechanical approach. The dipole moment, free energy, electrostatic potential, chemical hardness, and softness were calculated. Molecular docking and non-bonding interactions have been calculated to investigate the binding score, mode(s) and interactions between ligands and amino acid residues of $GABA_A$ receptor protein (4COF). Due to the insertion of different functional groups at the different positions of the the core structure, significant changes in thermodynamic properties, chemical stability, reactivity, binding affinity, interactions, and pharmacokinetic properties were observed, which can help to understand comparative studies among some BZ drugs, e.g., alprazolam (Al), bromazepam (BrZ), diazepam (DZ), flunitrazepam (FZ), and lorazepam (LZ).

2. Computational methods

2.1. Geometry optimization

Physicochemical properties help us to understand the chemical behavior of any compound. Computational chemistry methods were used to calculate the properties of the thermodynamic, molecular orbital, dipole moment, and molecular electrostatic potential to predict their stability, reactivity, and molecular recognition [7]. Initial geometries of all drugs were collected from the ChemSpider database [8]. The Gaussian 09 (Revision D.01) program package was utilized for geometry optimization [9].

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Table 1. Molecular formula, electronic energy, enthalpy, Gibb's free energy (Hartree) and dipole moment (Debye) of benzodiapene derivatives.

Drugs	Molecular formula	Electronic energy	Enthalpy	Gibbs free energy	Dipole moment
Alprazolam	$C_{17}H_{13}ClN_4$	-1327.49	-1327.49	-1327. 56	4.72
Bromazepam	$C_{14}H_{10}BrN_3O$	-3350.53	-3350.53	-3350.60	4.71
Diazepam	$C_{16}H_{13}ClN_2O$	-1255.56	-1255.55	-1255.63	2.35
Flunitrazepam	$C_{16}H_{12}FN_3O_3$	-1106.32	-1106.32	-1106.38	3.61
Lorazepam	$C_{15}H_{10}Cl_2N_2O_2$	-1748.69	-1748.68	-1748.75	5.82

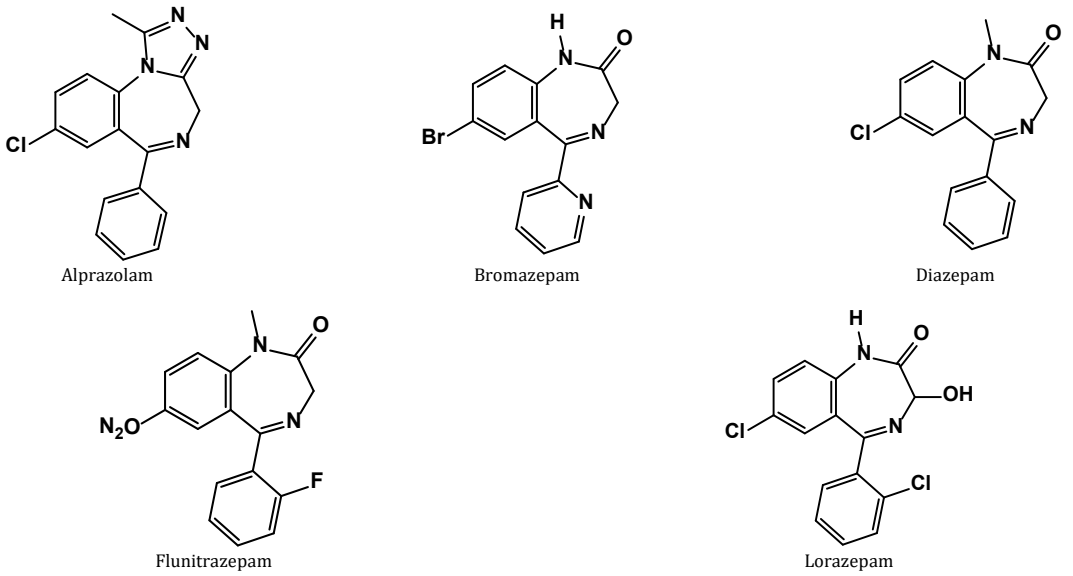

Figure 1. Chemical structure of selected benzodiazepine drugs.

