**Computational evolution of biological activities of selected bioactive compound library on The Angiotensin II Receptor Type 1 (AT1R) target**

**Abstract**

The Angiotensin II Receptor Type 1 (AT1R) is a key component of the renin-angiotensin system (RAS), primarily responsible for mediating the vasoconstrictive, hypertensive, and pro-inflammatory effects of angiotensin II. Understanding the structure of AT1R is essential in the development of therapeutic agents that target hypertension, cardiovascular diseases, and related metabolic disorders. A notable advancement is the AT1R nanobody antagonist AT118i4h32, a small, stable antibody fragment designed to bind selectively to AT1R, blocking its activity and offering high specificity and stability over traditional small-molecule inhibitors. The AT118i4h32 nanobody has significant potential in the development of targeted therapies due to its unique properties, including lower immunogenicity and better tissue penetration. By blocking AT1R, this nanobody can help mitigate adverse cardiovascular and renal effects associated with angiotensin II, making it a promising candidate for the treatment of cardiovascular diseases, inflammation, and fibrosis. Key molecular docking tools include BIOVIA Discovery Studio, which offers comprehensive molecular modeling and advanced visualization capabilities; PyRx, an open-source virtual screening tool that supports multiple docking engines and batch processing; PyMOL, a powerful software for analyzing and presenting protein-ligand interactions; and LigPlot, which generates schematic diagrams to illustrate binding interactions. For evaluating ADMET properties, ADMETlab provides systematic assessments with expanded prediction capabilities across various versions; ChEMBL serves as a large bioactivity database that facilitates virtual screening and structure-activity relationship studies; SWISSADME predicts physicochemical properties and ADME profiles to assess drug-likeness; ProtParam analyzes protein sequences to provide key physical and chemical parameters; and ChemSketch allows users to create chemical structures and calculate basic molecular properties.

Name - The Angiotensin II Receptor Type 1 (AT1R); Structure of angiotensin II type I receptor (AT1R) nanobody antagonist AT118i4h32

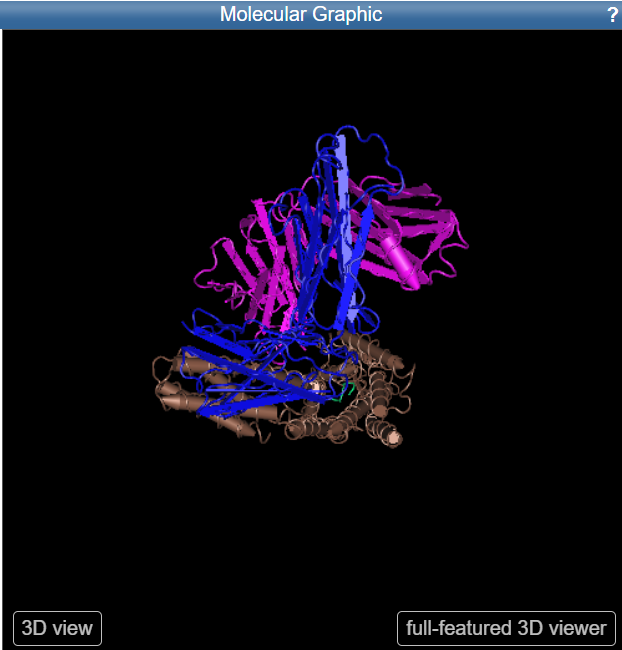
Keywords: Angiotensin II Receptor Type 1 (AT1R), ADMET Prediction, Molecular Docking, Drug-likeness, Bioactivity Database, Ligand-Receptor Interaction

**Introduction**

The Angiotensin II Receptor Type 1 (AT1R) is a pivotal component of the renin-angiotensin-aldosterone system (RAAS), which regulates critical physiological processes, including blood pressure, fluid balance, and vascular tone. AT1R is a G protein-coupled receptor (GPCR) primarily expressed in cardiovascular, renal, and adrenal tissues. Its activation by the endogenous ligand angiotensin II (Ang II) triggers a cascade of cellular responses that influence cardiovascular homeostasis, renal function, and immune system regulation.

**Structure and Molecular Biology**

AT1R is encoded by the *AGTR1* gene, located on chromosome 3 (3q21–q25) in humans. The gene spans approximately 55 kilobases and consists of five exons interspersed with four introns. The receptor itself is a seven-transmembrane domain GPCR with an extracellular N-terminus and an intracellular C-terminus. Specific amino acid residues within its transmembrane helices are critical for the binding of Ang II and subsequent receptor activation. While AT1R is the primary receptor mediating the effects of Ang II, it works in tandem with the Angiotensin II Receptor Type 2 (AT2R), which often opposes its actions, providing a balance in physiological processes.



**Physiological Role**

In the cardiovascular system, AT1R plays a vital role in maintaining blood pressure by inducing vasoconstriction and increasing systemic vascular resistance. It also contributes to pathological cardiac remodeling, including hypertrophy and fibrosis, particularly under conditions of chronic stress or disease. In the renal system, AT1R regulates sodium reabsorption in the proximal tubule and stimulates aldosterone secretion from the adrenal cortex, contributing to fluid and electrolyte balance. The receptor is also expressed in the central nervous system, where it influences thirst, salt appetite, and the sympathetic nervous system. Additionally, AT1R has a role in immune and inflammatory responses, promoting cytokine release and leukocyte recruitment, thereby linking it to inflammation and autoimmune conditions.

**Mechanism of Action**

AT1R is activated by the binding of Ang II, which induces conformational changes that activate associated G proteins, primarily Gq proteins. This activation leads to the stimulation of phospholipase C (PLC), which generates inositol triphosphate (IP3) and diacylglycerol (DAG). IP3 promotes calcium release from intracellular stores, while DAG activates protein kinase C (PKC), initiating a cascade of downstream signaling pathways. Besides classical G protein signaling, AT1R also engages β-arrestin-mediated pathways that modulate receptor internalization, desensitization, and alternative signaling mechanisms, including MAP kinase activation, further diversifying its functional outcomes.

**Clinical Relevance**

Dysregulation of AT1R activity is implicated in several pathological conditions. Overactivation of AT1R is a hallmark of hypertension, as it sustains vasoconstriction and promotes aldosterone-mediated sodium retention. In heart failure, chronic AT1R stimulation contributes to detrimental cardiac remodeling, fibrosis, and reduced cardiac function. Similarly, in chronic kidney disease (CKD), heightened AT1R activity exacerbates glomerular hypertension, proteinuria, and progressive renal damage. These clinical insights have made AT1R a major therapeutic target. Drugs known as angiotensin receptor blockers (ARBs), including losartan, valsartan, and candesartan, selectively inhibit AT1R. These medications not only lower blood pressure but also reduce inflammation, oxidative stress, and fibrosis, offering protective effects in cardiovascular and renal disorders.

**Pathophysiological Insights**

Genetic polymorphisms in the *AGTR1* gene can influence AT1R expression and function, affecting an individual’s susceptibility to cardiovascular and renal diseases. Beyond its traditional activation by Ang II, AT1R can also be activated by mechanical stress and alternative ligands, broadening its role in cellular signaling. This versatility allows AT1R to participate in non-canonical pathways that may contribute to disease progression, particularly in conditions like fibrosis and cancer.

**Research and Therapeutic Development**

Advances in AT1R research have led to the exploration of biased agonism, wherein ligands selectively activate certain signaling pathways while avoiding others. This approach aims to achieve therapeutic benefits while minimizing adverse effects associated with traditional ARBs. Furthermore, ongoing studies are investigating AT1R’s involvement in non-cardiovascular conditions, such as diabetes, neurodegenerative diseases, and certain cancers, expanding its therapeutic potential. Novel strategies targeting AT1R are also being developed to refine treatment options for complex diseases.

**Methods and techniques used**

Ligand library preparation is a crucial step in molecular docking studies to ensure that the ligands are in the correct format, conformation, and chemical state for accurate docking and binding affinity prediction.

1. Collect Ligand Structures

The first step in ligand library preparation involves gathering the structures of the compounds to be docked. These structures can be obtained from publicly available databases such as PubChem, ZINC, or ChEMBL, which host a wide range of small molecules. If you are working with novel compounds, you can design them using molecular drawing tools such as ChemDraw, MarvinSketch, or BIOVIA Draw. These tools allow for creating 2D representations that can later be converted to 3D structures.

2. Format Conversion

Once the structures are collected, they may need to be converted into formats suitable for docking, such as PDB, MOL2, or SDF. This conversion ensures compatibility with the docking software being used. Tools like Open Babel or RDKit are widely used for this purpose, providing efficient and accurate format transformation.

3. Generate 3D Structures

Molecular docking requires 3D structures of ligands. If the input structures are in 2D, they need to be converted to 3D. Tools like Open Babel, RDKit, and Avogadro can generate 3D structures while maintaining proper bond lengths, angles, and stereochemistry. This step is crucial to represent the actual spatial arrangement of atoms in the ligand.

4. Add Hydrogen Atoms

Hydrogen atoms, especially those affecting protonation states and binding interactions, must be explicitly added to the ligand structure. This ensures the correct representation of hydrogen bonding during docking. Tools such as Open Babel and PDBFixer can automate the addition of hydrogens

5. Assign Charges

The electronic state of the ligand is defined by assigning atomic charges, which significantly influence docking accuracy. Common charge assignment methods include AM1-BCC and Gasteiger charges. Tools like Antechamber (part of the AMBER suite) and Open Babel are widely used for charge assignment

6. Protonation State and Tautomer Preparation

Ligands should be prepared in their correct protonation states and tautomeric forms, especially at the physiological pH (~7.4). Tools like ChemAxon’s Marvin Suite and Epik (part of the Schrödinger suite) can predict and generate the most likely states based on pH conditions. This step is critical to mimic biological conditions during docking.

7. Energy Minimization

Energy minimization ensures that the ligand geometry is optimized, removing steric clashes and improving molecular stability. Tools like Open Babel and RDKit (using force fields such as MMFF94) or visualization software like Avogadro can be used to perform energy minimization. This helps prepare the ligand for accurate docking predictions.

8. Remove Redundant Conformations

If the ligand library contains multiple conformations of the same molecule, redundancy can lead to inefficiency in docking studies. Clustering or filtering redundant conformations helps streamline the library. Tools such as RDKit or Schrödinger’s LigPrep are effective for this task, ensuring a diverse and efficient set of ligands.

9. Save in Docking-Compatible Format

Docking software requires specific input formats. For example, AutoDock and AutoDock Vina require PDBQT files, while DOCK uses MOL2 files. After preparation, save the ligands in the required format using tools like AutoDockTools for PDBQT conversion or Open Babel for other formats.

10. Validation and Verification

The final step involves visualizing and checking the prepared ligands to ensure correctness. Molecular viewers like PyMOL and UCSF Chimera allow for manual inspection, enabling you to verify the geometry, charges, and protonation states. Proper validation minimizes errors and ensures that the ligands are ready for docking.

Computational drug discovery has become a vital component in the identification and development of new pharmaceuticals, particularly for targets like the Angiotensin II Receptor Type 1 (AT1R). This process involves various methods and tools, primarily focused on molecular docking, which helps predict the interaction between small molecules (ligands) and macromolecular targets (proteins). Below are the key techniques and tools utilized in this domain.

**a.) Molecular Docking**

Molecular docking is a computational technique used to simulate the interaction between a ligand and a protein. It helps in predicting binding affinities and the preferred orientation of ligands within the binding site of target proteins like AT1R. The main steps involved include:

Preparation of Protein and Ligand: This involves cleaning the protein structure (removing water molecules, adding hydrogens), optimizing ligand geometry, and calculating charges. Docking Algorithms: Various algorithms are employed, including:

AutoDock Vina: A popular tool for its efficiency in scoring ligand binding affinities.

