ProtacMLA: PROTAC Mutation and Ligand analysis tool

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ABOUT

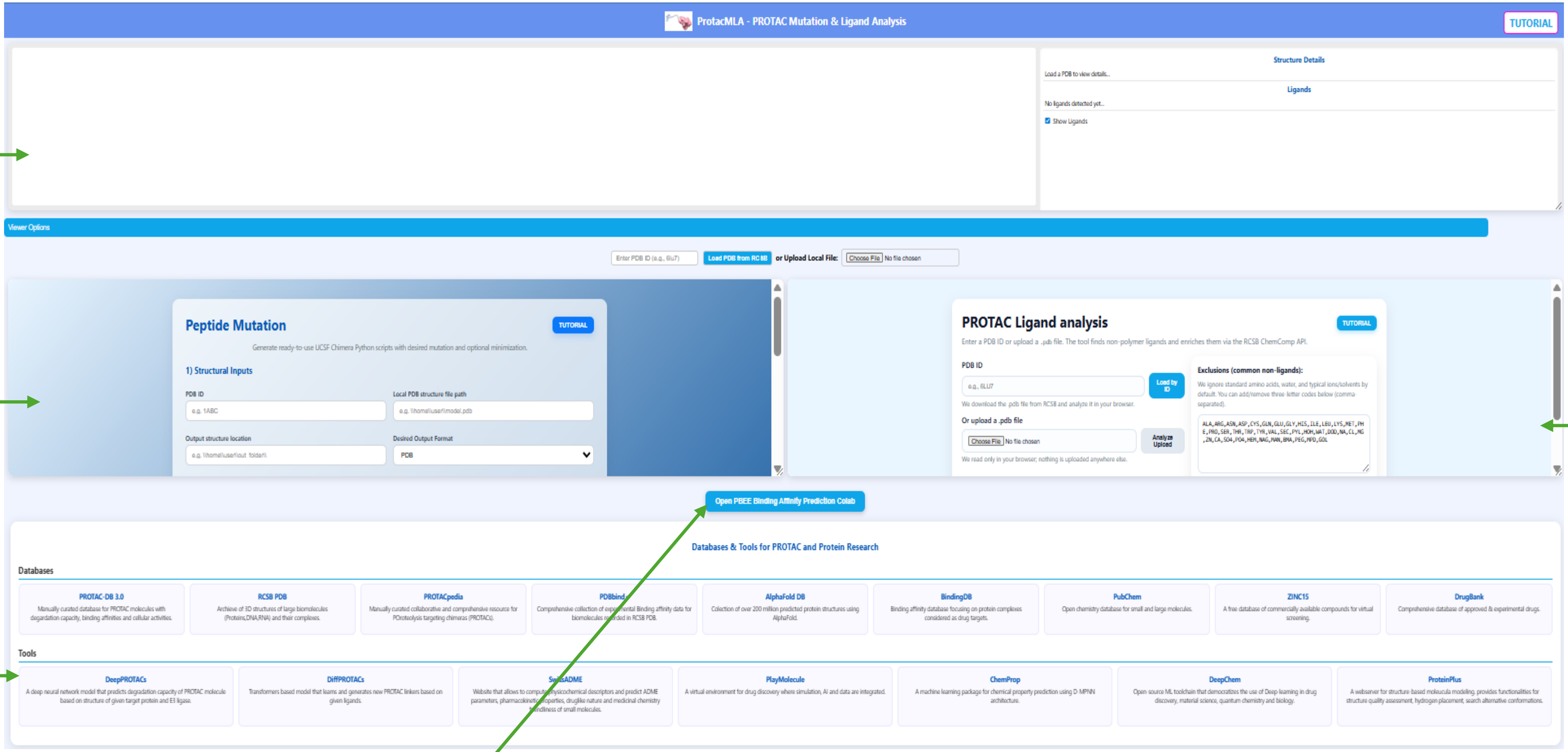
- ProtacMLA is an online web-based tool that helps users extract, visualize, and analyse the Proteolysis targeting chimeras (PROTACs).
- This online freely accessible web tool helps to extract the PDB format file of PROTAC or the PROTAC complex and analyze the PROTAC region.
- This tool helps to:
  - Extract and analyse ligands acting as the E3 ligase binding ligand and the linker
  - Mutate the amino acid region that acts like the target protein-binding region of the PROTAC molecule
- The tool also enlists databases and tools that are useful in the PROTAC and protein study.

