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Computational Screening and Identification ofEfficient Drug Candidates for Niemann-Pick Disease

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***Abstract*—**Niemann-Pick disease (NPD) is a rare genetic ail- ment that impairs the body's capacity to metabolise lipids, leadingto the accumulation of fatty substances in a number of organs, including the liver, spleen, lungs, bone marrow, and brain.There iscurrently no cure for NPD, and treatment is primarily focused on managing symptoms and providing supportive care. This study aims to provide an efficient drug candidate for NPD. By identifying the binding pockets of the NPD, suitable inhibitors were screened in PDB databases followed by molecular docking, molecular dynamics was performed to find its binding affinity and stability, followed by binding free energy estimation. The drug QDG has a high binding affinity of -7.95 kcal/mol with the NPD protein target. The 5U74-QDG complex was more stable, with an RMSD of 0.37 nm and two hydrogen bonds formed between ALA885 and LEU1045 of the 5U74 protein and theQDG drug. Additionally, it has the lowest binding free energy of
-41.63 kJ/mol. The effectiveness of pharmaceuticals is shown by employing computational tools to analyse various medications. These strategies include docking, molecular simulation, and binding free energy. Based on the findings, we conclude that medicine QDG is a far more potent inhibitor of Niemann-Pick disease than competing medications.

Index Terms—Niemann-Pick disease, Drug-inhibitor, Structure-based, Molecular Docking, Charge Calculation, Molecular Dynamic Simulation, Binding Free Energy.

I. Introduction

A set of inherited lysosomal storage illnesses known as Niemann-Pick disease (NPD). Inherited lysosomal storage disorders (LSDs) are a group of rare hereditary diseases caused by lysosomal enzyme deficiencies or malfunction. [1] These enzymes are responsible for breaking down and recycling certain molecules in the body. When they are not working properly, waste products build up in the lysosomes and cause damage to cells and organs. It impairs the body's capacityto transfer lipids (fats) such as cholesterol within cells. NPD is classified into four subtypes: typeA(which effects
infantile), B(less severe), C(effects adults), and E(less com- mon). Niemann-Pick disease type C (NPC) is caused by two genes, NPC1 and NPC2, which code for proteins involved in lipid transport and are the source of the disorder [2]. NPC1 primarily affects the cerebellum in the brain. [3]. A major membrane glycoprotein called NPC1 that is largelyfound in late endosomes is encoded by this gene, and around 95% of patients have mutations in it [4]. Lipids abnormally accumulate in a variety of organs and tissues, includingthe liver, spleen, and brain, when these proteins are not functioning properly. [4] A variety of symptoms, such as respiratory issues, liver malfunction, mobility difficulties, and developmental delays, can result from this [4]. Despite thefact that it can be compromised, the membrane protein NPC1, which is mostly found in late endosomes and lysosomes, is crucial for maintaining the cell's homeostasis of cholesterol, flict people of any age, NPC often manifests in childhood or adolescence.

[4] Individuals can have vastly different levels of disease severity and progression, with some suffering a quick deterioration in health and others a more gradual course of the illness. [5] NPC cannot yet be cured, and there are few effective treatments available. [6] However, there are a number of treatments that

could aid with symptom relief and quality of life enhancement, such as the drug miglustat, which can halt the progression of neurological symptoms [3].

The goal of this study is to identify the most effective medication based on the target protein's binding residues. Second, docking was carried out to as certain the binding affinity and examine how the drug's constituent parts inter- acted with the protein. Thirdly, to investigate the stabilityand physical motions of atoms and molecules, a simulation utilising molecular dynamics (MD) was carried out. Binding free energy was estimated to assess the change in free energy that takes place when a ligand binds to a protein.This work is motivated from our previous work on ProAll-D server, which predicts allergens and non allergens of proteins using a deep learning approach [7], and In silico method to predict multi- epitope design against norovirus were the study focuses on identifying novel epitopes against norovirus by using various databases [8].In this paper, they examined methodologies suchas drug-based, genome-based, chemical structure, and molec- ular information, and identified computational approaches that are commonly used in drug repositioning studies [9].The Cmapwas proposed and it has proven beneficial in predicting prospective treatment candidates for future experimental val- idation in several brain illnesses [10].Computational methods that calculate similarities between rare and non-rare diseases, taking into account biological factors such as genes, proteins, and symptoms, inspired this work [11].