FRED: Known for its speed and accuracy in predicting binding modes.

GOLD and FlexX: These tools are also used for their robust scoring functions.

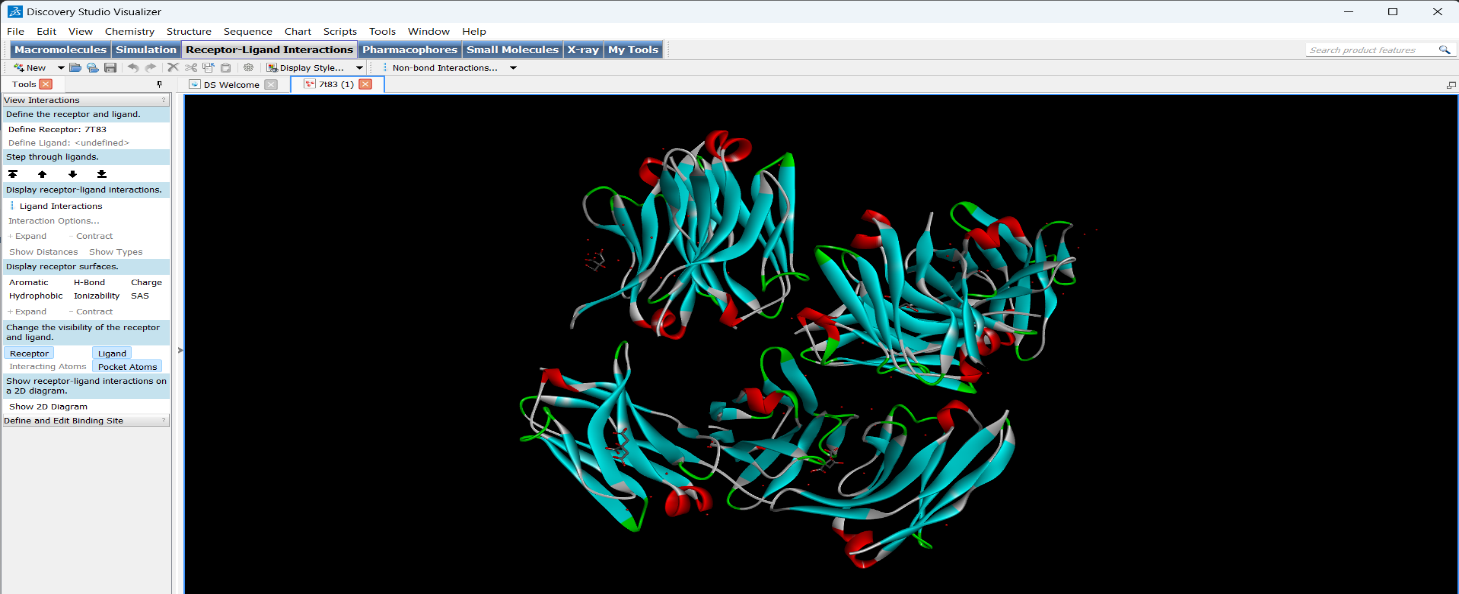
In the field of computational drug discovery, several specialized software tools are utilized to facilitate the docking process for targets like the Angiotensin II Receptor Type 1 (AT1R). This overview focuses on four prominent tools: BIOVIA Discovery Studio, PyRx, PyMOL, and LigPlot. Each tool offers unique functionalities that contribute to the molecular docking workflow.

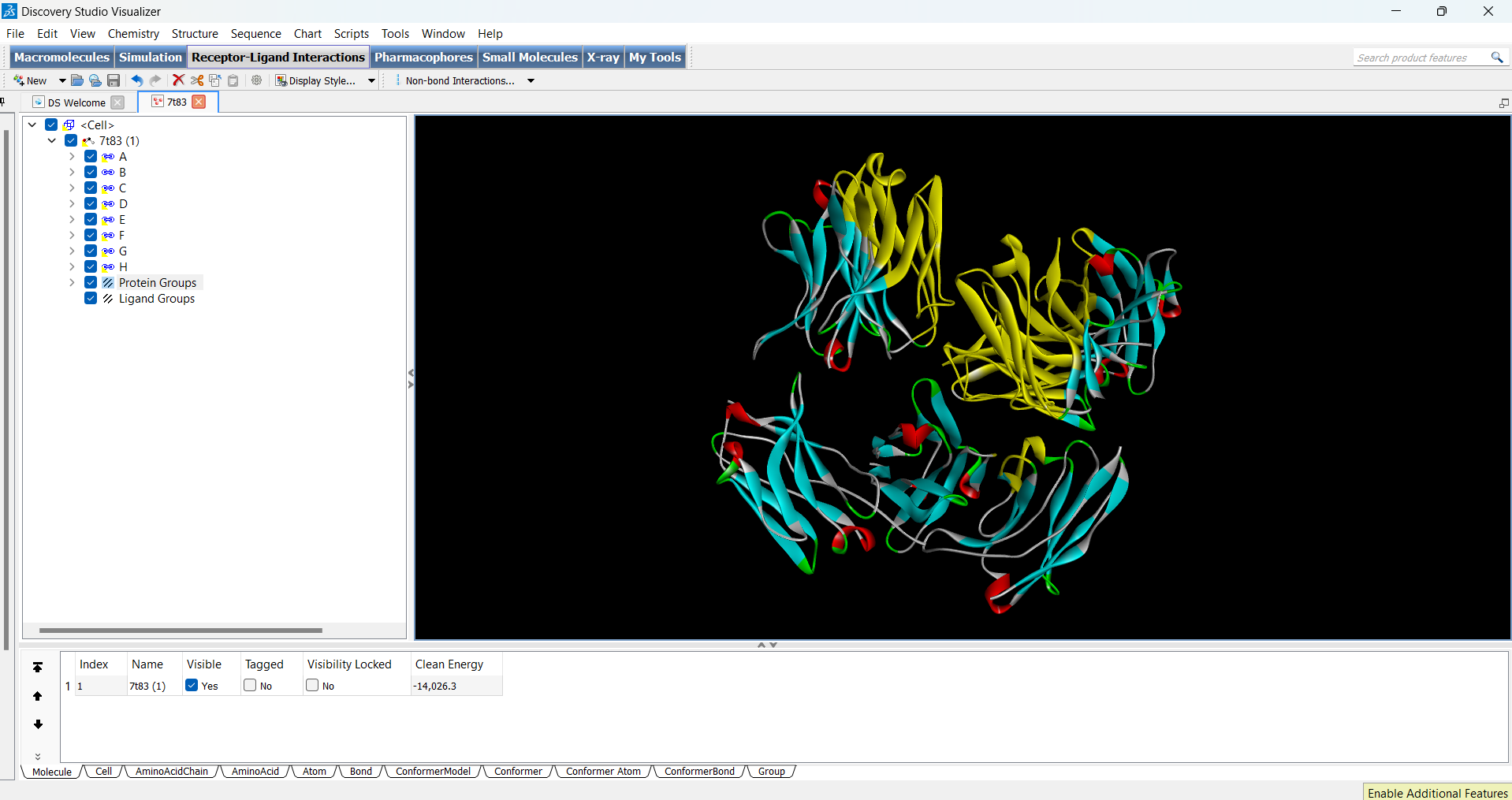
**1. BIOVIA Discovery Studio**

BIOVIA Discovery Studio (BDS) is a comprehensive software suite designed for molecular modeling and simulations. It provides a robust environment for performing molecular docking studies, particularly with its receptor-ligand interaction tools. Key Features include

Molecular Docking Protocols: BDS includes various docking protocols such as CDOCKER and GOLD, allowing users to perform flexible and rigid docking efficiently.

Visualization and Analysis: Users can visualize docking results in 3D, analyze binding interactions, and generate high-quality images suitable for publication. The interface allows customization of visual outputs to enhance clarity.

Binding Site Definition: BDS facilitates the definition of binding sites through an intuitive interface, where users can select ligand atoms or entire molecules to establish docking.



Usage in AT1R Studies: BDS is particularly useful for analyzing interactions between ligands and AT1R, providing insights into binding affinities and conformational changes upon ligand binding.

**2. PyRx**

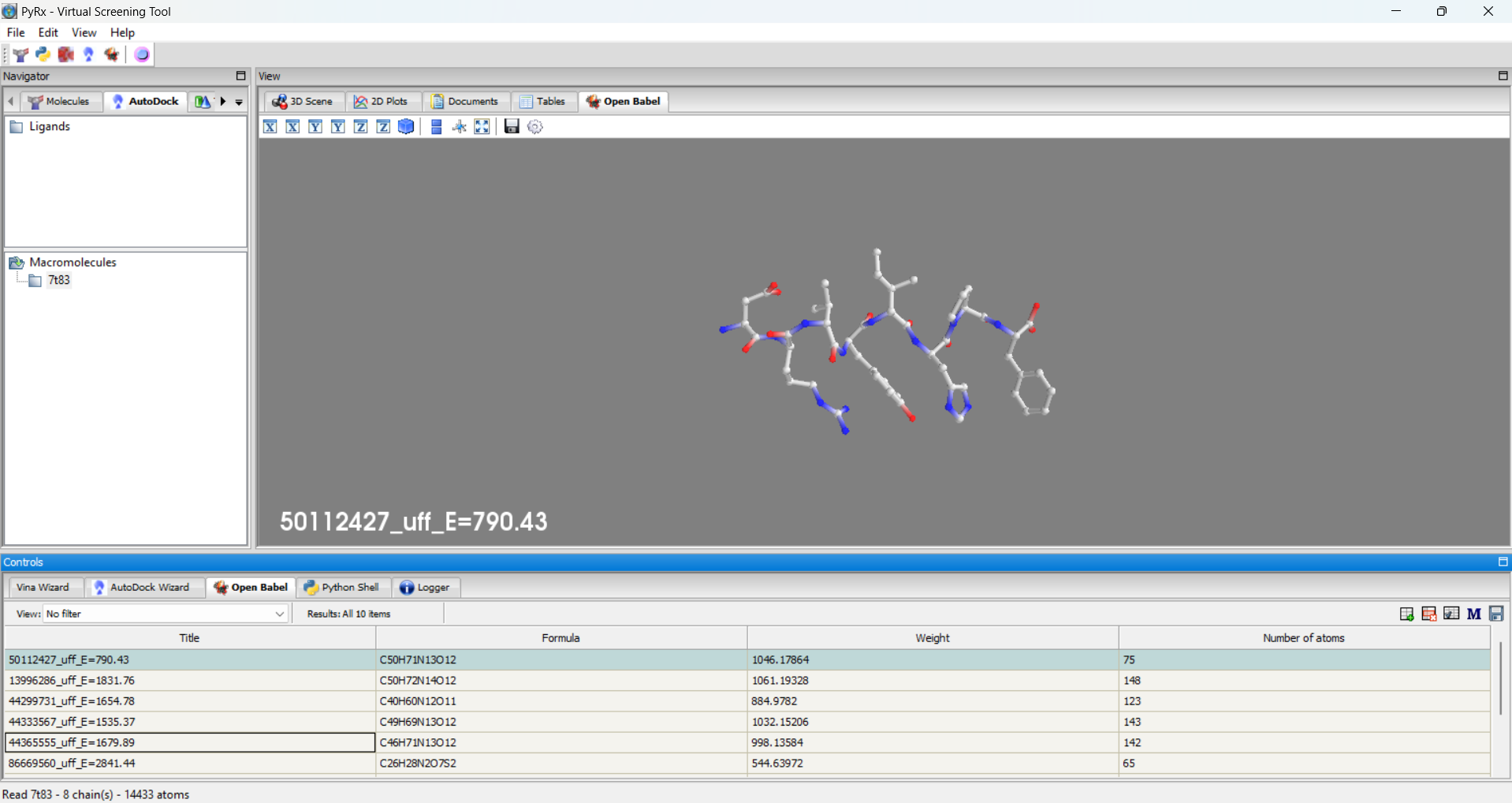
PyRx is an open-source virtual screening software that simplifies the process of molecular docking. It integrates various docking programs and provides a user-friendly interface. Key Features include

Multiple Docking Engines: PyRx supports different docking engines, including AutoDock Vina, which is known for its speed and accuracy in predicting ligand-receptor interactions3.