Homepage

PDB Viewer section

Mutation section

Database and Tools section



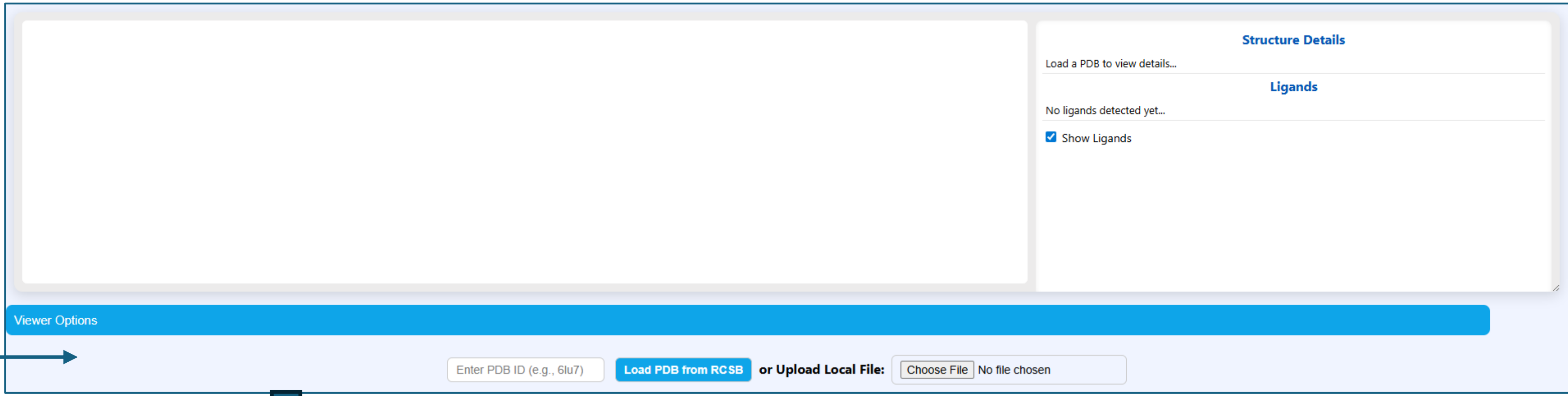
Ligand analysis section

PBEE protein-peptide binding affinity predictor

PDB structure viewer section

This section helps users visualize 3D structures along with their residues, chains, and involved ligands, allowing them to identify their target complex.

The viewer is designed in a way that it excludes common ions, water molecules, and uncommon ligands.

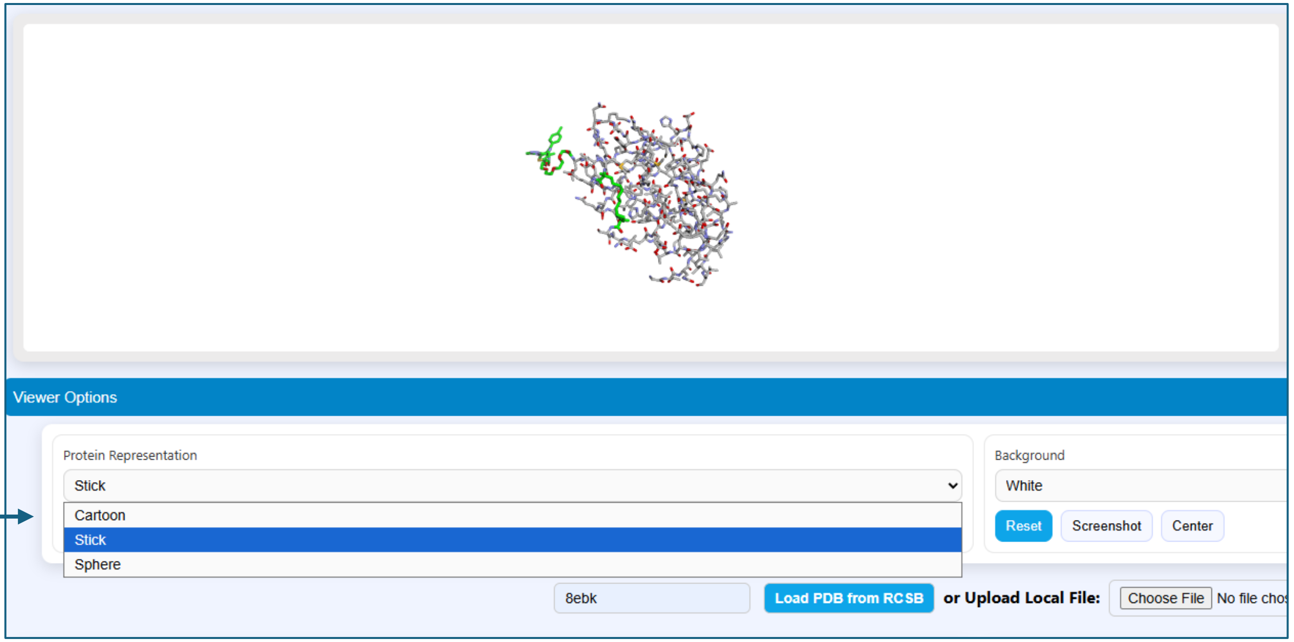


Users may enter the PDB ID or upload their PDB structure from the local system.

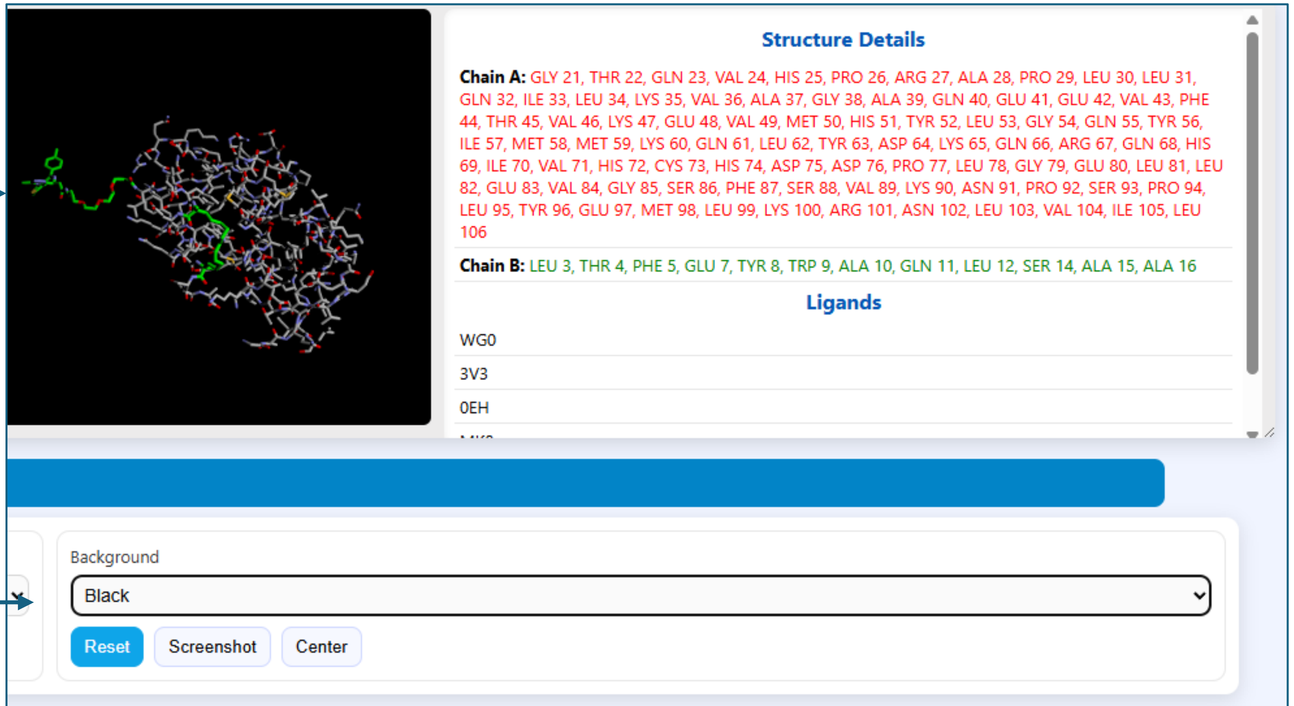
The 3D structure is loaded, which can be visualized here

