

Method Article

Illustrated Procedure to Perform Molecular Docking Using PyRx and Biovia Discovery Studio Visualizer: A Case Study of 10kt With Atropine

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Abstract: Molecular docking is a bioinformatic modeling technique used in structure-based drug design. It has been a vital tool in drug discovery and the study of biological systems. It plays a crucial role in predicting the interactions of small molecules (ligands) with the binding site of a protein of interest. This helps in designing more effective and specific drugs. This tutorial aimed at demonstrating a step-by-step procedure for the combined usage of PyRx and Biovia Discovery Studio visualizer in molecular docking.

Keywords: Biovia discovery studio visualizer; ligands; ligand-protein interactions; molecular docking; PyRx; small molecules

1. Introduction

Molecular docking is a common method employed in structure-based drug design^[1]. It is used in drug discovery to elucidate potential actions of uninvestigated bioactive compounds by identifying their molecular targets using bioinformatics along with systems biology approaches^[2]. It predicts how proteins interact with small chemical molecules or ligands to form a stable complex. In drug design and drug discovery the usefulness of molecular docking cannot be overemphasized^[3].

PyRx is a virtual screening tool for docking multiple small chemical molecules (ligands) with a target protein. It reveals the most suitable molecule that will bind to a protein with a strong orientation^[4]. PyRx enables medicinal chemists to run virtual screening from any platform and helps users in every step of this process - from data preparation to job submission and analysis of results. While it is true that there is no magic button in the drug discovery process, PyRx includes a docking wizard with an easy-to-use user interface which makes it a valuable tool for computer-aided drug design. PyRx also includes chemical spreadsheet-like functionality and a powerful visualization engine that is essential for rational drug design (<https://sourceforge.net/projects/pyrx/>). Biovia Discovery Studio (BDS) is a tool for viewing the 3-dimensional structure, residues, atoms, including the inter and intramolecular forces in a protein and the small chemical molecules^[5]. It is often used to prepare or convert a protein of interest into its protein data bank format (.pdb).

We have illustrated in this study, a simple stepwise and easy-to-practice procedure for carrying out a molecular docking analysis using PyRx^[6] and BDS visualizer^[7]. The procedural illustration was designed for non-bioinformaticians who may not have any prior experience with molecular docking studies^[8,9]. To make this tutorial applicable and generalizable, we started by downloading and installing all freely available prerequisite software, which was followed by subsequent illustrated step-wise procedures.

2. Methods

2.1 Basic Requirements

For this tutorial, a personal computer (laptop or computer system) of Windows Software 8 or 10, protein of interest (target protein), access to databases like RCSB PDB and PubChem, PyRx version 0.8 (un-licensed), BDS visualizer of any version, though version 16 was used for this tutorial. The PyRx has built-in AutoDock, AutoDock Wizard, Vina Wizard, and Open Babel. The first thing every user needs to do is download and install PyRx and BDS. Links to download PyRx and BDS are provided below:

<https://sourceforge.net/projects/pyrx/>

<https://discover.3ds.com/discovery-studio-visualizer-download>

Note: (accessed on 23-10-2023)

2.2 How to Download and Install PyRx

i. Copy and paste the link to download PyRx in any browser, and press 'ENTER' on your keyboard.

ii. Click on 'Download' and wait for a few minutes

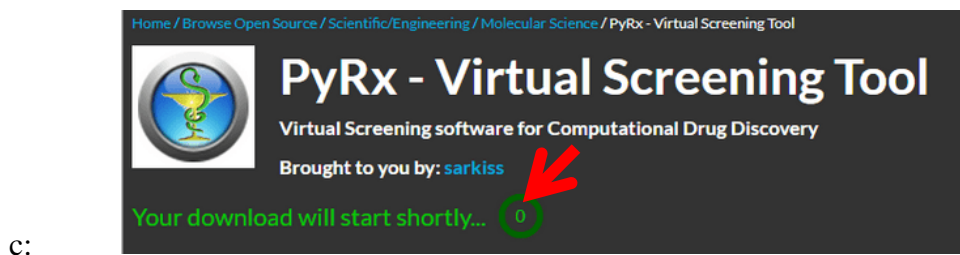
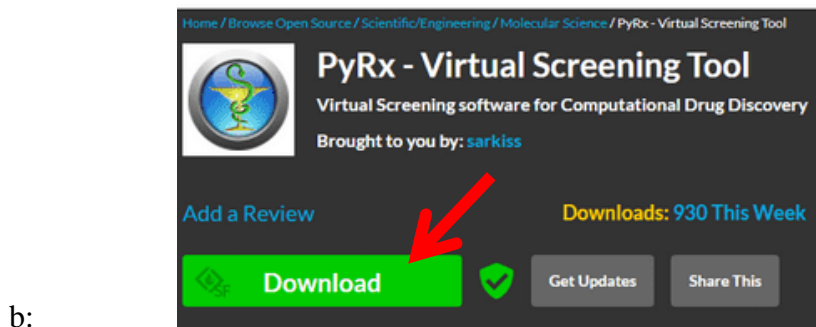
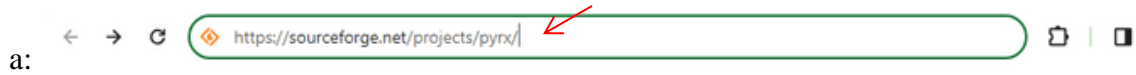
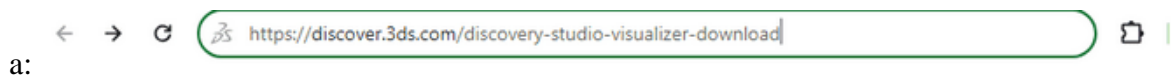


Figure 1. (a) PyRx link in the search bar. (b) Where to download PyRx. c. PyRx is downloading

2.3 How to Download and Install Biovia Discovery Studio

- i. Copy and paste the link to download Biovia Discovery Studio in any browser, and press 'ENTER' on your keyboard
- ii. Register to download and follow the instructions during registration.



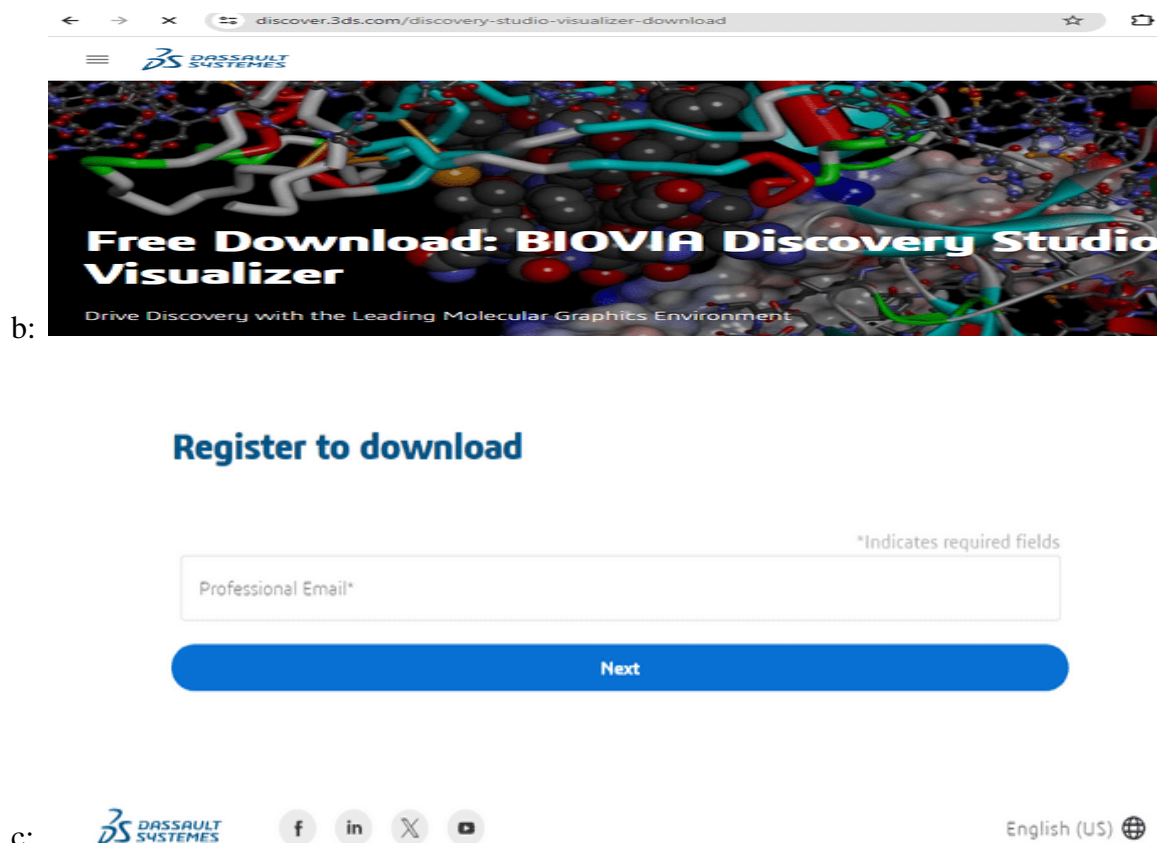


Figure 2. Biovia Discovery Studio link in the search bar. Where to download Biovia Discovery Studio
 Hint: Follow the instructions during registration, then you have it downloaded and installed into your system.



Figure 3. Windows 10 displaying PyRx and Biovia Discovery Studio icons

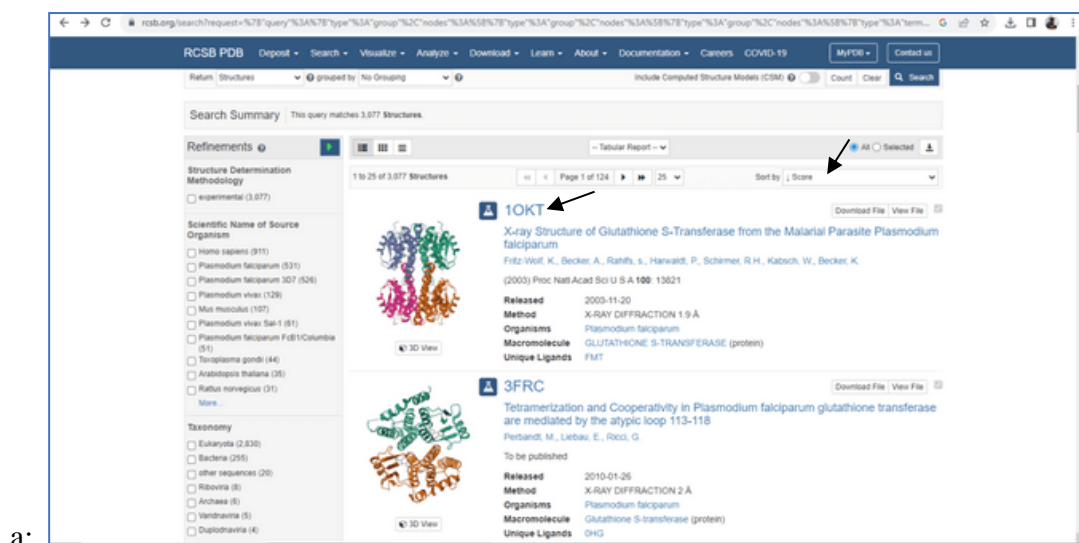
2.4 Protein of Interest (Target protein)

Protein of interest (target protein) depends on the research question you intend to answer. A fundamental knowledge from reviews of literature before selecting the protein of interest cannot be overemphasized. Target proteins in the three-dimensional structure are, in most cases, downloaded from the protein database, ‘rcsb protein data bank’ via <https://rcsb.org/>.



Figure 4. (a) RCSB PDB website display page

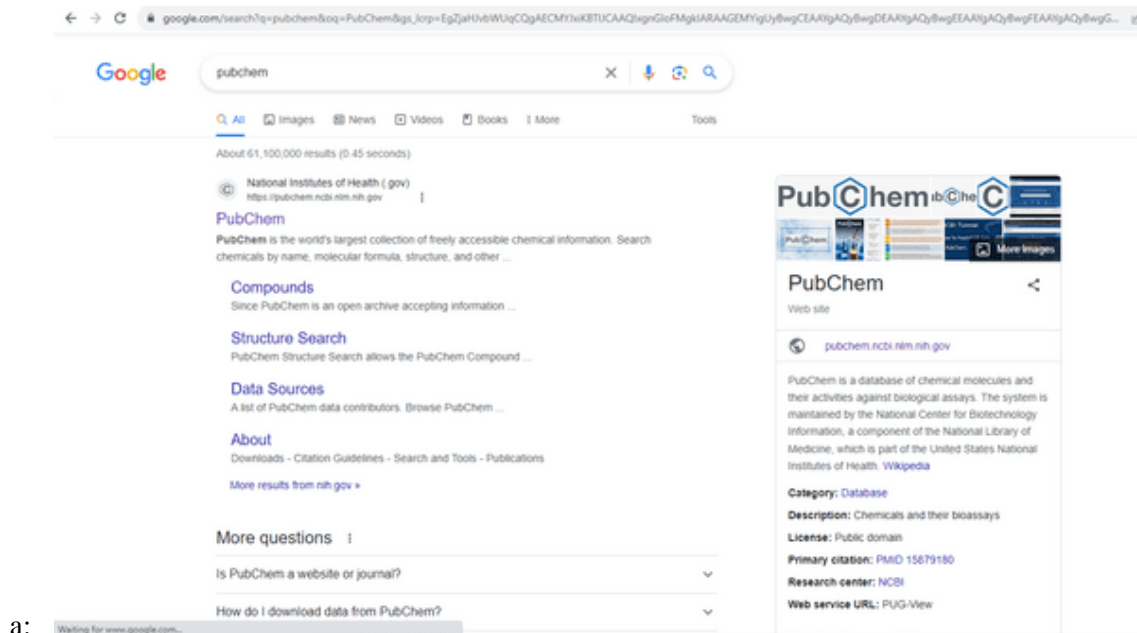
(b) Protein search display page



a:



Figure 5. (a), (b), (c). RCSB PDB display page and how to download 10KT in PDB format



a: Waiting for www.google.com...

