AIA STATEMENT OF PURPOSE.

Understanding protein-ligand interactions at a molecular level is crucial for drug development and disease treatment. However, the accurate prediction of binding affinities between small molecules and protein targets remains challenging in Molecular Biophysics and Structural Biology. Developing novel computational models and experimental approaches to precisely forecast and interpret protein-ligand binding and unraveling the intricate mechanisms influencing these interactions poses a significant research problem. Addressing this gap could revolutionize drug design and the understanding of disease pathways, potentially leading to the creation of more effective therapeutic interventions. Hence, this concern with needing additional and improved Molecular Biophysics and Structural Biology knowledge made me apply for this program. The doctoral program at the University of **XXXXXXXXX** program is my perfect program, and it is an excellent opportunity to hone my research skills and align with my career goals.

The pursuit of understanding and addressing the challenges of various diseases influencing humanity propelled my choice to pursue a Chemistry undergraduate program. At the Federal University of Technology Akure (FUTA) Nigeria, I realized the intrinsic link between theoretical and practical chemistry knowledge, envisioning how this expertise could make meaningful changes in human health issues. The diverse curriculum introduced me to various fields, particularly Organic Chemistry and Natural Products Chemistry, shedding light on the significance of bioactive compounds sourced from plants and their role in drug design. I maintained a high academic standing, securing the second-best result in my class in 2021 with a CGPA of 4.XX/5.00. My passion for research burgeoned during my fourth year at FUTA, driving me to collaborate on a study investigating the comparative quality of different paracetamol tablet brands in Nigeria. This exploration aimed to evaluate these tablets' physical and microbiological parameters, revealing that most brands passed physical parameters tests. The study emphasized the necessity of upholding Good Manufacturing Practices to ensure high-quality paracetamol products and consumer safety. Additionally, my Bachelor's thesis delved into monitoring the impact of stream water in the FUTA area on human health under the supervision of Prof. XXX. The research provided critical insights using methodologies involving assessing physicochemical properties and employing Atomic Absorption Spectrophotometry (AAS) to estimate heavy metal concentrations in water samples. It highlighted the unsuitability of the stream water for drinking without proper treatment, offering crucial information to the local community and individuals working in the stream's proximity. This endeavor equipped me with practical skills in sample collection, preservation, analysis of physicochemical parameters, and utilizing Statistical Package for the Social Sciences (SPSS) for data analysis.

After completing my undergraduate studies in 2021, I interned with the Computer-aided Therapeutic Drug Design and Discovery (CATDD) team at the FUTA under the supervision of XXXX. This internship provided me with extensive knowledge of various *In silico* tools, software, and databases crucial in drug design and discovery, including SwissADME, Protein Data Bank, ChemSketch, Schrodinger Work Station, PubChem, Chimera, Discovery Studio, PyRx, AutoDock, iGEMDock, PyMol, ProteinPlus, Plip, ADMETlab, and admetSAR. I learned that these tools leverage chemoinformatics to aid in designing medications for diverse diseases like diabetes and malaria. Motivated by my interest in human health and modern technologies, I engaged in a project using these *in silico* tools to investigate the potential antidiabetic properties of bioactive compounds found in "Effinrin," Cocoyam, and *Jatropha curcas L*. The research aimed to predict the therapeutic potential of these compounds through molecular docking, comparing them with established antidiabetic medications like Vildagliptin, Linagliptin, and Metformin, using a Human target DPP-4 complex with a novel heterocyclic DPP4 inhibitor (4A5S) protein. Employing SwissADME for drug-likeness screening and PyRx incorporating Autodock, Vina Wizard, and Openbarbel for molecular docking, I examined how these bioactive compounds bind to the target protein to inhibit type-2 diabetes and predicted their pharmacokinetic characteristics. Utilizing the admetSAR database, I found that Caffeic acid, Rosmarinic acid, Salvigenin, Catechin, Gallic acid, Pyrogallol, and Daidzein exhibited more favourable Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) characteristics compared to standard antidiabetic medications. The study's findings are undergoing further investigation using the Molecular Dynamics method.

