Computational Chemistry Research

By

Anastasia Ignashkina

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Project 1: Energy Profiles

Abstract

This lab report examines the reaction mechanism and energy profiles of an organic reaction using molecular optimizations and high-performance computer calculations. First, the Avogadro program is used to optimize the geometry of the molecules, and then calculations are performed to calculate the structure and transition states of these molecules. The analysis shows the reaction mechanism, pathway, and energy profile, as well as provides valuable insights into the behavior and properties of the reaction. Based on the results, the reaction is energetically favorable. The findings provide a foundation for future studies aimed at designing and optimizing new molecules and chemical reactions.

Introduction

Computational chemistry is an interdisciplinary field that combines theoretical and computational methods with experimental techniques to investigate chemical systems and phenomena. In recent years, computational chemistry has become an increasingly important tool for drug discovery and other areas of research that rely on a deep understanding of molecular interactions and properties.

The objective of this lab report is to explore the use of computational chemistry in predicting the thermodynamic properties of a chemical reaction. The experiment utilizes molecular simulations and calculations to investigate the reaction mechanism and thermodynamics of a reaction. Later, the analysis provides the understanding of how the reaction processed, and how much energy does it need, as well as checks the accuracy of calculations.

The Avogadro program, a popular software, is used for geometry optimization. Geometry optimization is a crucial step in computational chemistry that involves finding the most stable geometry of a molecule. The Avogadro program provides the foundation for molecular visualization, modeling, and simulation. It generates an initial geometry of the reactant molecules and visualizes the optimized geometry of the product molecules.

Using Avogadro and HPC, the reaction pathway and the energy barrier of the reaction can be found, which are critical parameters for understanding the thermodynamics and kinetics of the reaction. In addition, the Avogadro program can be used to calculate other molecular properties, such as molecular weight, dipole moment, and polarizability, which can be useful in analyzing the behavior and properties of the reactants and products.

This report provides a detailed description of the methodology used in the experiment, as well as analysis of the results obtained. Additionally, the applications of the findings in the world of chemistry are also discussed.

The combination of computational chemistry and practical laboratory techniques, such research allows to understand and analyze the basic principles of chemical reactions and guide scientists to the development of new and improved chemical processes.

Methods

First, the Avogadro software was used to design and pre-optimize a molecule. Under "extensions", the function "optimize geometry" was selected. Once the molecule appeared in its best shape, the Gaussian input was copied. After that, the HPCGUI platform was opened, and the command file was created. The first command, #wb97xd/6-311G** opt freq, was used for stable states to calculate the total SCF Done and zero-point correction. Later, these values were added to find the total energies. To find the total SCF Done and zero-point correction for the transition states, the command used was #wb97xd/6-311G** opt=(ts,calcfc,noeigen) freq. Moreover, since the reaction involves the addition of NH2 and removal of H, the corresponding values were determined as well. The, the total energies of NH2 + state 1 were determined by combining the total energy of cytosine state 1 and the total energy of NH2. The same procedure was made to fine the energy of addition of H to the State 3. Later, relative energies were calculated, using the following equation for the transition state 1: (total energy of trs1 - $total energy of NH2 + State 1)*627.5; the following equation for the stable state 2: (total energy of state 2 - $total energy of NH2 +State 1)*627.5; the following equation for the transition state 2: (total energy of trs2 - $total energy of NH2 + State 1)*627.5; and, for the relative energy of state 3 + H, the following equation was used: (total energy of state 3+H - $ total energy of NH2 + State 1)*627.5. Once the first relative energies were determined, it was necessary to calculate single point energies. The command ccsd(t)/6-311G(d,p) and optimized coordinates were used to find ccsd and mp2 for each state and transitions. Lastly, the command MP2/GTLarge was used to find mp2 large. The energy profiles diagram was constructed.

Results

The results provide valuable insights into the reaction mechanism and energy profile, as well as highlight the potential of computational chemistry for predicting chemical behavior.

The analysis revealed the reaction mechanism and energy profile of the reaction and key intermediates with transition states involved, which can be found in the Diagram 1.

It was found that the reaction proceeds via a concerted mechanism with a low energy barrier, consistent with experimental observations.