Details of the structure, including their residues, chain, and involved ligands, may be found here

Using the ‘Viewer option’, the user may change the structure representation to cartoon/stick/sphere for easy visualization of the structure components.



Using the ‘Viewer option’, the user may also change the background to white/black/soft blue to increase the visibility of small components.



The options for Reset (reset to default settings), Screenshot (save structure image in PNG format), and Center (move the structure to the center of the view window are also included.

PROTAC mutation section

This section of the tool helps the user to mutate the amino acid sequence of the target protein binding site of the PROTAC molecule.

1) Structure Input:

It takes the input of the PDB ID or structure from the local system, the output file saving location, and the desired output file format (PDB/mmCIF/mol2)

2) Minimization (optional):

Takes the number of steps of Steepest Descent and Conjugate Gradient to run minimization of the mutated structure. This step is optional.

(Note: An Increased number of steps and structure complexity may increase the time of minimization.)

3) Mutation mode:

Allows users to select the type of mutation they want to perform on the structure. It includes,

Single or multiple mutation: Mutate one or more amino acids with any other amino acid. (Discussed in detail in the next section)

Class-wise mutation: Mutate one or more amino acids to all amino acids of any class. (Discussed in detail in the next section)

Enter the number of amino acids that you want to mutate and generate fields for input entry.

The user may also visualize the generated Python script and download it to directly run in Chimera 1.19+ for mutation and minimization, and save the final structures in the desired folder in the desired format.

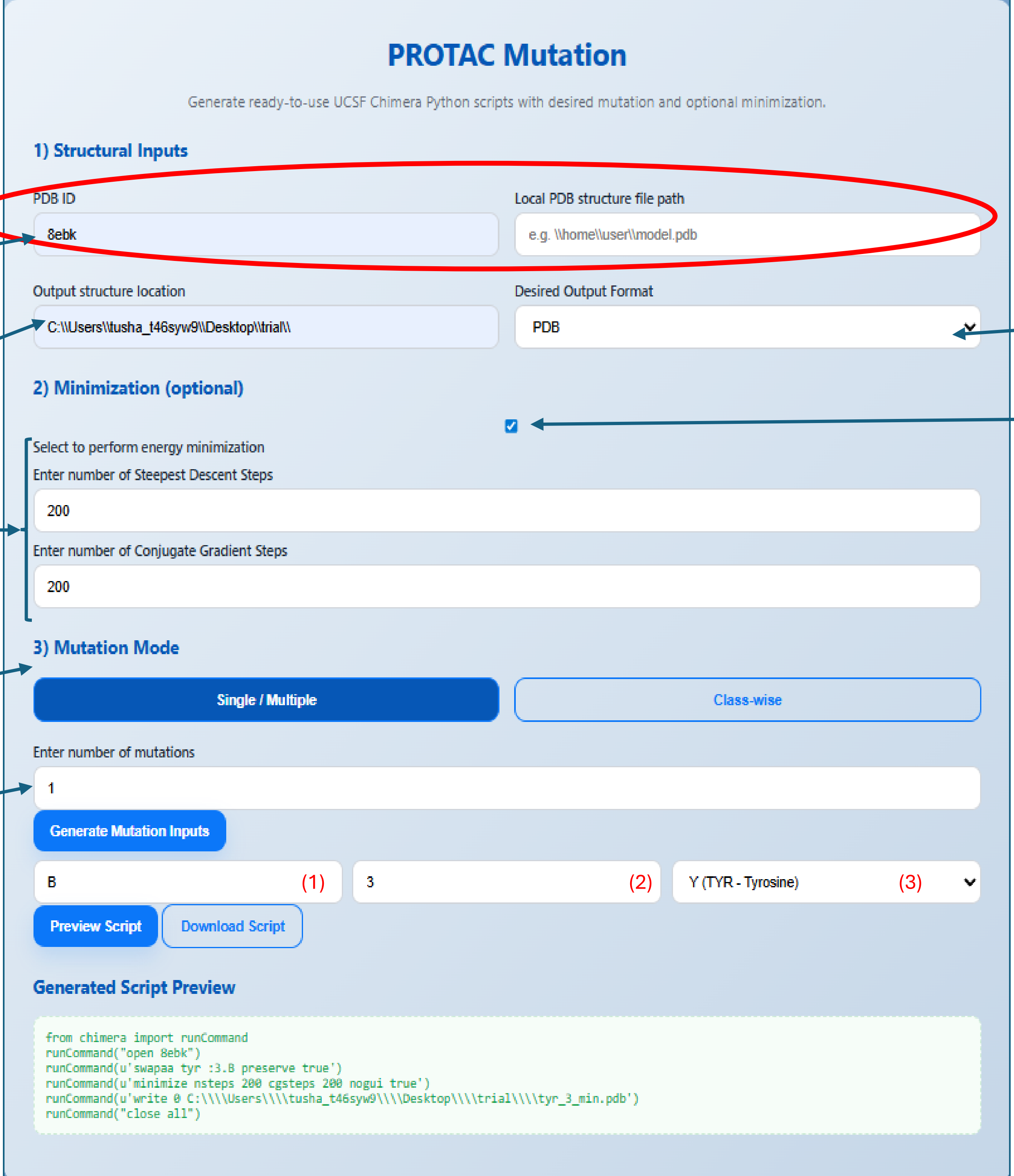
PDB ID or enter pdb structure location from local system