Density functional theory (DFT) along with Becke's (B) [10] three-parameter hybrid model, Lee, Yang and Parr's (LYP) correlation functional [11] under Pople's 6-311G+(d,p) basis set which has amply been proven to give very good ground state geometries [12]. The initial optimization of all drugs was performed in the gas phase.

Frontier molecular orbital features, the highest occupied molecular orbital (HOMO), and the lowest unoccupied molecular orbital (LUMO) were calculated at the same level of theory. For each of the drugs, hardness (η), softness (S), and chemical potential (μ) were calculated utilizing E_{HOMO} and E_{LUMO} as reported [13] considering Parr and Pearson interpretation [14,15] of the DFT and the Koopmans theorem [16] on the correlation of ionization potential (I) and electron affinities (E) with HOMO and LUMO energy (ε) as follows;

$$\eta = \frac{[E_{LUMO} - E_{HOMO}]}{2}; \ \mu = \frac{[E_{LUMO} + E_{HOMO}]}{2}; \ S = \frac{1}{\eta} \quad (1)$$

2.2. Protein preparation, docking, and analysis

The 3D crystal structure of the human gamma-amino-butyric acid receptor protein (PDB ID: 4COF) was collected from the online protein data bank (PDB) database [17]. To overcome improper bond order, chain geometry disorder, missing hydrogen atoms; the structure was checked and prepared by PyMOL (Educational version 1.7.4), and Swiss-Pdb viewer software (Version 4.1.0) was utilized for energy minimization [18,19]. Finally, the optimized drugs were subjected to molecular docking study against the human $GABA_A$ receptor protein (4COF) considering the protein as a macromolecule and the drug as ligand. In the current analysis, flexible docking was performed by PyRx software (Version 0.8) [20] where the center grid box was set at 64.84, 73.29 and 57.94 Å in/along x, y and z direction, respectively. Accelrys Discovery Studio (Version 4.1) was utilized to calculate, analyze, and visualize the interactions [21].

2.3. ADMET prediction

Absorption, distribution, metabolism, excretion, and toxicity are the important criterion for pharmaceutical analysis. AdmetSAR server was used to predict the ADMET properties of all Benzodiazepines (BZ) drugs [22].

3. Result and discussion

3.1. Thermodynamic properties analysis

Small modifications of any chemical structure significantly influence the structural properties including free energy, dipole moment, HOMO-LUMO gap, electrostatic potential, as well as binding property. Spontaneity of any chemical reaction and stability of a product related to the nature of Gibb's free energy and enthalpy [23]. Free energies significantly influence the binding affinity, where larger negative values are favorable for better binding interactions, and thermodynamic properties. The free energies of alprazolam and lorazepam are -1327.56 and -1748.68 Hartree, respectively. Meanwhile, bromazepam shows the highest free energy (-3350.60 Hartree) due to the presence of bromine and oxygen atoms, hence suggesting energetically and configurationally more stable. The optimized structures of the BZ drugs are shown in Figure 2.

In drug design, an increased dipole moment value is favorable to increase hydrogen bond and nonbonded interactions in drug receptor complexes which keep an important role to increase binding affinity. The polar nature of a molecule increases with the increase of the dipole moment [24]. The dipole moment of alprazolam and bromazepam is 4.72 and 4.71 Debye when lorazepam shows the highest value, 5.82 Debye (Table 1).

Table 2. Energy (eV) of HOMO, LUMO, Gap, hardness and softness of all drugs.

Drugs	E_{HOMO}	E_{LUMO}	Gap (E_{HOMO}/E_{LUMO})	E_{HOMO-1}	E_{LUMO+1}	Gap (E_{HOMO-1}/E_{LUMO+1})	Hardness	Softness
Alprazolam	-6.75	-1.93	4.82	-8.60	-4.67	3.93	2.41	0.42
Bromazepam	-6.72	-2.09	4.63	-7.15	-1.47	5.68	2.31	0.43
Diazepam	-6.37	-1.66	4.71	-6.41	-1.28	5.13	2.36	0.42
Flunitrazepam	-6.99	-2.97	4.02	-8.84	-4.79	4.05	2.01	0.50
Lorazepam	-6.75	-1.88	4.87	-7.02	-1.58	5.44	2.43	0.41

