RESEARCH PAPER

"COMPUTATIONAL STUDIES ON 1,5-BENZODIAZEPINES: DOCKING, ADME/T AND TOXICITY INSIGHTS FOR ANTIDEPRESSANT DEVELOPMENT"

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Abstract
There is ongoing interest in alternative CNS-active scaffolds since depression is still a major cause of disability worldwide and current antidepressants are hampered by delayed beginning of action, partial response, and side effects. In addition to their well-known anxiolytic, sedative, anticonvulsant, and anti-inflammatory qualities, 1,5-benzodiazepines have demonstrated developing antidepressant action associated with GABAergic regulation, which makes them appealing candidates for computational study as antidepressant drugs. In order to evaluate ligand-receptor interactions, a number of 1,5-benzodiazepine derivatives were molecularly docked against the human GABA-A receptor (PDB ID: 6X3X), a cryo-EM structure co-crystallized with diazepam that offers a physiologically relevant benzodiazepine-binding site. AutoDock Vina was used for docking, and the co-crystallized diazepam was used as a reference to examine the docked derivatives' binding affinities, hydrogen-bonding patterns, and important amino acid interactions. SwissADME was used to predict drug-likeness and pharmacokinetic behavior, such as gastrointestinal absorption, blood-brain barrier permeability, and cytochrome P450 interactions, while ProTox-III was used to assess acute toxicity and organ-specific toxicity endpoints. Promising antidepressant leads were found to have favorable binding affinities for the GABA-A receptor, compliance with Lipinski's rule of five, and acceptable anticipated toxicity profiles. A quick, economical, and animal-saving method for ranking 1,5-benzodiazepine derivatives for additional synthesis and pharmacological validation is provided by the integrated in-silico approach that combines molecular docking, ADME/T prediction, and toxicity profiling. These results provide a logical foundation for future structure-based optimization of GABA-A-targeted antidepressant candidates and validate the therapeutic repurposing potential of the 1,5-benzodiazepine scaffold beyond its traditional uses.

Keywords: 1,5-benzodiazepines; molecular docking; GABA-A receptor; ADME/T; toxicity prediction; antidepressant
How to cite this article: PRIYA GUPTA1 ANITA SINGH*1 ANIL KUMAR SAHDEV2. "COMPUTATIONAL STUDIES ON 1,5-BENZODIAZEPINES: DOCKING, ADME/T AND TOXICITY INSIGHTS FOR ANTIDEPRESSANT DEVELOPMENT". Int J Drug Deliv Technol. 2026;16(87s):608-625. DOI: 10.25258/ijddt.16.87s.62.

INTRODUCTION

Anhedonia, persistent poor mood, and reduced cognitive and physical functioning are the hallmarks of depression, a prevalent and crippling mental illness. The World Health Organization estimates that 280 million individuals worldwide—nearly 5% of all adults—have depression, with a significantly higher prevalence among women than males. Beyond its psychological effects, depression continues to be one of the main causes of suicide, which takes over 700,000 lives each year, and is strongly associated with increased morbidity from diabetes, cardiovascular disease, and other chronic illnesses. The majority of afflicted people, especially in low- and middle-income nations, do not receive proper care despite the availability of effective medicines, highlighting the critical need for easily available and efficient antidepressant therapies [1]. Currently, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) play a major role in the pharmacological treatment of depression [1]. Despite being the cornerstone of clinical management, these drugs have a number of side effects, such as sexual dysfunction, weight gain, gastrointestinal problems, and cardiotoxicity, as well as delayed onset of therapeutic action, incomplete remission rates, and treatment resistance in a significant portion of patients. These constraints continue to motivate research in medicinal chemistry to find new molecular scaffolds with enhanced safety and effectiveness profiles that can modify central nervous system (CNS) pathways linked to mood regulation [1].

One of the classes of CNS-active heterocycles that has been investigated the most is benzodiazepines. Benzodiazepines, which are structurally defined by a seven-membered diazepine ring fused with a benzene ring, primarily affect anxiety, seizure threshold, sedation, and muscle tone by allosterically modulating the gamma-aminobutyric acid type A (GABA-A) receptor complex. Among the different isomeric forms, 1,5-benzodiazepines

have garnered special interest in medicinal chemistry because of their simple synthesis, usually by condensing o-phenylenediamine with ketones or α, β-unsaturated carbonyl compounds, and their exceptional biological action, which goes beyond traditional anxiolytic and hypnotic effects to include anticonvulsant, analgesic, anti-inflammatory, and antidepressant properties. Potency and selectivity across various pharmacological domains have been demonstrated to be modulated by structural modification of the 1,5-benzodiazepine core via Mannich and Schiff base chemistry as well as the addition of electron-withdrawing substituents [2-5]. In preclinical behavioral models like the forced swim test and tail suspension test, a number of benzodiazepine analogs have shown notable antidepressant-like activity. Mechanistic studies have revealed a GABAergic component involving increased hippocampal GABA levels and upregulation of GABA-A receptor subunit expression in the prefrontal cortex [6]. 1,5-benzodiazepine derivatives are promising candidates for repurposing and rational design as novel antidepressant agents because of the well-established interaction between GABAergic and monoaminergic signalling in the regulation of mood and the favorable CNS-penetrant physicochemical character typical of the benzodiazepine scaffold. The traditional drug discovery process, which entails synthesis and in vivo pharmacological testing, is costly, time-consuming, and increasingly limited by ethical issues related to animal testing. Therefore, early-stage drug development now relies heavily on computer-aided drug design (CADD) techniques, such as molecular docking and in-silico prediction of absorption, distribution, metabolism, excretion, and toxicity (ADME/T) features. Programs like AutoDock Vina, which combine an effective search algorithm with an empirical scoring function, are frequently used for this purpose due to their favorable balance of speed and accuracy. Molecular docking allows prediction of the binding mode and relative binding affinity of candidate ligands within the active site of a biological target, allowing for quick virtual screening and prioritization of compounds prior to synthesis [7]. SwissADME and other complementary in-silico technologies enable quick, ligand-based prediction of physicochemical characteristics, drug-likeness, and pharmacokinetic behavior, including blood-brain barrier permeability, a crucial factor for CNS-targeted drugs [8]. Similar to this, toxicity prediction servers like ProTox-II provide a quick and less-animal-testing substitute for traditional toxicity screening by combining molecular similarity, toxicophore identification, and machine-learning models to estimate acute toxicity, hepatotoxicity, mutagenicity, and other toxicological endpoints [9]. A rigorous in-silico evaluation that combines molecular docking against pertinent antidepressant targets with thorough ADME/T and toxicity profiling of this scaffold is still lacking in the literature, despite the established pharmacological flexibility of 1,5-benzodiazepines. In addition to flagging compounds with unfavourable pharmacokinetic or toxicological liabilities early on, such an integrated computational approach can offer important mechanistic insight into ligand-receptor interactions, simplifying subsequent synthetic and biological evaluation efforts. With the overall goal of identifying promising lead candidates for additional experimental development as safe and effective antidepressant agents, the current study was conducted to investigate the antidepressant potential of a series of 1,5-benzodiazepine derivatives through molecular docking studies against pertinent CNS targets implicated in depression, coupled with in-silico prediction of their ADME/T properties and toxicity profiles.