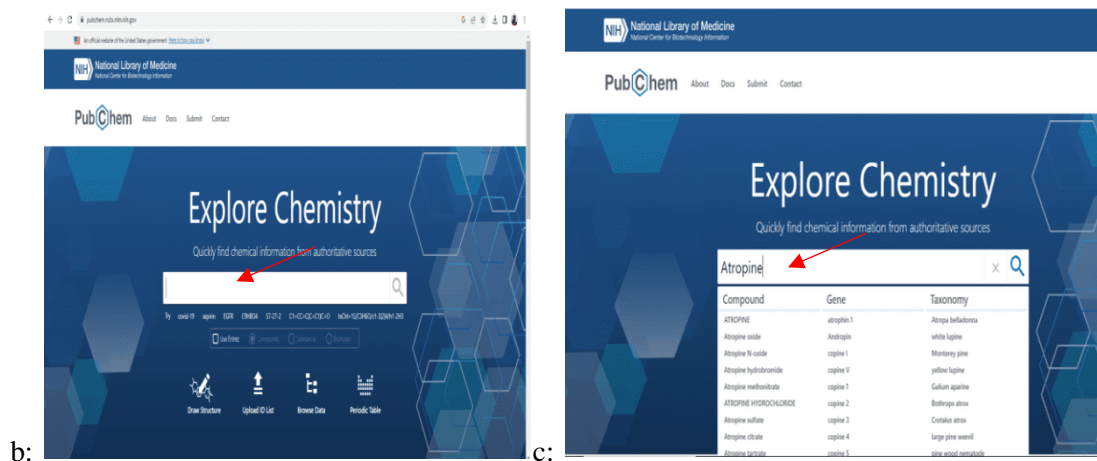
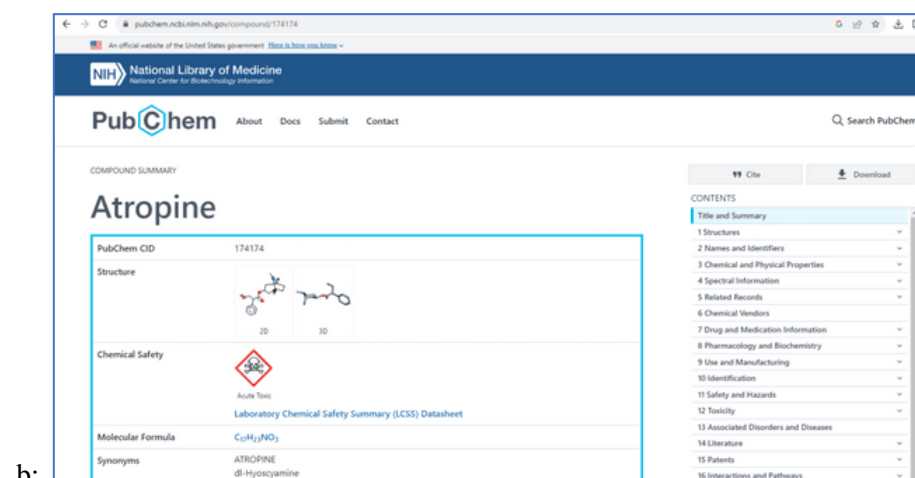
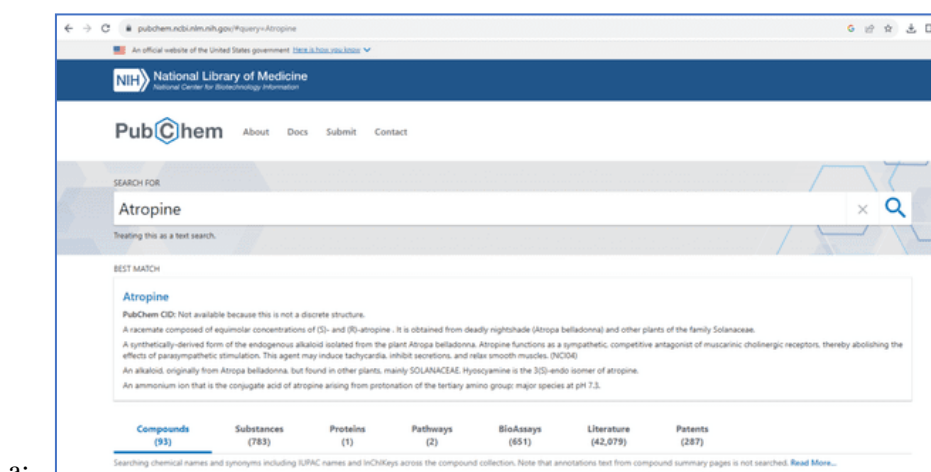
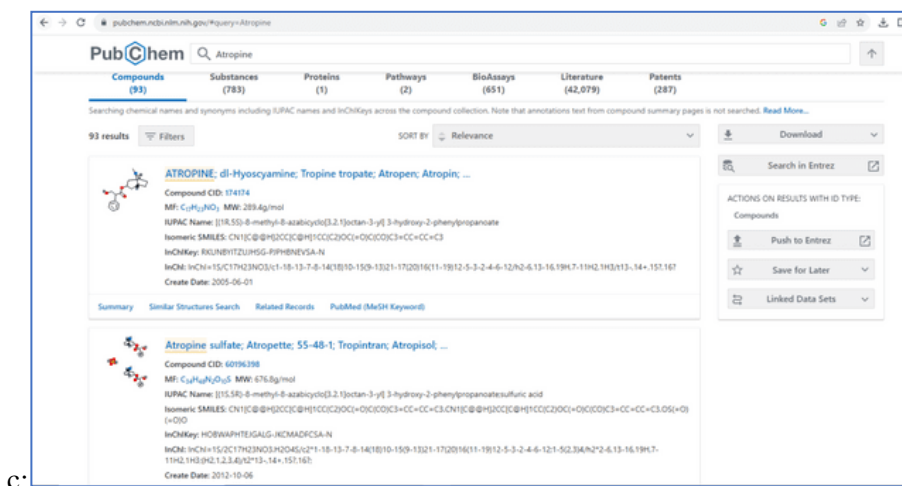


Figure 6. (a) PubChem webpage (b) Search page on PubChem (c) Atropine is searched for (as a case study).





C:

Figure 7. (a), (b), (c) Cheminformatics page of Atropine in PubChem

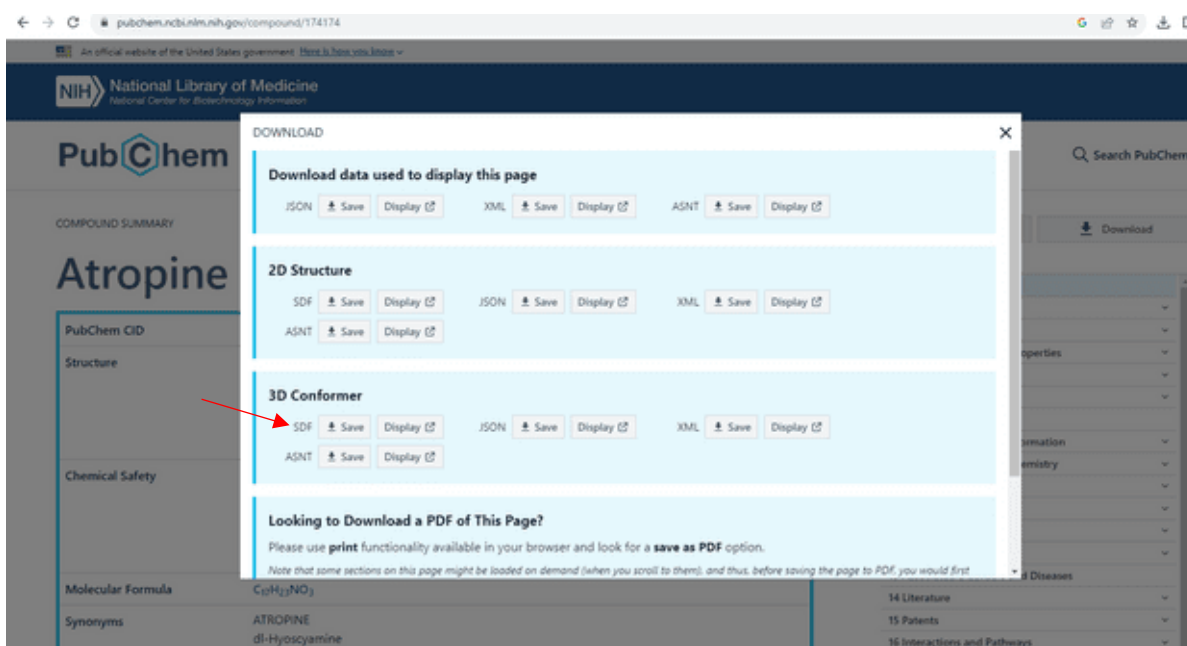


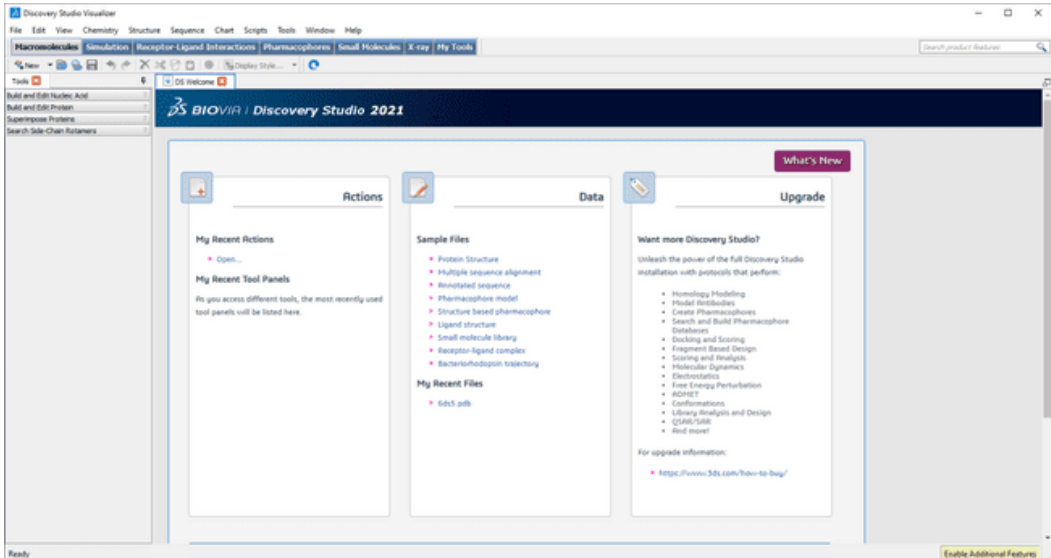
Figure 8. About to download the 3-D conformer (SDF) of Atropine in PubChem



Figure 9. 3-D conformer (SDF) of Atropine has been downloaded from PubChem



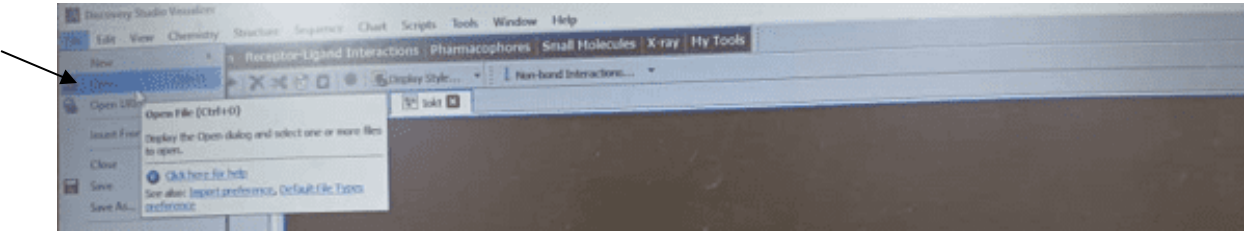
a:



b:

Figure 10. Biovia Discovery Studio Visualizer is launched.

Note: Show dropdown button image here
Hint: Click on 'File', then select 'CTRL+O' to import the downloaded protein of interest



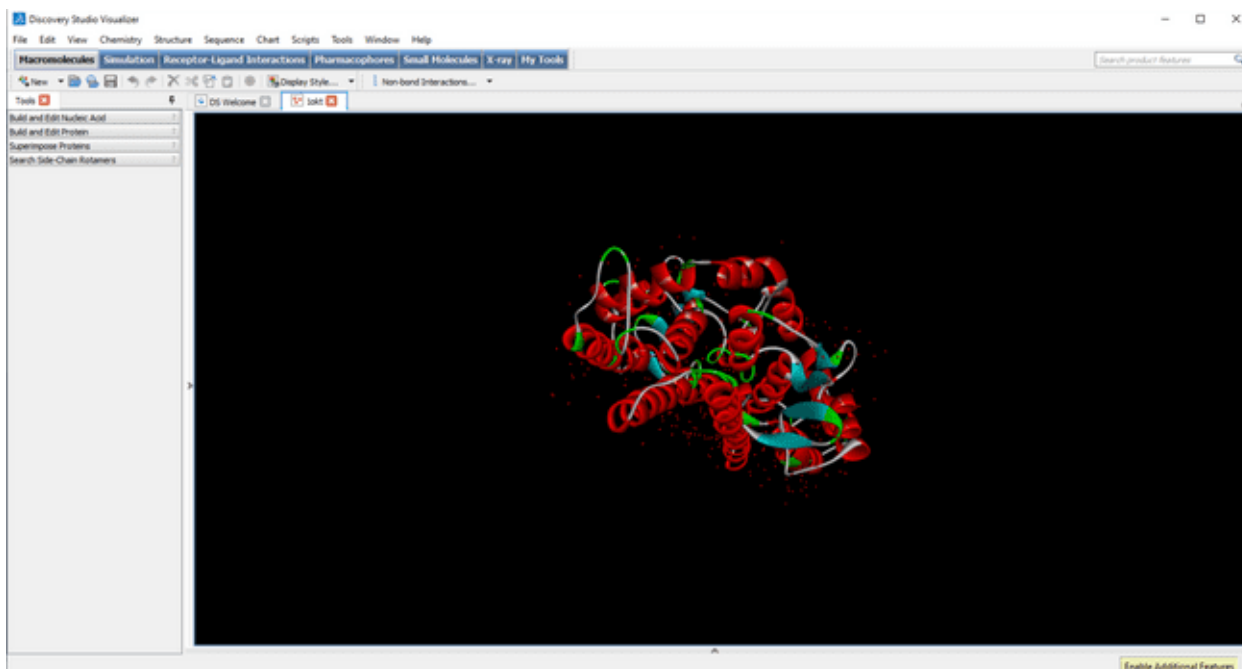
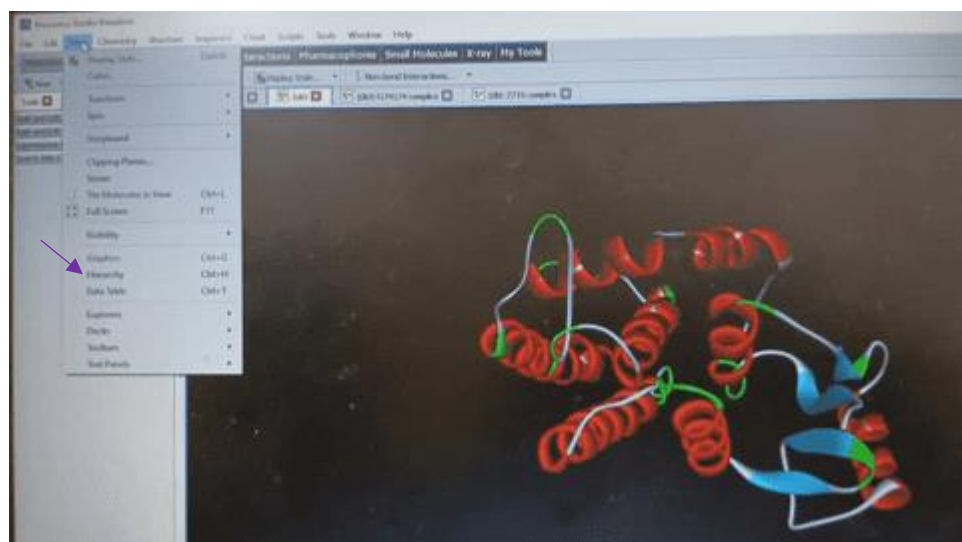


Figure 11. 10KT has been imported into Biovia Discovery Studio Visualizer.

