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Molecular docking analysis of α2-containing GABAA receptors with benzimidazoles derivatives

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Abstract:
It is of interest to study the binding capacity of "3-[2-(2-Amino-1H-benzo[d]imidazol-1-yl)ethyl]-1,3-oxazolidin-2-one" (OXB_2) with the active site of gamma-aminobutyric acid (GABA) located in the GABA type A receptor ($GABA_AR$) in comparison with different $GABA_A$ subtypes. Optimal binding features were observed with the $\alpha_2\beta_2\gamma_2$ isoform (-8 kcal/mol). This is similar (-7.3 and -7.2 kcal/mol, respectively) for subtypes ($\alpha_3\beta_2\gamma_2$ and $\alpha_1\beta_2\gamma_2$). This implies that OXB_2 binds preferentially to subtypes associated with anxiety (α_2- and/or α_3-containing receptors) linked molecules than with the subtype associated with sedation (α_1-containing receptors). It is further noted that molecular dynamics simulation data of the complex (OXB2-$GABA_AR$) shows adequate structural stability in aqueous environment. Moreover, relevant ADMET data is found adequate for further consideration.

Keywords: Benzemidazole, $GABA_A$, $GABA_A$ receptor, anxiety, docking

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Background:

There is increasing interest to molecules containing heterocyclic ring, constituting the basic skeleton for a wide variety of compounds with industrial and pharmacological activities **[1-2].** Heterocyclic compounds are the major chemicals, representing more than 60% of organic compounds and playing an important role in many biochemical processes **[3].** Benzodiazepines are the main heterocyclic compounds used in medical therapy. These classes of psychoactive drugs are widely used for treatment of psychotropic diseases, especially Generalized Anxiety Disorder (GAD) **[4-5].** Benzodiazepines are also known for their sedative and hypnotic properties **[6-7],** and also for their amnesic, muscle relaxant and sedative characteristics **[8-9].** Benzodiazepines act allosterically to enhance the central γ-amino-butyric acid (GABA)-mediated neurotransmission at the $GABA_A$ receptor **[10].** $GABA_A$ receptors are ionotropic receptors and ligand-gated ion channel. Generally, $GABA_A$ receptors are pentameric proteins composed of different subunits (α_{1-6}, β_{1-3}, γ_{1-3}, δ, ε, π and θ), α subunit being the most important one determining the pharmacology of the Benzodiazepines binding site [11]. The major Benzodiazepines - sensitive $GABA_A$ receptor subtypes in the brain are $\alpha_1\beta_x\gamma_2$, $\alpha_2\beta_x\gamma_2$, $\alpha_3\beta_x\gamma_2$ and $\alpha_5\beta_x\gamma_2$ and their distribution in the brain shows distinct regional variations **[11].** Benzodiazepines are non-selective drugs and interact with all $GABA_A$ subtypes with equivalent affinity and efficacy, and consequently exert their therapeutic actions by modulating the function of GABA at $GABA_A$ receptors containing α_1, or α_2, α_3 or α_5 subunit **[12-13].**

Interest was given to delineate which α-subunit-containing $GABA_A$ receptors subtypes are associated with particular aspects of the diverse pharmacology of nonselective benzodiazepines. The functional heterogeneity of $GABA_A$ receptor subtype was initially implied on the basis of regional differences in the expression of different α subunit containing $GABA_A$ receptors **[14-15]** along with the novel pharmacological profile of the α_1-subtype preferring hypnotic benzodiazepines drugs [16]. The functions of different $GABA_A$ receptor populations have been further clarified by the use of transgenic mice as well as subtype-selective compounds [17-18]. Hence, it is widely accepted that α_1-containing $GABA_A$ receptors play a role in the sedative properties of the nonselective benzodiazepines **[17; 19]** and anxiolytic properties are mediated by α_2 and/or α_3 subtypes **[18; 20-22].**

Thereafter, great efforts are made to develop new anxiolytic drugs devoid of the sedative properties associated with classical benzodiazepines. In this regards, some anxioselective benzodiazepines were developed with much reduced sedative liability but have a lower intrinsic efficacy than existing benzodiazepines and therefore a limited clinical utility [23-24]. Currently, most studies focus on the development of compounds with subtype-selective efficacy, able to bind to all four subtypes, but with higher efficacy to α_2- and α_3- as compared to α_1- and α_5-containing receptors **[25].**