Enter preferred output file saving location

Enter the steps of steepest descent and conjugate gradient for minimization

Select the type of mutation to conduct on desired amino acids

Enter the number of amino acids to mutate



Choose desired output format

Check the box if you want to run minimization on output structures

For the case of single/multiple mutation mode :

1. Enter the Chain ID of the desired amino acid to mutate
2. Enter the residue ID or residue number of the amino acid
3. Choose the amino acid you wish to mutate to

Repeat the same for all the entries

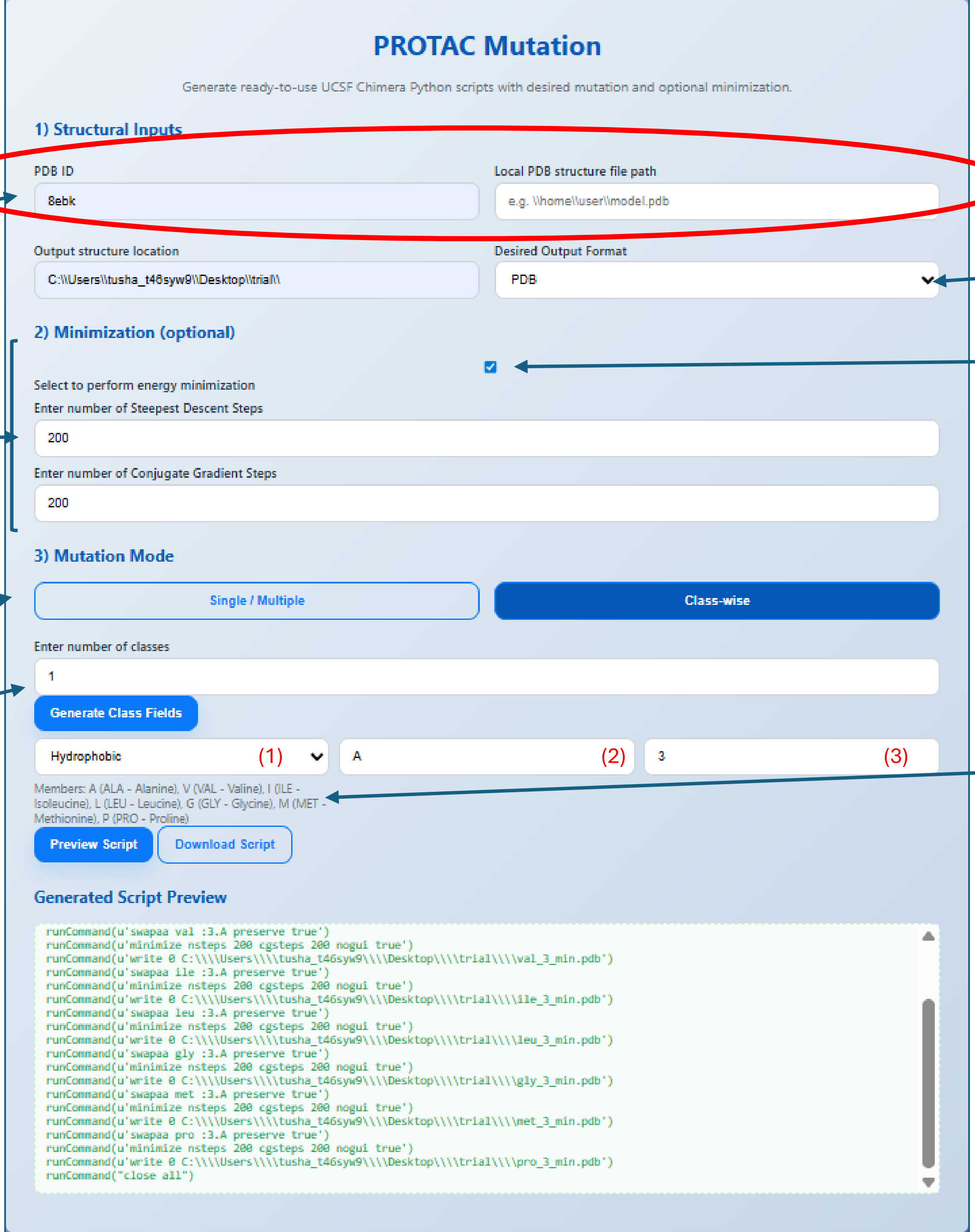
PDB ID or enter pdb structure location from local system