Note: Dropdown button shows how to navigate to 'hierarchy'.

Hint: Click on 'View', then select the 'hierarchy'



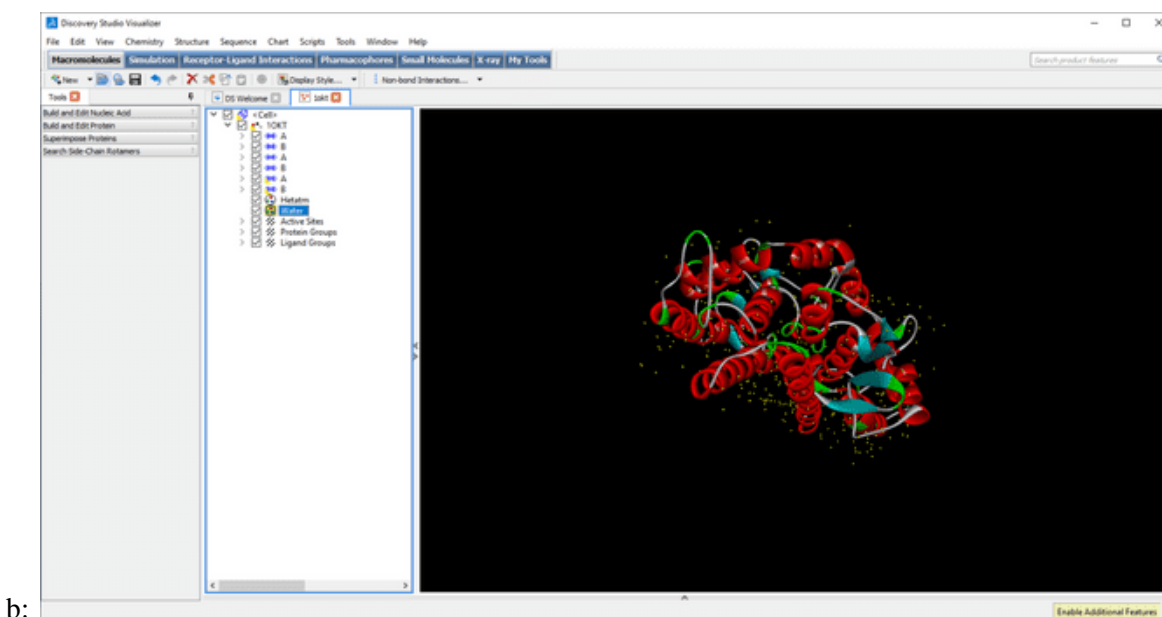
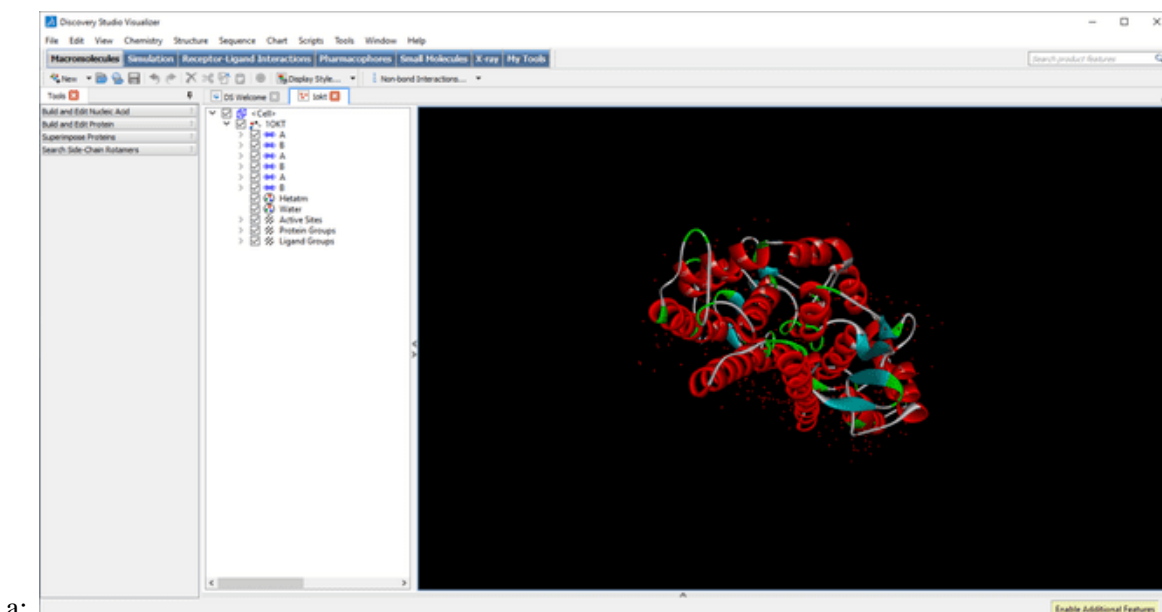
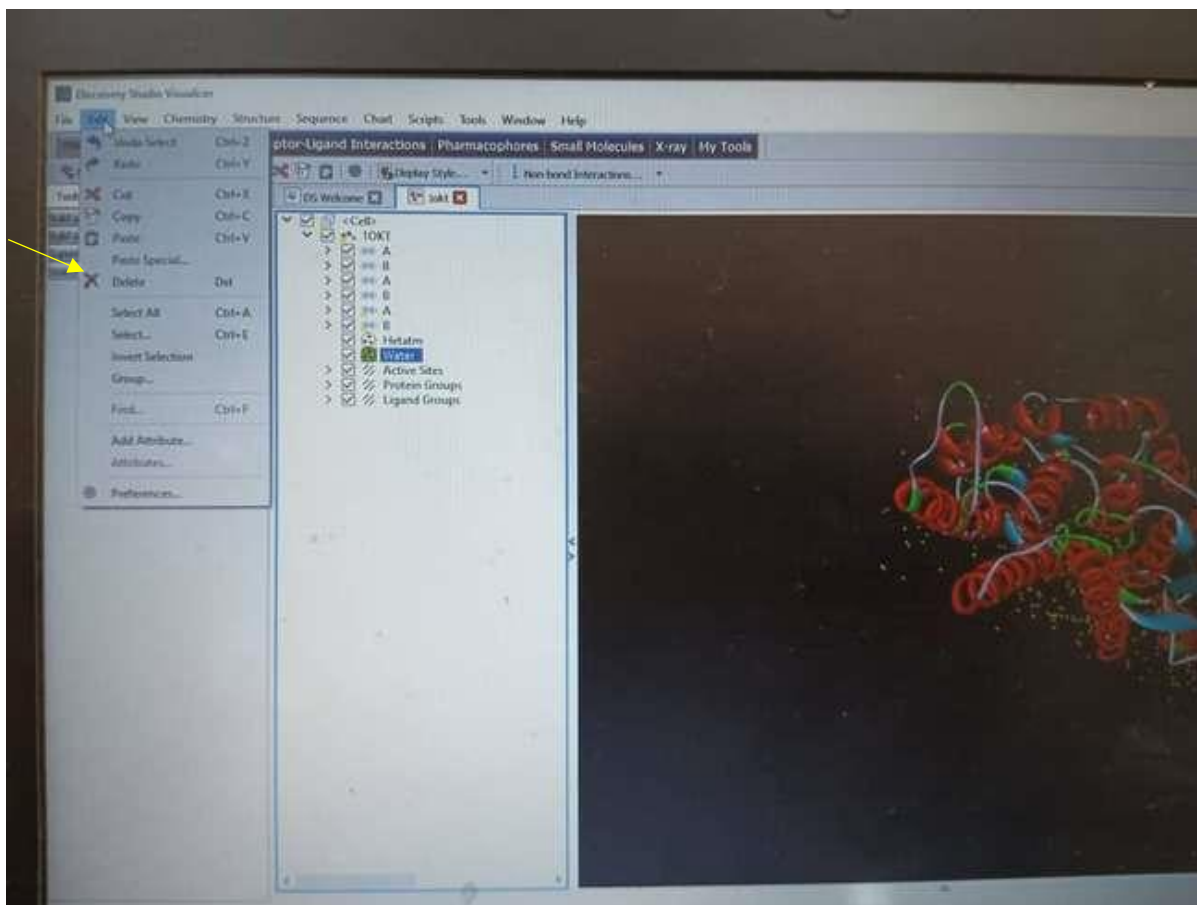
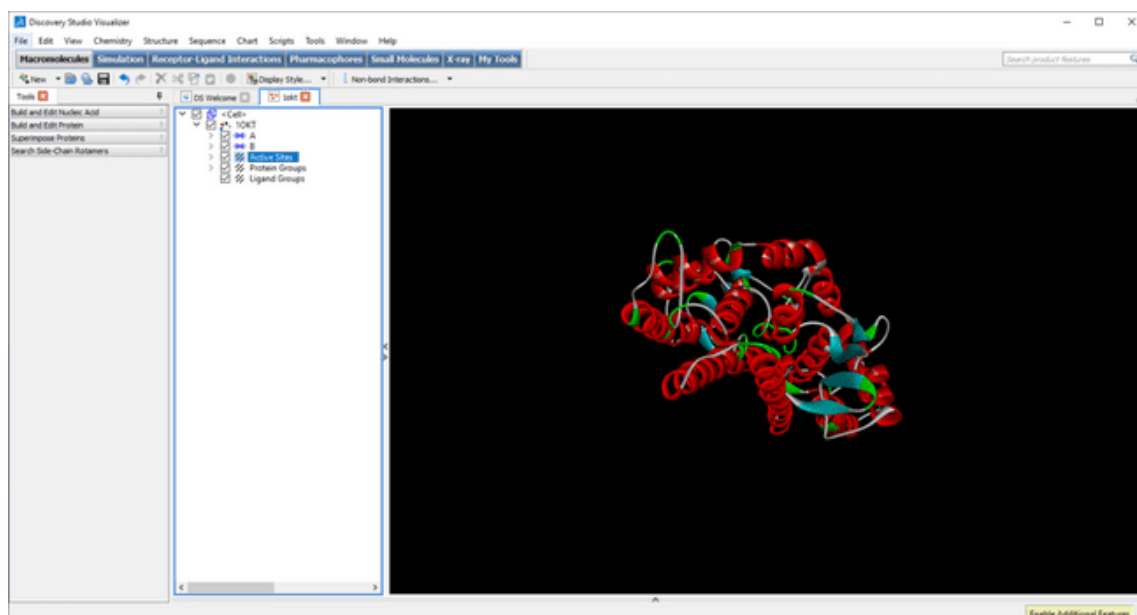


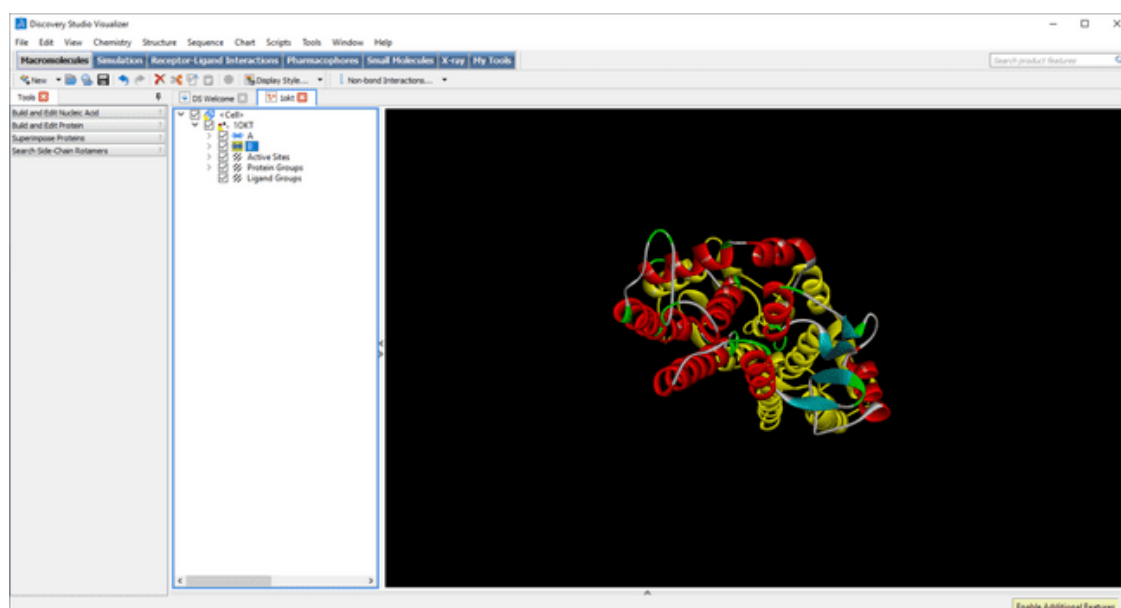
Figure 12. 10KT showing its peptide chains A, B, hetatoms, and water particles



Hint: Select 'Het-atoms' and 'water'; then select 'Delete'.



a:



b:

Figure 13. 10KT shows its chains A and B after deleting heteroatoms and water particles

Hint: Select a chain and delete it. Either chain can be deleted, but in this case, ‘Chain B’ was deleted.

Note: Only one protein chain should be used.