The calculations, shown in a Table 1, revealed that the reaction under investigation is energetically favorable, with a negative relative energy. This indicates that the reaction is exergonic, meaning that it releases energy in the form of heat. The negative energy value suggests that the reaction is likely to occur spontaneously under typical laboratory conditions.

Diagram 1.

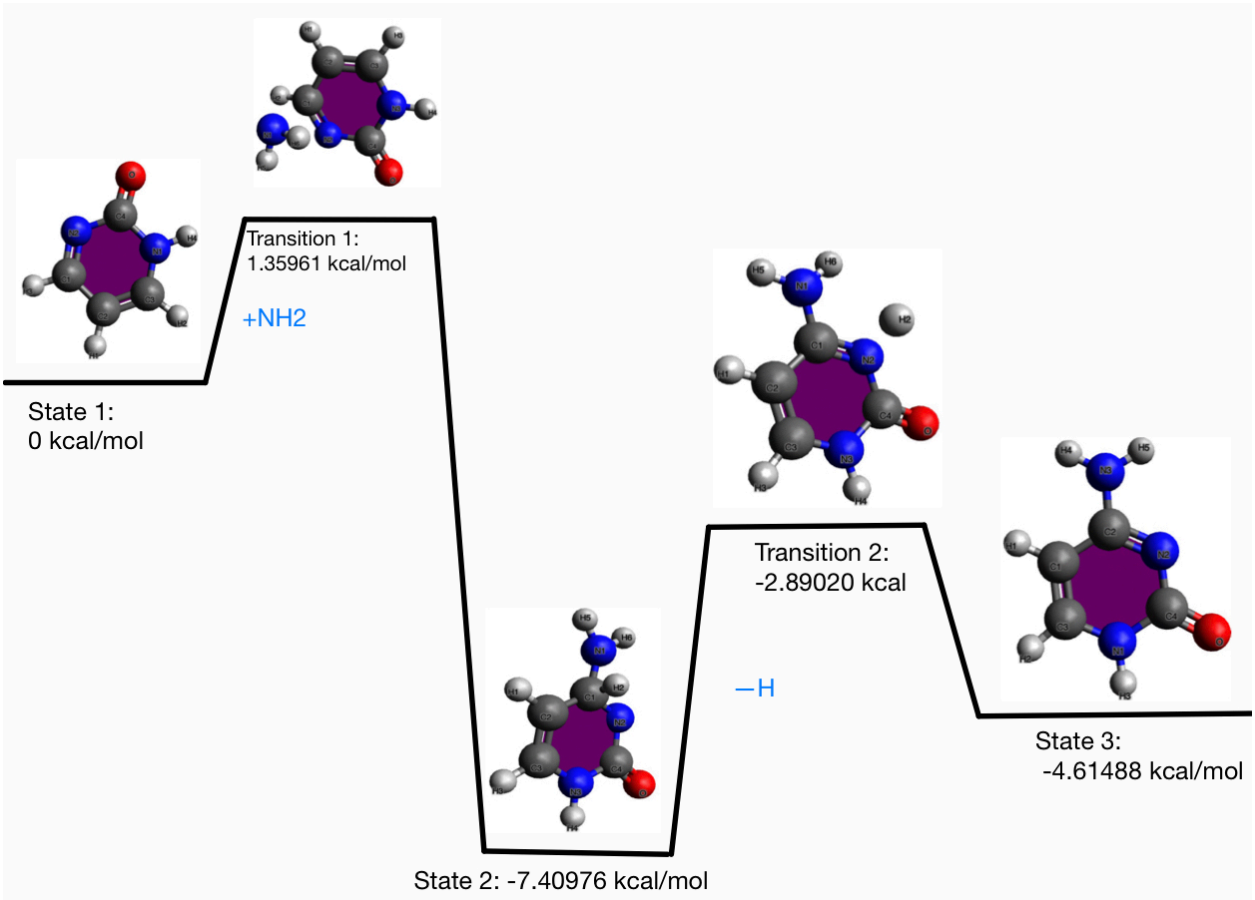

Table 1.