Enter preferred output file saving location

Enter the steps of steepest descent and conjugate gradient for minimization

Select the type of mutation to conduct on desired amino acids

Enter the number of amino acids to mutate



Choose desired output format

Check the box if you want to run minimization on output structures

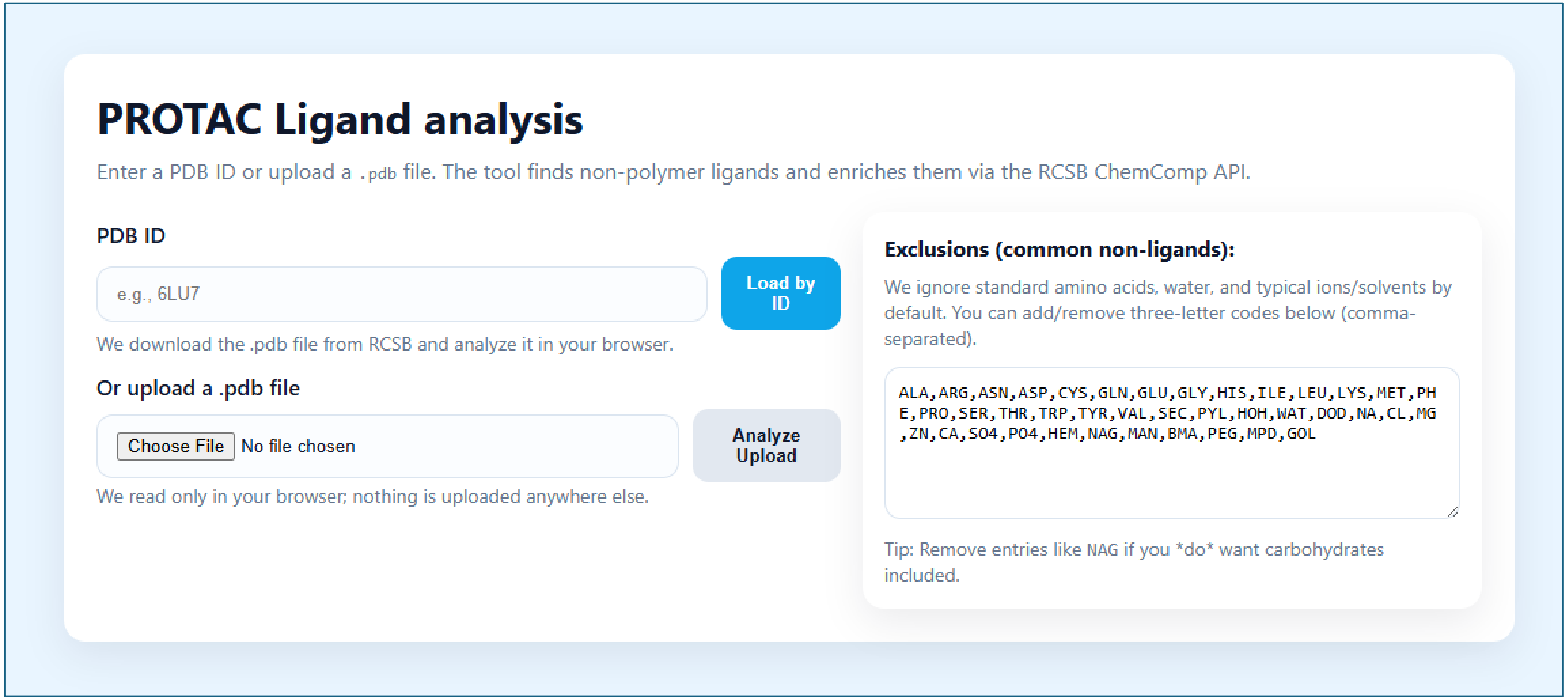
For the case of class-wise mutation mode :

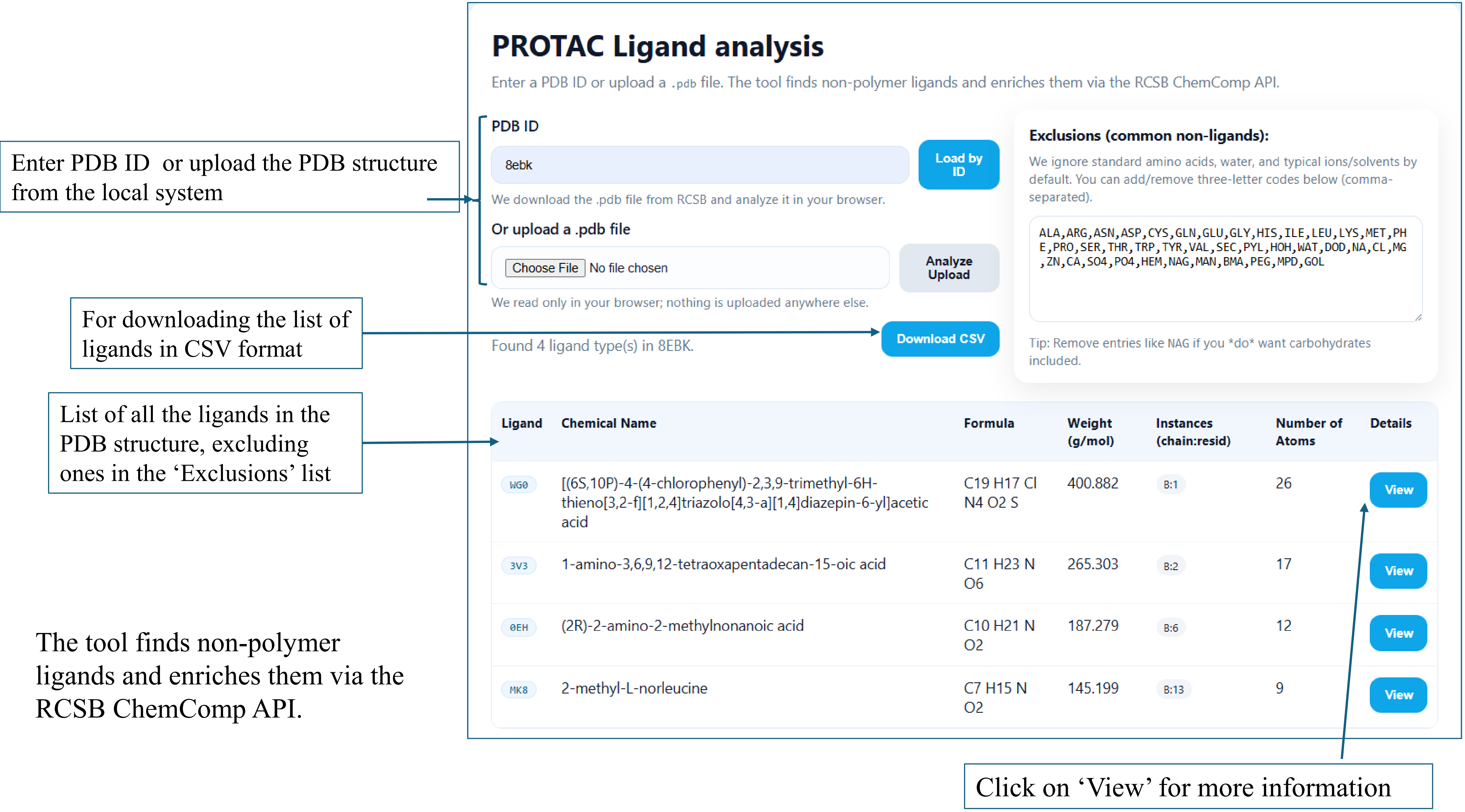
1. Enter the preferred class of amino acid (all amino acids of each class are listed for reference)
2. Enter the chain ID for the amino acid
3. Enter the residue ID or residue number of the amino acid