Figure 14. (a) 10KT shows its chains A after chain B has been deleted

Note: Click on ‘Chemistry’, navigate to ‘Hydrogen’, then select ‘Add Polar’

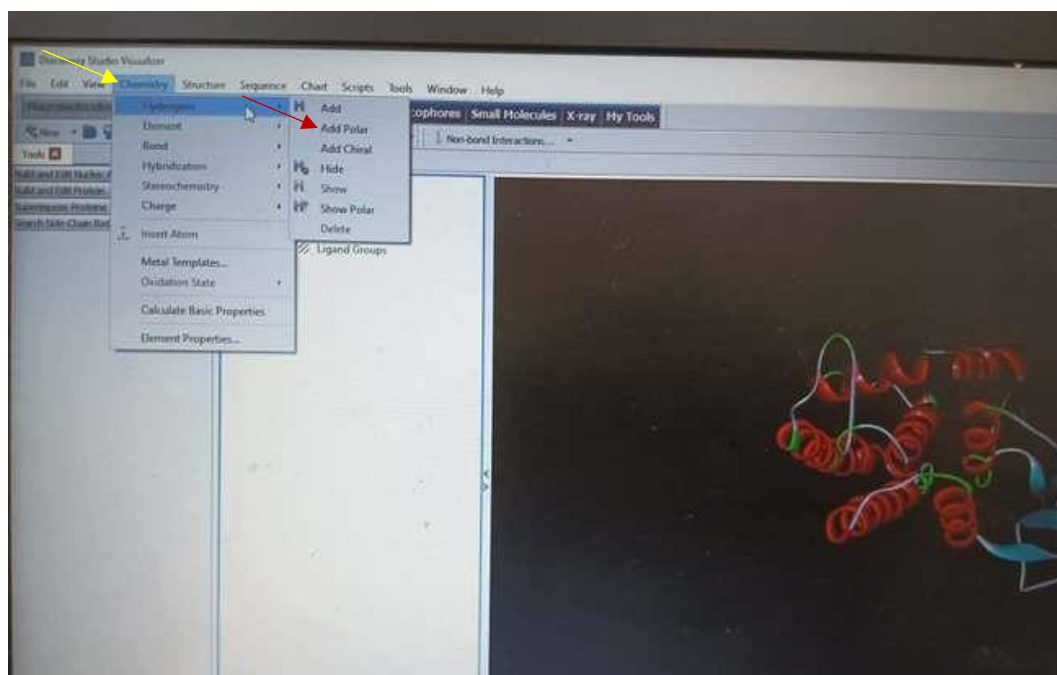


Figure 14 (b). Indicates the need to add polar hydrogen

Hint: Having done preparing the protein, save it by navigating to 'File' and select 'Save'.

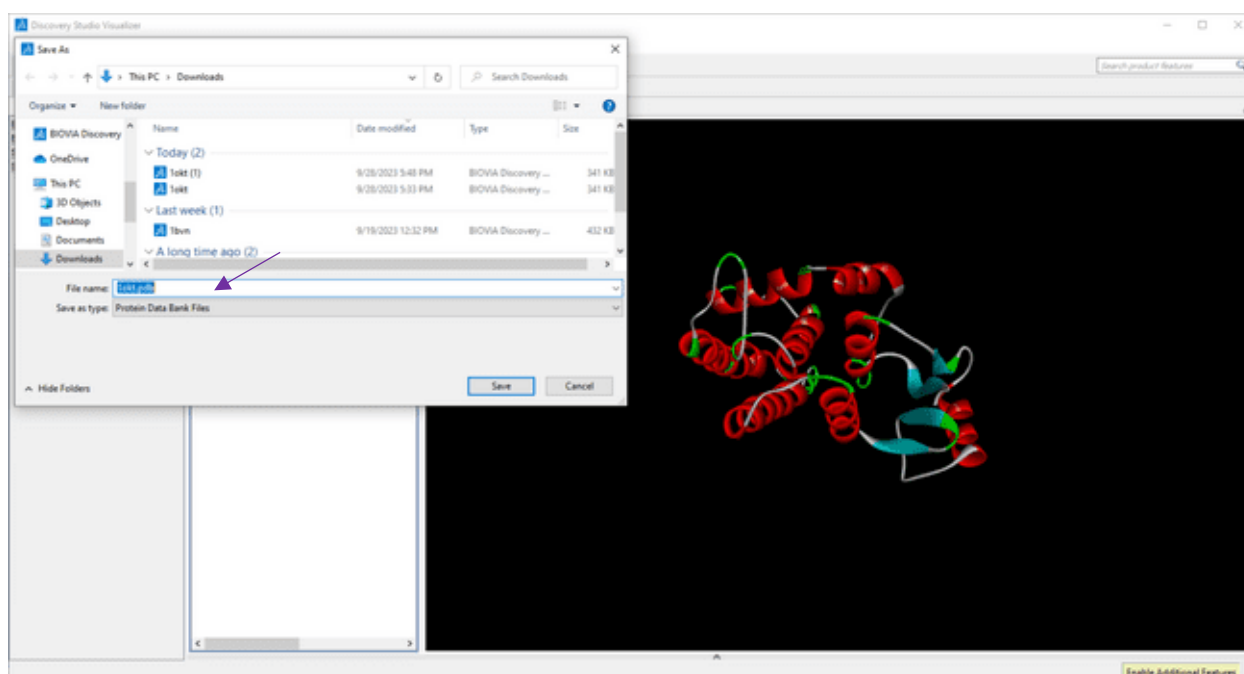
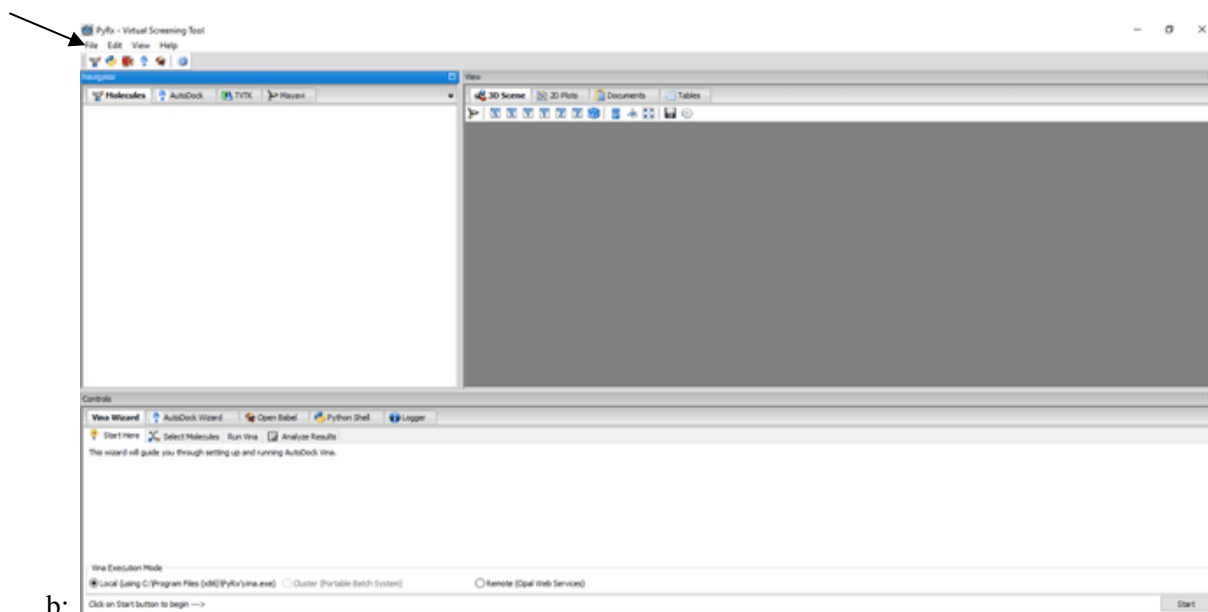


Figure 15. 10KT is saved as a protein data bank file and renamed as 10KT.pdb

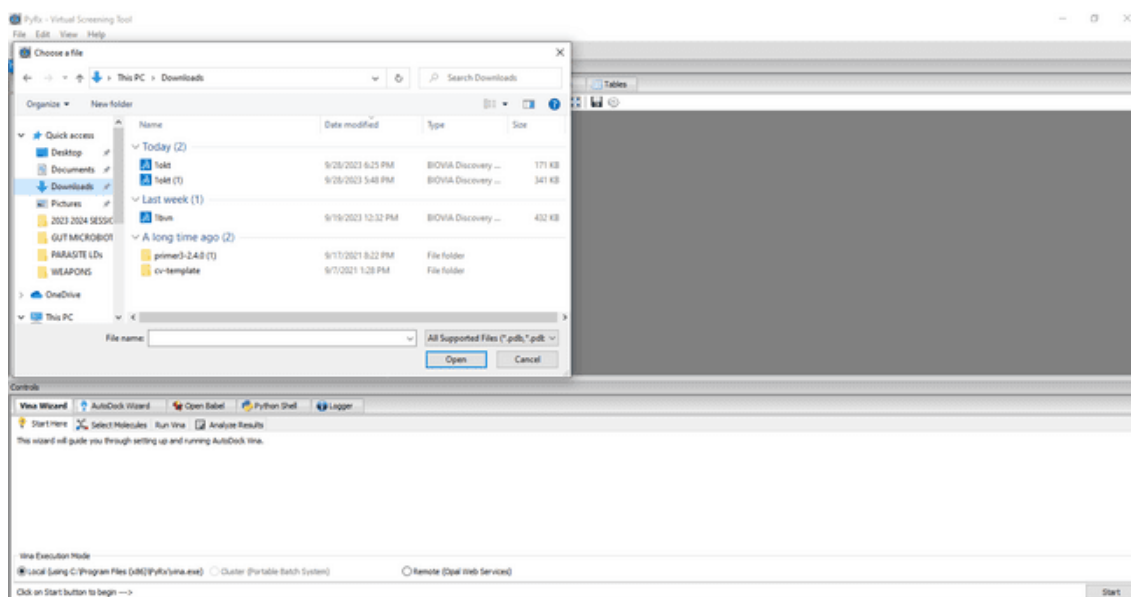


a:



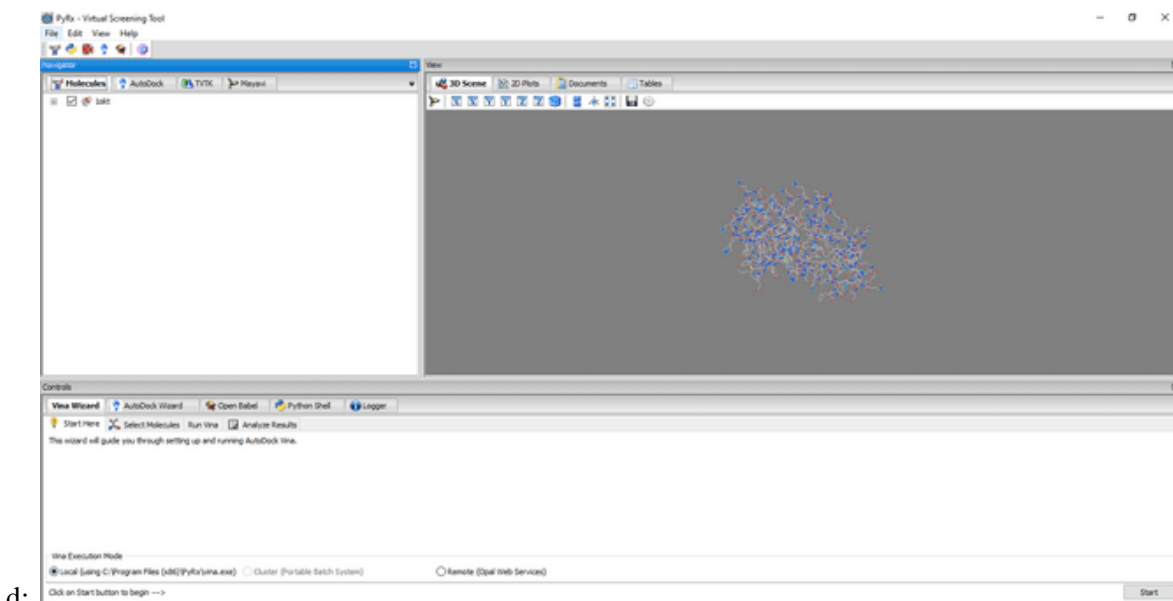
b:

Hint: Click on 'File' to import 10KT.pdb into PyRx

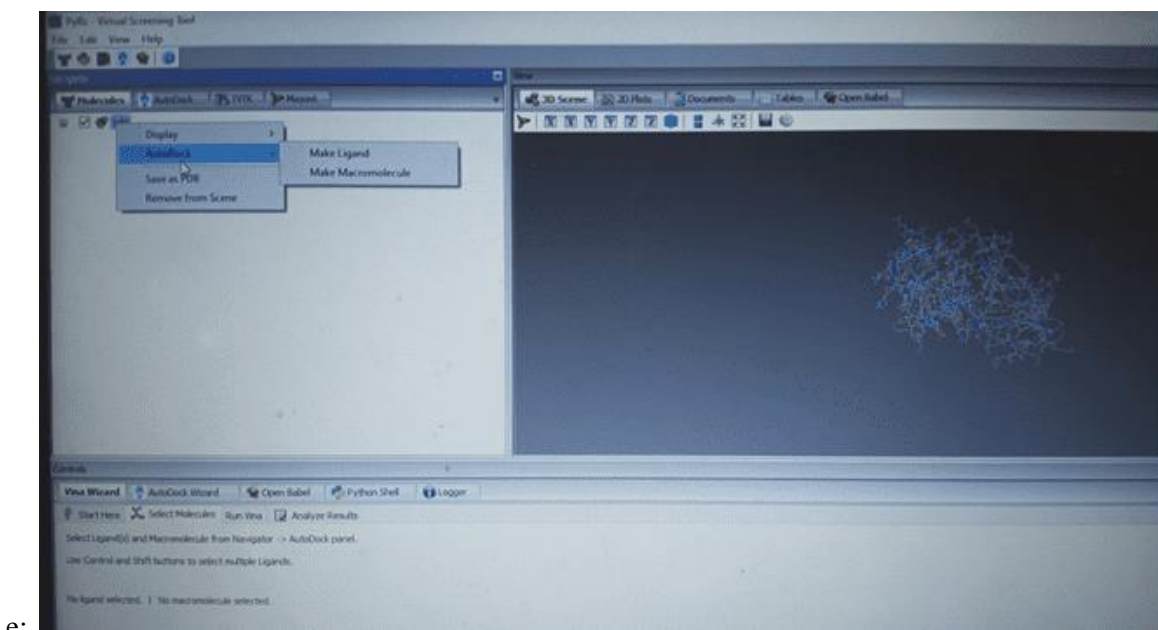


c:

Note: Uploading 10KT to PyRx

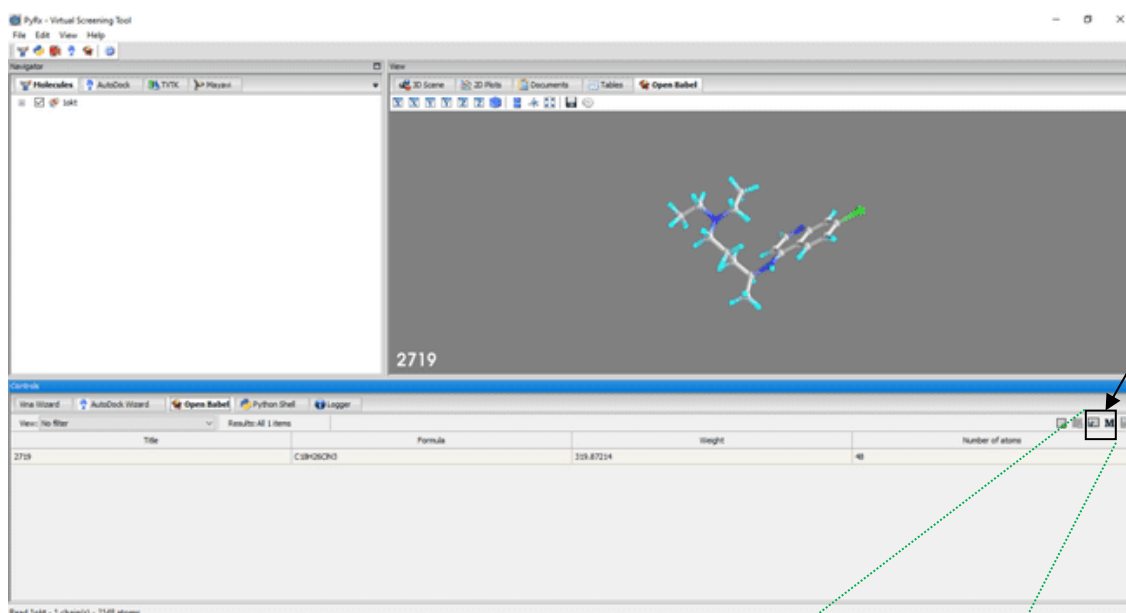


Hint: Right-click and select 'AutoDock', then navigate to 'Make Macromolecule'.

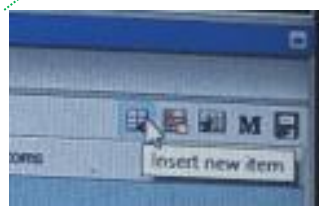


Note: The 10KT is automatically saved in pdbqt format

Figure16. (a) Launching page of PyRx (b) How to import 10KT to PyRx (c) Uploading 10KT to PyRx (d) How to convert 10KT to a macromolecule (e) Saving 10KT in pdbqt format



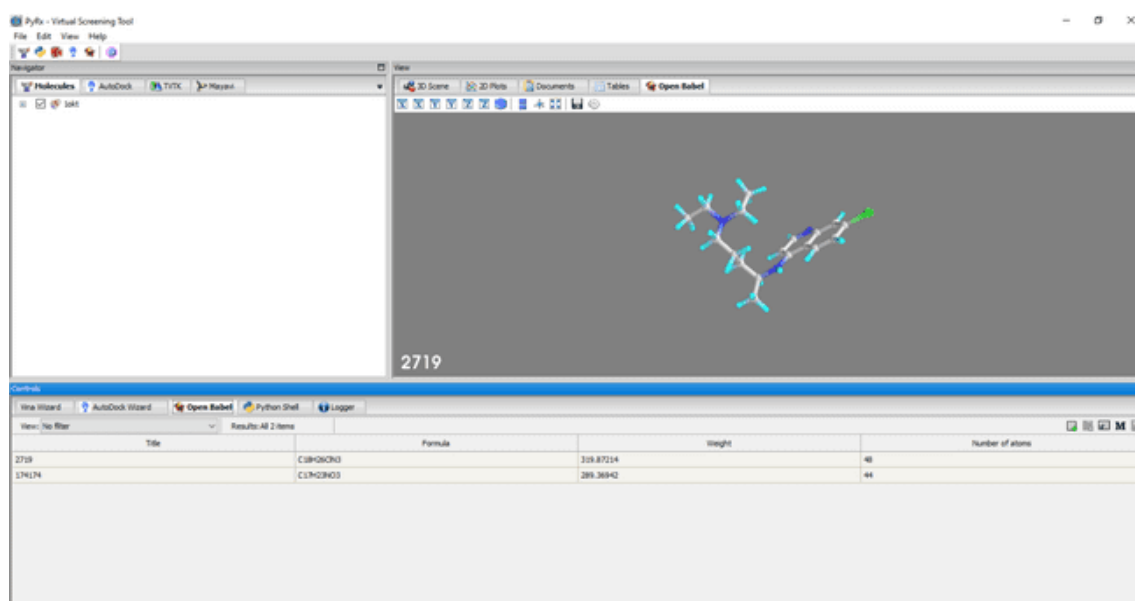
a: Read left - 1 chain(s) - 2148 atoms



Click on 'Open Babel' and select 'Insert new item'

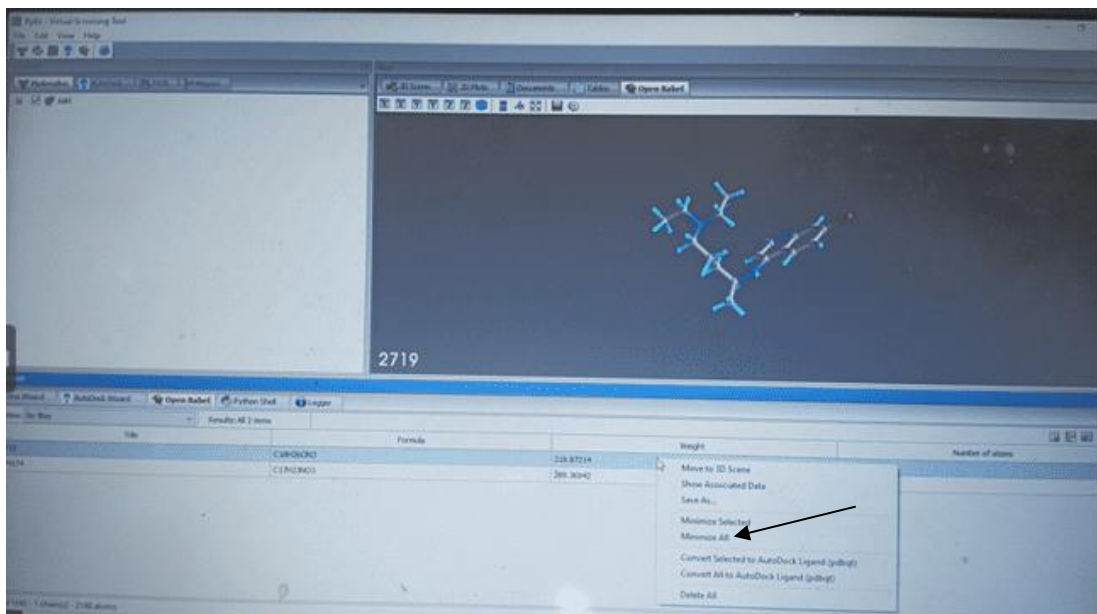
to import the downloaded ligands (from PubChem).

Note: Only one ligand can be imported at a time, so import others one after the other



b:

Right-click and select 'Minimize All'.

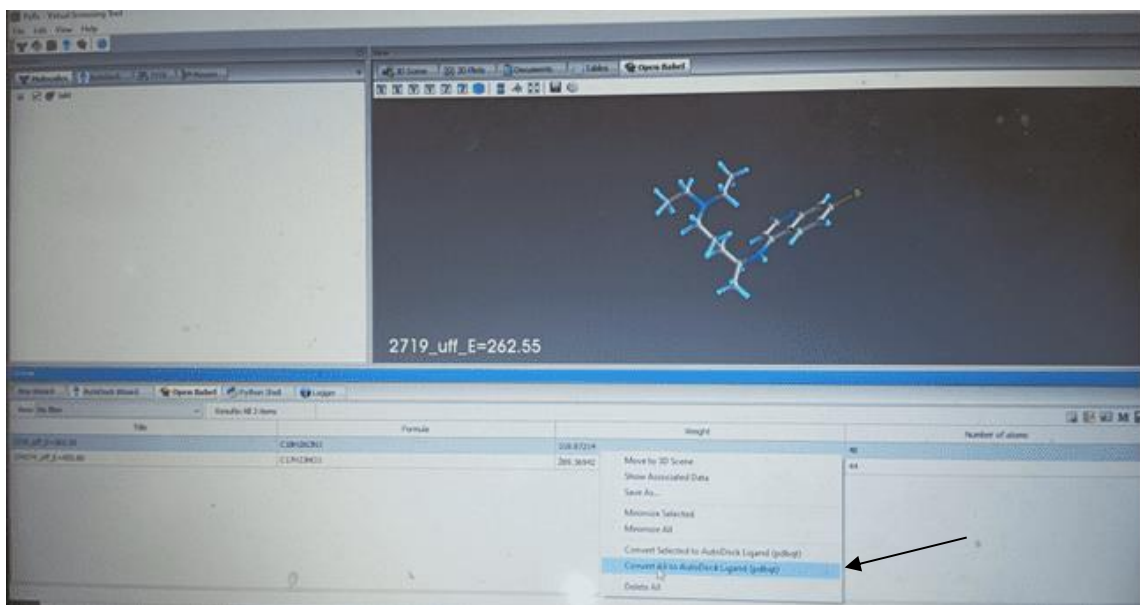


c:

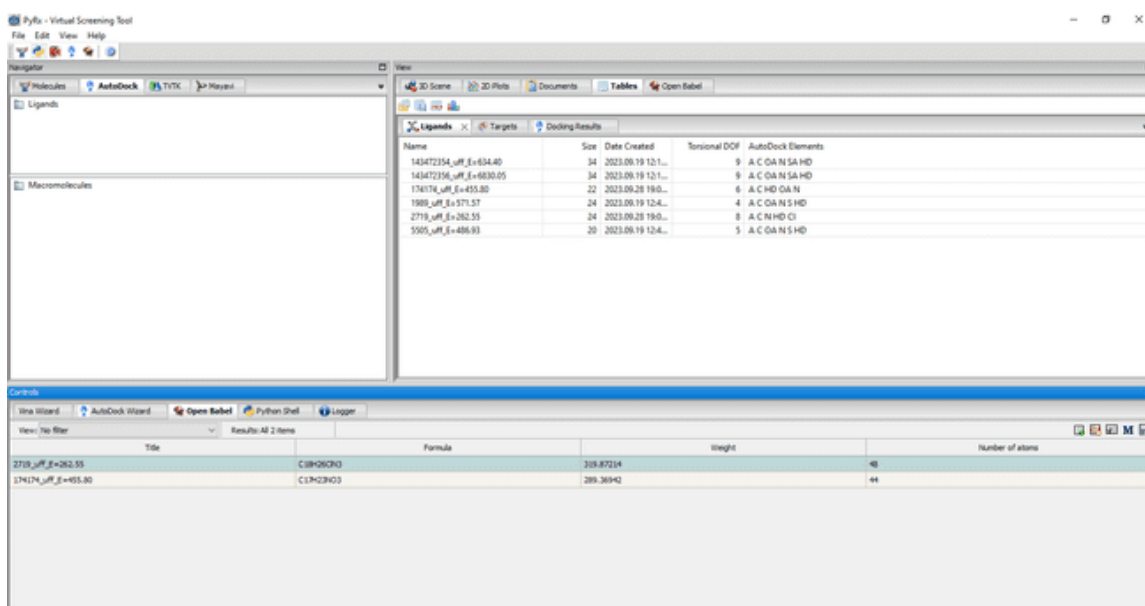


d:

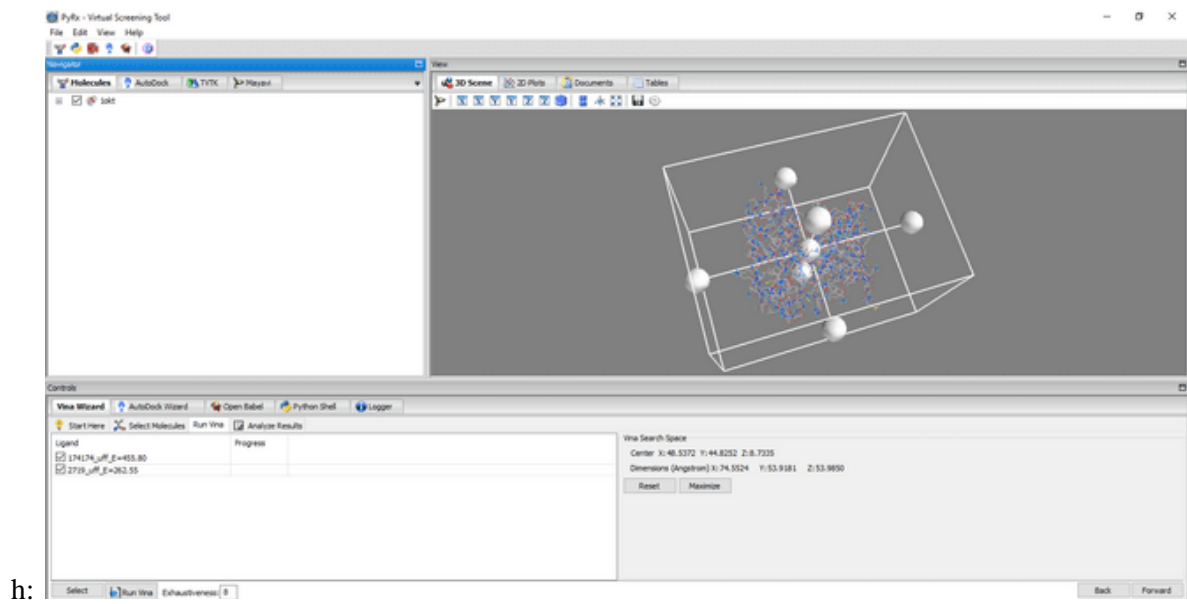
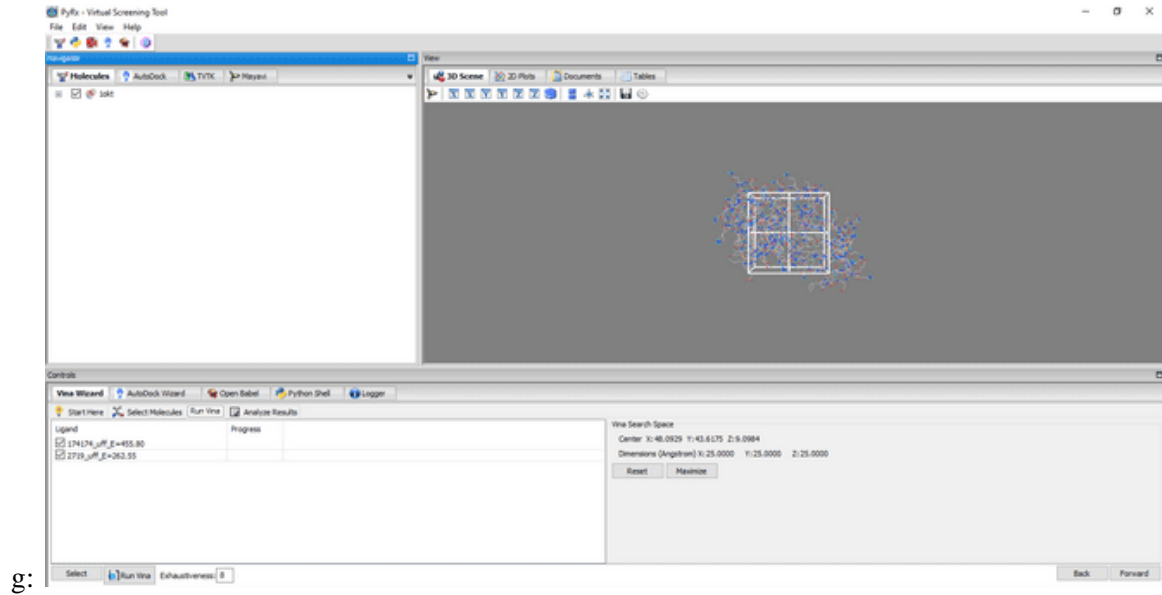
Hint: Right-click and select 'Convert all to AutoDock ligand (pdbqt).'