To enhance my research skills, in 2022, I collaborated on a study focusing on "*In silico* Studies of Bioactive Compounds from Four African Plants against Plasmodium falciparum Dihydrofolate Reductase-Thymidylate Synthase (pfDHFR-TS)." This research aimed to identify bioactive compounds from Bitter leaf, Lemongrass, Neem leaf, and Pawpaw leaf with superior binding affinity and pharmacokinetic properties compared to Artemether and Lumefantrine- common medication used in malaria treatments in Nigeria, known for side effects like headache and muscle pain. Using existing literature, I selected 20 bioactive compounds from Bitter leaf, Lemongrass, Neem leaf, and Pawpaw leaf. I used a chemical repository server-

PubChem, to obtain the 3D structure in structure data format (SDF) and the canonical SMILES of the bioactive compounds and the control medications (Artemether and Lumefantrine). I also gained valuable skills in target selection using the research collaboratory of structural bioinformatics (RCSB) protein databank web server. I cleaned and prepared the target protein using Chimera software. This research taught me other computational chemistry skills using the PyRx software for molecular docking, which is very important for binding score/binding affinity prediction. I used the PyMOL software, SwissADME, Molinspiration, and ADMETlab online tools for Molecular interaction analysis, druglikeness screening, bioactivity prediction, and Pharmacokinetics prediction, respectively. The results from this study propose that Nimbolide, Vernomygdin, Luteolin, and Emetine are the hit compounds, with a better binding affinity from the molecular docking with the target protein, compared to Artemether and Lumefantrine.

In pursuit of combating the persistent impact of COVID-19 despite various global treatment research, In 2022, I also engaged in collaborative research focused on "Evaluating Therapeutic Potentials of Bioactive Compounds from Selected African Plants Targeting SARS-CoV-2 Main Protease (Mpro): A Molecular Docking Study." We aimed to assess the therapeutic potential of bioactive compounds found in the Baobab tree, Alligator pepper, Billy goat weeds, and Frankincense tree against the SARS-CoV-2 Mpro. Utilizing in-silico tools, I contributed to various analyses encompassing ligand and protein selection, drug-likeness screening, molecular docking, visualization, bioactivity, and pharmacokinetics prediction. Leveraging resources such as PubChem, SwissADME, PyRx, PyMOL, ProteinPlus, and Plip webservers, I obtained 3D structures and canonical SMILES of bioactive compounds and a control medication (Remdesivir), conducted drug-likeness screenings as per Lipinski's Rule of Five, executed molecular docking, and visualized molecular interactions. The study highlighted that compounds Catechin, Epicatechin, Vitexin, Quercetin, Kaempferol, Gamma-Sitosterol, and Kaur-16-ene exhibited good binding affinity with the target protein, demonstrating favourable ADMET properties. This research has been accepted for publication in the Egyptian Journal of Medical Human Genetics. This endeavour significantly contributes to understanding potential treatment options against SARS-CoV-2, representing my commitment to addressing the global health challenge posed by the COVID-19 pandemic.

In my quest to understand and explore treatments for Type 2 diabetes, a condition marked by elevated blood sugar due to insulin resistance or insufficient insulin production, In 2023, I collaborated on a research project titled "Therapeutic Potential and Molecular Docking Perspective of Medicinal Plants against Human SIRT-6 Protein linked to Type-2 Diabetes." Our approach involved molecular docking, a simulation strategy utilizing protein and ligand structural features to predict their interactions. Within this study, I investigated bioactive compounds in African plants, including *Buchholzia coriacea*, *Vernonia amygdalina*, *Mimosa pudica*, *Momordica charantia*, *Bergenia ciliate*, and *Mangifera indica*. Utilizing *In silico* tools, I selected 29 bioactive compounds, obtaining their canonical SMILES and 3D structures via the PubChem Webserver. I employed Chimera software to prepare the co-crystallized SIRT-6 Protein, removing water molecules and assigning Gasteiger-Huckel charges. The project encompassed drug-likeness screening, molecular docking, molecular interaction analysis, bioactivity, and pharmacokinetic prediction using tools like SwissADME, AutoDock, PyMOL, Molinspiration, and ADMETlab. Notably, the results revealed that bioactive compounds such as Catechin, Luteolin, Chlorogenic acid, and Mimopudine exhibited superior binding affinity and favourable ADMET properties compared to control medications (Metformin and Miglitol). The research was published in the Journal of Advanced Pharmacy Research (JAPR) on 31/10/2023. This endeavour significantly contributes to understanding potential treatments for Type 2 diabetes, reflecting my dedication to addressing health challenges through scientific inquiry and collaborative research efforts.