Benzimidazoles are heterocyclic aromatic compounds with large biological effects. Some benzimidazoles derivatives have shown a strong efficacy to cure psychotic disorders. Of particular interest, these compounds showed a good affinity to $GABA_A$ receptor with a clear selectivity to α_2 and α_3 subunits **[26-29].** Recently, we have developed a new benzimidazole compound, 3-[2-(2-Amino-1H-benzo[d]imidazol-1-yl)ethyl]-1,3-oxazolidin-2-one" (OXB_2), with a potential antidepressant / anxiolytic activities [30-31]. Therefore, it is of interest to study the binding capacity of "3-[2-(2-Amino-1H-benzo[d]imidazol-1-yl)ethyl]-1,3-oxazolidin-2-one" (OXB_2), a newly synthesized and characterized Benzimidazole, on the active site of gamma-aminobutyric acid (GABA) located in the GABA type A receptor ($GABA_AR$) to compare with different $GABA_A$ subtypes.

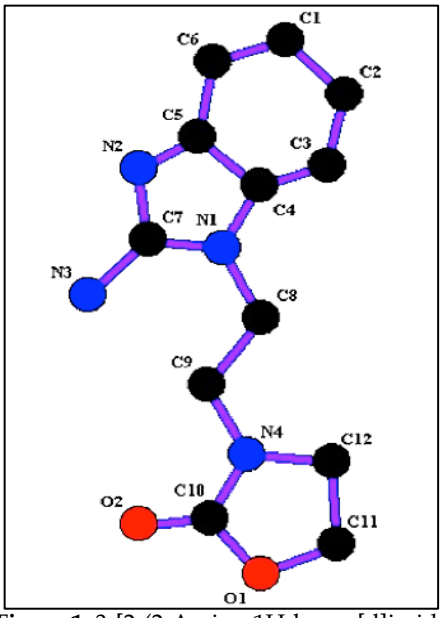

Figure 1: 3-[2-(2-Amino-1H-benzo[d]imidazol-1-yl) ethyl]-1,3-oxazolidin-2-one (OXB_2) represent in vivo effect on $GABA_A$ receptors generated by Ligplot

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Methodology:

Synthesis of compounds:

OXB_2 is a new Benzimidazole derivative synthesized by a new method PTC (Phase-Transfer Catalysis) by combining family of Benzemidazoles and Oxazolines. The purity of the newly synthesized compound was verified by melting point and on (Thin Layer Chromatography) TLC and the structure was determined by various analytical techniques such as IR spectral studies and 1H NMR (Spectroscopy Nuclear Magnetic Resonance). In OXB_2, the Benzimidazole ring is almost planar with the largest deviation from the mean plane being 0.039 (2) Å. However, the fused ring system is slightly folded at shared atoms with a dihedral angle of 3.4 (1)°. In contrast, the Oxazoline ring displays a twisted conformation on the adjacent carbon atoms. Moreover, the mean plane through the Oxazoline cycle makes a dihedral angle of 57.4 (2)° with the Benzimidazole ring. The molecules are linked together by two bifurcated N–H···O and C—H···N hydrogen bonds to form a three-dimensional network (**Figure 1**). There is also a weak C—H···π (benzene) interaction, which contributes to the stability of the crystal packing arrangement **[30-31].**

Structure of $GABA_A$ receptor:

The crystal structure of the human's $GABA_AR$ was downloaded from RCSB database bearing the following crystallization specificities: Code PDB 4COF, which is the Crystal structure of a human gamma-aminobutyric acid receptor, the $GABA_AR$-beta3 homopentamer published on 2014 by Miller, & Aricescu, by x-ray diffraction with resolution in order to 2.97 Å. R-Value Free: 0.226 and R-Value Work: 0.205

The Unit cell parameters were as:

Length [Å]: a = 174.10, b = 108.90 and c = 207.44.
Angles [°]: α = 90.00, β = 107.43 and γ = 90.00.