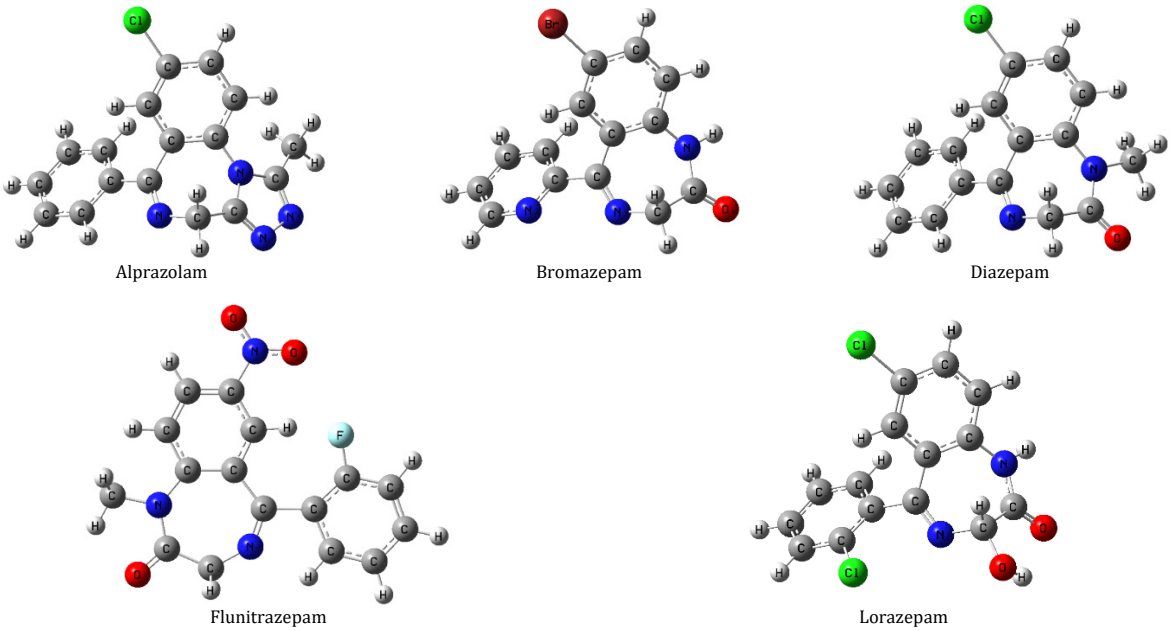

Figure 2. Most stable optimized structures of benzodiazepine drugs, optimized at B3LYP/6-311G+(d,p) level theory.