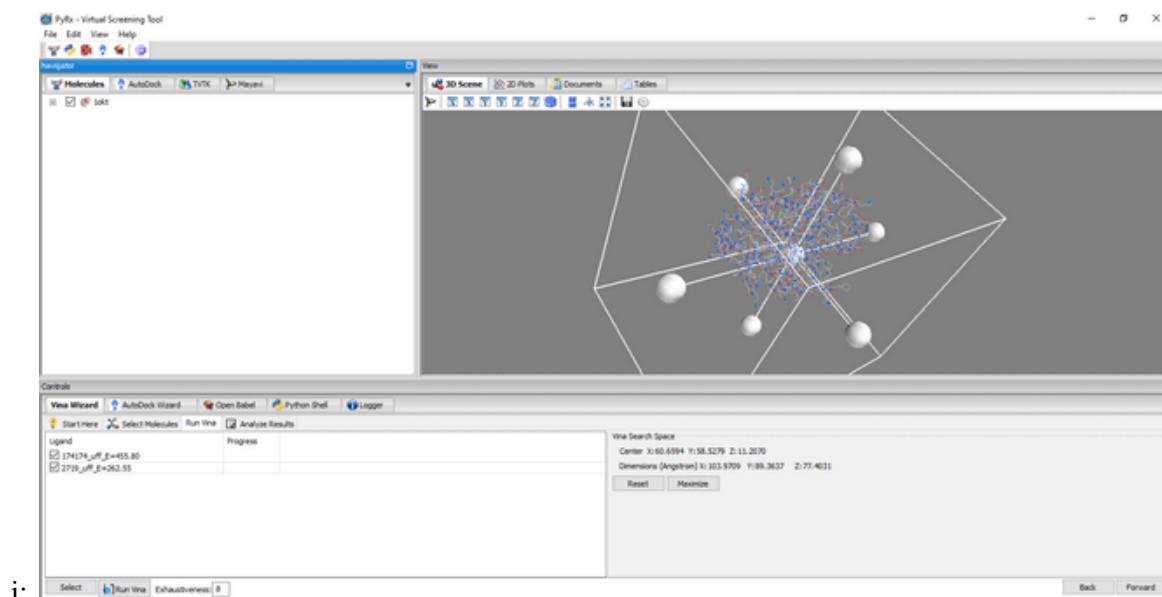


e:



f:

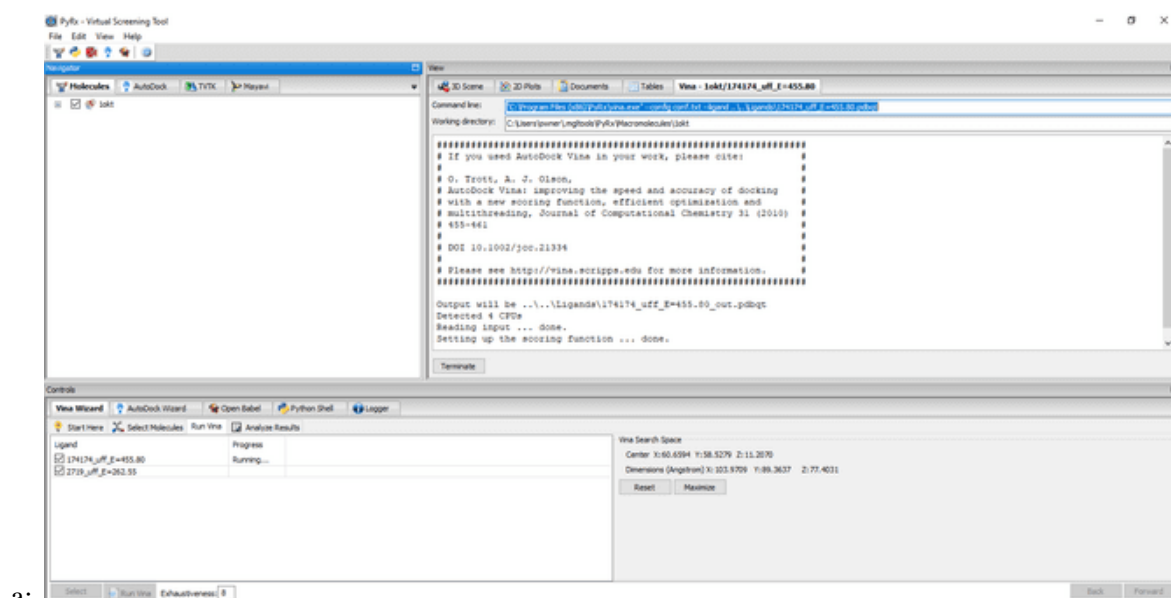




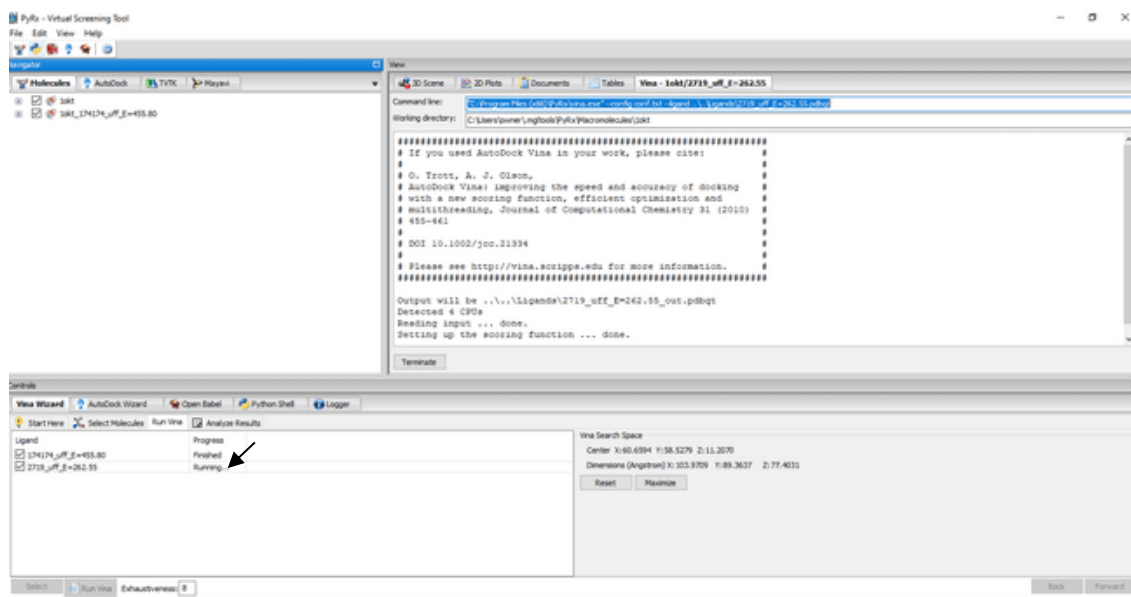
i:

Figure 17. Setting the grid box coordinates. (a) Inserting ligands. (b) Two ligands have already been inserted. (c) Reducing the energy field (UFF) of the inserted ligands. (d) Image after UFF of the ligands has been minimized. (e) Converting ligands to pdbqt format. (f) Ligands in AutoDock format. (g) Setting up a grid box for 10KT. (h) Adjust the grid box until 10KT is completely positioned within the grid box when viewed from all sides. (i) Image indicating the appropriate coordination or positioning of 10KT within grid box.

Note: Having achieved a relatively accurate positioning for 10KT within the grid box, then click on ‘Forward’ to initiate docking analysis



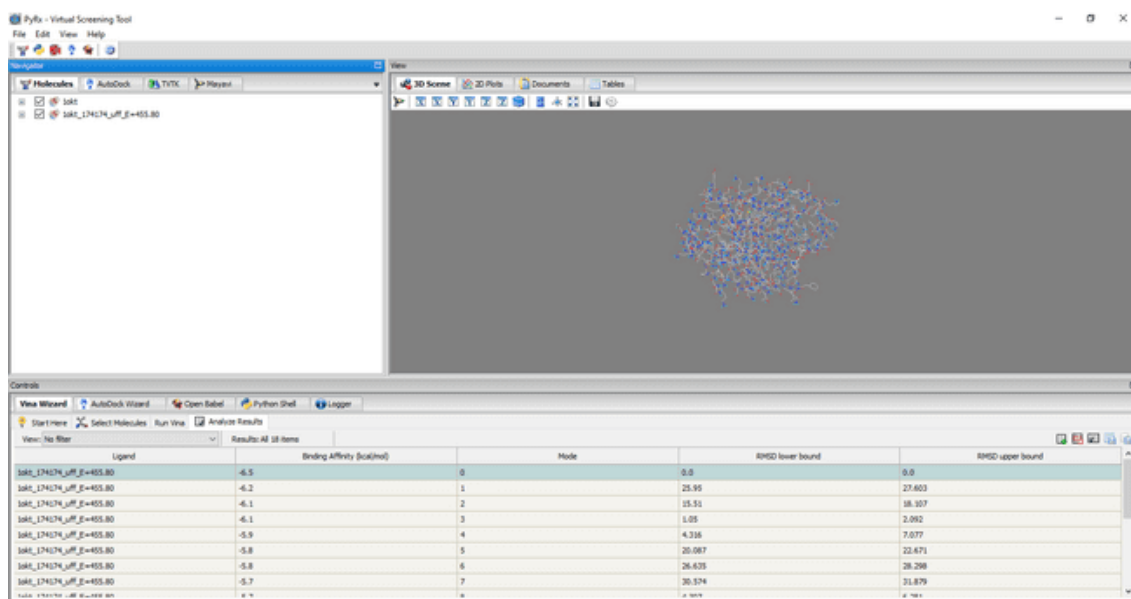
a:



b:

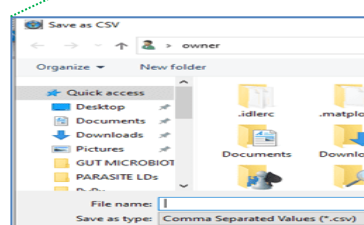
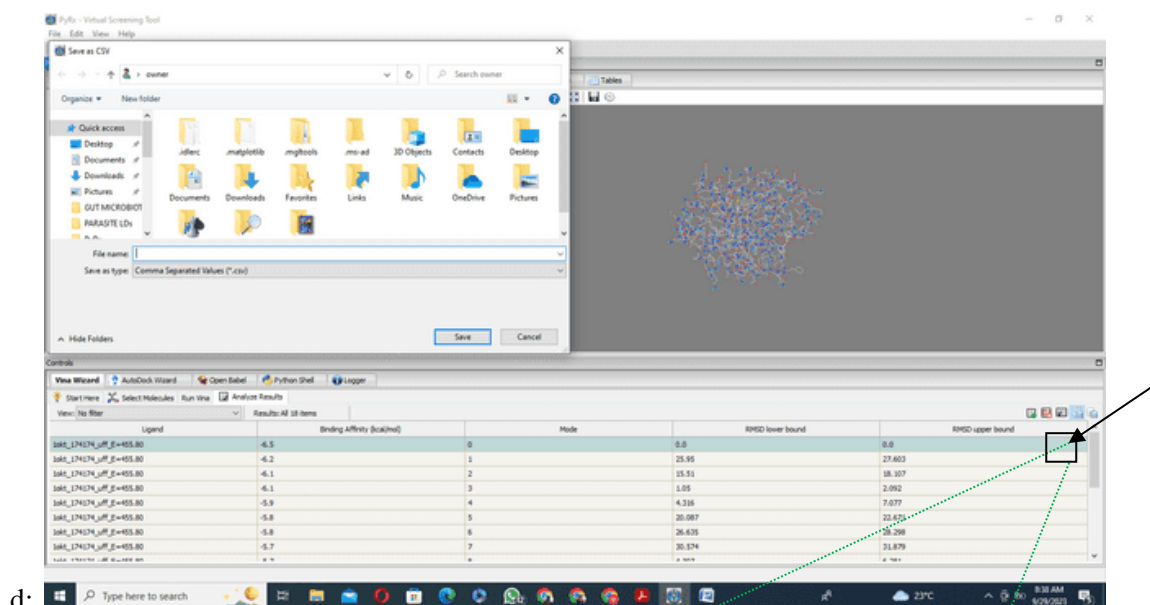
Docking is in progress

Note: Please wait patiently until the docking indicates ‘finished’ for all the ligands.



c:

Note: Click on ‘Comma Separated Value’ as indicated by the arrow in Fig. d below:



e:



Hint: This will automatically save the docking scores in an Excel file, as shown below.