II. Methodology

A. Identification of Target Protein and Finding Binding Pock-ets

The human Niemann-Pick C1 protein is involved in Niemann-Pick disease type C, a hereditary lysosomal storage disorder, has a structure that may be seen in the Protein Data Bank (PDB) and is denoted with the PDB ID 5U74 [12]. It's a lysosomal membrane protein that is involved in the metabolism of lipids. It is a member of the NPC protein family. To find the binding pockets of the protein, a Aggrescan [13], computational tool that predicts the location of aggregation- prone regions or "hot spots" by a combination of algorithms and statistical models is used. This tool considers variousfactors that are known to contribute to protein aggregation, including hydrophobicity, charge distribution, and the presence of specific amino acid residues that are prone to aggregation which aids in the development of more effective and stable protein-based therapeutics

B. Selecting ligands for the Target Protein

Based on the hot spots of the protein target, a similarity search was performed using the tool BLASTp [14]. The protein ID's which based on the search retrieved results with a100% query cover and 100% identity score were obtained from RCSB [15] .The ligands associated with the identified proteinswere selected as potential ligands for the target protein.

C. Molecular Docking

To achieve molecular docking, the Lamarckian Genetic Algorithm [LGA] with 25,000,000 steps and AutoDock v4.2 [16] were employed. For all ligands, the grid parameters were adjusted to size 62, 66, and 48 with centres of 30.3, 3.757, and -21.665 for all ligands [17]. The protein-ligand interactions were visualised through LigPlus tool, and the final docked structure was viewed using Chimera [18]. 2.4 Molecular Dynamics and Binding Free Energy Calculation. Gromacs 2021.3 was used to simulate molecular dynamics (MD) [19]. The Amber ff99SB-ILDN force field was used to construct the protein's gromacs architecture [20]. Antechamber [21] is a programme that generates force field parameters using AMBER 22 [22], was used to compute the drug's charge, and the drug's gromacs topology was created using acpype [23].Water molecules with extended simple point charges [24] were employed with a dodecahedron box 2.0.The steepest descent minimization procedure was used to conduct energy minimization for 50,000 steps. A 50-ns MD production run is followed by a 1-ns position-restrained dynamics simulation of the system (equilibration phase) at 300 K. Xmgrace was used to construct the RMSD plot [25].Chimera was used to create the 3D structures, and VMD was used to display them [26] .

III. Results

A. Binding Pockets of Protein Target and Selected ligands

Total 40 binding pockets of the protein targets are identified. The sequences of hot spots range from length 5 to 100. Based on the hot spots obtained from the protein target, seven ligands were screened from

RCSB and selected as drug candidates to check its binding affinity as shown in Table 1, which shows its structure, molecular name and formula with ligand id.

B. Molecular Docking Analysis

The 5U74-HC3 complex has the highest binding affinity with -9.18 kcal/mol, followed by the 5U74-QDG complexwith

-7.95 kcal/mol. The 5U74-HC3 complex has no H- bonds whereas the drug QDG complex has two H-bonds with ALA885 and LEU1045 of 5U74 protein. The remaining ligand along with the binding energy and interacting residues are as given in Table 1.

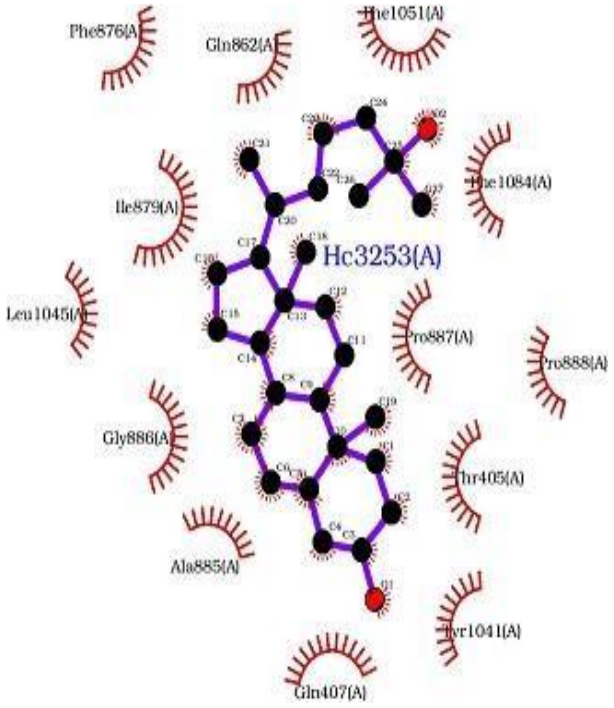


Figure. 1. (a) 5U74-HC3 complex Structure of human Niemann-Pick C1 protein with ligand HC3.