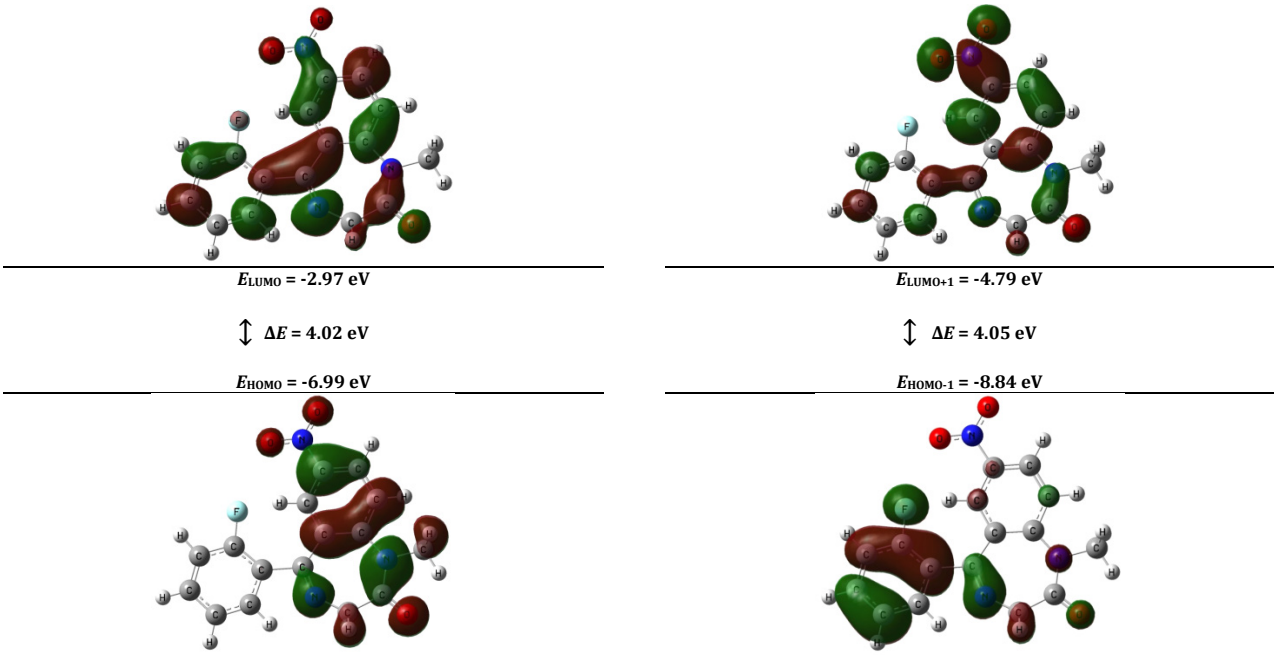

Figure 3. Frontier molecular orbitals and related energy of flunitrazepam.

3.2. Molecular orbital analysis

The HOMO and LUMO energies, energy gap, hardness, softness, chemical potential, electronegativity and electrophilic index of all drugs are presented in Table 2. The electronic transition from the ground to the first excited state mainly described by one electron excitation from HOMO to LUMO [25]. Frontier molecular orbital picture of flunitrazepam is displayed in Figure 3. Chemical reactivity and chemical potential are influenced by energies of HOMO and LUMO. The HOMO-LUMO gap is related to the chemical hardness, softness, chemical potential, and electrophilic index of a molecule [13,26]. Large HOMO-LUMO energy gap is responsible for high kinetic stability and low chemical reactivity. A small HOMO-LUMO energy gap is important for low chemical stability, because the addition of electrons to a high-lying LUMO and/or the removal of electrons from a low-lying HOMO are energetically favorable in any potential reaction.

Table 3. Binding energy and nonbonding interaction of benzodiazepine derivatives.

Ligand	Binding affinity (kcal/mol)	Residues in contact	Interaction type *	Distance (Å)
Alprazolam	-7.4	GLU52	C	4.79289
		GLU52	Pa	3.81763
		TYR220	PdH	2.84185
		THR271	PdH	2.97977
		TYR220	PpT	4.98649
		VAL53	PA	5.34154
Bromazepam	-6.4	GLN65	H	2.27068
		THR96	H	2.66812
		THR96	C	3.47936
		PHE98	PC	4.32935
		VAL106	PA	5.34822
		LEU128	PA	5.37012
Diazepam	-6.9	GLN65	H	2.19508
		THR96	C	3.27886
		PRO94	C	3.72636
		PHE98	PC	4.42984
		VAL106	A	4.42526
		VAL106	PA	5.34163
		LEU128	PA	5.21248
Flunitrazepam	-7.2	LEU294	Psi	3.70690
		PHE431	PpT	5.32222
		ILE423	A	5.19252
		PHE301	PA	4.83225
Lorazepam	-6.5	TYR126	H	2.37002
		LEU128	PA	5.27453

* H: Conventional hydrogen bond, C: Carbon hydrogen bond, PC: π-Cation, Pa: π-Anion, A: Alkyl, PA: π-Alkyl, Psi: π-Sigma, PPS: π-π Stacked, PdH: π-Donor hydrogen bond, PpT: π-π T-shaped.

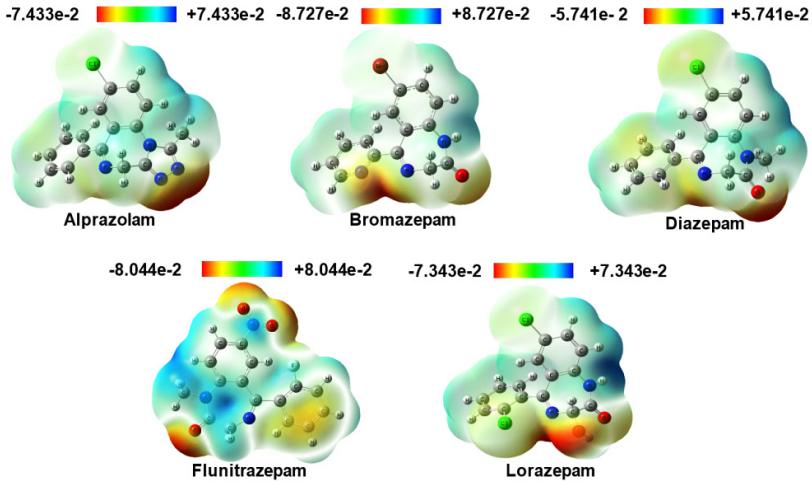

Figure 4. Molecular electrostatic potential map of all drugs.