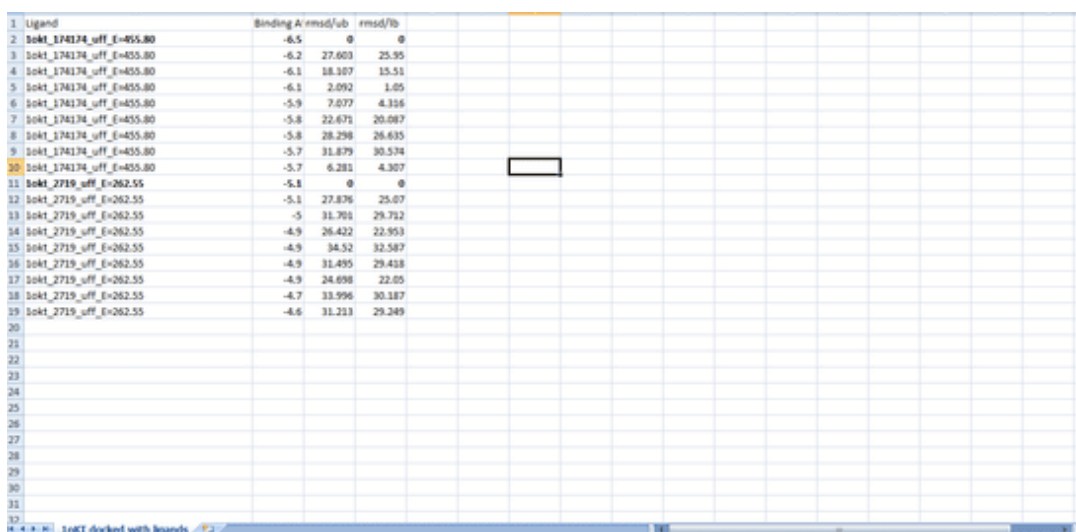
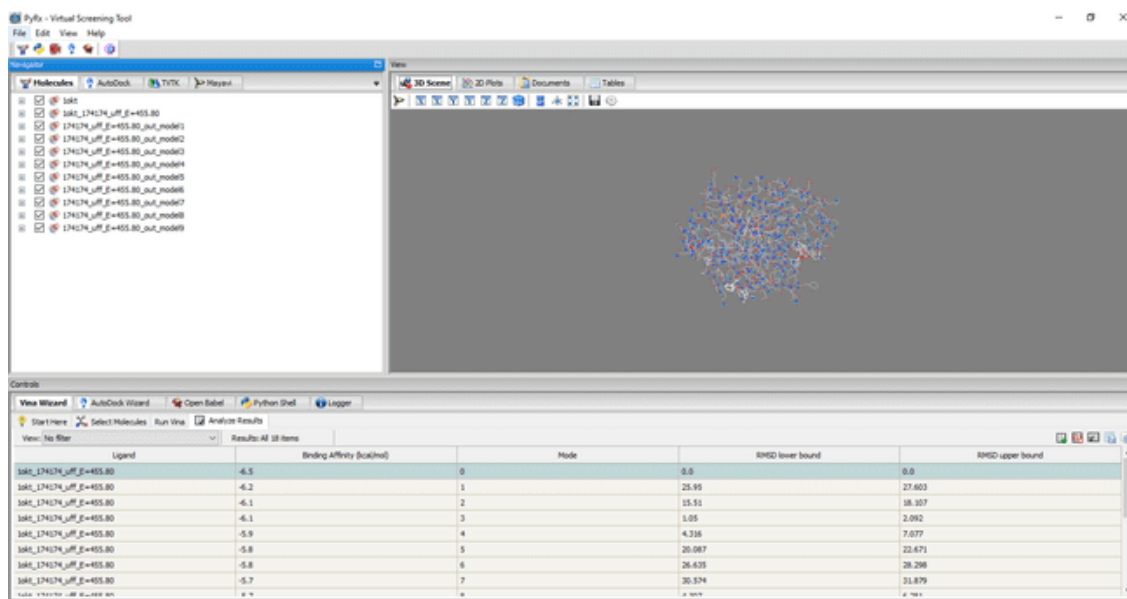
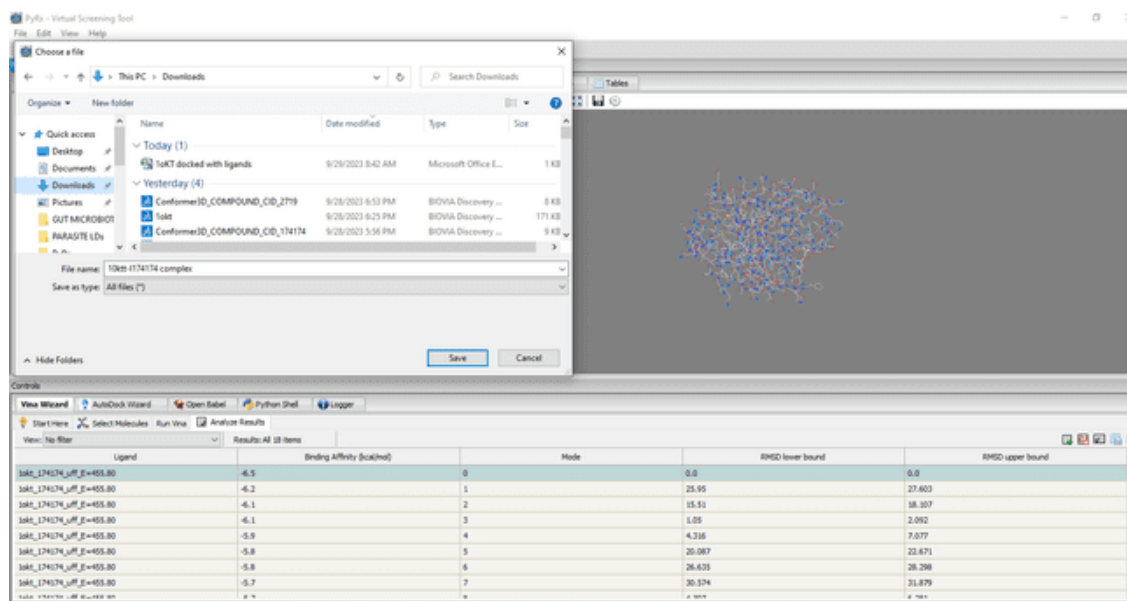


Figure 18. Docking scores are generated and saved (10k1 docked with ligands)



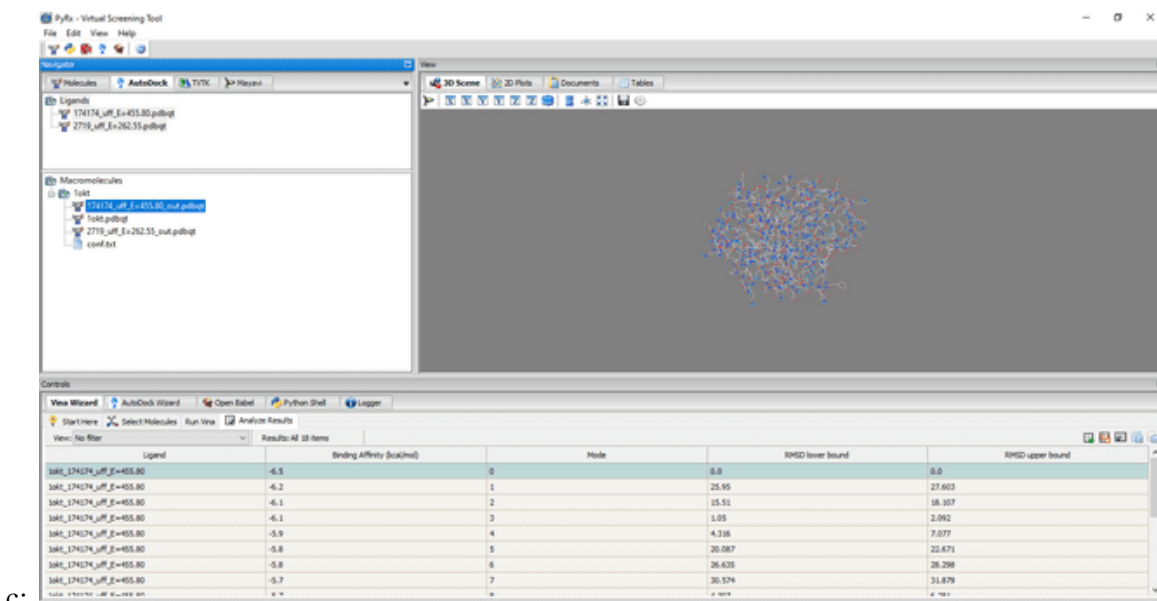
a:

Hint: Locate models of the interaction scores



b:

Note: Right-click on the identified structure with the lowest binding score and navigate to ‘Save as PDB’.



C:

Note: Repeat the same procedure above for other ligand(s)

Figure 19. Identification of interactions with the lowest binding score

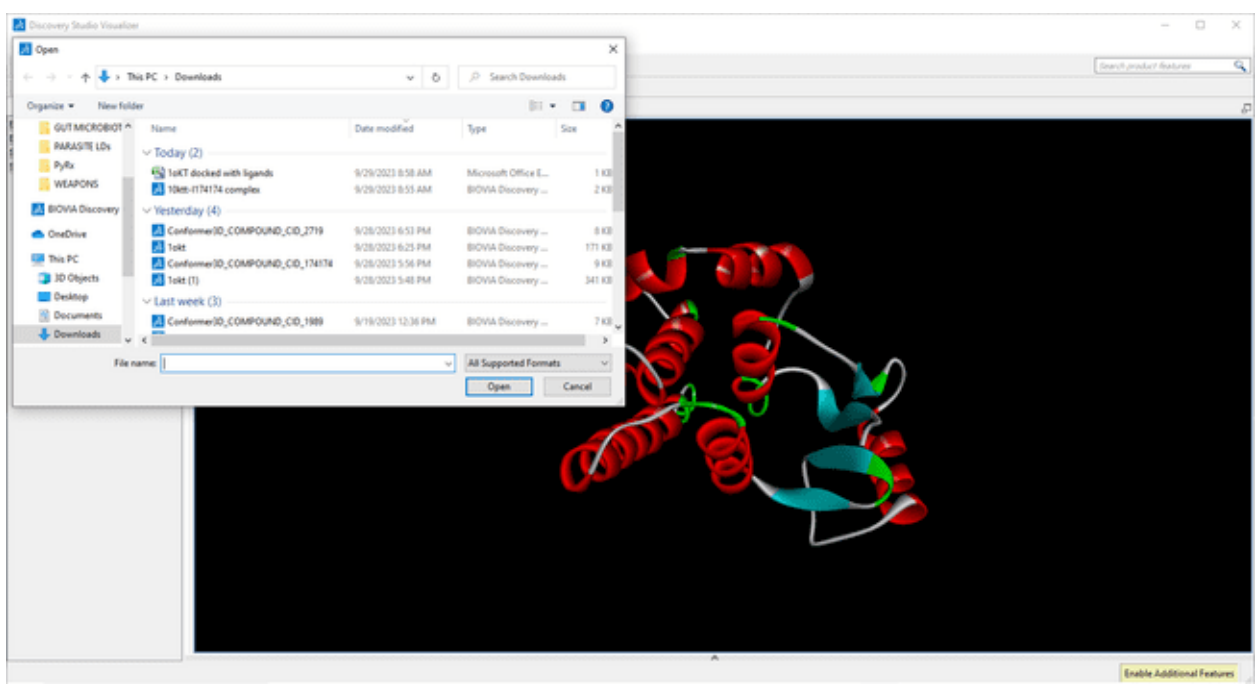
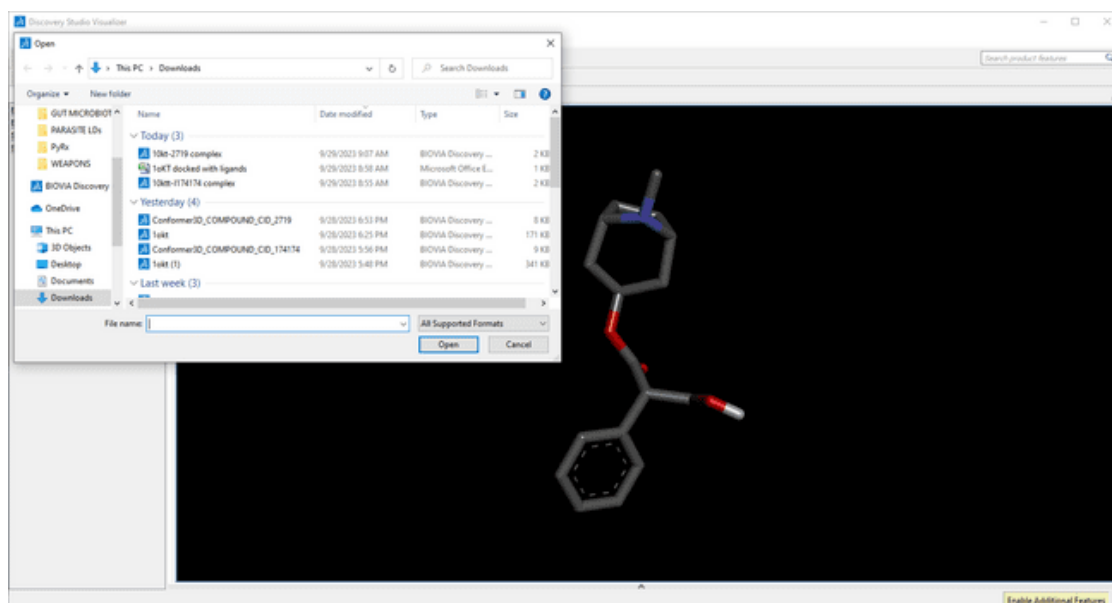
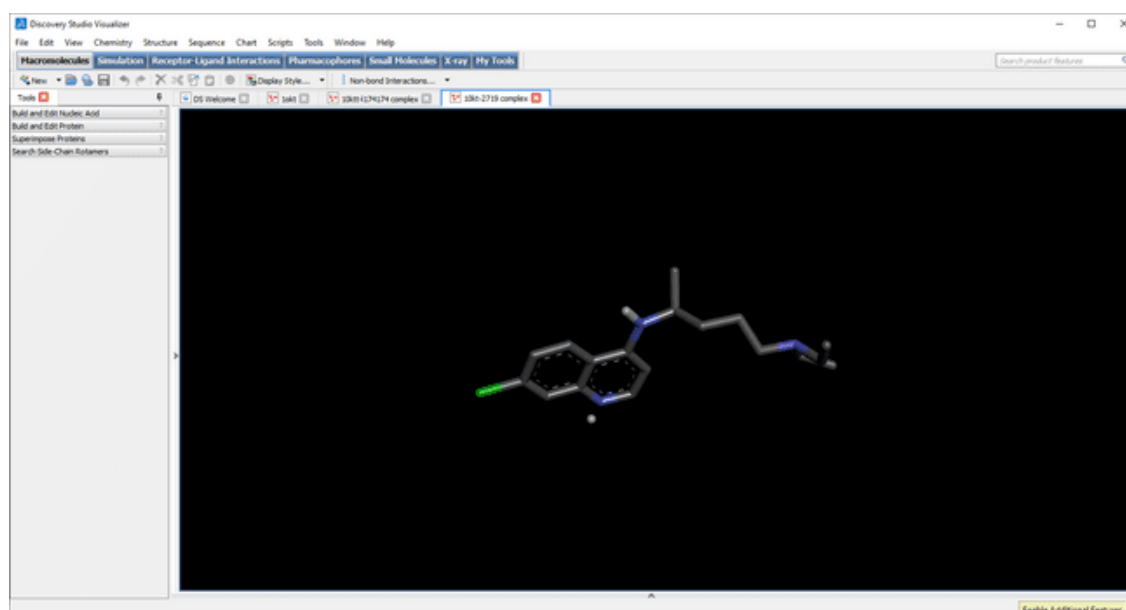


Figure 20: Importing the prepared 10KT and the docked ligands to Biovia Discovery Studio

Note: The 10KT will still be on the Biovia Discovery Studio if you do not close the Biovia Studio earlier.