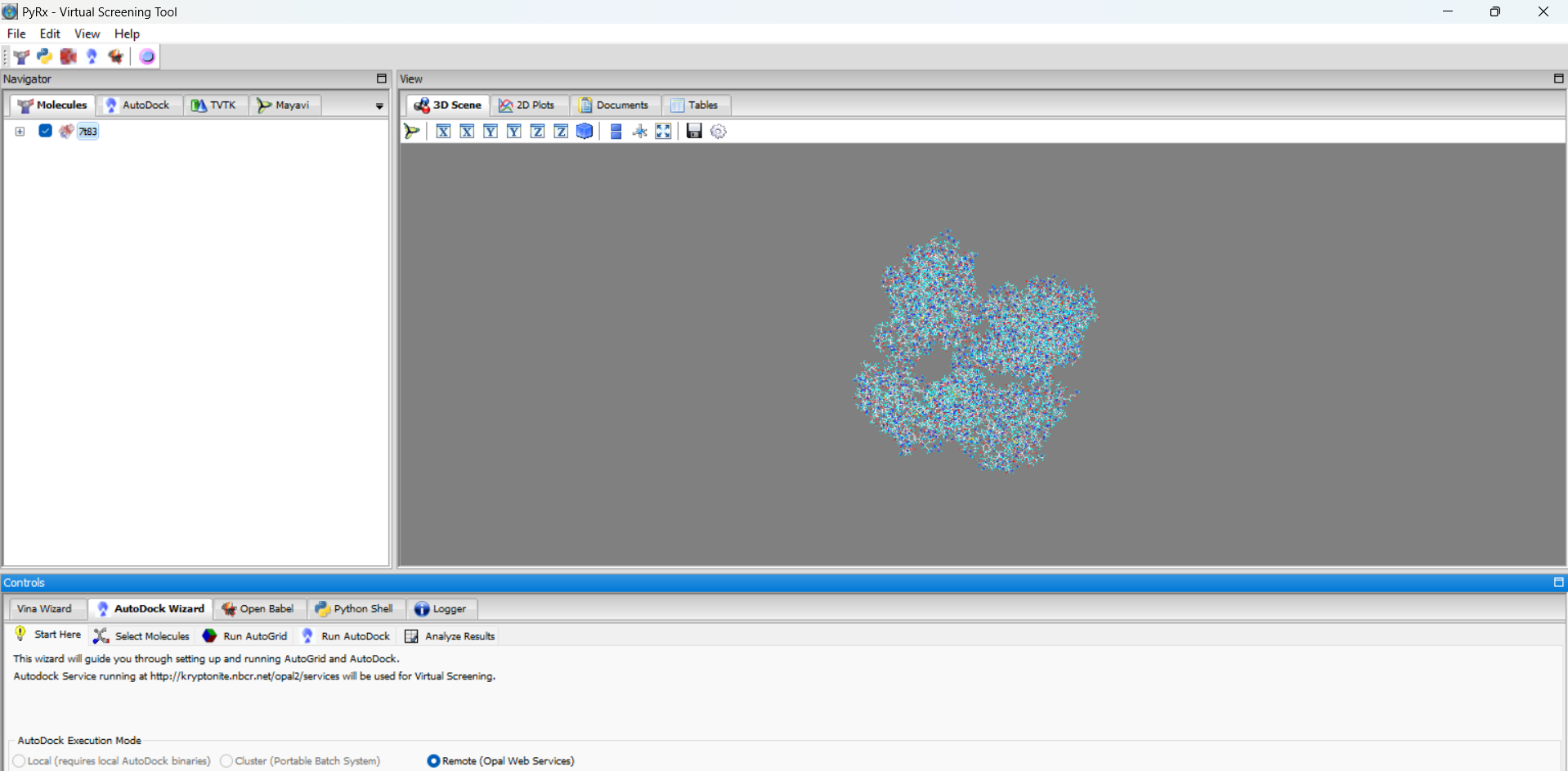
Batch Processing: Users can perform batch docking of multiple ligands against a target protein, which is essential for high-throughput screening in drug discovery.

Visualization Tools: PyRx allows users to visualize docked poses and analyze binding interactions directly within the software.

Usage in AT1R Studies: Researchers can use PyRx to screen large libraries of compounds against AT1R, quickly identifying potential drug candidates based on their binding scores.



PyRx – Balls and sticks model of the receptor



PyRx- Molecular surface of the receptor



PyRx- Line model of the receptor



**3. PyMOL**

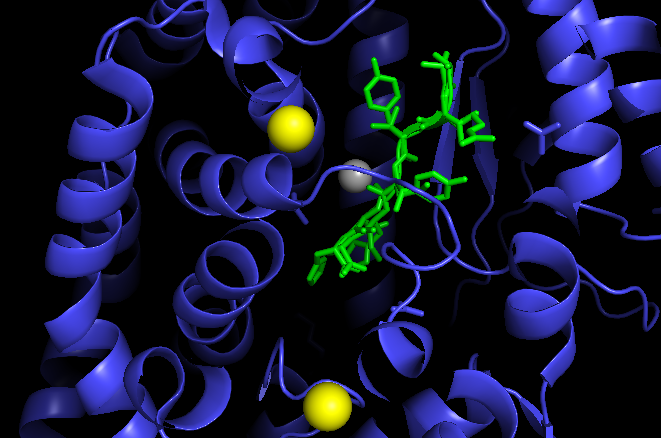
PyMOL is a powerful molecular visualization tool widely used in structural biology. While it does not perform docking itself, it plays a crucial role in analyzing and visualizing the results obtained from docking studies. Key Features include

High-Quality Visualization: PyMOL provides advanced rendering capabilities for visualizing protein-ligand complexes, allowing detailed inspection of molecular interactions.

Scripting Capabilities: Users can automate visualization tasks through scripting, making it easier to handle large datasets or repetitive analyses.

Integration with Other Tools: PyMOL can be used alongside other software like AutoDock or BDS to visualize docking results effectively.

Usage in AT1R Studies: After performing docking with tools like BDS or PyRx, researchers often use PyMOL to create publication-quality figures that highlight important interactions between ligands and AT1R.



**4. LigPlot**

LigPlot is a specialized tool designed for visualizing protein-ligand interactions in a clear and informative manner. Key Features include

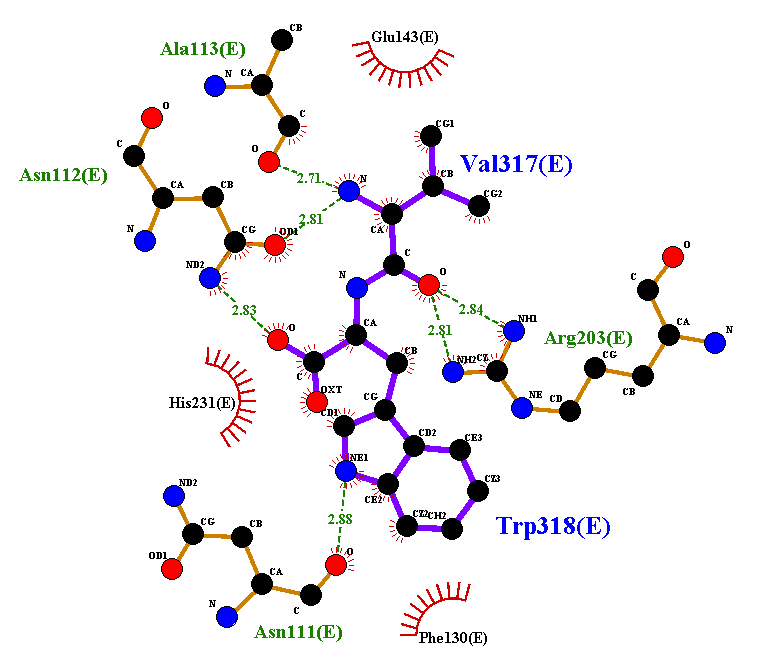
Interaction Mapping: LigPlot generates schematic diagrams that illustrate how ligands interact with their target proteins. It highlights hydrogen bonds, hydrophobic contacts, and other key interactions4.

User-Friendly Interface: The tool is straightforward to use, allowing researchers to input their protein-ligand complex files easily.

Export Options: Generated plots can be exported for use in publications or presentations.

Usage in AT1R Studies: LigPlot is particularly useful for summarizing the interaction data obtained from docking studies involving AT1R, providing a quick visual reference for understanding ligand binding modes.

Information on 10 molecules from SwissAdme, Chembl and ADMET lab.