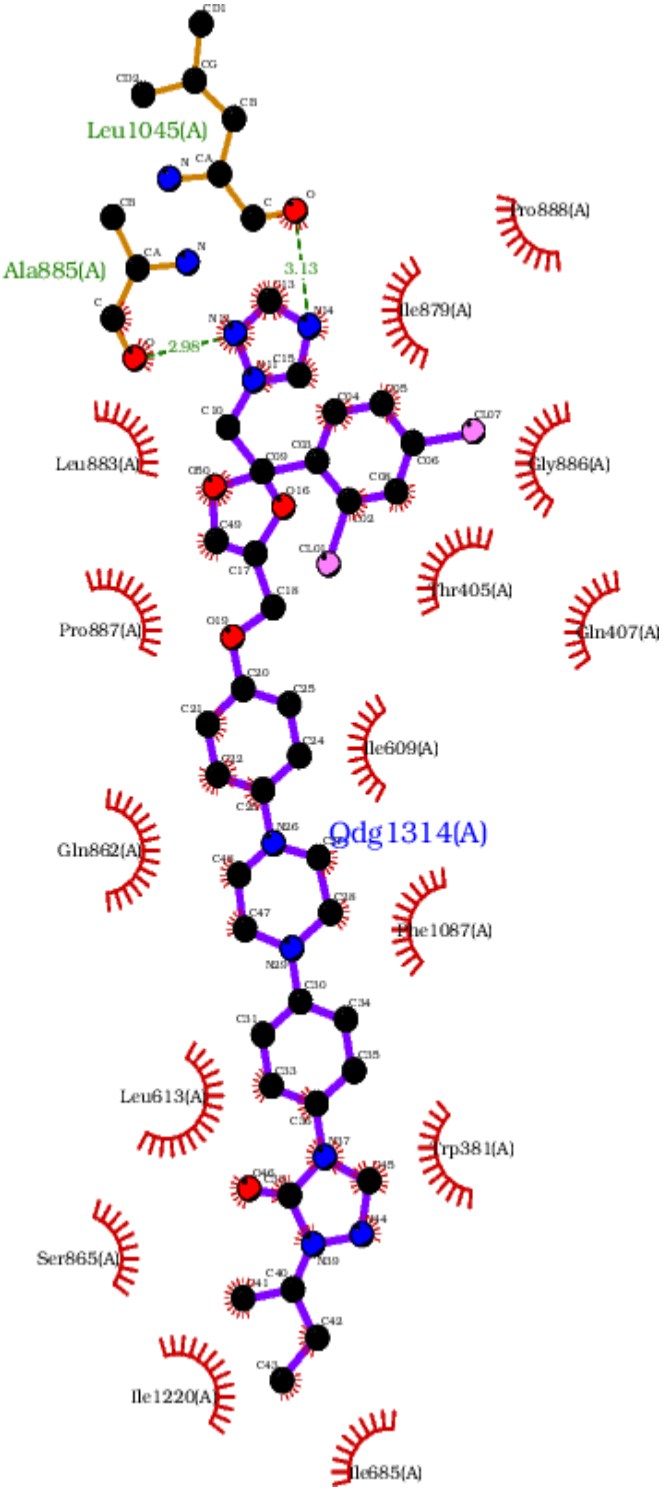


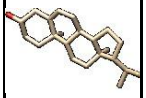
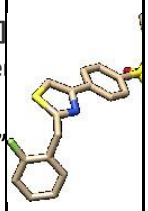
Figure. 1. (b) 5U74-QDG complex. Structure of human Niemann-Pick C1protein with ligand QDG.