1. Materials and Methods

2.1 Tools/ Software's used in *in-silico* studies

Chem Draw Ultra 12.0: This is used to compute molecular descriptors, create chemical structures, and optimize the proposed derivatives in three dimensions. It is also used for naming structures according to IUPAC. ChemDraw Ultra 12.0 is a specialized software program primarily used by chemists and chemical researchers. It is a part of the ChemDraw software package from PerkinElmer Informatics. It is commonly recognized that ChemDraw Ultra can create precise and well-designed chemical structures and diagrams.

RCSB PDB (Protein Data Bank): It is a crystallographic database designed to provide 3-D structural information about macromolecules like proteins and nucleic acids from X-ray crystallography and NMR spectroscopy. Scientists can save and arrange information about the morphology of tiny creatures using the RCSB PDB (Protein Data Bank), an online database. They use tools like X-ray machines and microscopes to view these shapes. The library has a plethora of information on each shape, including its composition and history.

Swiss ADME: The medications' Absorption, Distribution, Metabolism, and Excretion (ADME) properties were calculated using the Swiss ADME, which forecasts elements of organic molecules that are important from a physical and pharmacological standpoint. In order to predict the Lipinski rule of five, it will be utilized to compute the chemical characteristics and bioactivity. The Lipinski rule of five, often known as the rule of thumb, aids in assessing a compound's likelihood of possessing the chemical and physical characteristics necessary for oral bioavailability. By providing useful

information on the pharmacokinetic properties of substances, this program aids scientists in the search for and development of new medications.

Autodock Vina 1.5.7: For conducting docking studies and forecasting the intermolecular interactions of drugs with the receptor, an open-source docking program will be chosen. A molecular modelling program called AutoDock is used to forecast the interactions between tiny molecules (ligands) and proteins (receptors), which is essential for drug discovery. It uses methods such as the Lamarckian Genetic Algorithm for flexible docking of ligands and scores binding affinities. Analysis of docking findings is aided by visualization tools like AutoDock Tools [18].

Open Bable: Molecular docking will be helped by Open Babel, a computer programme and chemical expert system that is mostly used to translate chemical file types.

ProTox 3.0: ProTox is a predictive toxicology tool connected to cheminformatics. Its goal is to use molecular structure analysis to predict a chemical compound's potential toxicity. ProTox uses computer models and algorithms to evaluate a compound's toxicity against particular biological targets or endpoints. ProTox views itself as a complete, open-source computational platform for in-silico toxicity prediction that may be used by toxicologists, regulatory agencies, medicinal chemists, and computational chemists. The ProTox 3.0 web webserver is freely accessible to all users.

PubChem: Data on a variety of subjects, including identifiers, physical and chemical properties, biological activity, patents, health, safety, and toxicity, have been collected from this program.

BIOVIA Discovery Studio: For viewing, sharing, and analyzing protein and small molecule data, the free molecular modelling tool BIOVIA Discovery Studio Visualizer offers a wealth of features. The study of molecular docking studies heavily relies on molecular visualization.

2.2 Protein/Receptor preparation

For docking research, a clean protein must be prepared in order to obtain precise dock scores and accurate data. The protein's energy was minimized after it was downloaded from www.rcsb.org. The chosen receptor is a GABA A receptor, 6 HUP. The protein, which was saved in PDB format, was pre-processed to remove all bound water molecules, ligands, and cofactors. Small molecules that are attached to proteins must be removed before docking can take place. It is necessary to eliminate water molecules in addition to tiny ones. When making protein, polar hydrogens can also be added. With the AMBER force field, the resulting complex was reduced. The AMBER force field was used to reduce the resultant complex. After completing 5,000 steps or when the energy gradient fell below 0.05 kcal/mol, the reduction process was stopped. For the aforementioned objectives, Discovery Studio (BIOVIA) was utilized in this study [10].

2.3 Ligand preparation

Following a thorough review of the literature, new ligands were created. ChemDraw Ultra 12.0 was used to construct the compounds' two-dimensional structures. To find out if designed ligands exist, the SMILES of these ligands were duplicated and verified in the ZINC and PubChem databases. The Open Babel GUI was used to convert the ligands created in ChemDraw into PDBQT format. These conformations were then stored as PDB files for later usage after being opened in PyMOL [11,12].

2.4 Docking Methodology

Molecular docking is the computer technique of looking for a ligand that fits both physical and energetically into a protein's binding site. Molecular docking shows promise in both the first evaluation of binding affinity and the prediction of intermolecular interactions of novel medicines with receptors. A popular software program for simulating chemical interactions in computational chemistry and molecular modelling, "Optimized GABA A," was used to dock each ligand with Autodock 1.5.7. Predicting how a small substance, such as a ligand or drug, would bind to a particular receptor, like a protein target, is its primary goal. Each complex was assigned a docking score, which will be examined. PyMOL [13] and Discovery Studio [14] had been utilized to visualize the complexes and comprehend the ligands' binding sites. Both 2D and 3D conformations of the ligand and receptor have been shown to interact. To forecast how the medications will affect the receptor, an overall comparison of the docking scores and binding patterns was conducted. AutoDock explores the conformational space of the ligand and receptor using molecular docking techniques to predict the most energetically favorable binding modes [15]. Docking is completely automated and operates in response to commands and software. Finding the optimal ligand-receptor interaction was the primary motivation behind performing docking before any additional research. The energy released during ligand-receptor interaction is calculated using docking. Following docking, several dock scores were produced; the best dock score with the least energy (most negative) was chosen for additional research [16].