As illustrated in Figure 2, the $GABA_A$ receptor is a molecular target for numerous CNS depressants including: benzodiazepines (e.g. librium, valium, medazolam), benzodiazepine- like hypnotics: (zolpidem, eszopiclone and zalepon which selectively bind to the α_1 subunit of the $GABA_A$ receptor), Ethanol (at high & low affinity binding sites), barbiturates and anesthetics (e.g. isoflurane) **[14; 32].** As already mentioned, the $GABA_A$ receptors are composed by five subunits (2α, 2β, and 1γ). The GABA neurotransmitter bind in two sites (GABA site) localized between α and β subunit (top view). In other hand benzodiazepines like midazolam and benzodiazepine-like hypnotics like zolpidem bind in (BDZ site) localized between α and γ subunit (side view). Flumazenil (side view) is also BDZ receptor but has an antagonist characteristic, which can upset the effects of benzodiazepines and benzodiazepine-like hypnotics. The binding pocket is constructed from six regions, namely loops A–F. Experimental evidence reveals that the binding site in the $GABA_A$ receptor includes many residues (**Table 1**)

Molecular Docking:

Molecular docking was used to evaluate the affinity of OXB_2 to link to GABA (β_2/α_1, β_2/α_2, β_2/α_3) sites. The docking was performed on Autodock vina. The resulting structures were visualized using Chimera USCF [33] and PyMol **[34],** and 2D bond by LigPlus and Discovery Studio Visualization **[35].**

Pharmacokinetic study:

ADME-Tox (absorption, distribution, metabolism, elimination and toxicity) profile evaluation is widely used to evaluate the potential pharmacokinetic characteristics of chemical compounds describing the different processes followed by the chemical after administration. ADME-Tox properties of OXB_2 were studied using Pre-ADME and ADMET-Sar server **[36].** The interactions between OXB_2 and blood proteins were assessed by 3D-QSAR model.

Molecular dynamics:

The molecular dynamics simulation has been carried out by GROMOS software using the server MDWeb [A] and gromacs [b]. The simulation was done by AMBER99SB Force Field and the following parameters: Time (ns) 10 and 50, Δt (ps) 0.1, Output Frequency (steps) 100, Force Constant (Kcal/mol*Å²) 40, Distance between Alpha Carbon Atoms (Å)3.0. The mutations showed in the alignment results were investigated in MD to study their effects on the structure of the protein.

Table 1: amino acids and their characteristics in the binding site of $GABA_A$

Amino acids characteristics	Noun and position
Aromatic (Alpha and beta subunit)	α1Phe64, β2Tyr62, β2Tyr97 and β2Tyr205
Hydroxylated (Alpha and beta subunit)	α1Ser68, β2Thr160, β2Thr202, β2Ser204 and β2Ser209
Charged (Alpha and beta subunit)	α1Arg120, α1Asp183, α1Arg66 and β2Arg207

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Results & Discussion:

During last decades, pharmaceutical research has known a great evolution at both conceptual and methodological levels, using new technologies and innovative approaches. Bioinformatics and Cheminformatics tools have a special place in the process of valuing new synthetic components with cost and time gaining. In this study, bioinformatics tools were sued to evaluate the docking characteristics of OXB_2, a newly synthesized molecule, on $GABA_A$ (β_2/α_1, β_2/α_2, β_2/α_3) receptors, to evaluate the molecular dynamic of this link and to assess the ADEM-Tox profile of OXB_2.

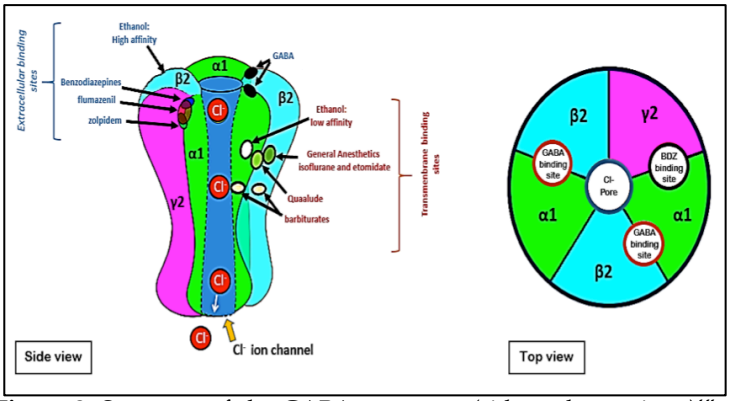

Figure 2: Structure of the $GABA_A$ receptor (side and top views)''' and position of the binding sites for different drugs.