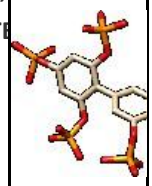
C.Molecular Dynamic Analysis and Binding energy estima- tion

- The Amber ff99SB-ILDN force field was used to perform a 50 ns molecular dynamics simulation of the 5U74 protein complexed with the medicines HC3 and QDG. The Gromacs topology was used for the protein, and Antechamber was used to calculate the charges and topol-ogy of the drugs. The SPC water model was employed for energy minimization. As illustrated in Figure-2(a), Root-mean-square-deviation (RMSD) calculations were utilised to estimate the stability of the 5U74-drug com- plexes.
- The findings show that, with an average RMSD of 0.37 nm against 0.39 nm, the 5U74-QDG complex was more stable than the 5U74-HC3 complex. The 5U74-HC3 complex exhibited the highest hydrogen bond occupancy of 11.28% between HC3 and TYR1041-5U74, followed by 7.88% between HC3 and TYR1088-5U74, and 6.52% between HC3 and GLN862-5U74. In contrast, the 5U74- QDG complex showed the highest hydrogen bond oc- cupancy of 17.15% between QDG and SER865-5U74, followed by 8.74% between QDG and THR604-5U74, and 3.48% between QDG and TYR875- 5U74.
- To evaluate changes in the 5U74 protein in combination with its medications, the root-mean-square fluctuation (RMSF) was computed, as shown in Figure 2(b). The results indicate that the QDG drug caused less fluctuation in the protein than the HC3 drug.
- As shown in Figure 2(c), the radius of gyration was calculated to assess the protein's compactness. The resultsshow that protein complexes with QDG are more compactthan protein complexes without QDG.
- In addition, as shown in Figure 3(a) and Figure 3(b), the binding free energies of the two complexes were determined. The 5U74-HC3 complex's binding free energy was determined to be -41.63 kJ/mol, whereas that of the 5U74- QDG complex was -42.57 kJ/mol. These results further confirm that the 5U74-QDG complex has alower bindingfree energy than the other complexes.

IV. Discussion

Niemann-Pick disease gives an overview of hereditary lysosomal storage disorders (LSDs), a group of uncommon genetic diseases brought on by a deficiency or inefficiency in lysosomal enzymes. The discussion focuses on Niemann-Pick disease (NPD), which is classified into four subtypes: type A, B, C, and E. Of these, NPC1 and NPC2 genes, which arein charge of creating proteins involved in lipid transport, are mutated in Niemann-Pick disease type C (NPC). In NPC1, the cerebellum is the brain region most impacted, and around 95% of patients have mutations in it. The present study aimed to investigate the stability and binding free energy of the5U74 protein (Niemann-Pick disease) complexed with two drugs, HC3 and QDG. The outcomes of molecular dynamics simulations performed with the Amber ff99SB-ILDN force

Name/Formula	3D Diagram	Binding Ene
" 2-acetamido-2-deo D-glucopyranose C8 H15 N O6 "		-9.18 kcal/r
" 4-(3-bromo ({(2R,4S)-2- (2,4-dichlorophenyl)- 1,2,4- triazol-1-yl) 1,3-dioxolan-4- yl}methoxy)phenyl]pi 1- yl}phenyl)-2-[(2S)- yl]-2,4- dihydro-3 triazol-3-one C35 H37 Br Cl2 N8 O4		-7.95 kcal/r
" N,N-diethyl- fluorophenyl)methyl] thiazol-4- yl}be sulfonamide C20 H21 F N2 O2 S2 "		-6.49 kcal/r
" 2-acetamido-2-deo D-glucopyranose C8 H15 N O6 "		-4.86 kcal/r
" methyl (R)-(6Z, octadeca- 6,9,12 ylphosphonofluoridat H34 F O2 P "		-4.35 kcal/r

" BIPHENYL 2, PENTAKISPHOSPHATE H15 O20 P5 "		-2.39 kcal/r

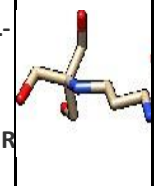
" 2-[3-(2-HYDR DIHYDROXYMETHYL-ETHYLAMINO)-PROPYLAMINO]-HYDROXYMETHYL-PR 1,3-DIOL C11 H26 N2 O6 "		-2.80 kcal/r

Table 1: Ligands used as drug candidates for the protein target along with its structure, molecular name and formula wit

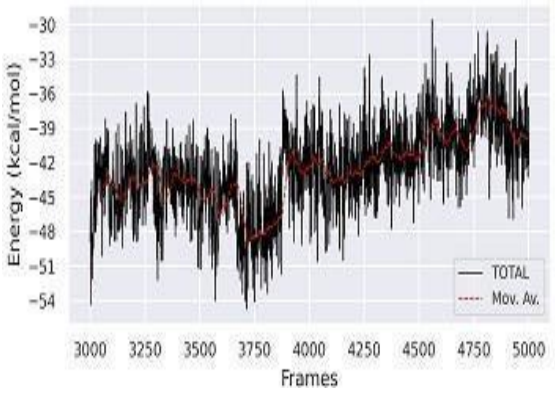


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Figure. 2. (a) RMSD of the two complex .