HOMO-LUMO gap as well as hardness, softness, and chemical potential were calculated for all the drugs (Table 2). In the current analysis, flunitrazepam shows the lowest HOMO-LUMO gap (4.02 eV), and the highest softness value (0.50 eV), which may contribute to show higher chemical activity and polarizability than others.

3.3. Molecular electrostatic potential analysis

The molecular electrostatic potential (MEP) calculation helps to search the position of possible electrophilic and nucleophilic attacks. It also helps to interpret the biological recognition process and the hydrogen bonding interaction [27]. Possible electrophilic attacks and negative potentiality are represented by red color. Meanwhile, the blue color discloses the possible nucleophilic attack and the positive potential area. Here, the maximum negative potentiality of bromazepam is -8.727 e^{-1} a.u. (deep red) for oxygen atoms and the maximum positive region is localized on the hydrogen atoms of the same having value +8.727 e^{-1} a.u. (deep blue). The molecular electrostatic potential map of all drugs is given in Figure 4.

3.4. Binding affinity and interactions of BZ drugs with 4COF

The binding affinities and drug-protein interactions of all drugs are summarized in Table 3. Prepared protein chains (4COF/A) and docked conformation of bromazepam and diazepam at the binding site of 4COF/A are shown in Figure 5. A higher negative value of the binding affinity indicates a stronger binding between the drugs and the receptor. Amino acid residues of 4COF/A; Pro94, Thr96, Phe98, Phe431, Val106, Val430, Leu128, Leu294, Leu297, Gln65, Ile423, Glu298, Ser427 are involved in binding sites with drugs. The binding affinity of alprazolam is -7.4 kcal/mol, where those of diazepam and flunitrazepam are -6.9 and -7.2 kcal/mol, respectively. Decreased binding affinity is found in bromazepam (-6.4 kcal/mol) and lorazepam (-6.5 kcal/mol), respectively. Among various factors, hydrogen bonding, carbon-hydrogen bond, and alkyl bonds can affect the selectivity of nucleotide incorporation by a DNA polymerase. Hydrogen bond of < 2.3 Å is able to increase the binding affinity by several magnitude [28]. Some significant hydrogen bonds and C-H bonds are observed in alprazolam with the amino acid residues; TYR220, THR271 and GLU52 (Table 3).

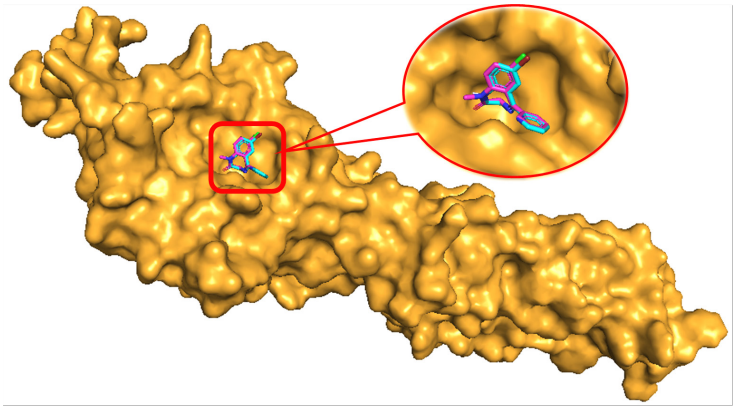

Figure 5. Docked conformation of bromazepam and diazepam at the binding site of receptor protein 4COF.