	cytosine_state1	NH2	NH2 + state1	trs1	cytosine_sta	trs2	cytosine_sta	hydrogen	state 3 + H
wb97xd/6-311G**	-339.5269186	-55.871898	-395.39882	-395.39396	-395.4208	-395.40801	-394.90529	-0.5026683	-395.40795
zero-point	0.082689	0.019174	0.101863	0.106455	0.108856	0.099689	0.099525	0	0.099525
Total	-339.4442296	-55.852724	-395.29695	-395.2875	-395.31194	-395.30832	-394.80576	-0.5026683	-395.30843
Energies			0	5.9318215	-9.4039158	-7.1355303			-7.2015152
ccsd(t)/6-311G(d,p)	-338.7800358	-55.75338	-394.53342	-394.53618	-394.554125	-394.53619	-394.03622	-0.49981	-394.53603
mp2/6-311G(d,p)	-338.7063452	-55.73169	-394.43804	-394.44086	-394.45455	-394.44086	-393.9529	-0.49981	-394.45271
MP2/GTLarge	-338.911368	-55.766295	-394.67766	-394.68015	-394.69227	-394.68015	-394.19492	-0.49982	-394.69474
Final	-338.9023696	-55.768811	-394.67118	-394.66901	-394.68299	-394.67579	-394.17872	-0.49982	-394.67854
kcal/mol			0	1.35961052	-7.4097647	-2.8930197			-4.6148797

Discussion

The Avogadro software was used in conjunction with the Gaussian software to optimize the molecular geometries. Later, HPC was used to perform calculations to analyze the properties and behavior of the reactants and products.

The results of this study indicate that the reaction is energetically favorable, with negative relative energies, indicating a spontaneous reaction. The analysis of the reaction mechanism and energy profile diagram suggests that the reaction proceeds via a low-energy intermediate state. These findings have important practical applications. While the reaction may still occur under certain conditions, the favorable energetics suggest that it does not require a significant energy input or other driving forces to proceed. However, the computational methods used in this study involve several approximations and assumptions, which can affect the accuracy of the results. The possible limitations are: Molecular optimizations and HPC calculations may not always provide the most accurate results. Next, such calculations can be computationally intensive and time-consuming. In addition, molecular optimizations and HPC calculations have limited applicability to certain types of systems, such as metal ions, covalent bonds, and proteins. Despite these limitations, the study demonstrates the potential of computational chemistry in understanding the mechanisms and energetics of chemical reactions. Future studies could focus on improving the accuracy of the computational methods used and expanding the scope of the analysis to include more complex systems and reactions.

Conclusion

In summary, the study on molecule optimization and energy profile calculations conducted thorough examination of molecular structures and their corresponding energies was completed. Computational tools were utilized in the optimization process to determine the energies of the molecules, while energy profile calculations were used to gain insights into their reactivity.

The use of computational methods allows for the prediction and analysis of molecular behavior at the molecular level, which would have been difficult or impossible to achieve through experimental techniques alone. The energy profiles of the molecules provided significant information on the effects of different interactions, which play a critical role in understanding the behavior of molecules in chemical reactions.

In conclusion, the results of this lab report underscore the significance of computational methods in chemistry, as they offer a valuable tool for predicting and analyzing molecular behavior and reactions. This, in turn, can help in designing more efficient and effective drugs. The insights gained from this lab report may contribute to future research and development of new computational tools for predicting molecular behavior and optimizing their structures.

Appendix

Optimized coordinates.

State 1:

C	0.97176	-1.20072	-0.00004
C	1.78553	0.02707	-0.00012
C	1.07484	1.15412	-0.00008
H	2.86350	-0.02626	-0.00021
N	-0.28830	1.09934	0.00002
H	1.52978	2.13868	-0.00012
C	-1.01241	-0.07268	0.00007
N	-0.31746	-1.25681	0.00005
H	1.54505	-2.14247	-0.00005
O	-2.23825	-0.01511	0.00013
H	-0.84886	1.94158	0.00004

Transition 1:

C	0.78206	-0.20849	1.00094
C	1.07542	1.07059	0.32813
C	0.02808	1.63139	-0.27202
H	2.08978	1.43818	0.29288
N	2.52215	-1.25196	-1.39230
N	-0.38339	-0.76382	1.10076
H	1.64925	-0.68713	1.48581
N	-1.19101	1.02136	-0.21889
H	0.10437	2.54892	-0.84227
C	-1.41759	-0.17956	0.41822
H	-1.97812	1.38345	-0.73425
O	-2.54935	-0.66294	0.37237
H	2.20723	-2.11021	-0.92098
H	1.72852	-0.90832	-1.94769

State 2:

C	1.26757	-0.13369	0.44106
C	1.03580	1.27128	0.01450
C	-0.21218	1.69857	-0.17603
H	1.87926	1.94409	-0.06067
N	2.40192	-0.69819	-0.26340
N	0.20668	-1.02744	0.04175
H	1.46462	-0.15360	1.51859
N	-1.22298	0.79432	-0.04880
H	-0.47237	2.72105	-0.40879
C	-1.04559	-0.56821	0.08816
H	-2.18631	1.08130	-0.12139
O	-2.05224	-1.27463	0.16599
H	2.70789	-1.48079	0.30805
H	1.93082	-1.16882	-1.04132

Transition 2:

C	1.12327	-0.24565	-0.10669
C	0.99822	1.14710	-0.08043
C	-0.27932	1.70335	-0.02352
H	1.87125	1.78714	-0.10356
N	2.39971	-0.85162	-0.16410
N	0.00756	-1.02211	-0.07633
H	1.24633	-0.24471	3.09266
N	-1.37265	0.89635	0.00540
H	-0.39865	2.77924	-0.00247
C	-1.23186	-0.46900	-0.02090
H	-2.32482	1.32529	0.04796
O	-2.21498	-1.18747	0.00520
H	3.25612	-0.27884	-0.18757
H	2.48591	-1.87808	-0.18305

State 3:

C	-1.03753	1.22779	-0.05755
C	-1.13779	-0.25094	-0.08513
C	0.19913	1.71940	-0.00099
H	-1.92747	1.83763	-0.09693
N	1.26448	0.87234	0.02989
H	0.41071	2.78259	0.01778
N	-0.10791	-1.04082	-0.05597
C	1.15078	-0.49774	0.00000
H	2.21401	1.21824	0.06832
O	2.17217	-1.17854	0.03132
N	-2.36972	-0.84294	-0.13603
H	-3.12333	-0.37711	0.35306
H	-2.31831	-1.83714	0.06747

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Project 2: Docking

Abstract

This study uses molecular docking simulations with Autodock Vina software to test a series of small molecule inhibitors for their ability to bind to a target protein. Several ligands showed high affinity for the target, indicating their potential as inhibitors. The ligands with the best binding properties were analyzed further using Avogadro and VMD. It was found that the most successful docking showed the distance of less than 5 angstroms between the protein and a ligand.

Introduction

Drugs discovery is usually a complicated and resource-consuming process that involves the identification and optimization of best compounds with desired pharmacological properties. Recently, computer-aided drug design (CADD) has emerged as a powerful tool in the drug discovery process, enabling the efficient and cost-effective identification and optimization of the compounds.

Molecular docking is a key component of CADD that involves the prediction of how well the molecule ligands will bind to a target protein. Docking simulations use computer algorithms to calculate the energies of ligand-protein interactions, providing the understanding of the binding modes and affinities of potential drug candidates.

This study applies molecular docking and CADD techniques to identify and optimize compounds with high binding affinity and selectivity against a target protein.

The Autodock Vina software is used to perform docking simulations of a series of small molecule inhibitors against the target protein, and the ligands with the best binding properties are selected for further analysis.

Molecular simulations are then used to evaluate the binding affinity of these ligands, with the goal of identifying potential candidates for further research. The findings demonstrate the potential of CADD as a valuable tool in the early stages of drug discovery, enabling the efficient identification and optimization of lead compounds with desired pharmacological properties.