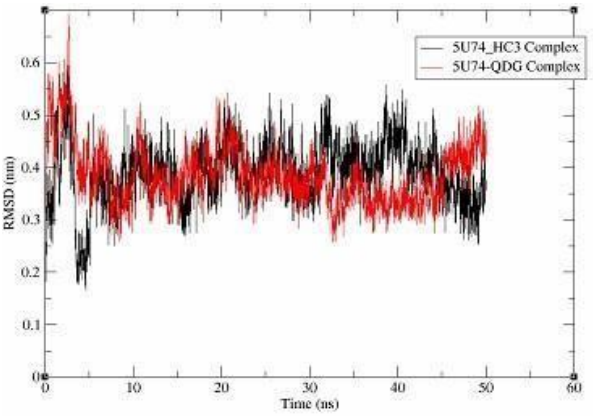
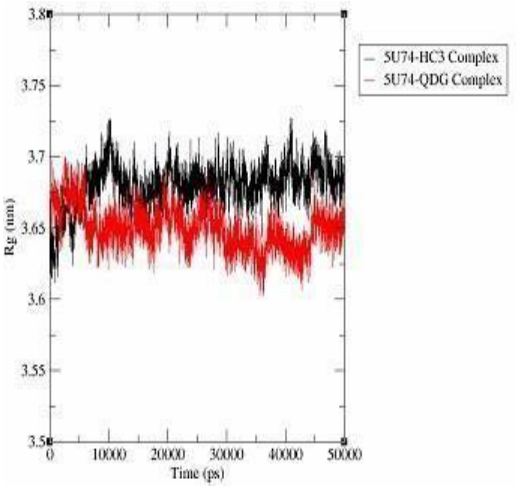


Figure. 2. (b) RMSF of the two complex .



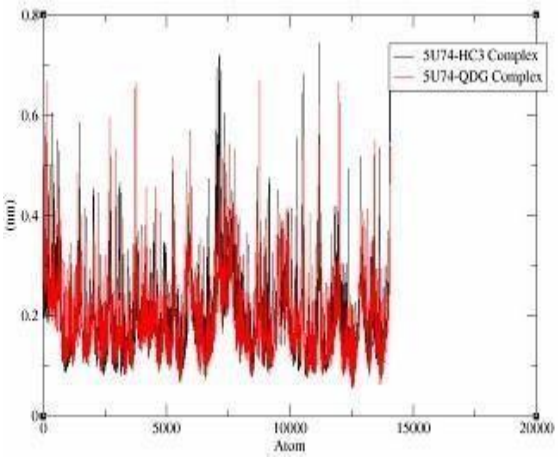


Figure. 3. (a) 5U47-HC3 Complex

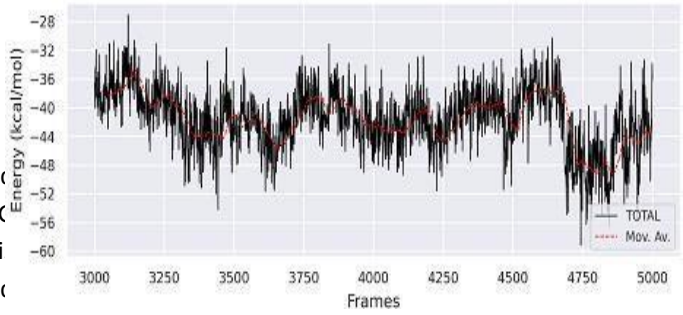


Figure.3 .(b)5U74-QDG Complex

field and the Antechamber tool for drug charge and topology calculations suggest that the 5U74-QDG complex is more sta-ble than the 5U74-HC3 complex. This conclusion is supported by the lower RMSD values and the higher hydrogen bond occupancy observed in the 5U74-QDG complex. Moreover, the radius of gyration calculations revealed that the protein complex with QDG is more compact than in other complexes. The lower RMSF values observed for the QDG complex also indicate that QDG is more tightly bound to the protein than HC3. These findings suggest that QDG could be a more effective drug candidate for the 5U74 protein. Furthermore, the binding free energy calculations showed that the 5U74- QDGcomplex has a lower binding free energy than the5U74- HC3 complex. This result further confirms that the 5U74- QDG complex is more stable and has a stronger binding affinity to the 5U74 protein. In conclusion, our research sheds light on the stability and binding characteristics of the 5U74 protein when it is complexed with the medicines HC3 and QDG. The results suggest that QDG could be a promising drug candidate for the 5U74 protein and could serve as a starting point for further drug discovery studies. To support the study's computational results, additional experimental validation is needed.