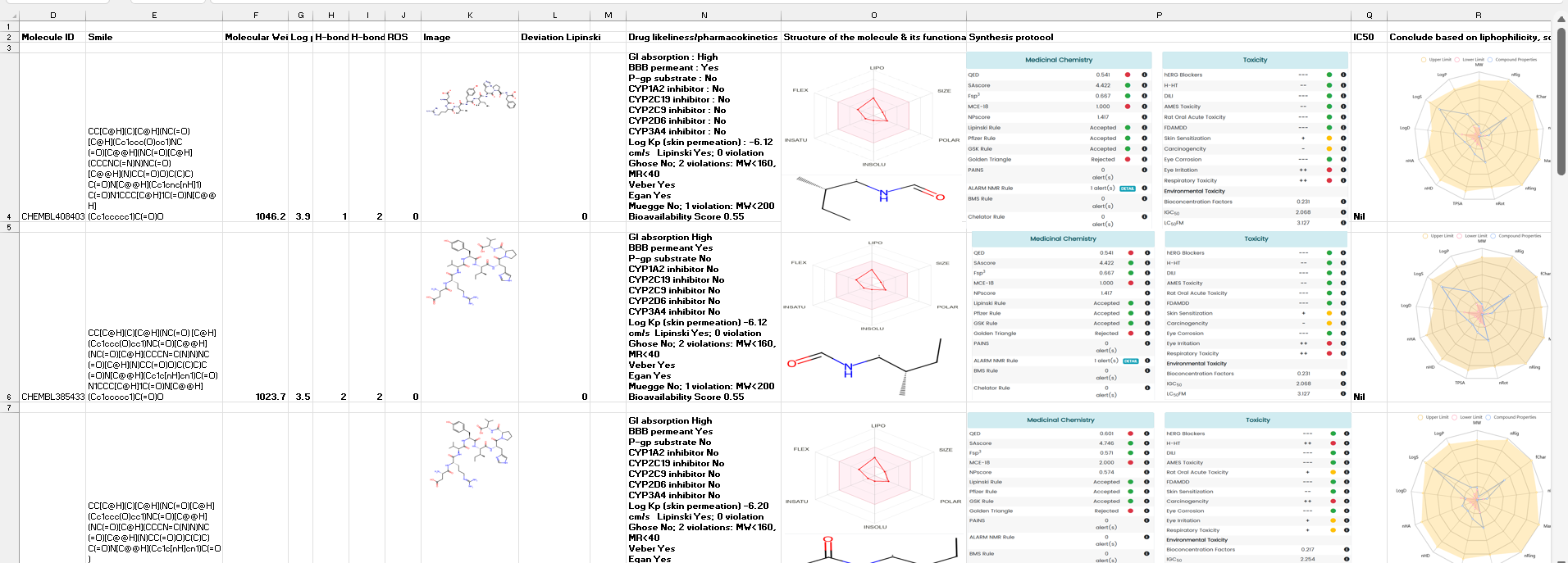


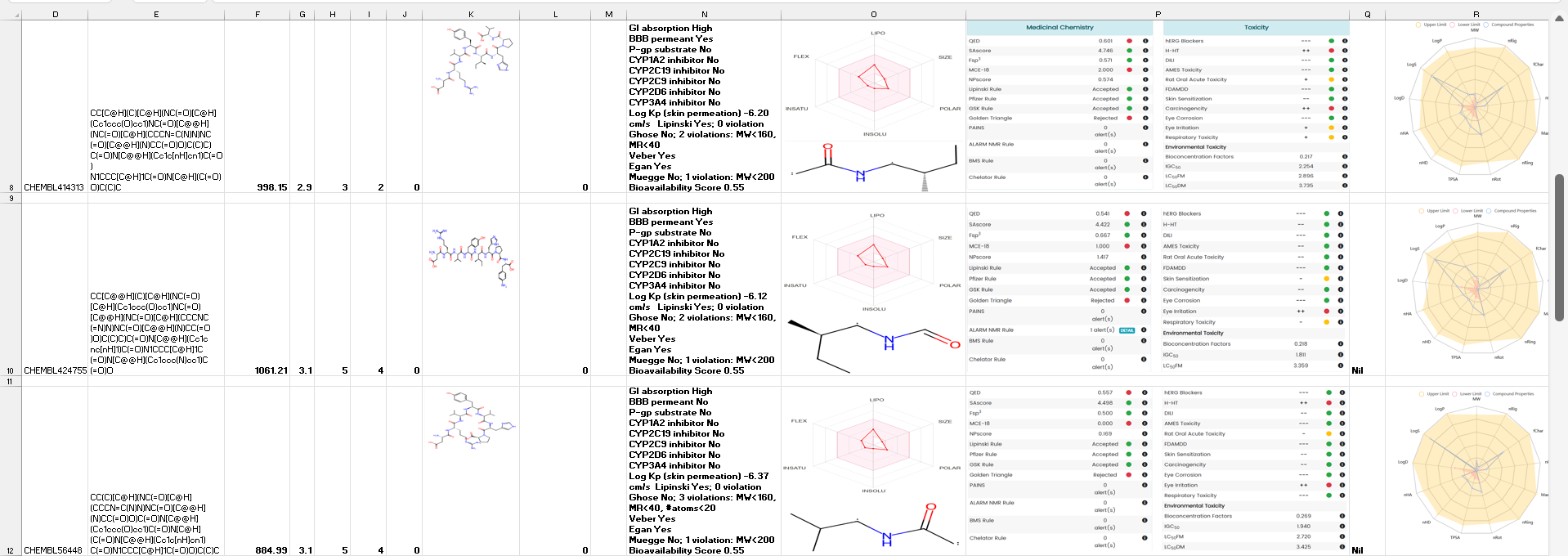
**Overview of Computational Tools for ADMET Prediction and Molecular Docking**

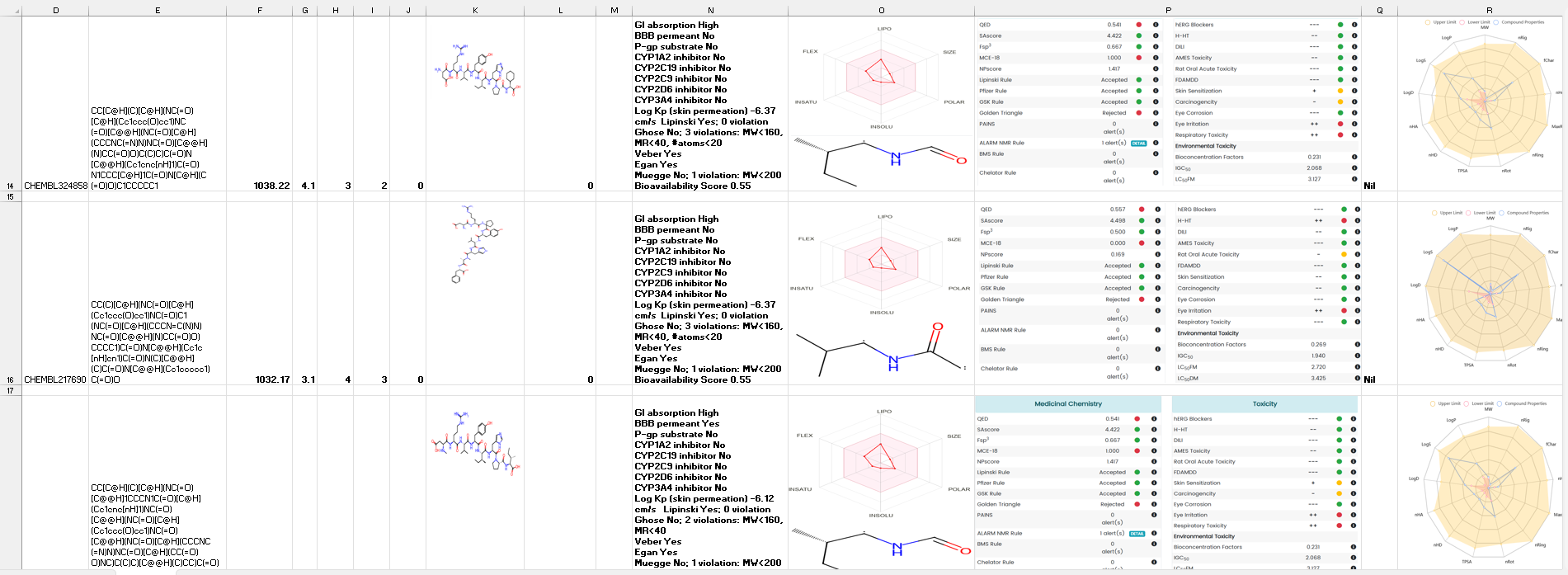
In drug discovery, the evaluation of Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties is crucial for assessing the viability of potential drug candidates. Several computational tools have been developed to facilitate these evaluations, including ADMETlab, ChEMBL, SWISSADME, ProtParam, and ChemSketch. This section details these tools and their applications in the context of molecular docking and drug design.

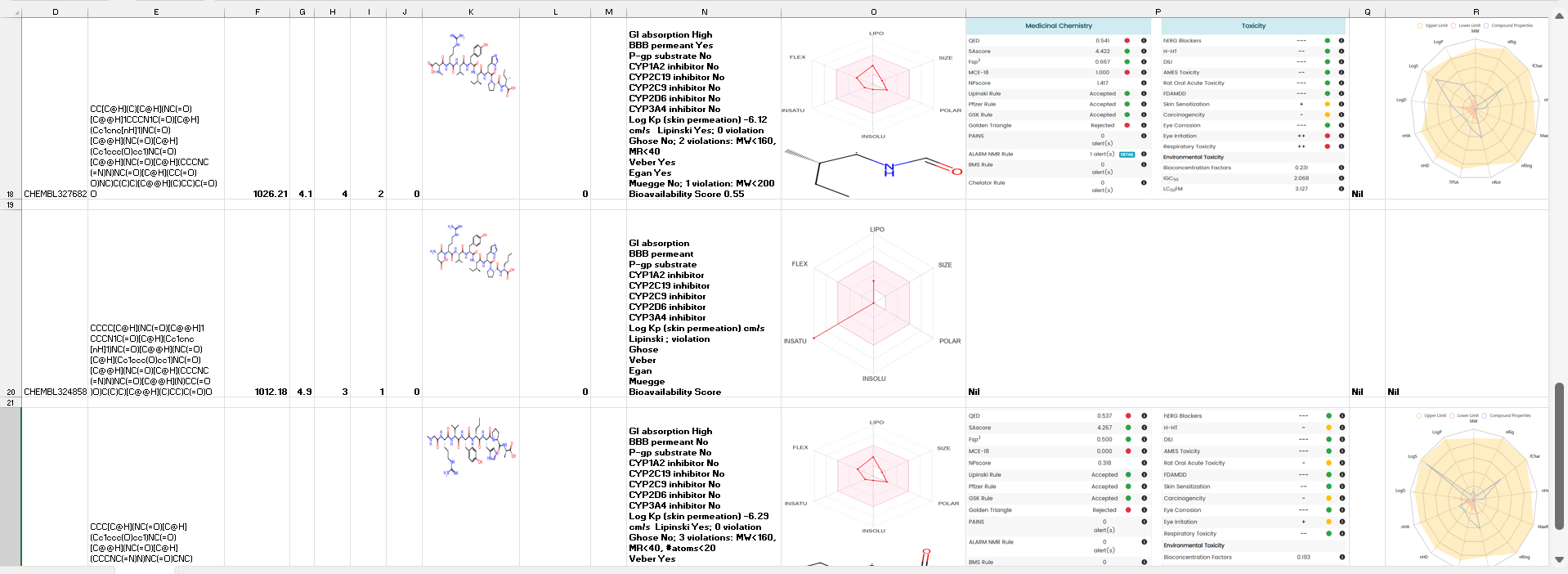
**1. ADMETlab**

ADMETlab is an online platform designed for systematic evaluation of ADMET properties and physicochemical characteristics of chemical compounds.









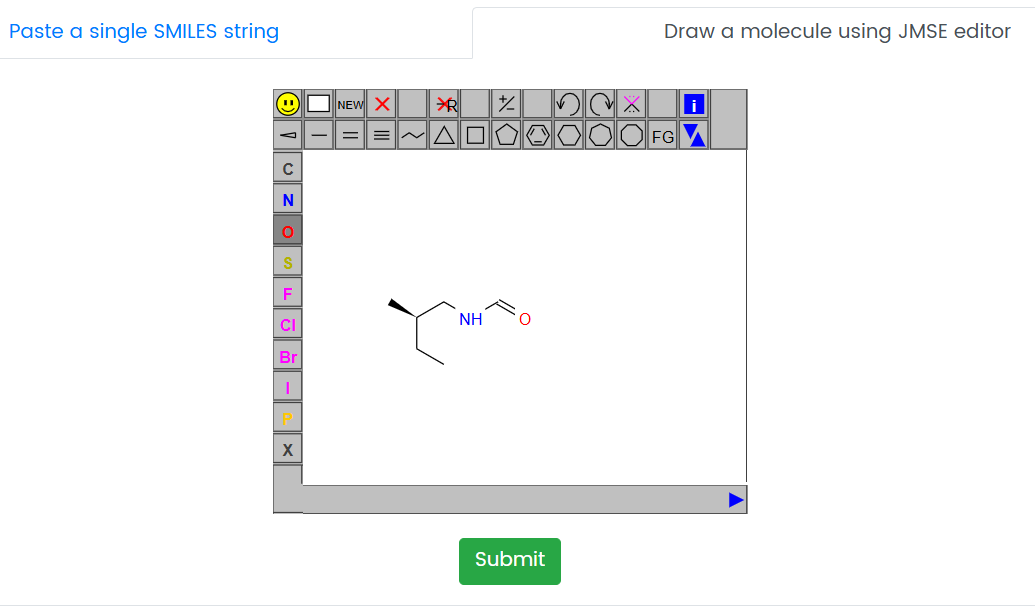
Versions:

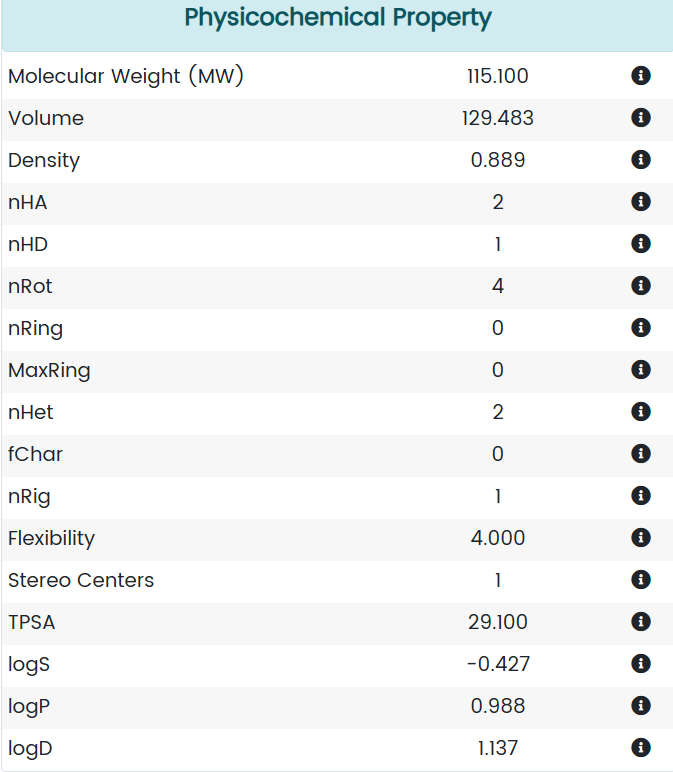
ADMETlab 1.0: The original version focused on basic ADMET predictions.