Table 2: Docking results of OXB_2 with $GABA_A$ isoforms (α_1, α_2 and α_3)

α_1*	-7.2 kcal/mol
α_2**	-8.0 kcal/mol
α_3**	-7.3 kcal/mol

*Crystal structure **Modeled structure

$GABA_A$ ($2\alpha_2$, $2\beta_2$, and $1\gamma_2$) and $GABA_A$ ($2\alpha_3$, $2\beta_2$, and $1\gamma_2$) were modeled using I-TASSER server, using $GABA_A$ ($2\alpha_1$, $2\beta_2$, and $1\gamma_2$) (Id: 4COF) as a template. The total energy variation showed that for the 3 $GABA_A$ isoforms, the energy was around -7/-8 Kcal/mol, indicating that OXB_2 is able to link to both $GABA_A$ receptors. Specific energy liaison of OXB_2 to the 3 $GABA_A$ isoforms is reported in **Table 2** and showed that the high energy score was obtained with the isoform $GABA_A$ (α_2) giving a score of -8 kcal/mol.

Interactions between OXB_2 and $GABA_AR$ (α_1), $GABA_AR$ (α_2) and $GABA_AR$ (α_3) are represented in Figure 3. Overall, OXB_2 component forms fewer bonds with the active sites and all formed bonds are non-covalent type. The absence of covalent bonds can be explained by compatibility of the shape of the OXB_2 with the active site. The

Table 3 shows the residues involved in binding with the ligand and three isoforms of alpha subunit GABAA receptor. Eleven amino acids GLN64, PHE200, TYR62, ALA201, ALA88, TYR126, ARG114, VAL106, ARG114, LEU91 and ALA88 residues of template are involved in interaction.

Table 3: $GABA_A$ active site residues involved in docking interactions with the compounds.

α_1	α_2	α_3
GLN64	ALA88	ARG114
PHE200	TYR126	LEU91
TYR62	ARG114	ALA88
ALA201	VAL106	LEU91
	ASN138	ASP39
	THR140	

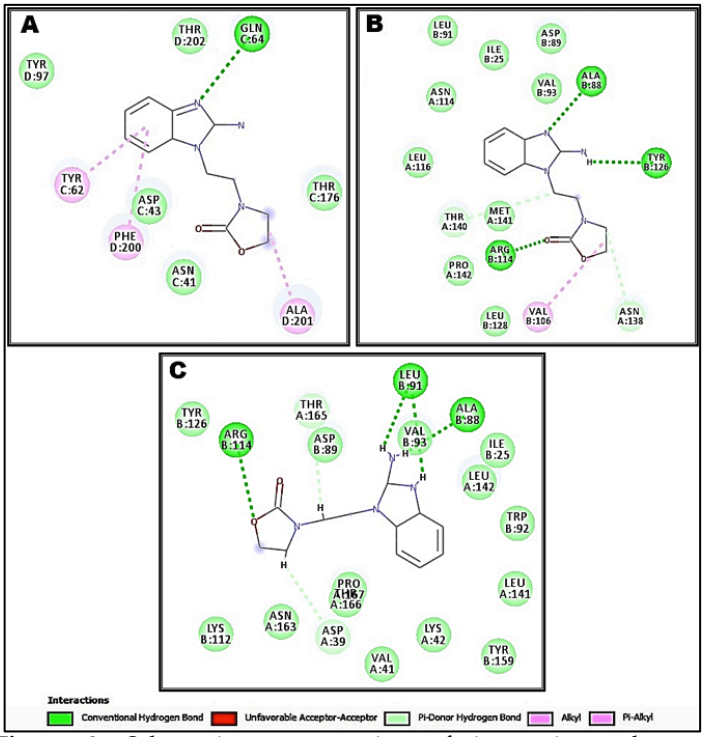

Figure 3: Schematic representation of interactions observed between OXB_2 and $GABA_A$ (α_1) *A*, $GABA_A$ (α_2) *B* and $GABA_A$ (α_3) *C* generated by discovery studio visualize