2.5 ADME and toxicity prediction

Absorption, distribution, metabolism, excretion, and toxicity are predicted for the selected 1,5-benzodiazepine derivatives using the Pre ADMET predictor server [17]. Using Swiss ADME, ADME properties were anticipated. The table that follows

provides a thorough overview of the compounds' different characteristics. The website www.swissadme.ch provides free access to Swiss ADME. SwissADME offers a variety of computer models for predicting properties such as solubility, permeability, and adherence to Lipinski's Rule of Five. These predictions can be used by researchers to rank substances for further testing and development based on their likelihood of working as potential drugs. Through the user-friendly online interface offered by SwissADME, users can directly construct molecular structures or upload data in various forms. After submitting a molecule, users receive a detailed report detailing the expected attributes of the complex. While working on drug development projects, researchers can make better selections by consulting this paper [18].

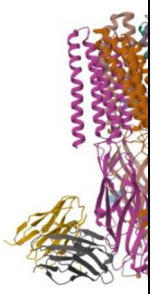
2. Results and Discussion

3.1 Docking Results/Score

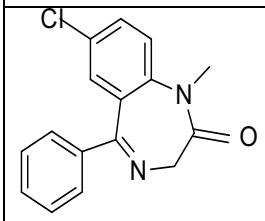
A docking score was determined after each drug molecule was docked with the target receptor in AutoDock Vina. In following docking, the docking score forecasts the binding affinity between a ligand and a protein. The better the docking, the lower the docking score. After docking with the GABAA receptor, we obtained 68 docking scores for 68 molecules. Among all the BZDs taken into consideration, it was projected that GABAA would have the strongest binding affinity with **D20** and **D21** based on the docking score from AutoDock Vina (Table 1). In order to examine the results and estimate the potential binding site of the BZDs to the receptor, the 3D binding conformations were viewed in BIOVIA Discovery Studio.

The prepared and cleaned structures and PDB ID of receptor are shown in the table below:

RECEPTOR USED IN DOCKING STUDIES

S. NO.	PDB ID	STRUCTURE	DESCRIPTION
1.	6X3X https://doi.org/10.2210/pdb6X3X/pdb		**Classification:** Membrane Protein **Organism:** Homo sapiens **Expression system:** Homo sapiens **Resolution:** 2.92 Å **Molecule:** Human GABAA receptor α1-β2-γ2 subtype in complex with GABA plus diazepam.

STANDARDS USED IN DOCKING STUDIES

STANDARD 2	Binding Affinity (kcal/mol) with 6X3X
 Diazepam	-8.8

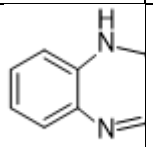
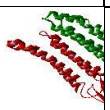
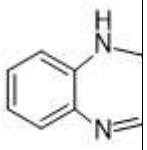
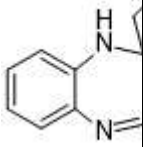
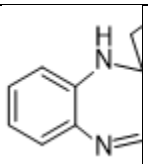
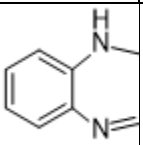
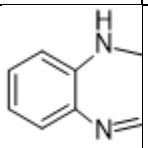
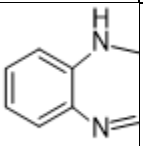
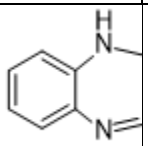
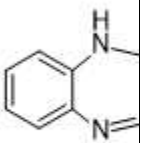
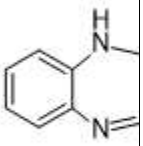
Diazepam is taken as Standard 1.

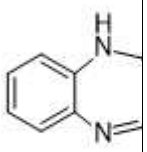
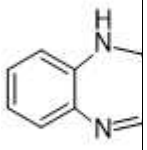
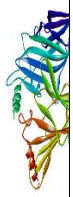
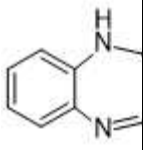
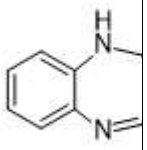
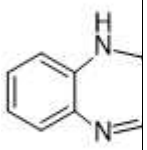
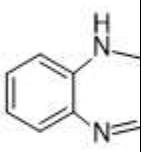
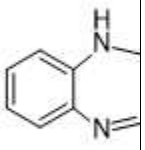
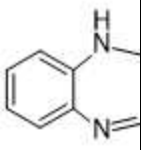
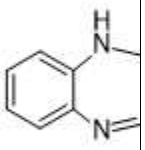
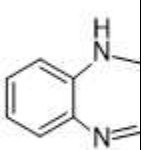
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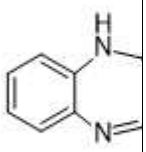
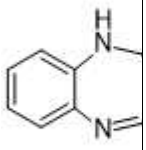
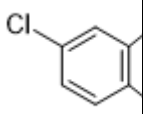
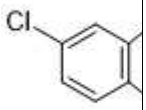
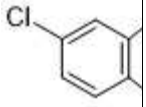
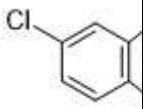
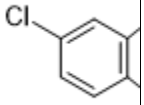
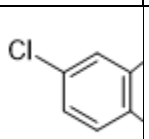
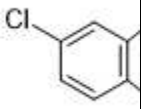
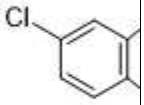
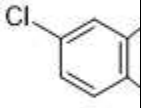
Total 80 ligands were designed and are chosen for docking studies. The designed ligands are provided below along with their IUPAC names and binding affinities:

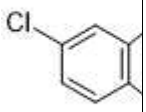
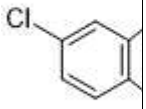
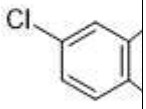
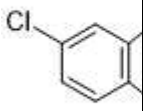
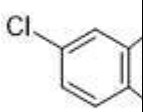
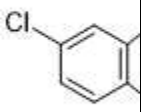
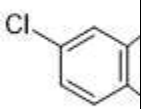
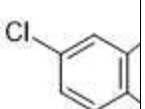
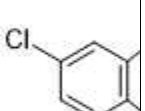
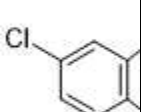
Table No. 01: AUTO DOCK SCORE, IUPAC, STRUCTUR, 3-D INTERACTIONS OF DERIVATIVES OF 1,5-BENZODIAZEPINES [18]

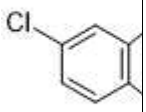
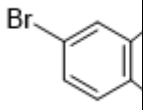
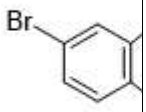
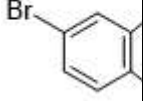
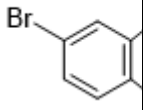
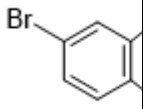
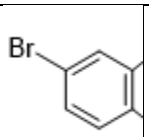
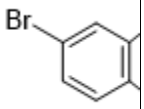
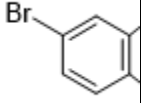
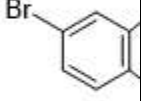
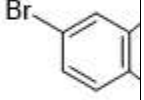
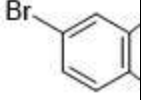
S. No.	Structure	IUPAC	3-D structure with protein(6X3X)	Binding Affini

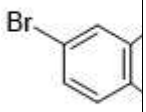
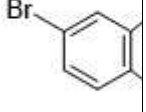
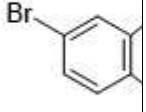
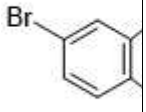
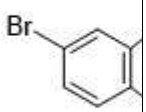
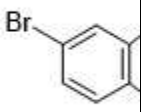
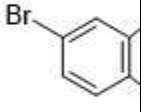
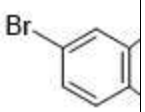
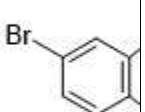
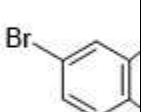
				ty (kcal/mol)
1.		2,2,4-Trimethyl-1H-1,5-benzodiazepine		-8.8
2.		2-Methyl-2,4-diphenyl-1,3-dihydro-1,5-benzodiazepine		-9.2
3.		1',2',3',4',10',11a'-Hexahydrospiro[cyclohexane-1,11'-dibenzo[b,e][1,4]diazepine]		-9.1
4.		2′,3′,3a′,10a′-Tetrahydro-1′H-spiro[cyclopentane-1,10′-benzo[b]cyclopenta[e][1,4]diazepine]		-8.9
5.		2,4-Diethyl-2-methyl-1,3-dihydro-1,5-benzodiazepine		-8.8
6.		2-Ethyl-2,3,4-trimethyl-1H-1,5-benzodiazepine		-9.3
7.		2,2-Diethyl-3,4-dimethyl-2,3-dihydro-1,5-benzodiazepine		-8.9
8.		2,2,4-Triethyl-1,3-dihydro-1,5-benzodiazepine		-8.4
9.		2-Ethyl-2,4-diphenyl-1,3-dihydro-1,5-benzodiazepine		-7.9
10.		2,3-Dimethyl-2,4-diphenyl-1H-1,5-benzodiazepine		-8.6

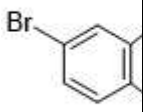
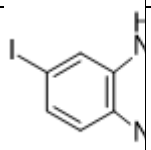
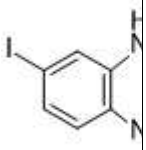
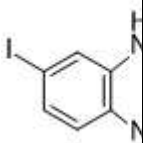
11.		2,4-Bis(4-chlorophenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-8.7
12.		2,4-Bis(4-bromophenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-8.1
13.		2,4-Bis(4-iodophenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-7.8
14.		2,4-Bis(4-hydroxyphenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-10.0
15.		2,4-Bis(4-methoxyphenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-9.1
16.		2,4-Bis(4-ethoxyphenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-9.5
17.		2-methyl-2,4-bis(4-methylphenyl)-1,3-dihydro-1,5-benzodiazepine		-11.1
18.		2,4-Bis(4-ethylphenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-11.0
19.		2,4-bis(4-nitrophenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-10.6
20.		2,4-Bis(4-cyanophenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-12.2

21.		4,4'-(2-Methyl-2,3-dihydro-1H-1,5-benzodiazepine-2,4-diyl)dibenzoic acid		-11.8
22.		4,4'-(2-Methyl-2,3-dihydro-1H-1,5-benzodiazepine-2,4-diyl)dianiline		-10.0
23.		8-Chloro-2,2,4-trimethyl-1,3-dihydro-1,5-benzodiazepine		-8.4
24.		8-Chloro-2-methyl-2,4-diphenyl-1,3-dihydro-1,5-benzodiazepine		-9.5
25.		8′-Chloro-1′,2′,3′,4′,11′,11a′-hexahydro-10′H-spiro[cyclohexane-1,11′-dibenzo[b,e][1,4]diazepine]		-8.4
26.		8-Chloro-2,2,3,4-tetramethyl-1H-1,5-benzodiazepine		-8.8
27.		8-Chloro-2,4-Diethyl-2-methyl-1,3-dihydro-1,5-benzodiazepine		-8.5
28.		8-Chloro-2,2-Diethyl-4-methyl-1,3-dihydro-1,5-benzodiazepine		-9.6
29.		8-Chloro-2,2-Diethyl-3,4-dimethyl-1H-1,5-benzodiazepine		-9.3
30.		8-Chloro-2,4-Diphenyl-2-ethyl-1,3-dihydro-1,5-benzodiazepine		-8.5
31.		8-Chloro-2,4-Diphenyl-2,3-dimethyl-1,3-dihydro-1,5-benzodiazepine		-8.1
32.		8-Chloro-2,4-bis(4-chlorophenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-8.7