Repeat the same for all the entries

PROTAC ligand analysis section

This section of the tool helps users analyse features of ligands present in the structure playing role as E3 ligase binding ligand and linker.
This section also includes an exclusion list that enlists all the amino acids, small, uncommon ligands, and ions that may be changed by the user.
It takes the input pdb structure or is fetched using the PDB ID from RCSB PDB and displays ligands, including ones involved in E3 ligase binding ligand and as a linker for E3 ligase binding ligand and target protein binding region.



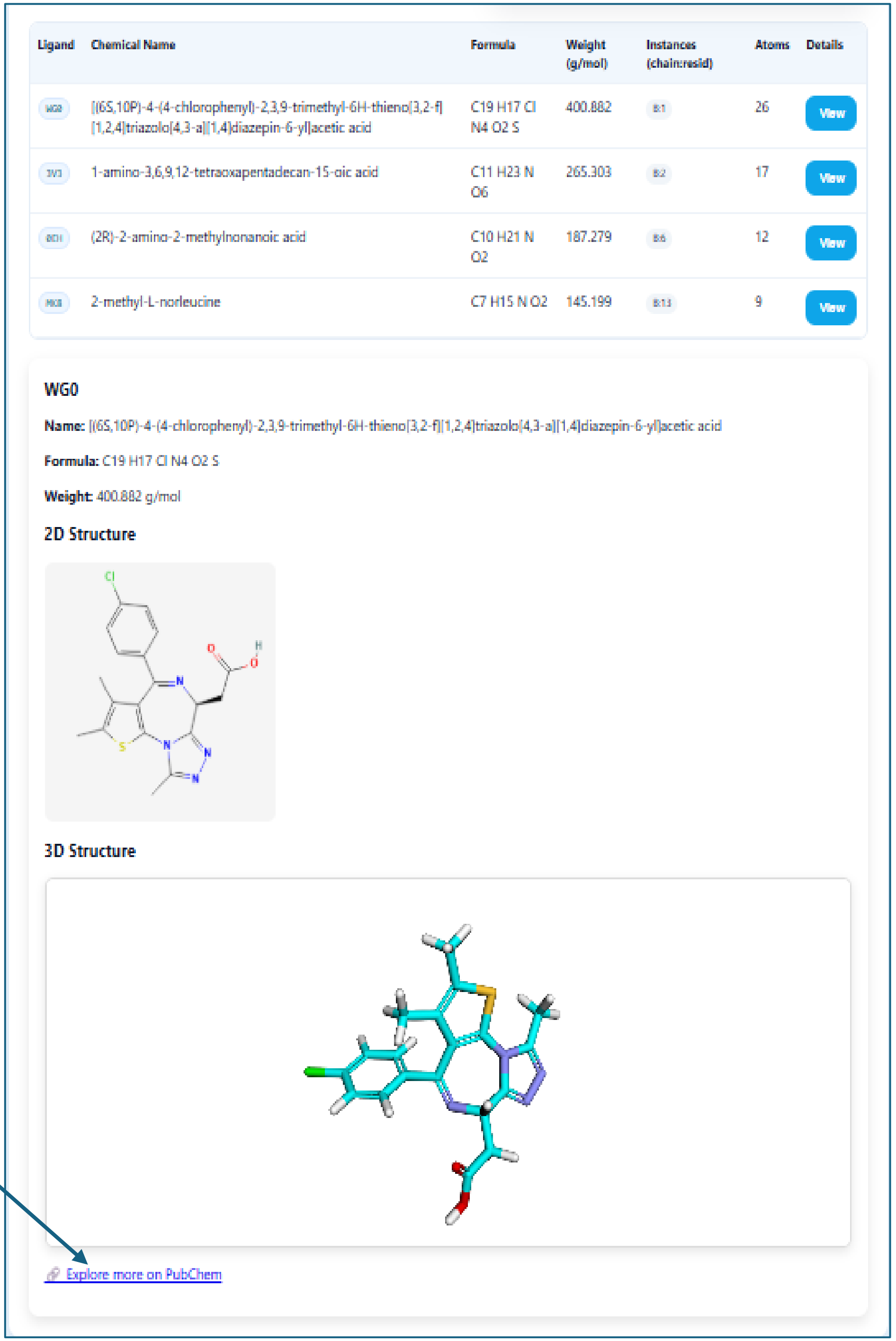


PROTAC Ligand analysis
Enter a PDB ID or upload a .pdb file. The tool finds non-polymer ligands and enriches them via the RCSB ChemComp API.
PDB ID
8ebk
Load by ID
We download the .pdb file from RCSB and analyze it in your browser.
Or upload a .pdb file
Choose File No file chosen
Analyze Upload
We read only in your browser; nothing is uploaded anywhere else.
Download CSV
Found 4 ligand type(s) in 8EBK.
Exclusions (common non-ligands):
We ignore standard amino acids, water, and typical ions/solvents by default. You can add/remove three-letter codes below (comma-separated).
ALA,ARG,ASN,ASP,CYS,GLN,GLU,GLY,HIS,ILE,LEU,LYS,MET,PHE,PRO,SER,THR,TRP,TYR,VAL,SEC,PYL,HOH,WAT,DOD,NA,CL,MG,ZN,CA,SO4,PO4,HEM,NAG,MAN,BMA,PEG,MPD,GOL
Tip: Remove entries like NAG if you *do* want carbohydrates included.
Ligand
Chemical Name
Formula
Weight (g/mol)
Instances (chain:resid)
Number of Atoms
Details
WG0
[(6S,10P)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl]acetic acid
C19 H17 Cl N4 O2 S
400.882
B:1
26
View
3V3
1-amino-3,6,9,12-tetraoxapentadecan-15-oic acid
C11 H23 N O6
265.303
B:2
17
View
0EH
(2R)-2-amino-2-methylnonanoic acid
C10 H21 N O2
187.279
B:6
12
View
MK8
2-methyl-L-norleucine
C7 H15 N O2
145.199
B:13
9
View
Enter PDB ID or upload the PDB structure from the local system
For downloading the list of ligands in CSV format
List of all the ligands in the PDB structure, excluding ones in the 'Exclusions' list
The tool finds non-polymer ligands and enriches them via the RCSB ChemComp API.
Click on 'View' for more information

Downloaded ligand table with features

Ligand	Name	Formula	Weight_g_mol	Instances_chain:resid	TotalAtoms
WG0	[(6S,10P)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl]acetic acid	C19 H17 Cl N4 O2 S	400.882	B:1	26
3V3	1-amino-3,6,9,12-tetraoxapentadecan-15-oic acid	C11 H23 N O6	265.303	B:2	17
0EH	(2R)-2-amino-2-methylnonanoic acid	C10 H21 N O2	187.279	B:6	12
MK8	2-methyl-L-norleucine	C7 H15 N O2	145.199	B:13	9