The proposed binding mode OXB_2 revealed an affinity value of -7.2 kcal/mol with the isoforms α_1. The N-atoms of OXB_2 interacted with active sites of $GABA_A$ (α_1) by forming H-bond with GLN64 at distances of 2.69996 A˚. Also, Pi-Alkyl type of interaction observed

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between aromatic rings and TYR62 and PHE200 with distances 4.34717 A˚ and 4.8423 A˚ respectively. Alkyl type of interaction was observed between (ALA201) and "carbon 11" of the ligand with bond lengths of 3.8367 A˚ (Fig. 3A). In $GABA_A$ (α_2) isoform, the proposed binding mode OXB_2 revealed an affinity value of -8 kcal/mol. OXB_2 interact with many amino acids residues by forming hydrogen bonds with ALA88 (3.35142A˚), TYR126 (2.46278A˚), ARG114 (2.75004A˚), THR140 (3.40151A˚) and ASN138 (4.97569A˚). Also Alkyl type of interaction was observed between VAL 106 and carbon 12 of the ligand with bond lengths of 3.8367 A˚ (Fig. 3B). Otherwise, OXB_2 revealed an affinity value of -7.3 kcal/mol with the isoforms of $GABA_A$ (α_3). Exclusively, H-bond type of interaction was indicated with different amino acids. LEU91 forms two bonds with NH- OXB_2 with bond lengths of 2.61522 A˚ and 2.46548 A˚. Also ARG114, THR 165, ASP39 and ALA88 form the same type of bond with OXB_2 with distance 2.26162 A˚, 2.82758 A˚, 3.04107 A˚ and 2.38929 A˚ respectively (**Figure 3C**).

The non-covalent bonds established between the chemical compound and $GABA_A$ receptors are of particular interest to favor the placement of the proper ligand at the active site with competition and reversibility, whereas covalent bonds are highly stable and mostly associated with irreversible effects **[37].** The liaison between OXB_2 and $GABA_A$ receptors exhibited an endothermic reaction, which thermodynamically favors the good orientation of the compound in the system due to the increase in the enthalpy effect according to the law of Internal Energy **[38].** The increase in Van Der Waals (VdW) energy is an obvious result as the new components are characterized by the presence of nitrogen atom and core aromatics of 5, making the attractive effect of the components more significant **[39].**

It's widely accepted that knowledge at an atomic level of the structural and dynamic aspects of organized systems is particularly important for better understanding the functions of these complex molecular structures. In many cases, obtaining the microscopic details by conventional experimental techniques proves impossible. However, the true explosion of the computerized means initiated for about ten years, and the development of efficient algorithms, make possible the study of supra molecular assemblies of increasing complexity by the methods of theoretical chemistry **[40].**

The complexes obtained by molecular docking were submitted to a simulation of 20 ns (Figure 4). Molecular dynamic results show stability of protein-ligand complex, characterized by thermal stability during the simulation conditions. The fluctuation of the protein complex is more stable for both complex and proteins; however the binding energy is more suitable for the complex than the protein alone. The simulations are done in a constant pressure system for the different cell dimension, which allowed having a prototypical simulation of the cellular activity during the whole dynamic simulation period. The energies of bonds, partially and VdW are very close, which lead to a high Van der Waals energy, just like a large number of hydrogen bonds since they pull the atoms closer than their normal Van der Waals contact distance.