ADMETlab 2.0: Released in 2021, this version significantly expanded its capabilities by offering approximately twice the number of endpoints compared to its predecessor. It supports predictions for 88 ADMET-related parameters, including physicochemical properties, medicinal chemistry properties, and toxicity endpoints using a multi-task graph attention framework for robust modeling 12.

ADMETlab 3.0: The latest update enhances performance with over 400,000 entries and 119 prediction endpoints. It incorporates a deep learning architecture (DMPNN) for improved accuracy and speed, along with API functionality for batch evaluations 1.

Usage in Drug Discovery: ADMETlab is widely used to predict pharmacokinetic properties and toxicity profiles early in the drug development process, helping researchers prioritize compounds for further testing.





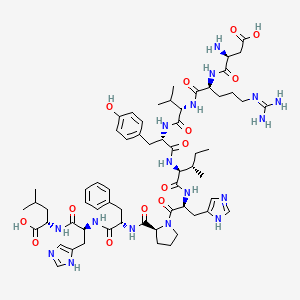
**2. ChEMBL**

ChEMBL is a large-scale bioactivity database that provides information on the biological activities of small molecules. Key Features include

Contains data on drug-like compounds, including their chemical structures, bioactivity data against various targets, and pharmacological information.

Facilitates virtual screening by allowing researchers to search for compounds based on specific biological activities or chemical properties.

Usage in Drug Discovery: ChEMBL is instrumental in identifying potential lead compounds for AT1R by providing access to a wealth of experimental data that can inform structure-activity relationships (SAR).



**3. SWISSADME**

SWISSADME is an online tool for the prediction of physicochemical properties and ADME profiles of small molecules. Key Features include

Offers predictions for lipophilicity, solubility, permeability, and various other pharmacokinetic properties.

Provides a user-friendly interface where users can input SMILES strings or upload molecular files to receive detailed reports on predicted ADME characteristics.

Usage in Drug Discovery: SWISSADME assists researchers in evaluating the drug-likeness of compounds early in the design process, ensuring that selected candidates possess favorable pharmacokinetic profiles.

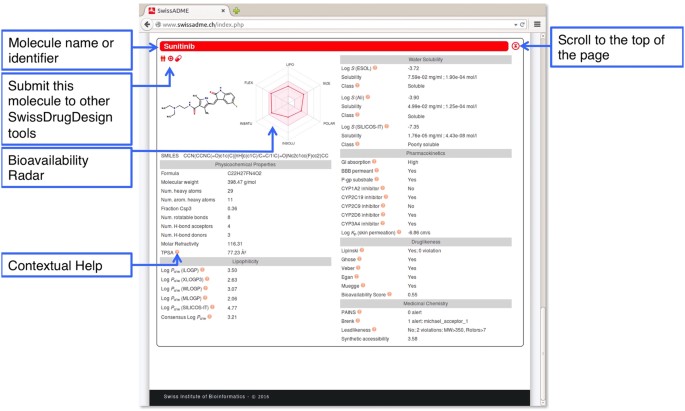
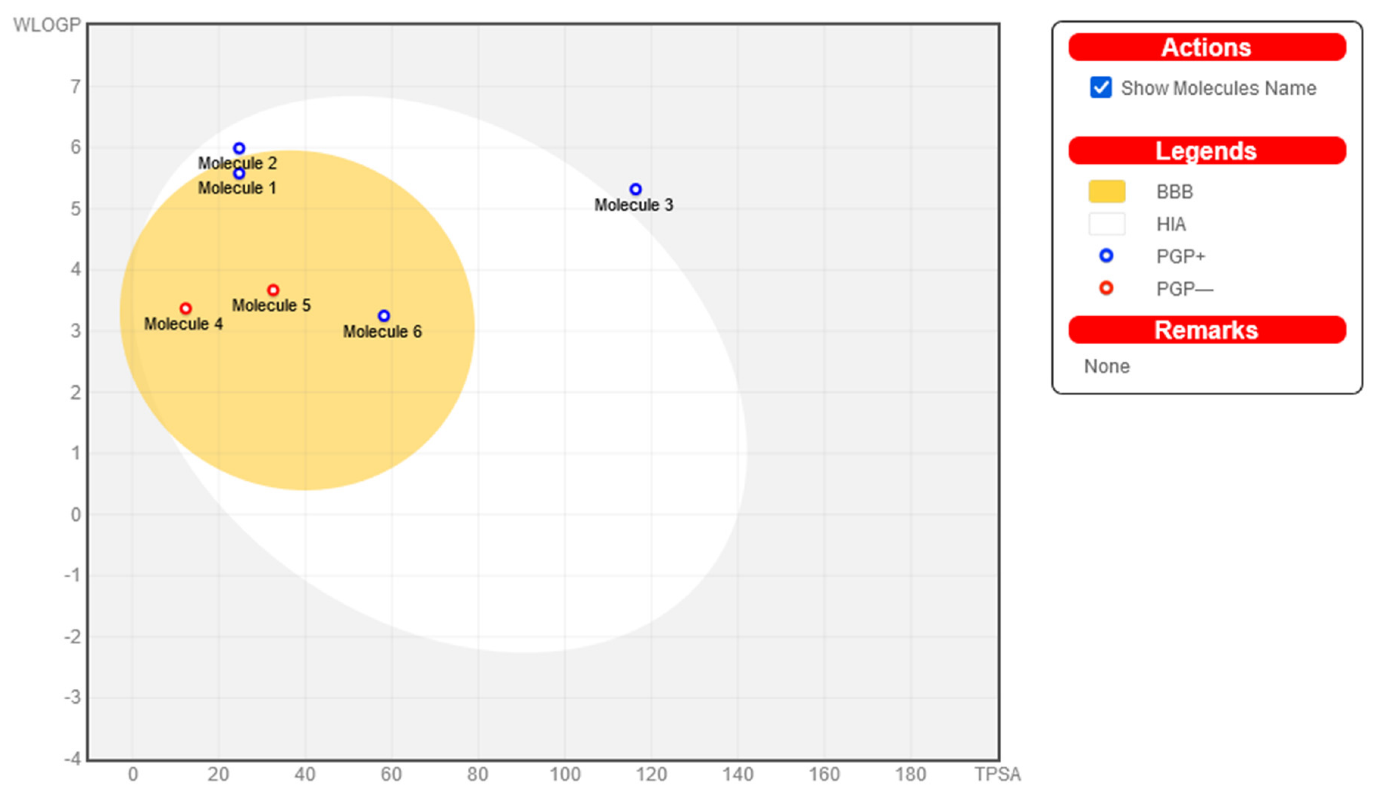


Image courtesy: <https://www.nature.com/articles/srep42717>



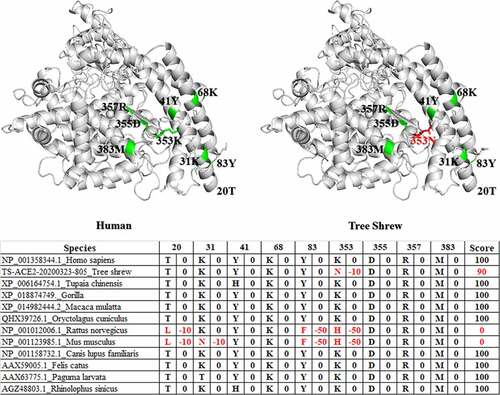
**4. ProtParam**

ProtParam is a web-based tool that provides various physical and chemical parameters for proteins. Key Features include

Analyzes protein sequences to predict molecular weight, amino acid composition, extinction coefficients, and other relevant parameters.

Offers insights into the stability and solubility of proteins which can be critical when assessing receptor-ligand interactions.

Usage in Drug Discovery: ProtParam can be used to analyze AT1R sequences to understand structural features that may influence ligand binding during docking studies.



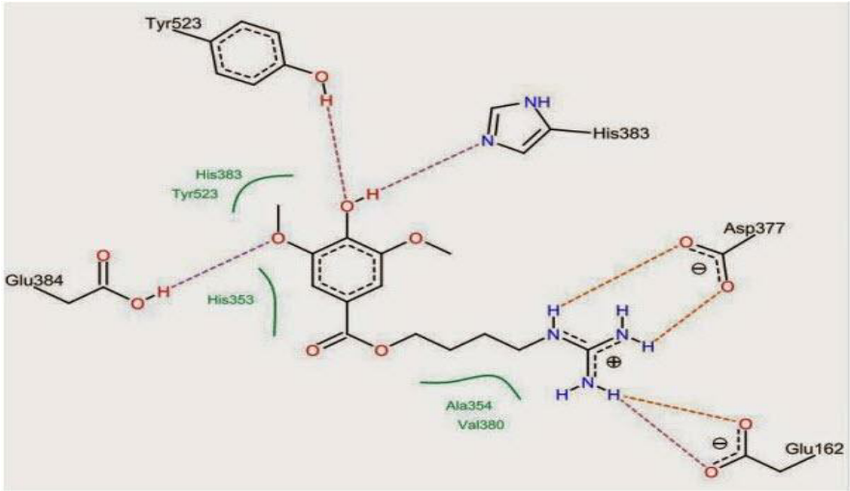
**5. ChemSketch**

ChemSketch is a chemical drawing software that allows users to create chemical structures and perform basic molecular modeling tasks. Key Features include

Provides tools for drawing complex chemical structures with ease.

Includes functionalities for calculating molecular properties such as molecular weight and logP values.

Usage in Drug Discovery: ChemSketch is often used in the initial stages of drug design to visualize potential ligands before conducting docking studies or ADMET evaluations.



**Result**

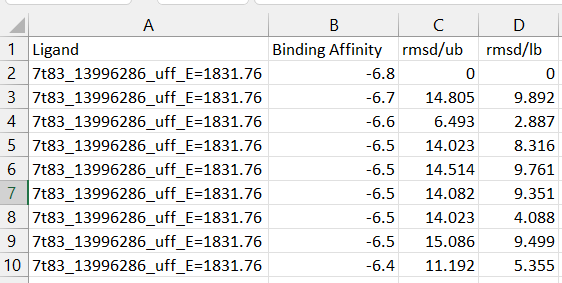
The computational studies surrounding the Angiotensin II Receptor Type 1 (AT1R) have yielded significant insights into its potential as a therapeutic target, particularly for conditions like hypertension and diabetes. Recent research highlights the successful identification of promising ligands derived from Nigella sativa, specifically Beta-amyrin and Taraxerol, which demonstrated strong binding affinities to AT1R, surpassing those of the standard drug Losartan. These compounds not only exhibited favorable pharmacokinetic profiles but also showed no acute toxicity, as assessed through comprehensive ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling.