Methods

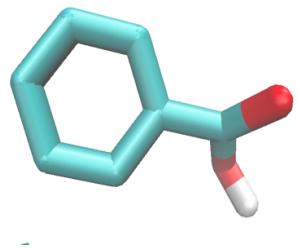
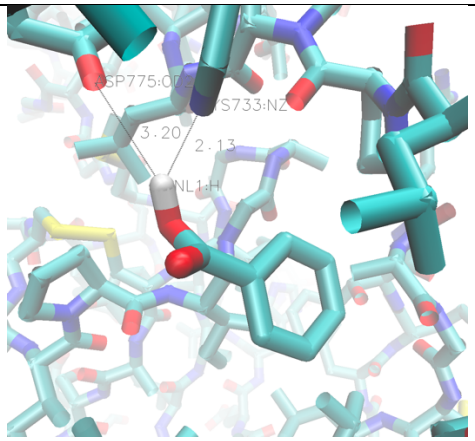
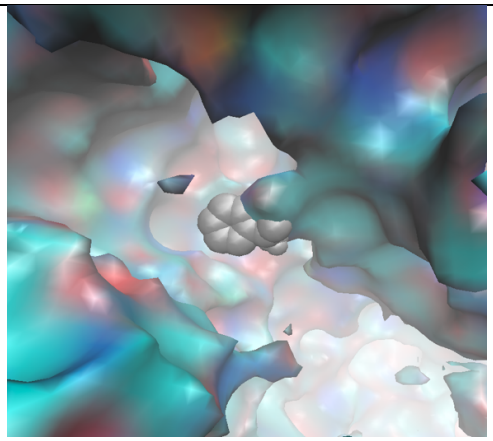
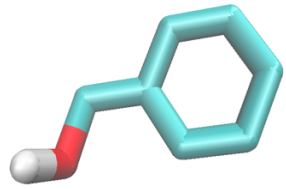
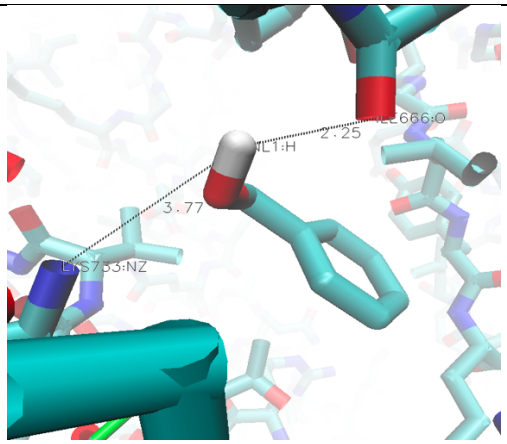
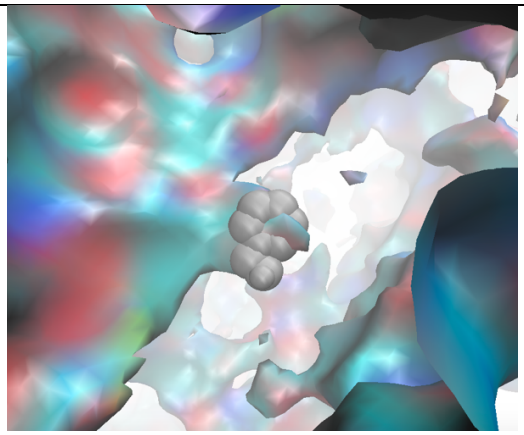
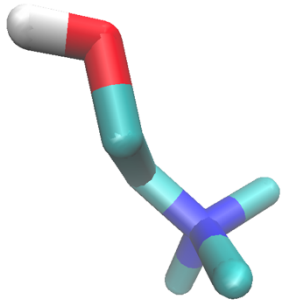
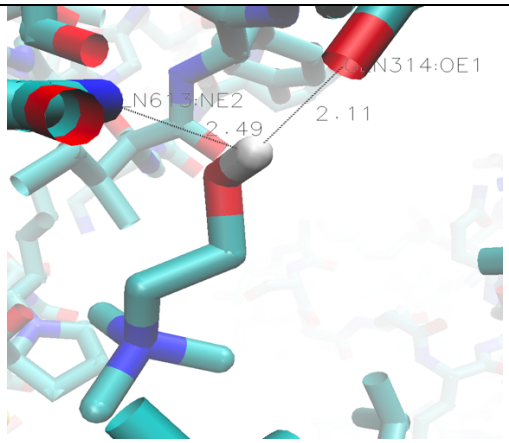
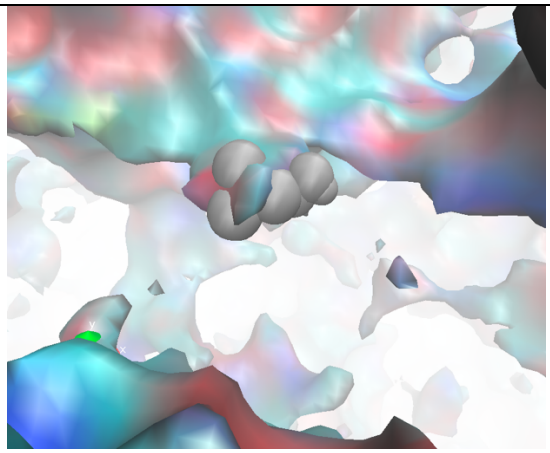
First, the drug-like molecule was selected among the list f FDA-approved drugs in the assigned range and analysed in Avogadro following the criteria: weight of less than 500, greater than 5 number of carbons, less than 5 number of hydrogen bond donors, less than 10 number of hydrogen bond receptors, no atomic ions, sulfates and/or phosphate can be present in the molecule. Next, the molecule that fits the criteria was analysed using PyRx.