33.		8-Chloro-2,4-bis(4-bromophenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-8.4
34.		8-Chloro-2,4-bis(4-iodophenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-8.0
35.		8-Chloro-2,4-bis(4-hydroxyphenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-9.0
36.		8-Chloro-2,4-bis(4-methoxyphenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-11.1
37.		8-Chloro-2,4-bis(4-ethoxyphenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-10.9
38.		8-Chloro-2,4-bis(4-methylphenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-8.6
39.		8-Chloro-2,4-bis(4-ethylphenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-8.5
40.		8-Chloro-2,4-bis(4-nitrophenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-11.2
41.		8-Chloro-2,4-bis(4-cyanophenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-11.5
42.		4,4'-(8-Chloro-2-methyl-2,3-dihydro-1H-benzo[b][1,4] diazepine-2,4-diyl) dibenzoic acid		-8.9

43.		8-Chloro-2,4-bis(4-aminophenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-8.5
44.		8-Bromo-2,2,4-trimethyl-1,3-dihydro-1,5-benzodiazepine		-8.4
45.		8-Bromo-2-methyl-2,4-diphenyl-1,3-dihydro-1,5-benzodiazepine		-9.5
46.		8′-Bromo-1′,2′,3′,4′,11′,11a′-hexahydro-10′H-spiro[cyclohexane-1,11′-dibenzo[b,e][1,4]diazepine]		-7.8
47.		7-Bromo-2,3,9,10a-tetrahydro-1H-spiro[benzo[b]cyclopenta[e][1,4]diazepine-10,1’-cyclopentane]		-7.0
48.		8-Bromo-2,2,3,4-tetramethyl-1H-1,5-benzodiazepine		-9.0
49.		8-Bromo-2,4-diethyl-2-methyl-1,3-dihydro-1,5-benzodiazepine		-8.4
50.		8-Bromo-2,2-diethyl-4-methyl-1,3-dihydro-1,5-benzodiazepine		-9.2
51.		8-Bromo-2,2-diethyl-3,4-dimethyl-1H-1,5-benzodiazepine		-9.2
52.		8-Bromo-2,4-diphenyl-2-ethyl-1H-1,5-benzodiazepine		-8.3
53.		8-Bromo-2,4-diphenyl-2,3-dimethyl-1H-1,5-benzodiazepine		-7.9
54.		8-Bromo-2,4-bis(4-chlorophenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-8.7

55.		8-Bromo-2,4-bis(4-bromophenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-8.4
56.		8-Bromo-2,4-bis(4-iodophenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-8.0
57.		8-Bromo-2,4-bis(4-hydroxyphenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-8.6
58.		8-Bromo-2,4-bis(4-methoxyphenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-10.7
59.		8-Bromo-2,4-bis(4-ethoxyphenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-10.2
60.		8-Bromo-2,4-bis(4-methylphenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-8.8
61.		8-Bromo-2,4-bis(4-ethylphenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-8.8
62.		8-Bromo-2,4-bis(4-nitrophenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-10.3
63.		8-Bromo-2,4-bis(4-cyanophenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-11.2
64.		4,4'-(8-Bromo-2-methyl-2,3-dihydro-1H-benzo[b][1,4] diazepine-2,4-diyl) dibenzoic acid		-10.6

65.		8-Bromo-2,4-bis(4-aminophenyl)-2-methyl-1,3-dihydro-1,5-benzodiazepine		-8.5
66.		8-Iodo-2,2,4-trimethyl-1,3-dihydro-1,5-benzodiazepine		-8.4
67.		8-Iodo-2-methyl-2,4-diphenyl-1,3-dihydro-1,5-benzodiazepine		-8.5
68.		8′-Iodo-1′,2′,3′,4′,11′,11a′-hexahydro-10′H-spiro[cyclohexane-1,11′-dibenzo[b,e][1,4]diazepine]		-7.4

Ligands estimation profile:

All the ADME/T parameters of designed ligands were checked using various software's, their pharmacokinetic profile was obtained. The ligand estimation profile of most all ligands is provided in the table below:

Table 2: Derivatives (Swiss ADME Parameter)

S. No.	GI Absorption	BBB Permeability	Log P	Water Solubility	Lipinski Rule	Molecular Wt.	Molecular formula	Synthetic Accessibility
D1.	High	Yes	2.27	Soluble	Yes	188.27 g/mol	$C_{12}H_{16}N_2$	3.23
D2.	High	Yes	3.02	Moderately Soluble	Yes	312.41 g/mol	$C_{22}H_{20}N_2$	3.87
D3.	High	Yes	3.04	Soluble	Yes	268.40 g/mol	$C_{18}H_{24}N_2$	4.56
D4.	High	Yes	2.80	Soluble	Yes	240.34 g/mol	$C_{16}H_{20}N_2$	4.34
D5.	High	Yes	2.65	Soluble	Yes	216.32 g/mol	$C_{14}H_{20}N_2$	3.83
D6.	High	Yes	2.68	Soluble	Yes	216.32 g/mol	$C_{14}H_{20}N_2$	4.12
D7.	High	Yes	2.94	Soluble	Yes	230.35 g/mol	$C_{15}H_{22}N_2$	3.96
D8.	High	Yes	2.93	Soluble	Yes	230.35 g/mol	$C_{15}H_{22}N_2$	3.48
D9.	High	Yes	3.44	Moderately Soluble	Yes	326.43 g/mol	$C_{23}H_{22}N_2$	3.96
D10.	High	Yes	3.31	Moderately Soluble	Yes	326.43 g/mol	$C_{23}H_{22}N_2$	4.24
D11.	High	Yes	3.64	Poorly Soluble	Yes	381.30 g/mol	$C_{22}H_{18}Cl_2N_2$	3.86