V. Conclusions

In conclusion, this study aimed to identify an efficient drug candidate for Niemann-Pick disease (NPD), a rare inherited disorder that affects lipid metabolism. By performing molecular docking, molecular dynamics, and binding free energy.estimation, the drug QDG was identified as having a high binding affinity and stability with the NPD protein target.The 5U74-QDG complex demonstrated strong binding with two hydrogen bonds, and QDG had the lowest binding free energy. The results of this study suggest that QDG can act asa highly effective inhibitor of NPD and may be a promising drug candidate for further investigation and development. Thecomputational techniques used in this study can also be appliedto screen other potential drugs for NPD and other diseases, providing a valuable tool for drug discovery and develop-ment. We have proposed a potential drug candidate for Niemann-pick disease which can be further tested experimentally. Also a peptide based drug candidate can be designed which are naturally occurring from amino acids for the treatment of Niemann-pick disease.

References

[1] Sun, "Lysosomal storage disease overview," *Annals of translational medicine*, vol. 6, no. 24, 2018.

[2] H. Bajwa and W. Azhar, "Niemann-pick disease," in *StatPearls [Inter- net]*, StatPearls Publishing, 2021.

[3] W. Li, M. R. Pergande, C. A. Crutchfield, B. C. Searle, P. S. Backlund,

[4] J. A. Picache, K. Burkert, N. M. Yanjanin-Farhat, P. S. Blank, C. L. Toth, *et al.*, "A differential proteomics study of cerebrospinal fluid from individuals with niemann-pick disease, type c1," *Proteomics*, p. 2200378, 2023.

[5] M. T. Vanier, F. M. Platt, E. R. Eden, and M. C. Patterson, "Niemann- pick disease type c," *Lysosomal Storage Disorders: A Practical Guide*, pp. 134–143, 2022.

[6] T. Rego, S. Farrand, A. M. Goh, D. Eratne, W. Kelso, S. Mangelsdorf,

[7] Velakoulis, and M. Walterfang, "Psychiatric and cognitive symptoms associated with niemann-pick type c disease: neurobiology and manage- ment," *CNS drugs*, vol. 33, pp. 125–142, 2019.

[8] Mengel, M. C. Patterson, R. M. Da Riol, M. Del Toro, F. Deodato,

[9] M. Gautschi, S. Grunewald, S. Grønborg, P. Harmatz, B. Héron, *et al.*, "Efficacy and safety of arimoclomol in niemann-pick disease type c: re-sults from a double-blind, randomised, placebo-controlled, multinational phase 2/3 trial of a novel treatment," *Journal of inherited metabolic disease*, vol. 44, no. 6, pp. 1463–1480, 2021.

[10] P. M. Shanthappa and R. Kumar, "Proall-d: protein allergen detection using long short term memory-a deep learning approach," *ADMET and DMPK*,

vol. 10, no. 3, pp. 231–240, 2022.

[11] P. M. Shanthappa, R. Suravajhala, P. Suravajhala, G. Kumar, and

[12] N. Melethadathil, "In silico based multi-epitope vaccine design against norovirus," *Journal of Biomolecular Structure and Dynamics*, pp. 1–11, 2022.

[13] T. N. Jarada, J. G. Rokne, and R. Alhajj, "A review of computational drug repositioning: strategies, approaches, opportunities, challenges, and directions," *Journal of cheminformatics*, vol. 12, no. 1, pp. 1–23, 2020.

[14] J. Zhou, Q. Li, W. Wu, X. Zhang, Z. Zuo, Y. Lu, H. Zhao, and

[15] Z. Wang, "Discovery of novel drug candidates for alzheimer's disease by molecular network modeling," *Frontiers in Aging Neuroscience*, vol. 14, 2022.