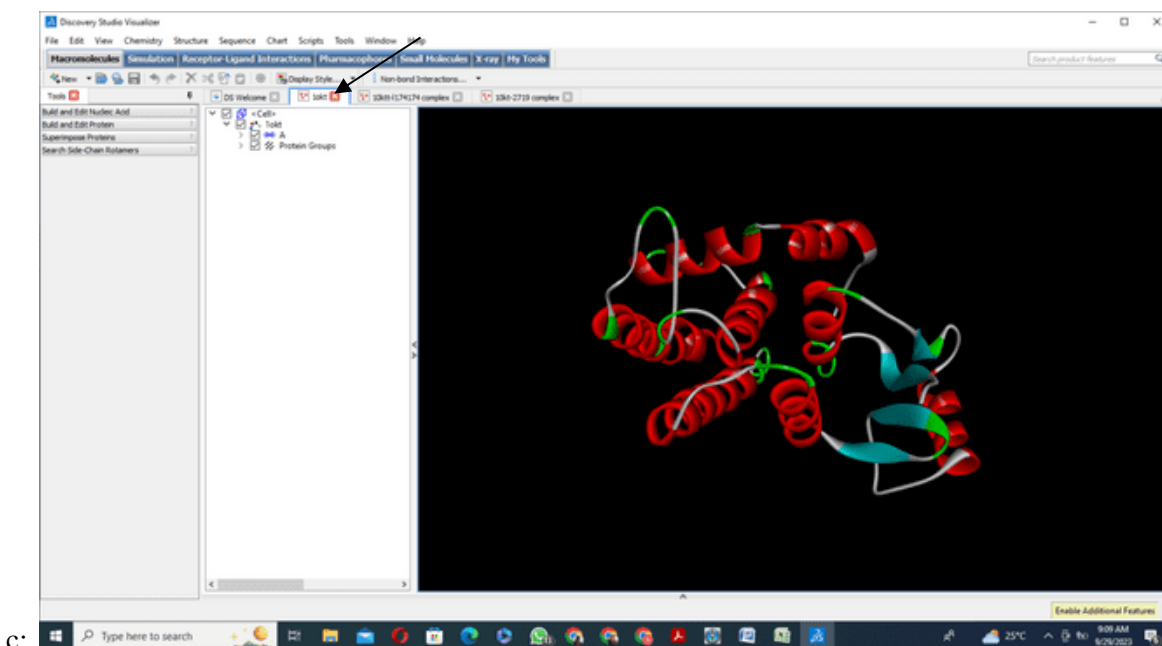


a:

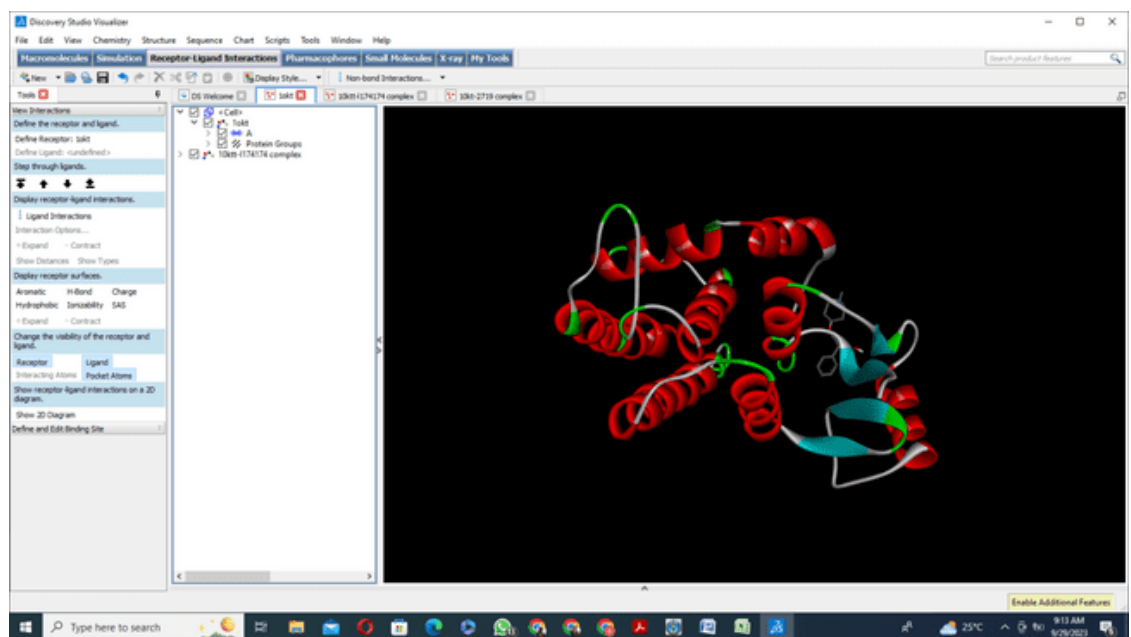


b:

Note: Click on 'View' and navigate to 'Hierarchy'. Right-click on the docked ligand, select 'Copy' to copy the docked ligand, then paste it in 'Hierarchy' of 10KT or your protein which is directly beside 'DSWelcome' as shown below:



c:



d:

Figure 21. (a), (b), (c), (d) How to copy and paste docked ligands into the hierarchy of 10KT or protein of interest

Hint: Select the ligand to define it

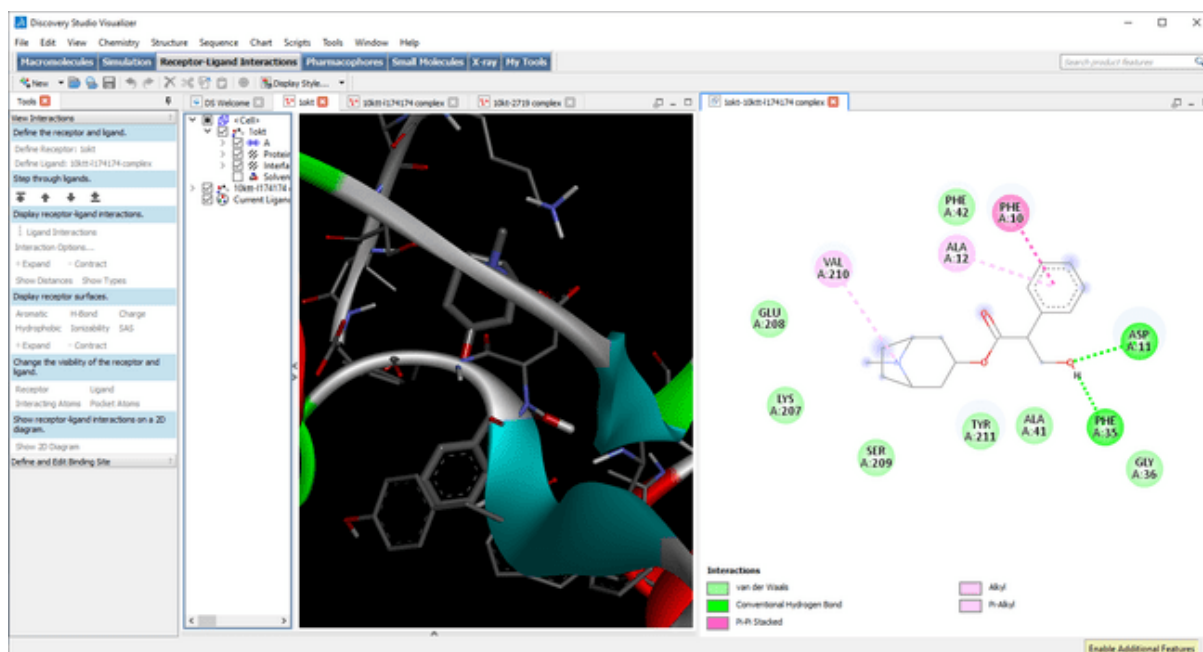


Figure 22. Defining 10Kt-Atropine (receptor-ligand) interaction

Note; 2-D and 3-D conformers of the 10KT-Atropine complex displaying the amino acid residues involved in the interaction.

Hint: 2-D conformer on the right-hand side and 3-D conformer on the left-hand side.

Copy both separately and paste them into a document or PowerPoint for presentation, as shown below:

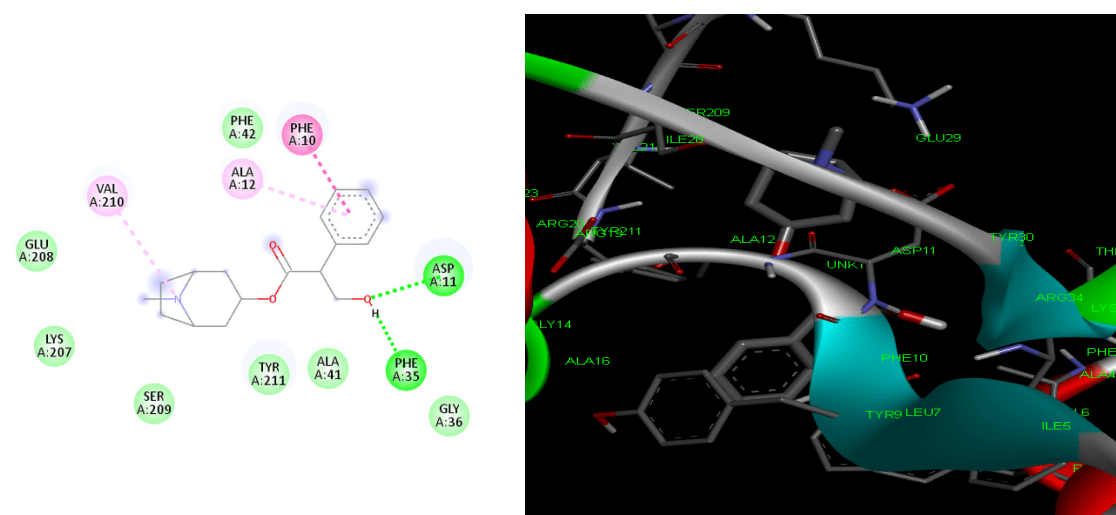


Figure 23. Extracted images of the 2D and 3D conformers of the 10KT-Atropine complex

3. Discussion

Figures 1 and 2 show how to download PyRx and Biovia Discovery Studio Visualizer, following the suggested links. With these two software programs, molecular docking can be performed for any structure-based ligand and protein of interest. PyRx has an advantage over other docking software program because it has built-in AutoDock, Vina Wizard and Open Babel, and can be used to dock more than one ligand with a single protein of interest.

Figure 3 shows the icons for PyRx and Biovia Discovery Studio. There are several and more-to-come software programs, but with different programmers and purposes. The icons (Figure 3) show the exact software tools used in this article.

Figure 4 shows the RCSB PDB website display page and how to search for a protein of interest. 10KT is the protein of interest used in this tutorial. RCSB PDB is a database of proteins.

Figure 5 shows how to download 10KT protein in PDB format.

Figure 6 shows the webpage for PubChem, where ligands can be downloaded. PubChem is a database that contains structural information, chemical names, molecular formulas, and weights of chemical compounds.

Figure 7 shows the general information of Atropine in PubChem.

Figure 8 shows how to download the structural data file (SDF) 3-D conformer of Atropine in PubChem.

Figure 9 shows the location in the system where the SDF conformer is downloaded.

Figure 10 shows the launch page of Biovia Discovery Studio and how to import 10KT or protein of interest.

Figure 11 shows the imported 10KT in Biovia Discovery Studio.

Figure 12 shows the two chains A and B, heteroatoms, and water molecules present in 10KT.

Figure 13 shows chains A and B after heteroatoms and water molecules have been deleted.

Figure 14 shows a single polypeptide chain for 10KT and how to add polar hydrogens.

Figure 15 shows a prepared 10KT, and how to save it as a protein data file.

Figure 16 shows the launch page of PyRx, how to import a 10KT or protein of interest to PyRx, and how to save the protein in pdbqt format.

Figure 17 shows how to accurately position 10KT or protein of interest within a grid box.

Figure 18 shows the docking process and how to generate docking scores.

Figure 19 shows how to identify the 10KT-ligand interaction with the lowest binding score.

Figure 20 shows how to import the prepared 10KT and the docked ligands into Biovia Discovery Studio.

Figure 21 shows how to copy a docked ligand to the hierarchy of 10KT or protein of interest, in Biovia Discovery Studio.

Figure 22 shows how to define 10KT-Atropine (receptor-ligand).

Figure 23 shows the 2-D and 3-D conformers of the 10KT-Atropine complex

As described elsewhere^[1], this study also explains a simple approach that involves docking drug-like small molecules to a protein of interest in order to gain insight into their binding affinity^[10]. The approach begins with downloading and installing the necessary software as the basic requirements. This tutorial explains a simple approach that involves docking drug-like candidate ligands to a protein of interest, in order to gain insight into their binding affinity.

4. Conclusion

Our step-wise procedural tutorial in molecular docking, using PyRx and Biovia Discovery Studio Visualizer, is, to the best of our knowledge, sufficient to assist anyone interested in molecular docking studies.

Author contributions: PFA, ATB, OOB, and IAA conceived the study, researched literature and methodology; EST, AJS, and STF reviewed and edited the manuscript; PFA and ATB wrote the first draft of the manuscript. All authors approved the final version of the manuscript.

Acknowledgments: We acknowledge the graphical and photography expertise of our departmental colleagues.

Conflicts of Interest: The authors declare no conflict of interest to this work.

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