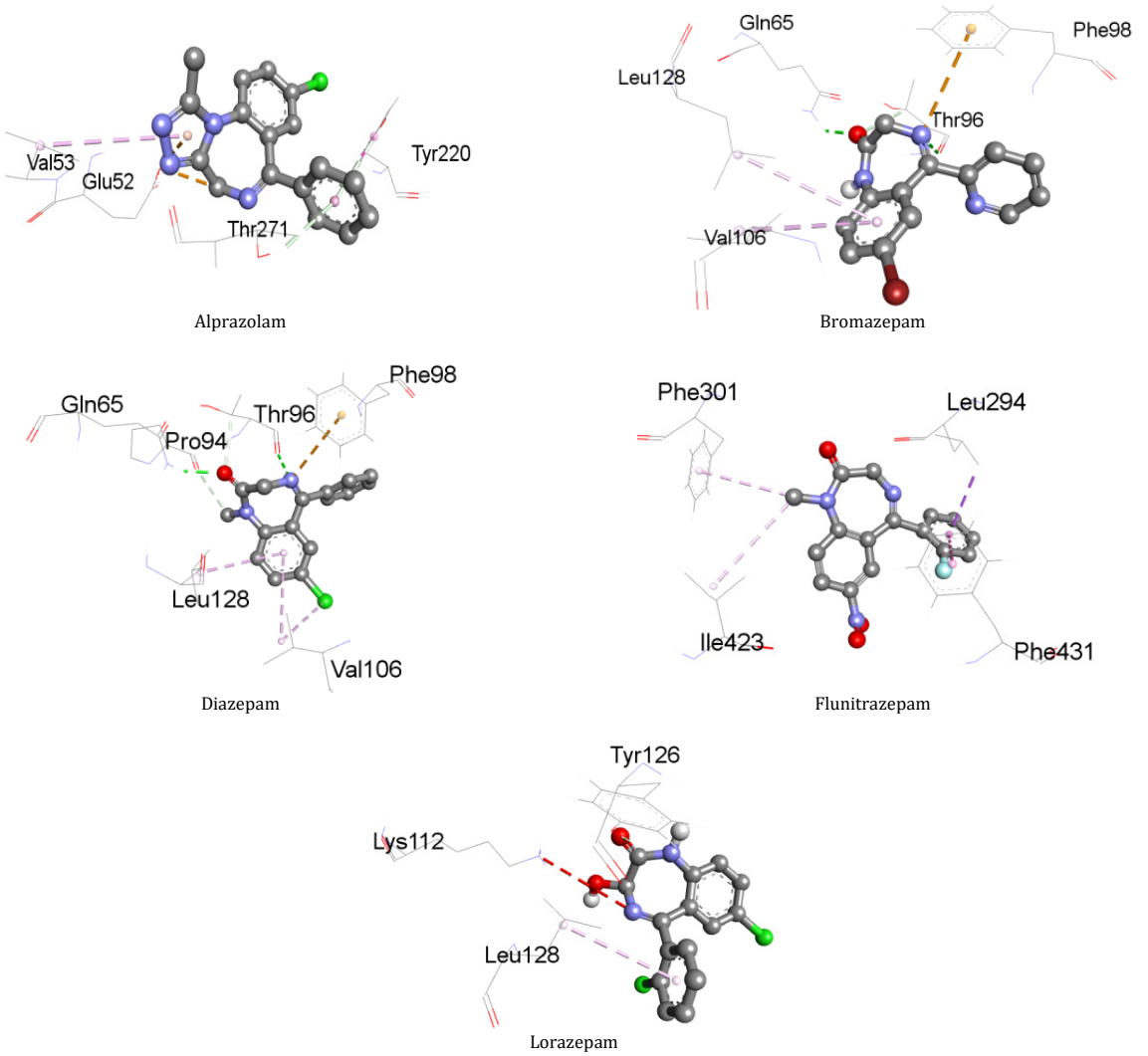

Figure 6. Nonbonding interactions of all drugs with 4COF generated by Discovery Studio.

Non-bonding interactions of all drugs and the hydrogen bond surface of bromazepam and diazepam with 4COF are shown in Figures 6 and 7, respectively. In the alprazolam -4COF docked structure, multiple non-bonded interactions were observed and the bond distance increases with VAL53 and TYR220 due to π-alkyl interaction. In addition, some non-covalent interactions such as hydrogen bonds and hydrophobic interaction are involved in the binding of the examined drugs. No hydrogen bond interaction was found in the case of flunitrazepam, instead alkyl and -sigma bond interactions with ILE423 and LEU294 residues, respectively, were observed. A special type of π-π T shaped PpT interaction with Phe431 is supposed to increase the binding affinity of flunitrazepam. Improved hydrogen bonding observed in alprazolam not only contributes in increasing binding affinity but also increase binding specialty [29,30].