[16] Otero-Carrasco, L. Prieto Santamaría, E. Ugarte Carro, J. P. Caraça- Valente Hernández, and A. Rodríguez-González, "Repositioning drugs for rare diseases based on biological features and computational ap- proaches," in *Healthcare*, vol. 10, p. 1784, MDPI, 2022.

[17] X. Li, F. Lu, M. N. Trinh, P. Schmiege, J. Seemann, J. Wang, and

[18] Blobel, "3.3 a˚ structure of niemann–pick c1 protein reveals insights into the function of the c-terminal luminal domain in cholesterol transport," *Proceedings of the National Academy of Sciences*, vol. 114, no. 34, pp. 9116–9121, 2017.

[19] Nygaard, A. Løland, M. Holden, M. Langaas, H. Rue, F. Liu,

[20] O. Myklebost, Ø. Fodstad, E. Hovig, and B. Smith-Sørensen, "Effects of mrna amplification on gene expression ratios in cdna experiments estimated by analysis of variance," *Bmc Genomics*, vol. 4, no. 1, pp. 1– 13, 2003.

[21] A. Mahram and M. C. Herbordt, "Fast and accurate ncbi blastp: Acceleration with multiphase fpga-based prefiltering," in *Proceedings of the 24th ACM International Conference on Supercomputing*, pp. 73– 82, 2010.

[22] P. W. Rose, A. Prlić, A. Altunkaya, C. Bi, A. R. Bradley, C. H. Christie,

[23] L. D. Costanzo, J. M. Duarte, S. Dutta, Z. Feng, *et al.*, "The rcsbprotein data bank: integrative view of protein, gene and 3d structural information," *Nucleic acids research*, p. gkw1000, 2016.

[24] S. M. D. Rizvi, S. Shakil, and M. Haneef, "A simple click by click protocol to perform docking: Autodock 4.2 made easy for non-bioinformaticians," *EXCLI journal*, vol. 12, p. 831, 2013.

[25] R. Huey, G. M. Morris, and S. Forli, "Using autodock 4 and autodock vina with autodocktools: a tutorial," *The Scripps Research Institute Molecular Graphics Laboratory*, vol. 10550, no. 92037, p. 1000, 2012.

[26] W. L. Whelan and C. E. Ballou, "Sporulation in d-glucosamine aux- otrophs of saccharomyces cerevisiae: meiosis with defective ascospore wall formation," *Journal of bacteriology*, vol. 124, no. 3, pp. 1545–1557, 1975.

[27] M. J. Abraham, T. Murtola, and R. Schulz, "Pa´ ll s, smith jc, hess b, et al. gromacs: High performance molecular simulations through multi- level parallelism from laptops to supercomputers. softwarex. 2015; 1–2: 19–25."

[28] C.-Y. Zhou, F. Jiang, and Y.-D. Wu, "Residue-specific force field based on protein coil library. rsff2: modification of amber ff99sb," *The journal of physical chemistry B*, vol. 119, no. 3, pp. 1035–1047, 2015.

[29] A. Case, R. E. Duke, R. C. Walker, N. R. Skrynnikov, T. E. Cheatham III, O. Mikhailovskii, C. Simmerling, Y. Xue, A. Roitberg,

S. A. Izmailov, *et al.*, "Amber 22 reference manual," 2022.

[31] J. Wang, W. Wang, P. A. Kollman, and D. A. Case, "Antechamber: an accessory software package for molecular mechanical calculations," *J. Am. Chem. Soc*, vol. 222, no. 1, 2001.

[32] A.W. Sousa da Silva and W. F. Vranken, "Acpype-antechamber python parser interface," *BMC research notes*, vol. 5, pp. 1–8, 2012.

[33] Y. Wu, H. L. Tepper, and G. A. Voth, "Flexible simple point-charge water model with improved liquid-state properties," *The Journal of chemical physics*, vol. 124, no. 2, p. 024503, 2006.

[34] B. BIÇ AK and S. K. GUNDUZ, "Conformational analysis of tyrosyl- lysyl-threonine tripeptide using mm, md and qm methods and its hy-perpolarizability study," *Sakarya University Journal of Science*, vol. 26, no. 4, pp. 745–756.

[35] W. Humphrey, A. Dalke, and K. Schulten, "J. l\/lolec," *J Mol Graphics*, vol. 14, pp. 33–38, 1996.