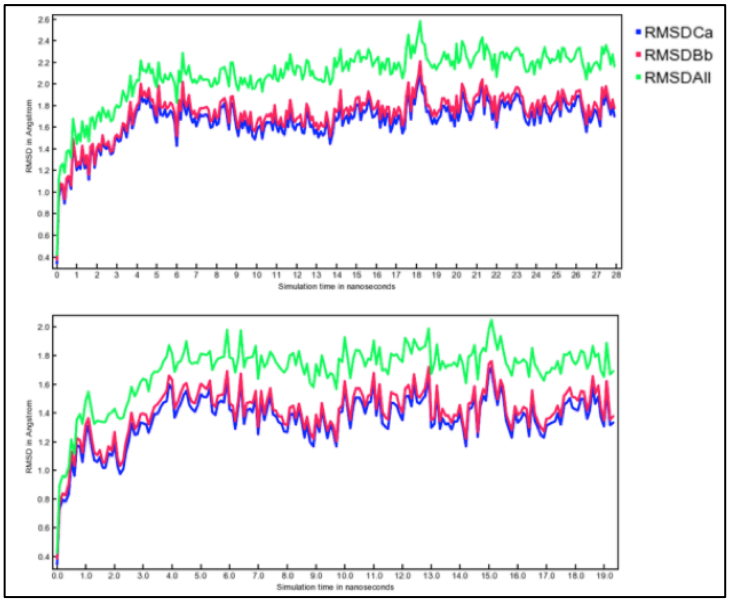

Figure 4: Molecular dynamic results

The total potential energies were calculated for each snapshot (**Figure 5**) and showed a fluctuation of about 1000 kcal / mol (about 0.5% of the total potential energy), indicating the stabilization of all the systems in MD simulations. In addition, the potential energies of complex models for each ligand subtype were quite similar, suggesting that the influence of local mutations on potential energy could be neglected in MD simulations. RMSD values were further calculated for each snapshot to study the relative movement of the backbone atoms of the proteins and ligands. RMSD values fluctuated largely when whole protein structures were considered in the calculation. Most of the RMSD values were less than 2 Å, and some of them even reached 0.6 Å (the complex model), indicating that the receptors showed less significant structural changes during the simulations. Since most parts of the complexes are less rigid and stable, the fluctuation of the RMSD values is mainly due to the loop. Thus, the RMSD values, excluding the complex, the structures were recalculated in **Figure 4.** The new RMSD values were

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generally less than 6 Å, demonstrating that the high RMSD values of the full-length receptors were attributed to the high flexibility of loops telling the active site.

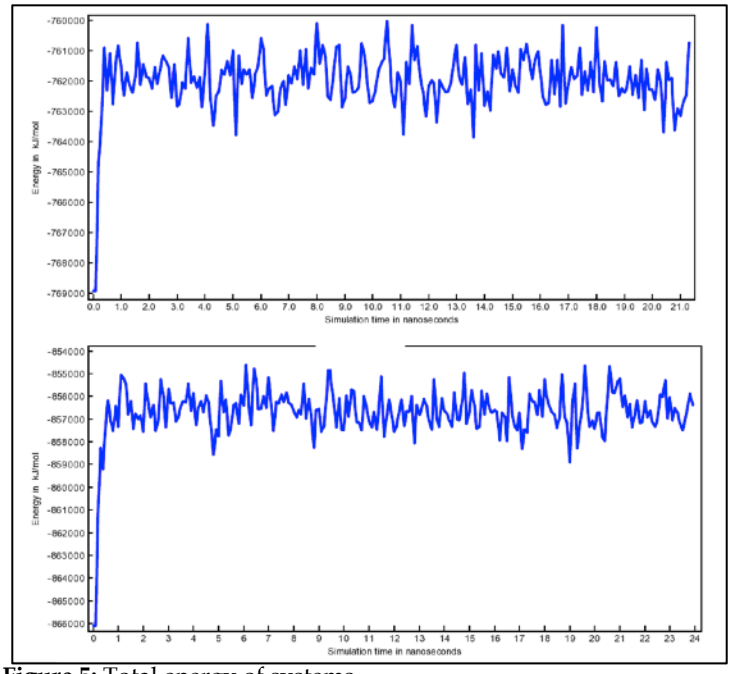

Figure 5: Total energy of systems

A high value of factor B indicates more flexibility, while a low value of factor B indicates more stability. The helices had very low B-factor values, but the loops had moderate or high B-factor values, indicating large conformational changes in the loop regions during the MD simulations. These results were consistent with the inference of the RMSD values and explained that the high RMSD value of the complex was caused by a major conformational change, such as rotation. Although the flexibility of the loop has decreased the stability of the system, it would not affect inter-complex interactions because the loop was located far from the link interface. Thus, the reliability of further analysis can be guaranteed. ΔEvdW and ΔEelec oppose binding, but ΔGGB enhances binding to the complex by switching from CP to AP ligand, while ΔEvdW and ΔEelec improve binding. The sum of AEvdW and AEelec could overcome the term AGBG and cause the net link change. Decomposition analysis of binding energies In order to explore how mutations influence binding energies, binding energies are decomposed into each residue.