After clicking the 'View' button, the window expands to list features of the specific ligand, including IUPAC name, chemical formula, molecular weight, and 2D structure.
3D structure of the ligand is displayed using PubChem, which may be extended further to see other features of the ligand by clicking the link 'Explore more on PubChem'.



Databases and Tools for PROTAC and Protein Research

This section of the tool is designed to help users access various available resources for computational drug discovery and bioinformatics using PROTAC.

The included databases and tools range from several PROTAC-specific resources to general ones.

Databases

- PROTAC-DB 3.0
- RCSB PDB
- PROTACpedia
- PDBbind+
- AlphaFold DB
- BindingDB
- PubChem
- ZINC15
- DrugBank

Tools

- DeepPROTACs
- DiffPROTACs
- SwissADME
- PlayMolecule
- ChemProp
- DeepChem
- ProteinPlus

DATABASES

PROTAC-DB 3.0

- **Purpose:** A manually curated database specifically for PROteolysis-TArgeting Chimeras (PROTACs). It's a specialized resource for researchers working on targeted protein degradation.
- **Key Features:** It provides detailed information on PROTAC molecules, including their chemical structures, and crucial biological data like degradation capacity (DC50 and Dmax), binding affinities (IC50, Ki, Kd), and cellular activities. The updated version, 3.0, has expanded its entries and now includes pharmacokinetic data, which is essential for assessing the druggability of these molecules. The database also categorizes the components of a PROTAC: the warhead (the part that binds to the target protein), the E3 ligase ligand, and the linker.

RCSB PDB (Protein Data Bank)

- **Purpose:** The central global archive for 3D structures of large biomolecules. It serves as a fundamental resource for structural biologists, providing a detailed view of the atomic coordinates of proteins, DNA, RNA, and their complexes.
- **Key Features:** PDB entries are derived from experimental methods like X-ray crystallography, NMR spectroscopy, and cryo-electron microscopy. The database is a go-to source for understanding molecular function, interactions, and for structure-based drug design. It includes extensive annotations, visualizations, and tools for searching and analyzing structures.

PROTACpedia

- **Purpose:** A collaborative, high-quality, and freely accessible resource for PROTACs. Unlike commercial databases, it's designed to be a community-driven platform.
- **Key Features:** It provides a manually curated collection of data on PROTAC molecules. The collaborative nature of the platform means that registered users can contribute new data, helping to expand the resource. This makes it a dynamic and up-to-date source of information for the PROTAC research community.