Table 4. Selected pharmacokinetic parameters of benzodiazepine and its derivatives. Probability values related to each of the parameters are given in parentheses *.

Parameters	Alprazolam	Bromazepam	Diazepam	Flunitrazepam	Lorazepam
Blood brain barrier	+ (0.98)	+ (0.98)	+ (0.99)	+ (0.97)	+ (0.96)
Human intestinal absorption	+ (1.00)	+ (0.99)	+ (0.99)	+ (1.00)	+ (0.98)
P-glycoprotein inhibitor	NI (0.73)	NI (0.72)	NI (0.84)	NI (0.90)	NI (0.91)
Human ether-a-go-go-related gene inhibition	NI (0.97)	NI (0.99)	NI (0.99)	NI (0.98)	NI (0.99)
Carcinogen	NC (0.6)	NC (0.87)	NC (0.83)	NC (0.68)	NC (0.77)
Acute oral toxicity	III	III	II	II	III
Rat acute toxicity, LD_{50} (mol/Kg)	2.37	2.24	2.59	2.85	1.82

* NI: Non-inhibitor, NC: Non-carcinogenic.

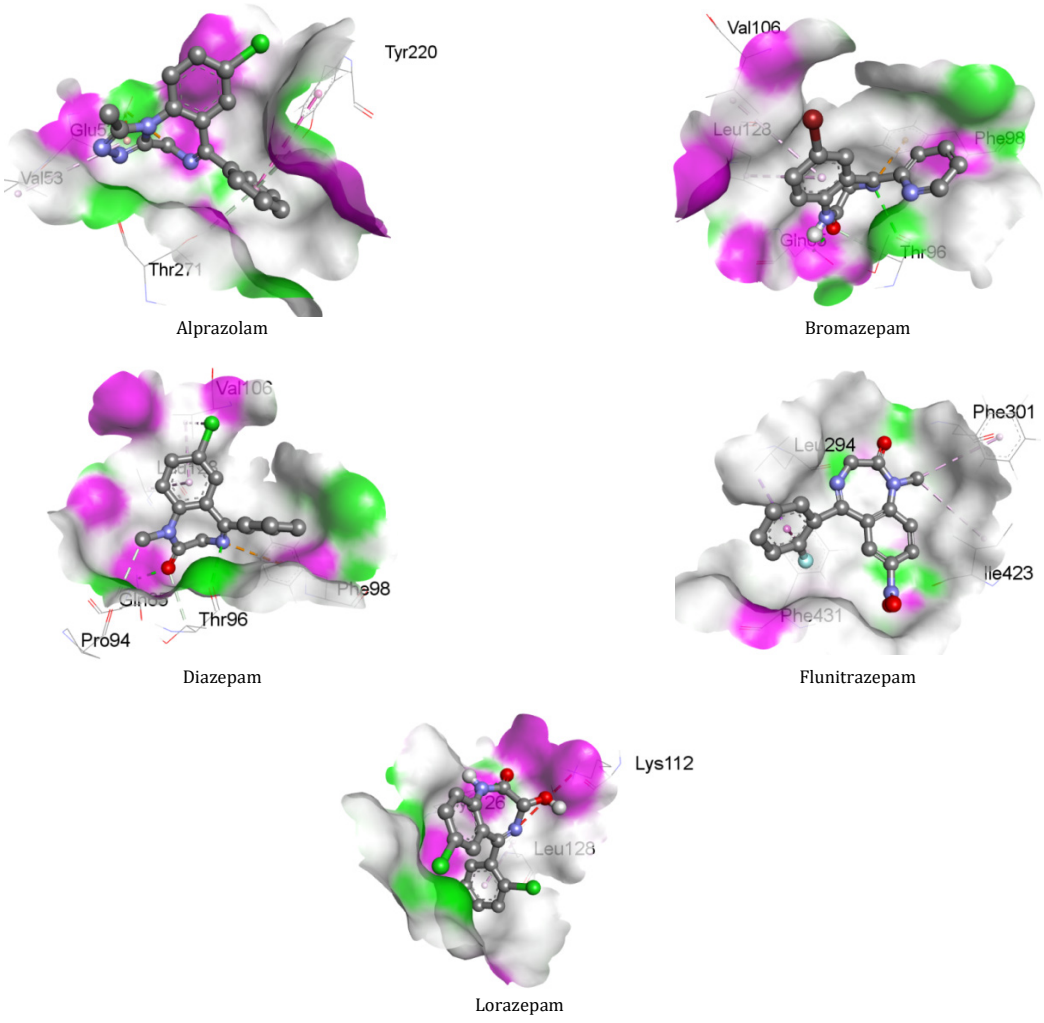

Figure 7. Hydrogen bond surface of 4COF with drugs.