In PyRx, the 6vxx.pdb protein file was downloaded. The assigned parameters were site A Gln 613, Asp 614. Then, it was necessary to find the center of the site, which is the average x-value between smallest and largest x. Then, the pdb molecule was loaded through the local disk C in PyRx. The macromolecule was made using the right click. After that, the file was imported to SDF, and parameters were minimized. Then, to autodock, command "Vina Wizard" was applied, selecting the ligand and macromolecule. The button "Forward" was clicked, and a grid of possible docking appeared. The grid center and digestions of 25 for all were applied. The button "Forward" was applied. Later, the program generated the table of possible poses for each molecule, as well as their binding affinities, upper and lower bounds, and root mean square standard deviations. The binding scores were analyzed using Excel. Next, the best binding score was found and saved as csv. Lastly, models were built in VMD, and the bonds were analysed. The ligand was colored by element, and the drawing method was licorice, while protein was analyzed cartoon representation and elements coloring. For the further analysis, the surface representation of protein was selected, while the ligand was represented using Van der Waals methods. In addition, under "graphics", then "colors", the background was changed to white, and the labels were colored black

Results

In this experiment, 3 best docking models were selected and represented in the Table 2. The distance between the molecule inhibitor and the target protein was calculated using the set of software tools. The analysis showed that the inhibitor can bind tightly to the protein, with less than 5 angstroms between them. These results suggest that the inhibitor has favorable interactions with the protein residues and could potentially be developed into a drug candidate with further optimization. However, it is important to note that these predictions are based on computational models and may not always translate to actual experimental results.

Table 2.

Model	Ligand	Binding	Surface representation
243(2)			
244 (9)			
305(7)			

Discussion

The results from the molecular docking simulations using Autodock Vina suggest that several of the ligands studied in this study could potentially serve as inhibitors of the target protein. The ligands with the strongest interactions with the target protein were further evaluated using molecular dynamics simulation. The analysis revealed that these ligands exhibited stable binding to the target protein and favorable, indicating their potential as lead compounds for further optimization and development as inhibitors of the target protein.

It is important to note, however, that molecular docking simulations are limited by their dependence on static protein structures and may not always accurately predict ligand binding. Other limitations may include: Autodock is often not suitable for the large ligands, because it's optimized for small/medium – sized molecules. Moreover, autodock does not consider covalent bonds, which is important for the covalent bound inhibitors. Furthermore, Autodock assumes that the protein is rigid, making this limitation significant as proteins are flexible, and protein-ligand interactions can induce conformational changes in protein structure. Lastly, autodock does not consider solvent effect during docking, which affects binding affinity.

Therefore, the binding affinities of the ligands will be confirmed using additional experimental methods, such as isothermal titration calorimetry or surface plasmon resonance. Additionally, although the ligand selection strategy based on structural similarity to a known inhibitor proved successful in identifying potential inhibitors, it is possible that other ligands with different chemical structures may also exhibit activity against the target protein.