The pharmacodynamics and pharmacokinetic of newly synthesized drugs are of a great interest to evaluate the target and the undesirable effects and to appreciate the metabolization, bio-distribution, elimination and toxicity of the drug and its derivatives. In this study, the ADME-Tox profile of OXB_2 was evaluated and results are reported in **Table 4.** In ADME-Tox analysis, the main parameter is the characterization of blood-brain barrier (BBB), evaluating the ability of drugs to cross this barrier and go insight the brain **[41].** The role of BBB is to maintain brain homeostasis and to protect nerve tissue from circulating blood microorganisms, toxins, cellular factors and humoral immune system **[42].** However, the presence of BBB prevents the treatment of many diseases of the central nervous system, and therefore in the perspective of psychotropic diseases therapy, all potential drugs have to cross the BBB and link to the target sites. ADME-Tox results showed that BBB permeability index was 0.554267, considered as medium to low **[43],** suggesting that OXB_2 is able to cross the BBB and acts on $GABA_A$ receptors as target sites. Other important pharmacokinetic parameters were also predicted by Pre-ADME and ADMET-Sar and showed that OXB_2 exhibited no AMES mutagenic and carcinogenic effects by Ames assay and possessed better human intestinal absorption. OXB_2 had also Middle Caco2 permeability had a well human intestinal absorption. Predictive results showed that OXB_2 weakly bounds to Plasma protein binding (PPB) and had lower MDCK permeability. These results suggest that OXB_2 ligand has adequate pharmacokinetic characteristics and could be a promising candidate to be used as a drug.

Table 4: ADMET prediction of OXB_2

Parameter	Value / Predictive result	Parameter	Value / Predictive result
Ames mutatest	Negative	HIA	96.623102
SK log S pure	-1.9298	CYP3A4 substrate	Weakly
SK log S buffer	-1.59987	CYP3A4 inhibition	Non
SK log P value	1.15268	CYP2D6 substrate	Non
SK log D value	1.15268	CYP2D6 inhibition	Non
Skin Permeability	-4.1626	CYP2C9 inhibition	Non
Pure water solubility mg/1	2894.73	CYP2C19 inhibition	Non

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Plasma Protein Binding	52.137421	Caco2	19.5815
Pgp inhibition	Non	Buffer solubility mg/l	6187.83
MDCK	17.4024	BBB	0.554267

BBB (Blood Brain Barrier): High absorption CNS >2.0, Middle absorption CNS 2.0–0.1, Low absorption CNS <0.1 Caco2: High permeability >70, Middle permeability 4–70, Low permeability <4 HIA (Human Intestinal Absorbance): Well absorbed compounds 70–100%, moderately absorbed compounds 20–70%, Poorly absorbed compounds 0–20%. PPB (Plasma Protein Binding): Strongly Bound >90%, Weakly Bound <90%, MDCK: Higher permeability >500, Medium Permeability 25–500, lower permeability <25.

Conclusion:

We document the molecular docking analysis of α_2-containing $GABA_A$ receptors with a benzimidazole derivative for further consideration.

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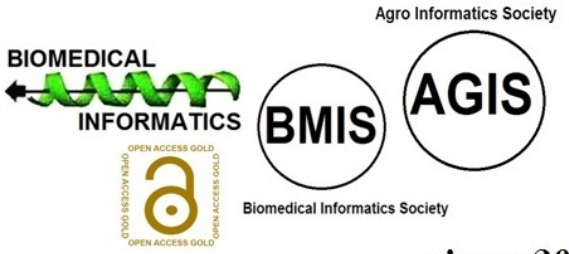

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