				e		l		
D12.	High	Yes	3.97	Poorly Soluble	Yes	470.20 g/mol	$C_{22}H_{18}Br_2N_2$	3.91
D13.	High	Yes	3.96	Poorly Soluble	No	564.20 g/mol	$C_{22}H_{18}I_2N_2$	3.98
D14.	High	Yes	2.41	Moderately Soluble	Yes	344.41 g/mol	$C_{22}H_{20}N_2O_2$	3.86
D15.	High	Yes	3.87	Moderately Soluble	Yes	372.46 g/mol	$C_{24}H_{24}N_2O_2$	4.04
D16.	High	Yes	4.48	Moderately Soluble	Yes	400.51 g/mol	$C_{26}H_{28}N_2O_2$	4.27
D17.	High	Yes	3.69	Moderately Soluble	Yes	340.46 g/mol	$C_{24}N_{24}N_2$	4.08
D18.	High	Yes	4.26	Poorly Soluble	Yes	368.51 g/mol	$C_{26}H_{28}N_2$	4.30
D19.	High	No	2.43	Moderately Soluble	Yes	402.40 g/mol	$C_{22}H_{18}N_4O_4$	4.03
D20.	High	Yes	2.96	Moderately Soluble	Yes	362.43 g/mol	$C_{24}H_{18}N_4$	3.98
D21.	High	No	2.34	Moderately Soluble	Yes	400.43 g/mol	$C_{24}H_{20}N_20_4$	4.00
D22.	High	Yes	2.47	Moderately Soluble	Yes	342.44 g/mol	$C_{22}H_{22}N_4$	3.99
D23.	High	Yes	2.55	Soluble	Yes	222.71 g/mol	$C_{12}H_{15}ClN_2$	3.18
D24.	High	Yes	3.58	Moderately Soluble	Yes 1Violation	346.85 g/mol	$C_{22}H_{19}ClN_2$	3.86
D25.	High	Yes	3.34	Moderately Soluble	Yes 1Violation	302.84 g/mol	$C_{18}H_{23}ClN_2$	4.52
D26.	High	Yes	3.05	Moderately Soluble	Yes	274.79 g/mol	$C_{16}H_{19}ClN_2$	4.30
D27.	High	Yes	2.69	Soluble	Yes	236.74 g/mol	$C_{13}H_{17}ClN_2$	3.73
D28.	High	Yes	3.08	Soluble	Yes	250.77 g/mol	$C_{14}H_{19}ClN_2$	3.79
D29.	High	Yes	3.00	Soluble	Yes	250.77 g/mol	$C_{14}H_{19}ClN_2$	3.36

D30.	High	Yes	3.22	Moderately Soluble	Yes	264.79 g/mol	$C_{15}H_{21}ClN_2$	3.92
D31.	High	Yes	3.75	Poorly Soluble	Yes 1Violation	360.88 g/mol	$C_{23}H_{21}ClN_2$	3.96
D32.	High	Yes	3.63	Poorly Soluble	Yes 1Violation	360.88 g/mol	$C_{23}H_{21}ClN_2$	4.23
D33.	Low	No	3.99	Poorly Soluble	Yes 1Violation	415.74 g/mol	$C_{22}H_{17}Cl_3N_2$	3.88
D34.	Low	No	4.18	Poorly Soluble	No	504.64 g/mol	$C_{22}H_{17}Br_2ClN_2$	3.90
D35.	High	No	4.12	Poorly Soluble	No	598.65 g/mol	$C_{22}H_{17}ClI_2N_2$	3.96
D36.	High	Yes	2.60	Moderately Soluble	Yes	378.85 g/mol	$C_{22}H_{19}ClN_2O_2$	3.86
D37.	High	Yes	4.16	Moderately Soluble	Yes	406.90 g/mol	$C_{24}H_{23}ClN_2O_2$	4.04
D38.	High	No	4.67	Poorly Soluble	Yes 1Violation	434.96 g/mol	$C_{26}H_{27}ClN_2O_2$	4.27
D39	High	Yes	4.0	Poorly	Yes 1V	374.91	$C_{24}H_{23}ClN$	4.08

.			4	Soluble	iolation	g/mol	$_2$	
D40.	High	No	4.49	Poorly Soluble	Yes 1Violation	402.96 g/mol	$C_{26}H_{27}ClN_2$	4.30
D41.	Low	No	2.59	Moderately Soluble	Yes	436.85 g/mol	$C_{22}H_{17}ClN_4O_4$	4.02
D42.	High	No	3.23	Moderately Soluble	Yes	396.87 g/mol	$C_{24}H_{17}ClN_4$	3.97
D43.	High	No	2.65	Moderately Soluble	Yes	434.87 g/mol	$C_{24}H_{19}ClN_2O_4$	4.00
D44.	High	No	2.65	Moderately Soluble	Yes	376.88 g/mol	$C_{22}H_{21}ClN_4$	3.98
D45.	High	Yes	2.69	Soluble	Yes	267.16 g/mol	$C_{12}H_{15}BrN_2$	3.33
D46.	High	Yes	3.53	Poorly Soluble	Yes 1Violation	391.30 g/mol	$C_{22}H_{19}BrN_2$	3.96
D47.	High	Yes	3.50	Moderately Soluble	Yes 1Violation	347.29 g/mol	$C_{18}H_{23}BrN_2$	4.66
D48.	High	Yes	3.14	Moderately	Yes	319.24 g/	$C_{16}H_{19}BrN_2$	4.45