Molecular docking simulations conducted using tools like PyRx and Discovery Studio confirmed the stability and efficacy of these ligands in binding to AT1R over extended molecular dynamics simulations (100 ns), indicating their potential as effective inhibitors. The binding affinities ranged from -3.1 to -10.7 kcal/mol, suggesting robust interactions with the receptor.

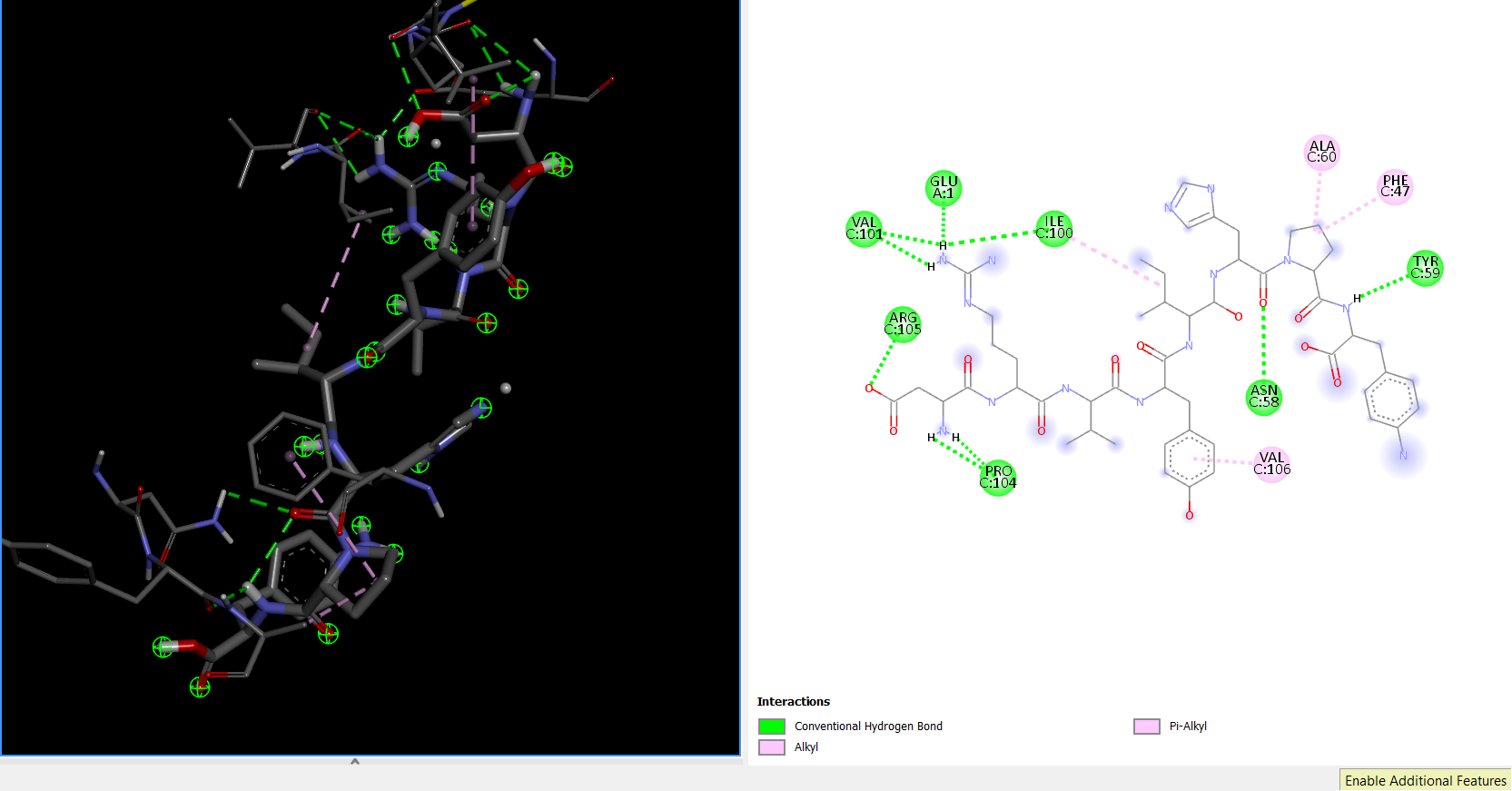
Further structural analysis revealed critical interactions within the AT1R ligand-binding pocket, emphasizing residues that are crucial for ligand binding. The presence of conserved motifs and specific amino acids involved in these interactions underscores the complexity of receptor-ligand dynamics and provides a foundation for designing more effective AT1R-targeted therapies.

Additionally, tools such as ADMETlab, ChEMBL, and SWISSADME have been instrumental in evaluating the drug-likeness of these compounds, ensuring that selected candidates possess desirable pharmacokinetic properties. The integration of advanced computational methods, including deep learning approaches like Deep Docking, enhances the efficiency of virtual screening processes, allowing for rapid assessment of vast chemical libraries against AT1R.