PDBbind+

- **Purpose:** A specialized database that bridges structural and energetic information. It's a comprehensive collection of experimentally determined binding affinity data for protein-ligand complexes that have a corresponding 3D structure in the RCSB PDB.
- **Key Features:** It is an invaluable resource for developing and validating computational methods in drug discovery, such as docking and scoring functions. The database provides a "refined set" of high-quality data, which is a standard benchmark for testing the performance of molecular modeling algorithms.

AlphaFold DB

- **Purpose:** A collection of over 200 million predicted protein structures generated by Google DeepMind's AlphaFold AI system. It dramatically expands the number of available protein structures beyond those determined experimentally.
- **Key Features:** For many organisms, it provides a comprehensive predicted proteome. Each structure comes with a per-residue confidence score (pLDDT), allowing users to assess the reliability of the prediction for different regions of the protein. This database is accelerating research by providing structural models for proteins that have not yet been experimentally characterized.

BindingDB

- **Purpose:** A publicly accessible database focused on the binding affinities of small molecules to proteins, particularly those considered to be drug targets.
- **Key Features:** It contains millions of data points, including Ki, Kd, IC50, and EC50 values. This data is critical for medicinal chemists and computational modelers for developing Structure-Activity Relationships (SAR), training machine learning models, and validating docking methods. It also provides links to related information in other databases like RCSB PDB and PubChem.

PubChem

- **Purpose:** An open chemistry database maintained by the National Institutes of Health (NIH). It's a foundational resource for a vast array of chemical information.
- **Key Features:** It includes a massive collection of information on chemical structures, physical properties, biological activities, and more. Data is contributed by a wide range of sources, including government agencies and vendors. It's a go-to resource for chemical searching, whether by structure, name, or other identifiers.

ZINC15

- **Purpose:** A free and comprehensive database of commercially available chemical compounds. It is optimized for virtual screening.
- **Key Features:** ZINC15 contains over 230 million purchasable compounds, all in "ready-to-dock," 3D formats. This is a crucial feature for computational chemists who need to quickly prepare large libraries of molecules for docking simulations. It also provides various filters based on molecular properties like molecular weight and LogP, making it easy to create focused screening libraries.

DrugBank

- **Purpose:** A unique bioinformatics and cheminformatics resource that combines detailed drug information with comprehensive drug target data.
- **Key Features:** It includes data on approved and experimental drugs, providing their chemical, pharmacological, and pharmaceutical details. It also offers a wealth of information on the drugs' protein targets, including sequences and pathways. This database is a powerful tool for linking drugs to their mechanisms of action and for drug repurposing studies.

TOOLS

DeepPROTACs

- **Purpose:** A deep neural network model designed to predict the degradation capacity of a PROTAC molecule.
- **Key Features:** It takes the 3D structures of the target protein and the E3 ligase as input, along with the PROTAC molecule's structure. The model uses a combination of Graph Convolutional Networks (GCNs) and other neural network architectures to predict whether a given PROTAC will effectively degrade its target. This tool helps in the early-stage rational design of PROTACs, as it can filter out potentially ineffective molecules before synthesis.

DiffPROTACs

- **Purpose:** A generative AI model based on diffusion and transformer architectures for designing new PROTAC linkers.
- **Key Features:** This tool addresses a major challenge in PROTAC design: the linker. It can learn the properties of existing linkers and generate novel ones that connect a given target ligand and E3 ligase ligand. It's a powerful approach for exploring the vast chemical space of potential linkers to find ones that optimize the properties of the PROTAC molecule.

SwissADME

- **Purpose:** A web-based tool for computing physicochemical descriptors and predicting Absorption, Distribution, Metabolism, and Excretion (ADME) parameters for small molecules.
- **Key Features:** It helps researchers quickly assess the "druglike" nature of their compounds. It predicts properties such as water solubility, gastrointestinal absorption, blood-brain barrier penetration, and adherence to rules like Lipinski's Rule of Five. This is an essential tool for early-stage drug discovery to filter out molecules with poor pharmacokinetic properties.

PlayMolecule

- **Purpose:** A virtual environment for drug discovery that integrates simulations, AI, and data. It provides a comprehensive platform for various computational workflows.
- **Key Features:** It offers a suite of applications for tasks like protein and small molecule preparation, virtual screening, binding mode analysis, and relative binding affinity predictions. It can be accessed via a graphical user interface, a Python API, or the command line, providing flexibility for different user needs. It's designed to streamline complex drug discovery processes.

ChemProp

- **Purpose:** An open-source machine learning package for chemical property prediction, specifically using Directed Message Passing Neural Networks (D-MPNNs).
- **Key Features:** This is a coding-focused tool for researchers who want to build their own predictive models. It simplifies the process of training and using powerful graph neural networks on molecular data. It can predict a wide range of properties for single molecules, reactions, and multi-molecule systems, making it highly versatile for cheminformatics tasks.

DeepChem

- **Purpose:** An open-source machine learning toolchain that aims to democratize the use of deep learning in drug discovery, materials science, quantum chemistry, and biology.
- **Key Features:** It provides high-level APIs for building and deploying deep learning models on molecular datasets. It includes a wide variety of models and data featurizers, making it easy to get started with complex machine learning tasks. It's a foundational library for researchers who want to apply AI to scientific problems.

ProteinPlus

- **Purpose:** A web server for structure-based molecular modeling, focusing on supporting life scientists who work with protein structures.
- **Key Features:** It provides a suite of functionalities for preparing and analyzing protein structures, especially in the context of protein-ligand interactions. Key tools include structure quality assessment, hydrogen placement, binding site prediction (DoGSiteScorer), and the generation of aligned protein structure ensembles. It also features tools for 2D ligand interaction diagrams and finding alternative conformations.