				Soluble		mol		
D49.	High	Yes	2.81	Soluble	Yes	281.19 g/mol	$C_{13}H_{17}BrN_2$	3.89
D50.	High	Yes	3.20	Moderately Soluble	Yes	295.22 g/mol	$C_{14}H_{19}BrN_2$	3.93
D51.	High	Yes	3.02	Moderately Soluble	Yes	295.22 g/mol	$C_{14}H_{19}BrN_2$	3.51
D52.	High	Yes	3.31	Moderately Soluble	Yes	390.16 g/mol	$C_{15}H_{21}BrN_2$	4.07
D53.	High	Yes	3.83	Poorly Soluble	Yes 1Violation	405.33 g/mol	$C_{23}H_{21}BrN_2$	4.06
D54.	High	Yes	3.70	Poorly Soluble	Yes 1Violation	405.33 g/mol	$C_{23}H_{21}BrN_2$	4.34
D55.	Low	No	4.16	Poorly Soluble	Yes 1Violation	460.19 g/mol	$C_{22}H_{17}BrCl_2N_2$	3.95
D56.	Low	No	4.45	Poorly Soluble	No	549.10 g/mol	$C_{22}H_{17}Br_2N_2$	3.99
D57.	Low	No	4.36	Poorly Soluble	No	643.10 g/mol	$C_{22}H_{17}BrI_2N_2$	4.06
D58.	High	Yes	2.81	Moderately Soluble	Yes	423.30 g/mol	$C_{22}H_{19}BrN_2O_2$	3.96
D59.	High	Yes	4.14	Poorly Soluble	Yes	451.36 g/mol	$C_{24}H_{23}BrN_2O_2$	4.14
D60.	High	No	4.78	Poorly Soluble	Yes 1Violation	479.41 g/mol	$C_{26}H_{27}BrN_2O_2$	4.37
D61.	High	No	4.35	Poorly Soluble	Yes 1Violation	419.36 g/mol	$C_{24}H_{23}BrN_2$	4.18
D62.	High	No	4.65	Poorly Soluble	Yes 1Violation	447.41 g/mol	$C_{26}H_{27}BrN_2$	4.40
D63.	Low	No	2.65	Poorly Soluble	Yes	481.30 g/mol	$C_{22}H_{17}BrN_4O_4$	4.12
D64.	High	No	3.49	Moderately Soluble	Yes	441.32 g/mol	$C_{24}H_{17}BrN_4$	4.07
D65.	High	No	2.69	Moderately Soluble	Yes	479.32 g/mol	$C_{24}H_{19}BrN_2O_4$	4.10
D66.	High	No	2.77	Moderately Soluble	Yes	421.33 g/mol	$C_{22}H_{21}BrN_4$	4.09
D6	High	Yes	2.	Sobl	Yes	314.1	$C_{12}H_{15}I$	3.41

7.			64	e		7 g/mol	N_2	
D68.	High	Yes	3.73	Poorly Soluble	Yes 1Violation	438.30 g/mol	$C_{22}H_{19}IN_2$	4.02

In-silico toxicity data:

This data was collected from ProTox 3.0. The toxicity class, LD_{50}, type of active toxicity is provided in the table below:

Table 3: Oral Toxicity Prediction Results

Derivative	**LD_{50}**	**Predicted Toxicity Class**	**Hepatotoxicity**	**Nephrotoxicity**	**Cardiotoxicity**	**Carcinogenicity**
D1.	400 mg/kg	4	Inactive	Inactive	Inactive	Inactive
D2.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D3.	400 mg/kg	4	Inactive	Inactive	Inactive	Inactive
D4.	400 mg/kg	4	Inactive	Inactive	Inactive	Inactive
D5.	400 mg/kg	4	Inactive	Inactive	Inactive	Inactive
D6.	400 mg/kg	4	Inactive	Inactive	Inactive	Inactive
D7.	400 mg/kg	4	Inactive	Inactive	Inactive	Inactive
D8.	400 mg/kg	4	Inactive	Inactive	Inactive	Inactive
D9.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D10.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D11.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D12.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D13.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D14.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D15.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D16.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D17.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D18.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D19.	3000 mg/kg	5	Active	Inactive	Inactive	Active
D20.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D21.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D22.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D23.	800 mg/kg	4	Inactive	Inactive	Inactive	Inactive
D24.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D25.	400 mg/kg	4	Inactive	Inactive	Inactive	Inactive
D26.	400 mg/kg	4	Inactive	Inactive	Inactive	Inactive
D2	800	4	Inacti	Inacti	Inacti	Inacti

7.	mg/kg		ve	ve	ve	ve
D28.	800 mg/kg	4	Inactive	Inactive	Inactive	Inactive
D29.	800 mg/kg	4	Inactive	Inactive	Inactive	Inactive
D30.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D31.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D32.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D33.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D34.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D35.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D36.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D37.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D38.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D39.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D40.	3000 mg/kg	5	Active	Inactive	Inactive	Inactive
D41.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D42.	3000 mg/k	5	Inactive	Inactive	Inactive	Inactive
	g					
D43.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D44.	1300 mg/kg	4	Inactive	Inactive	Inactive	Inactive
D45.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D46.	1300 mg/kg	4	Inactive	Inactive	Inactive	Inactive
D47.	1300 mg/kg	4	Inactive	Inactive	Inactive	Inactive
D48.	1300 mg/kg	4	Inactive	Inactive	Inactive	Inactive
D49.	1300 mg/kg	4	Inactive	Inactive	Inactive	Inactive
D50.	1300 mg/kg	4	Inactive	Inactive	Inactive	Inactive
D51.	1300 mg/kg	4	Inactive	Inactive	Inactive	Inactive
D52.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D53.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D54.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D55.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D56.	3000 mg/kg	5	Inactive	Inactive	Inactive	Inactive
D57.	3000m	5	Inactive	Inactive	Inactive	Inactive

	g/kg					
D58.	3000mg/kg	5	Inactive	Inactive	Inactive	Inactive
D59.	3000mg/kg	5	Inactive	Inactive	Inactive	Inactive
D60.	3000mg/kg	5	Inactive	Inactive	Inactive	Inactive
D61.	3000mg/kg	5	Inactive	Inactive	Inactive	Inactive
D62.	3000mg/kg	5	Active	Inactive	Inactive	Inactive
D63.	3000mg/kg	5	Inactive	Inactive	Inactive	Inactive
D64.	3000mg/kg	5	Active	Active	Inactive	Inactive
D65.	3000mg/kg	5	Inactive	Inactive	Inactive	Inactive
D66.	400 mg/kg	4	Inactive	Inactive	Inactive	Inactive
D67.	3000mg/kg	5	Inactive	Inactive	Inactive	Inactive
D68.	400 mg/kg	4	Inactive	Inactive	Inactive	Inactive