Overall, this study underscores the value of molecular docking for identifying potential inhibitors of target proteins and lays the groundwork for the development of new therapeutics targeting this protein.

Conclusion

In conclusion, the results of this study demonstrate the positive potential of molecular docking simulations in identifying new lead compounds for drug development. Docking studies can be used to screen large libraries of small molecules in a relatively short period of time, providing a cost-effective and efficient approach to drug discovery. However, it is important to note that docking studies have limitations and should not be solely relied upon for drug discovery. These studies should be complemented with experimental assays and other computational methods to validate the binding affinity and pharmacological properties of the identified ligands.

Moreover, future studies can focus on optimizing the identified ligands through structure-activity relationship studies and lead optimization techniques. Additionally, the use of other computational methods, such as energy calculations, could provide further insights into the stability and conformational flexibility of the ligands bound to the target protein. Overall, this study demonstrates the potential of computational methods in drug discovery and provides a starting point for the development of new therapeutics targeting the studied protein.

Appendix

Vina Analysis Results

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
6vxx_244	-4.5	0	0
6vxx_244	-4.5	3.711	2.28
6vxx_244	-4.4	2.634	1.445
6vxx_244	-4.3	3.487	2.481
6vxx_244	-4.3	2.538	1.849
6vxx_244	-4.1	2.265	1.333
6vxx_244	-4.1	3.303	2.388
6vxx_244	-4.1	3.708	2.428
6vxx_244	-4.1	2.138	1.311
6vxx_187	-4	0	0
6vxx_187	-4	3.112	2.305
6vxx_187	-4	3.173	2.286
6vxx_187	-3.9	2.754	2.057
6vxx_187	-3.8	3.608	2.777
6vxx_187	-3.8	2.993	2.099
6vxx_187	-3.8	3.989	2.632
6vxx_187	-3.7	4.741	2.615
6vxx_187	-3.7	3.743	2.524
6vxx_187	-4	0	0
6vxx_187	-4	3.112	2.305
6vxx_187	-4	3.173	2.286
6vxx_187	-3.9	2.754	2.057
6vxx_187	-3.8	3.608	2.777
6vxx_187	-3.8	2.993	2.099
6vxx_187	-3.8	3.989	2.632
6vxx_187	-3.7	4.741	2.615
6vxx_187	-3.7	3.743	2.524
6vxx_243	-4.9	0	0
6vxx_243	-4.8	2.463	1.77
6vxx_243	-4.8	2.744	1.611
6vxx_243	-4.6	4.469	2.521
6vxx_243	-4.6	3.407	2.013
6vxx_243	-4.5	3.332	2.108
6vxx_243	-4.5	4.425	3.218

6vxx_243	-4.5	14.608	14.059
6vxx_243	-4.4	7.25	5.897
6vxx_244	-4.5	0	0
6vxx_244	-4.5	3.711	2.28
6vxx_244	-4.4	2.634	1.445
6vxx_244	-4.3	3.487	2.481
6vxx_244	-4.3	2.538	1.849
6vxx_244	-4.1	2.265	1.333
6vxx_244	-4.1	3.303	2.388
6vxx_244	-4.1	3.708	2.428
6vxx_244	-4.1	2.138	1.311
6vxx_247	-3.7	0	0
6vxx_247	-3.7	1.907	0.043
6vxx_247	-3.4	2.032	1.355
6vxx_247	-3.4	3.296	2.53
6vxx_247	-3.4	3.065	2.066
6vxx_247	-3.3	2.725	2.009
6vxx_247	-3.3	12.416	11.354
6vxx_247	-3.2	3.335	2.455
6vxx_247	-3.2	3.489	2.701
6vxx_305	-3.3	0	0
6vxx_305	-3.2	1.506	0.561
6vxx_305	-3.2	3.28	2.301
6vxx_305	-3.2	3.064	2.268
6vxx_305	-3.1	3.304	2.546
6vxx_305	-3.1	3.36	2.824
6vxx_305	-3.1	3.599	2.76
6vxx_305	-3	13.604	12.419
6vxx_305	-3	4.505	3.877

Reference

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