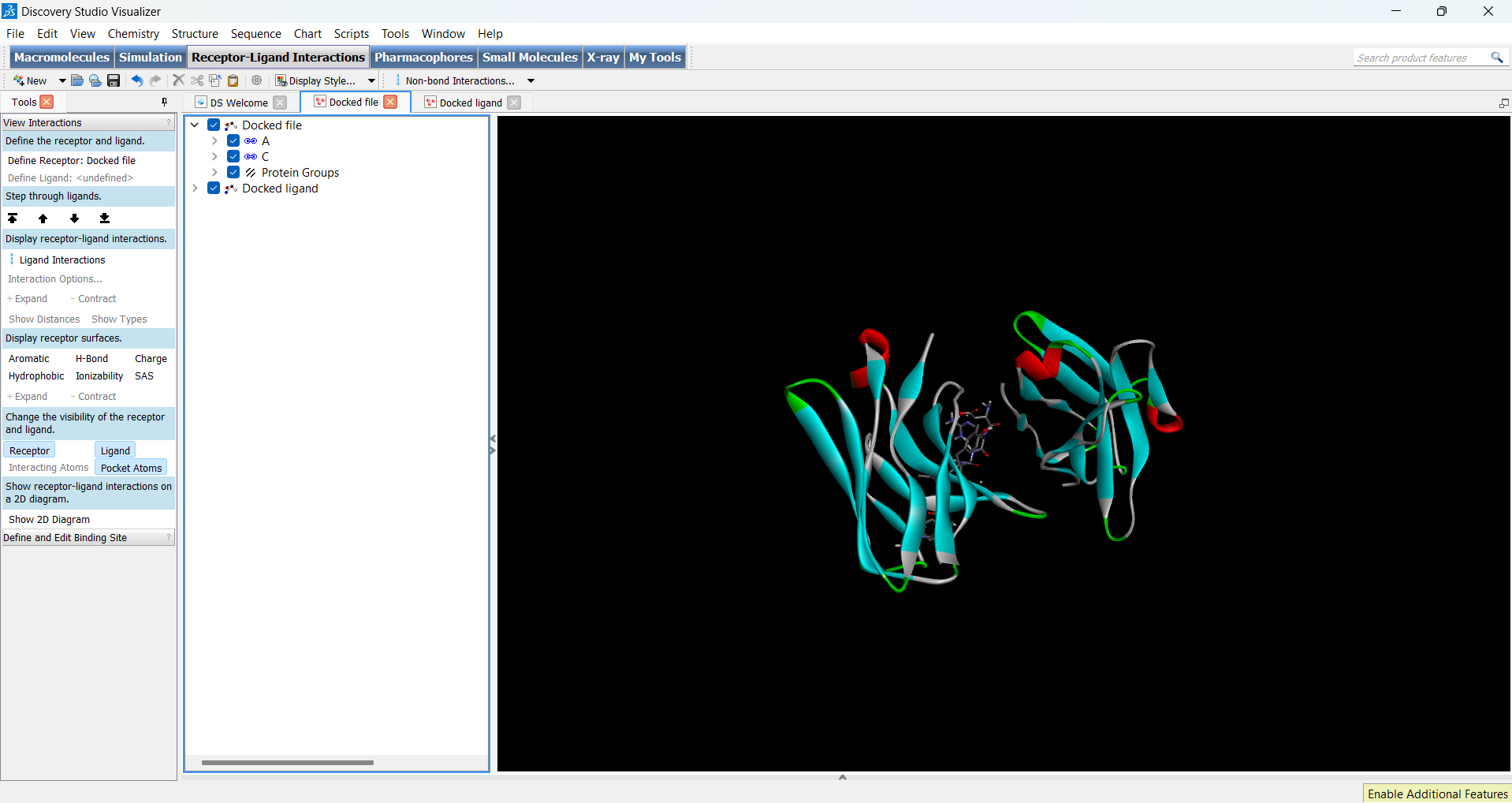
Docking results of compounds

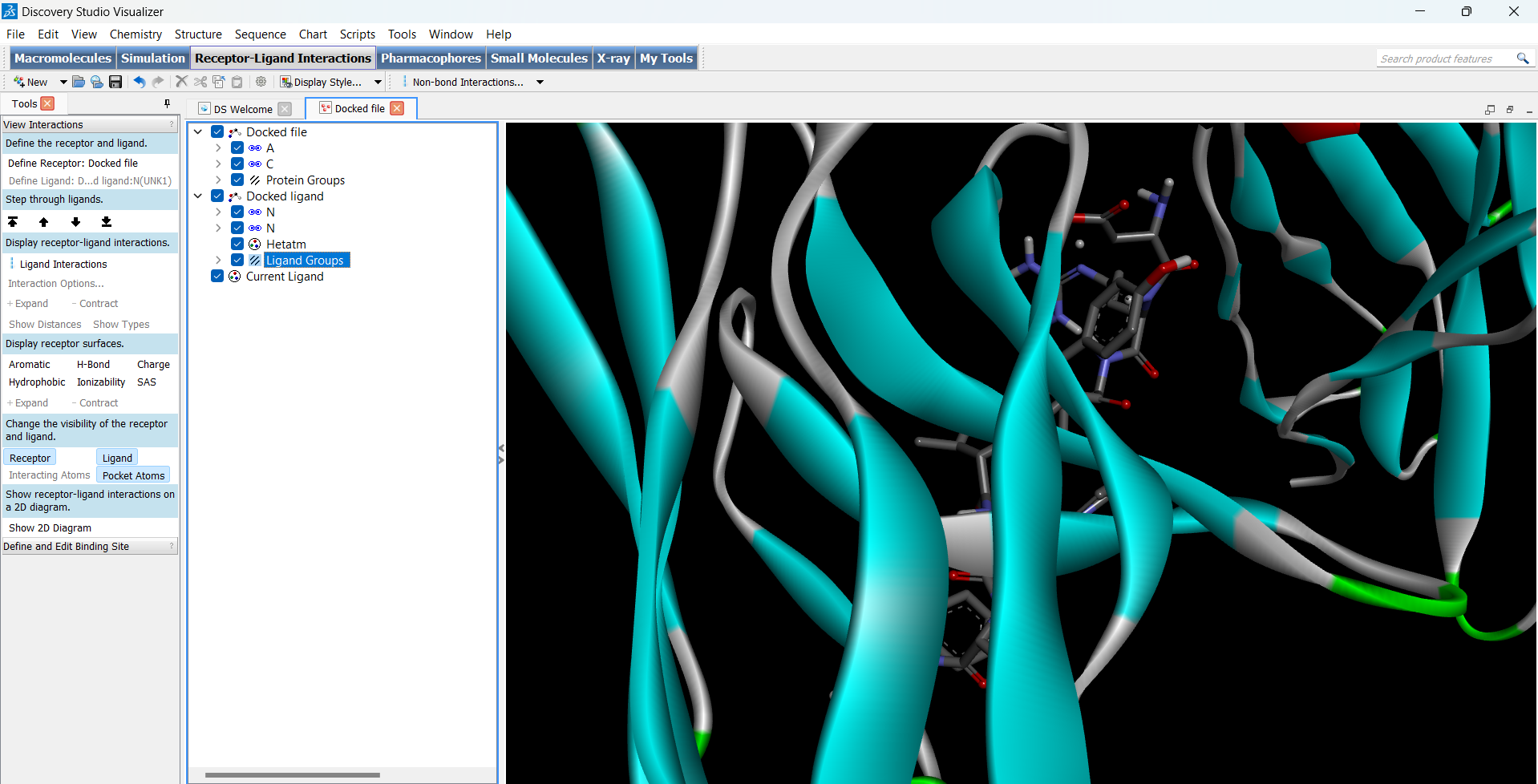


3D v/s 2D diagram

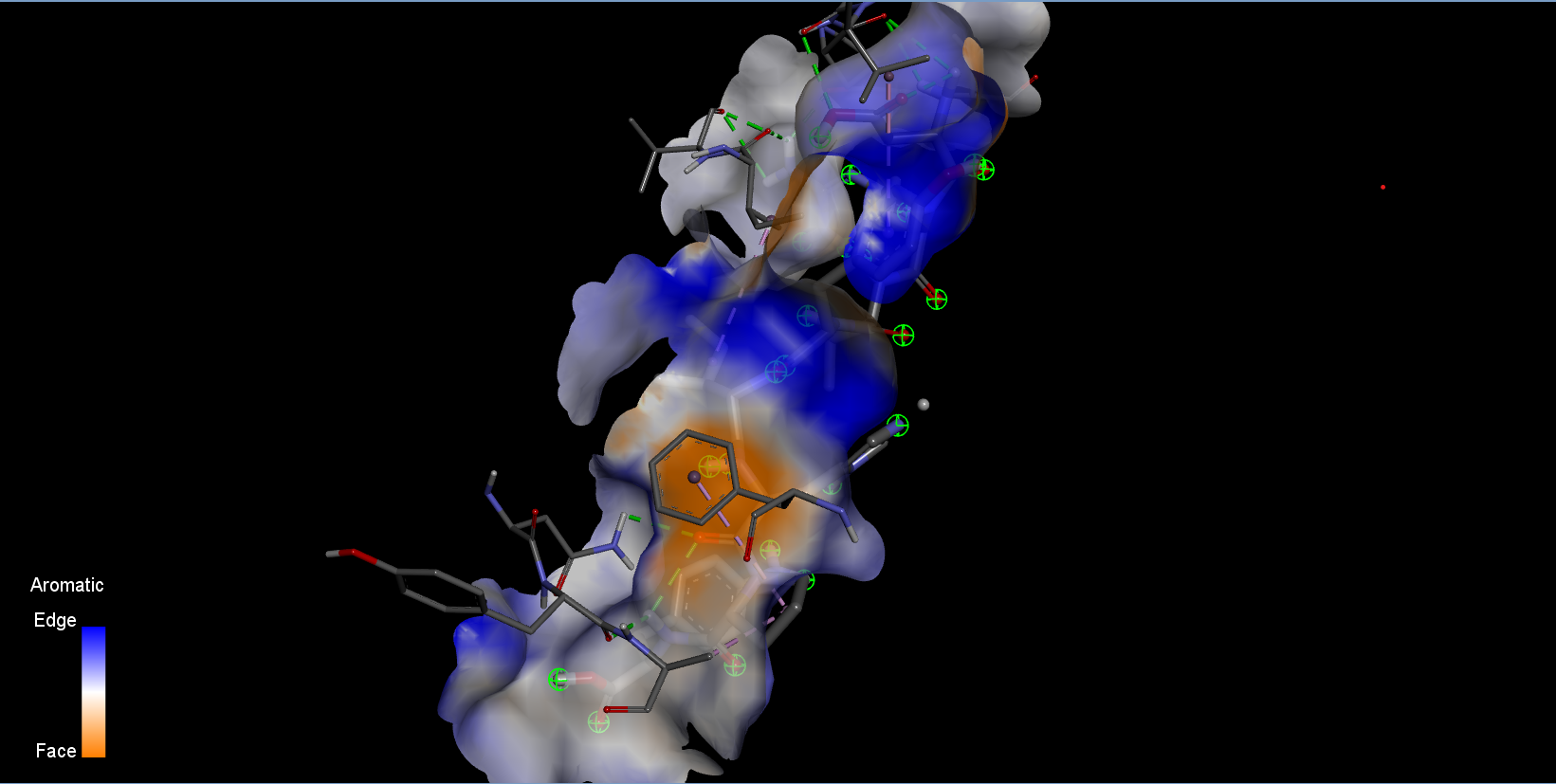


Docked ligand inserted in docked receptor

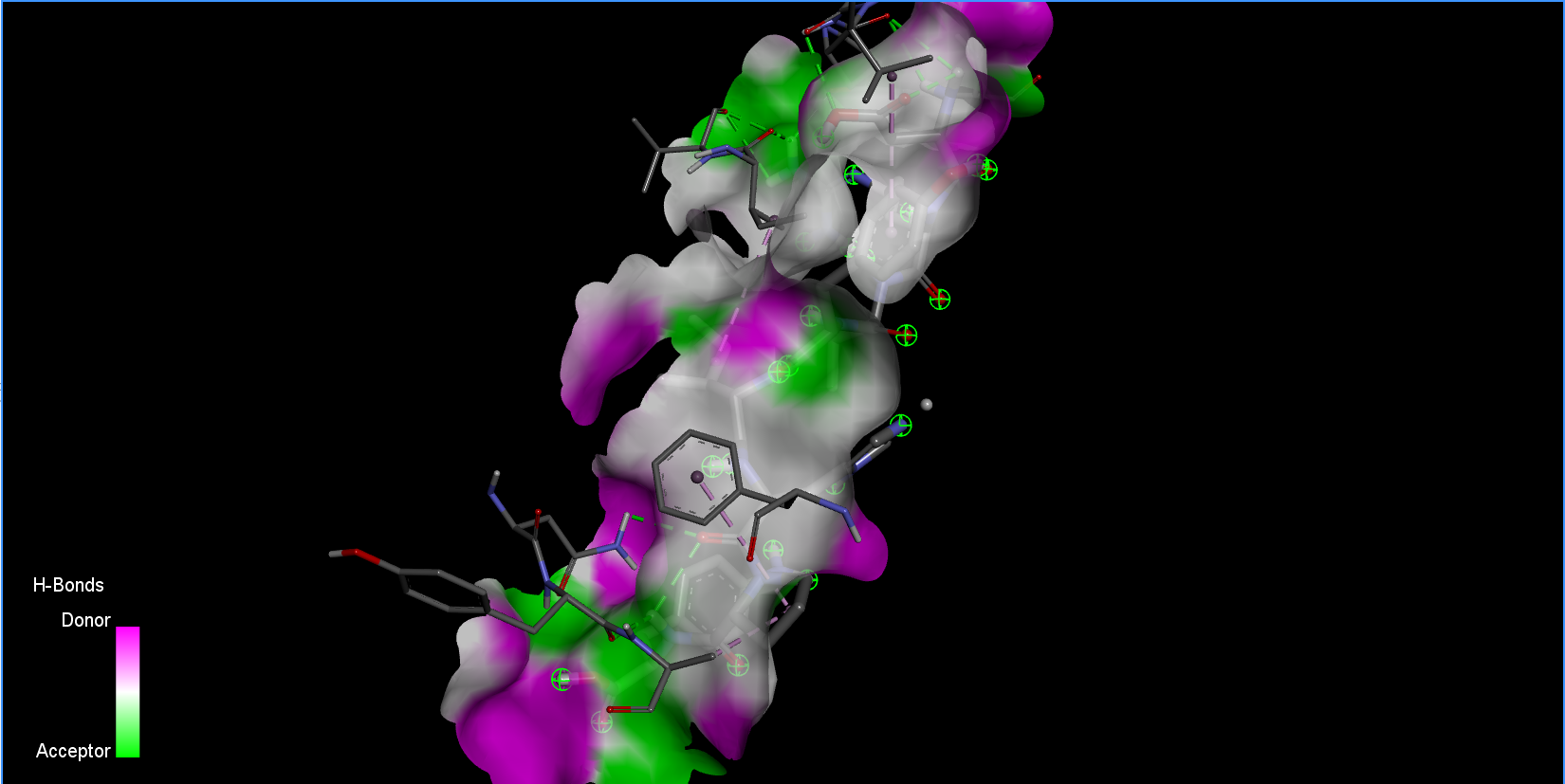




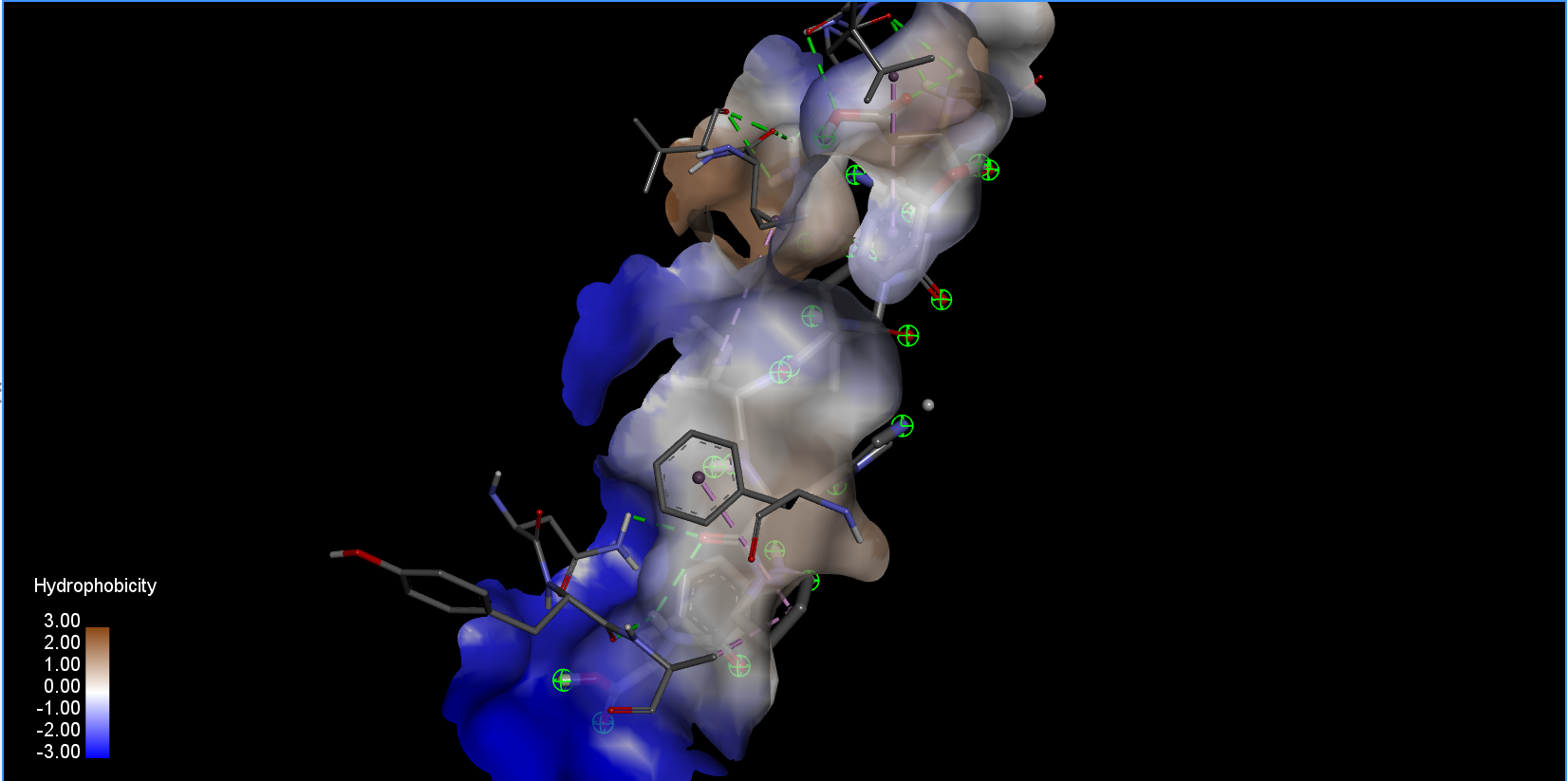
Aromatic receptor surface



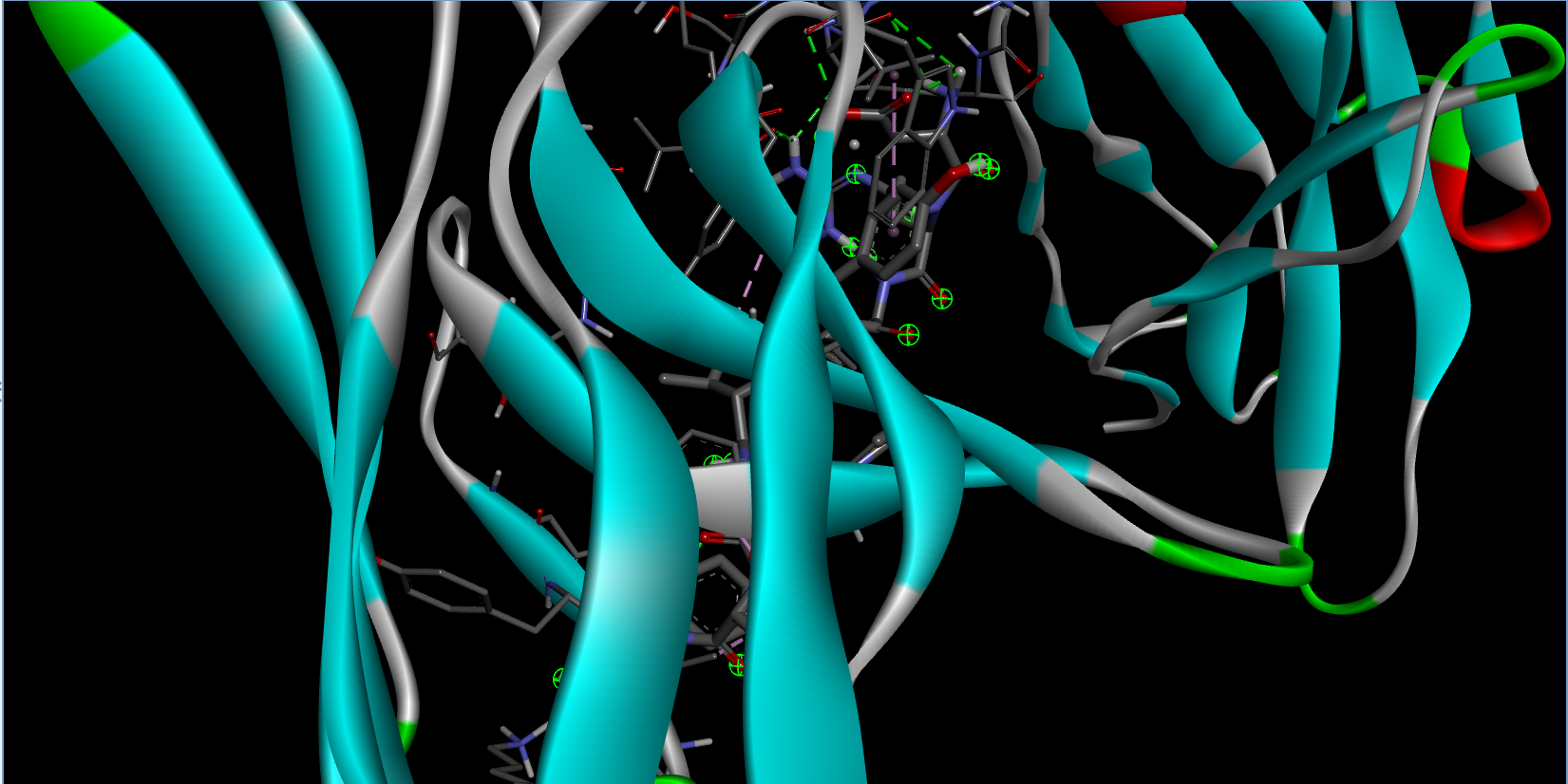
Hydrogen receptor surface



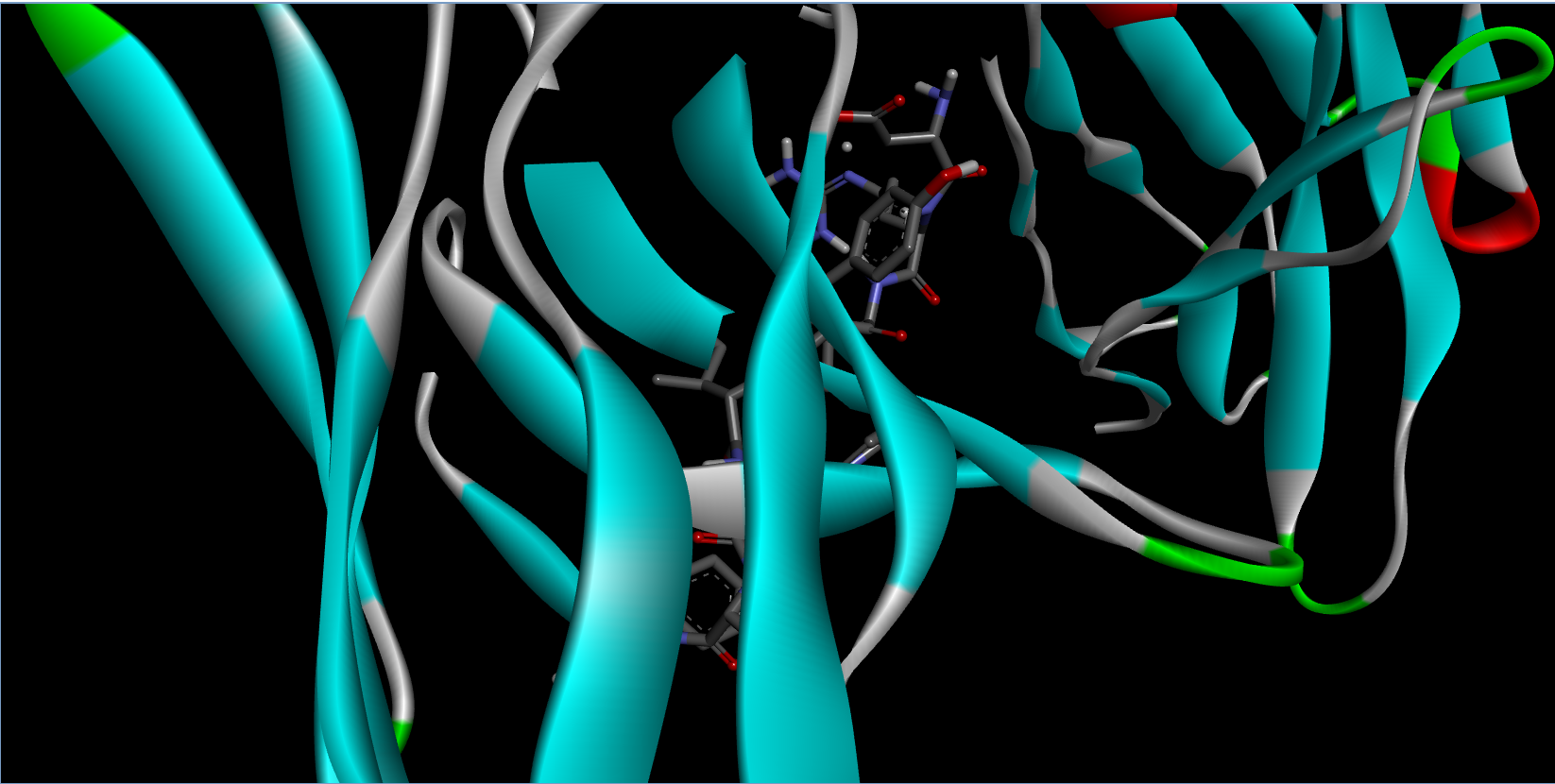
Hydrophobic receptor surface

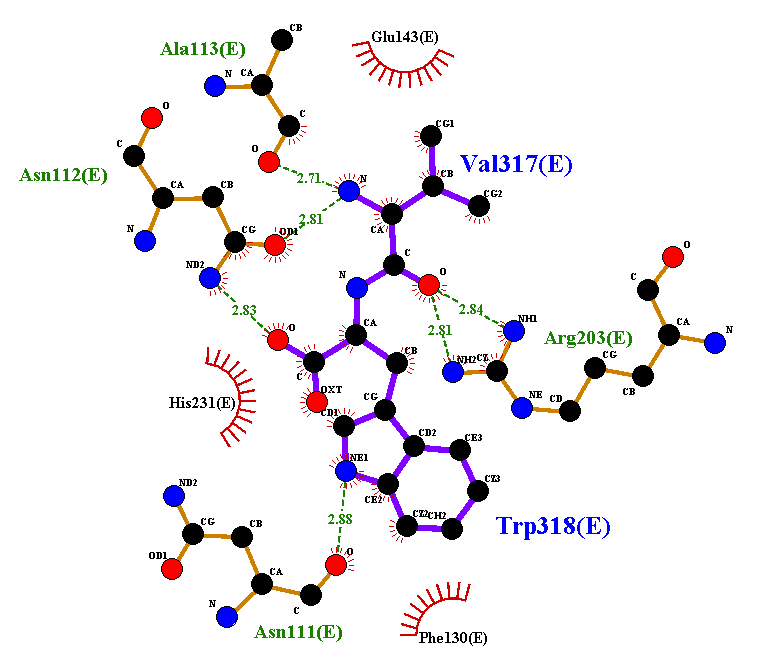


Pocket atoms



Interacting atoms





### **Conclusion**

The Angiotensin II Receptor Type 1 (AT1R) is integral to the regulation of cardiovascular, renal, and immune functions, serving as a critical mediator of Ang II’s effects. Its dysregulation is associated with a range of diseases, from hypertension and heart failure to chronic kidney disease. The development of AT1R-targeted therapies, such as ARBs, has significantly advanced the management of these conditions. The integration of advanced computational techniques, including molecular docking, deep learning approaches, and robust post-docking analyses, significantly enhances the drug discovery process targeting AT1R. These methodologies not only streamline the identification of potential drug candidates but also provide critical insights into their interactions at a molecular level, paving the way for effective therapeutic developments. The integration of tools like ADMETlab, ChEMBL, SWISSADME, ProtParam, and ChemSketch enhances the efficiency of the drug discovery process by providing essential data on ADMET properties and molecular characteristics. he findings from computational docking studies and ADMET evaluations present a promising avenue for developing new therapeutic agents targeting AT1R. The combination of strong binding affinities, favorable pharmacokinetic profiles, and advanced computational methodologies positions these ligands as potential candidates for further development in treating hypertension and related disorders.

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