Conclusion

The current in-silico study used molecular docking against the human GABA-A receptor (PDB ID: 6X3X), a cryo-EM structure co-crystallized with diazepam, to assess 80 new 1,5-benzodiazepine derivatives as possible antidepressant candidates. Many of the derivatives showed binding affinities that were significantly higher than the diazepam standard (-8.8 kcal/mol). The lead compound with bis(4-cyanophenyl) substitution had the highest score of -12.2 kcal/mol, closely followed by a number of 4-cyanophenyl and 4-methoxyphenyl analogs that were substituted with chloro and bromo in the range of -10.7 to -11.8 kcal/mol, suggesting stable and energetically advantageous interactions within the benzodiazepine-binding pocket. The majority of derivatives have high gastrointestinal absorption, and nearly two-thirds exhibit blood-brain barrier permeability and adherence to Lipinski's Rule of Five, supporting their suitability as orally bioavailable, CNS-penetrant candidates, according to in-silico ADME profiling using SwissADME. With high predicted LD50 values and mostly inactive profiles for hepatotoxicity, nephrotoxicity, cardiotoxicity, and carcinogenicity, toxicity prediction using ProTox 3.0 further classified the majority of compounds under toxicity Class 4–5, indicating an acceptable overall safety margin. Only a few derivatives were flagged for organ-specific toxicity concerns. The electron-withdrawing-substituted 1,5-benzodiazepine derivatives are promising lead candidates for the development of GABA-A-targeted antidepressants due to their superior docking scores, favorable pharmacokinetic behavior, and low predicted toxicity. This provides a logical foundation for their prioritization in subsequent synthesis, in-vitro binding assays, and in-vivo antidepressant efficacy studies.

Acknowledgement

The authors gratefully acknowledge the Department of Pharmaceutical Sciences, Sir J.C. Bose Technical Campus, Kumaun University, Nainital, for providing the necessary facilities and support to carry out this research work.

Conflict of Interest

The author has no conflict of Interest.

References:

1. World Health Organization. Depressive disorder (depression) [Internet]. Geneva: WHO; 2023 [cited 2026 Sep 26]. Available from: https://www.who.int/news-room/fact-sheets/detail/depression
2. Pandeya SN, Rajput N. Synthesis and Anticonvulsant Activity of Various Mannich and Schiff Bases of 1, 5-Benzodiazepines. International Journal of Medicinal Chemistry. 2012;2012(1):237965. https://doi.org/10.1155/2012/237965
3. Bhat I, Kumar A. Synthesis and anti-inflammatory activity of some novel 1, 5 benzodiazepine derivatives. Asian Journal of Pharmaceutical and Clinical Research. 2016 Jul 1:63-6.
4. Dhiaa SM, Mohammed SK, Bahir H, Hameed AH, Abdulkareem Mahmood E, Abedinifar F, Babazadeh Rezaei E. Recent Advances in Bioactive 1, 5-Benzothiazepine-Based Compounds: Highlights From 2012 to 2022. Chemical Review and Letters. 2023 Nov 1;6(3):390-402. https://doi.org/10.22034/crl.2023.427609.1262

5. Pavlović G, Ahmedova A, Marinov M. From 2-acetyl-indan-1, 3-dione to 2 H-1, 5-benzodiazepines and their versatile applied features. Structural Dynamics. 2025 Sep 1;12(5_Supplement):A64-. https://doi.org/10.1063/4.0000856
6. Haq FU, Shoaib M, Ali Shah SW, Hussain H, Zahoor M, Ullah R, Bari A, Alotaibi A, Hayat MF. Antidepressant activities of synthesized benzodiazepine analogues in mice. Brain Sciences. 2023 Mar 21;13(3):523. https://doi.org/10.3390/brainsci13030523
7. Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of computational chemistry. 2010 Jan 30;31(2):455-61. https://doi.org/10.1002/jcc.21334
8. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific reports. 2017 Mar 3;7(1):42717. https://doi.org/10.1038/srep42717
9. Banerjee P, Eckert AO, Schrey AK, Preissner R. ProTox-II: a webserver for the prediction of toxicity of chemicals. Nucleic acids research. 2018 Jul 2;46(W1):W257-63. https://doi.org/10.1093/nar/gky318
10. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, Li Q, Shoemaker BA, Thiessen PA, Yu B, Zaslavsky L. PubChem 2023 update. Nucleic acids research. 2023 Jan 6;51(D1):D1373-80. https://doi.org/10.1093/nar/gkac956
11. Schrödinger L, DeLano W. PyMOL. http://www. pymol. org/pymol,(2020). There is no corresponding record for this reference. 2020.
12. Pawar SS, Rohane SH. Review on discovery studio: An important tool for molecular docking. Asian Journal of Research in Chemistry. 2021;14(1):1-3. http://dx.doi.org/10.5958/0974-4150.2021.00014.6
13. Ding J, Tang S, Mei Z, Wang L, Huang Q, Hu H, Ling M, Wu J. Vina-GPU 2.0: further accelerating AutoDock Vina and its derivatives with graphics processing units. Journal of chemical information and modeling. 2023 Mar 20;63(7):1982-98. https://doi.org/10.1021/acs.jcim.2c01504
14. Holik HA. The molecular interaction and ADMET prediction of modified Jph203 as a potential radiopharmaceutical kit for molecular imaging of cancer: an in silico research. International Journal of Applied Pharmaceutics. 2021 Jan 1. https://dx.doi.org/10.22159/ijap.2021.v13s4.43860
15. Gaieb Z, Liu S, Gathiaka S, Chiu M, Yang H, Shao C, Feher VA, Walters WP, Kuhn B, Rudolph MG, Burley SK. D3R Grand Challenge 2: blind prediction of protein–ligand poses, affinity rankings, and relative binding free energies. Journal of computer-aided molecular design. 2018 Jan;32(1):1-20. https://doi.org/10.1007/s10822-017-0088-4
16. Loganathan V, Akbar I, Ahamed A, Alodaini HA, Hatamleh AA, Abuthkir MH, Gurusamy R. Synthesis, antimicrobial and cytotoxic activities of tetrazole N-Mannich base derivatives: Investigation of DFT calculation, molecular docking, and Swiss ADME studies. Journal of Molecular Structure. 2024 Mar 15;1300:137239. 10.1016/j.molstruc.2023.137239
17. Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. InChemical biology: methods and protocols 2014 Dec 22 (pp. 243-250). New York, NY: Springer New York. https://doi.org/10.1007/978-1-4939-2269-7_19
18. Trott O, Olson AJ. Software news and update AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function. Effic. Optim. Multithreading. 2009;31:455-61.