There is hydrogen bond interaction with TYR126 and C-H interaction with Ser427 acid residue in lorazepam. There are lower hydrogen bond distances with GLN65 and THR96 and the C-H bond interaction with THR96 in bromazepam. Decreased binding affinity of both bromazepam and lorazepam also complies with their dipole moment and softness. There are several pi-alkyl interactions observed in all drugs.

3.5. Structural activity relationship on binding affinity

Binding affinity with receptor protein decreases by the order: alprazolam (-7.4 kcal/mol) > flunitrazepam (-7.2 kcal/mol) > diazepam (-6.9 kcal/mol) > lorazepam (-6.5 kcal/mol) > bromazepam (-6.4 kcal/mol). It is revealed that substituents at N1, C5 and C7 (Figure 1) have a remarkable influence on binding affinity with receptor protein. Exceptionally, alprazolam contains a fused triazole ring and a methyl group at N1 which are responsible for its higher binding affinity. In flunitrazepam there are N1-methyl, C5-F-Ph and C7-NO_2 groups that create its binding affinity high. N1-methyl has a dominant effect than C5-Cl-Ph and C7-Cl and hence diazepam has higher affinity than lorazepam and bromazepam. Lorazepam having C5-Cl-Ph and C7-Cl shows higher affinity than bromazepam.

3.6. ADMET analysis

From AdmetSAR data (Table 4), it is shown that all drugs exhibit a positive response to the blood brain barrier, and human intestinal absorption. All drugs are non-carcinogenic, and alprazolam, bromazepam, and lorazepam show III category acute oral toxicity. They are P-glycoprotein non-inhibitor where, inhibition can interrupt the absorption, permeability and retention of drug [31]. Lorazepam shows highest rat acute

toxicity (LD_{50} = 1.822) when flunitrazepam shows lowest rat acute toxicity (LD_{50} = 2.846). Improved rat acute toxicity is found for fluorinated drug. So, all the drugs show higher to median lethal dose (LD_{50}) values compared to flunitrazepam. Sequence of their toxicity is as decreasing order: Lorazepam > bromazepam > alprazolam > diazepam > flunitrazepam. However, all the drugs show weak inhibitory feature for human ether-a-go-go-related gene (hERG) which can lead to long QT syndrome [32,33]. Therefore, further study of this aspect is necessary.

4. Conclusion

In this investigation, five selected benzodiazepines have been studied to explore their thermal properties, molecular orbital characteristics, binding affinity, molecular interactions, and ADMET properties. Among them alprazolam shows the lowest HOMO-LUMO energy gap with the largest softness and the highest binding affinity (-7.4 kcal/mol) with protein chains (4COF/A) as compare to other examined drugs. The maximum energy gap is found for flunitrazepam with the smallest rat acute toxicity, (LD_{50}). Enhanced free energy is observed in bromazepam with the dipole moment 4.71 Debye, which makes it thermodynamically more stable. The prediction of ADMET prediction suggests that all drugs are non-carcinogenic and safe for oral administration.

Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: Not applicable

CRediT authorship contribution statement

Conceptualization: Mohammad Nasir Uddin; Methodology: Monir Uzzaman; Software: Monir Uzzaman; Validation: Monir Uzzaman; Formal Analysis: Monir Uzzaman, Amrin Ahsan; Investigation: Mohammad Nasir Uddin; Resources: Monir Uzzaman; Data Curation: Monir Uzzaman; Writing - Original Draft: Monir Uzzaman; Writing - Review and Editing: Mohammad Nasir Uddin; Visualization: Amrin Ahsan; Supervision: Mohammad Nasir Uddin; Project Administration: Mohammad Nasir Uddin.

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