Moreover, I actively participated in the Chemoinformatics Summer School at Universite Paris Cite, where I joined a team for a Hackathon session utilizing Openeye Orion software. I conducted Molecular Modelling tasks within this session, generating FastROCS hits and conformations for Entrectinib, an anti-cancer medication, and conducted docking experiments with the ALK kinase domain from PDB entry 5FTO. This experience illuminated the differences between docked and re-docked compounds. Additionally, I collaborated with a diverse team from the University of Padova, the University of Zagreb, the University of Ljubljana, and the University of Giessen on the DigiChem project, emphasizing sustainability, Green Chemistry principles, and rational modeling. This project fostered my understanding of sustainability's core tenets and the metrics essential to Green Chemistry.

In nurturing comprehensive skills in research and teaching, scientists must excel in conducting research, effectively communicating scientific knowledge, and mentoring students. My academic journey and experiences have allowed me to cultivate proficiency in these crucial areas. Throughout my academic pursuits, I engaged in teaching roles that honed my ability to impart scientific knowledge. As a chemistry course instructor in a secondary school, I shared foundational concepts with students,

offering guidance in General, Organic, Inorganic, Physical, and Analytical Chemistry during my undergraduate years. Beyond academic settings, I volunteered for the Africa Climate and Environment Foundation (ACEF) as their Environmental Chemist for the Africa region. This opportunity enabled me to raise awareness in various communities regarding climate change's impact and the management of diseases affecting individuals. Moreover, I took the initiative to design and lead a training series focused on Computer-aided drug design and discovery. Over four cohorts, I successfully trained 20 students in library preparation, target selection and preparation, drug-likeness screening, molecular docking, molecular visualization, bioactivity, and ADMET prediction. These experiences have significantly enhanced my ability to conduct research, effectively communicate scientific concepts, and mentor aspiring students in science.

On the back of my academic, research experience, and internship experience, this is the golden moment for me to pursue my doctoral degree in **XXXXXXX**, and the University of **XXXXXX** program is my perfect program. The well-designed program curriculum, which includes the Foundation of Biomedical Science, Molecular Biophysics I, II, and III, Scientific Ethics, and Introduction to Statistical Methods, perfectly aligns with my career objective. Also, the opportunity to take part in a Lab rotation will provide a good relationship with a potential dissertation advisor and to learn various laboratory techniques. This program will equip me with skills in using contemporary facilities such as X-ray, NMR, and Electron Microscopy, critical tools in structural biology for high-resolution, three-dimensional structural analysis of proteins and protein complexes. Furthermore, the computational resources of the university will help me understand the functioning or malfunctioning of proteins and biological complexes as Computational tools play an increasingly important role in biophysical and structural research. Furthermore, the Programming Proficiency organized by the program will help me to improve my HTML/CSS, PHP, and Python programming skills, which I am currently working on; further improvement of these skills will improve my computer literacy skill and improve my skills on the use of these programming skills to solve different biophysical problems. This program will also allow me to attend the weekly Molecular Biophysics and Structural Biology Seminar Series and the bimonthly Data and Literature Club. This seminar will provide me an excellent opportunity to meet high-caliber scientists engaged in Biophysics and Structural Biology research from inside and outside of the XXXXX area XXXXXXX to discuss and learn more about this subject. This program will allow me to learn and work with world-class Professors in top-notch research laboratories and a body of students who share a similar goal of improving the world of science.

The emergence of new diseases, like SARS-CoV-2, continually burdens science to catch up with cures and vaccines and the molecular mechanism of the diseases. In my doctorate, I aim to learn XXXXX at the University of XXXXXX. Hence, based on my research interest, I aim to follow the Chemical Structure and Dynamics and Principles of Protein Structure and Dynamics track and to join XXXXXX research group, XXXX Lab, based his research on developing and applying techniques related to computer-aided drug discovery (CADD) and molecular-dynamics simulations. XXXX Lab research on Small-Molecule Ligand Identification and Molecular Visualization is significant in disease processes and answers biological questions such as how does the Ligands bind to grooves and pockets in viral, bacterial, parasitic, and cancer-related proteins?, how does Ligand binding changes protein function, thus interfering with associated disease/biological processes? My experience with Molecular docking and scoring and molecular visualization using different software such as Autodock, Chimera, iGEM dock, Glides, PyMOL, Plip, Protein Plus, and Discovery Studio from my previous projects will help me with his project on Small-Molecule Ligand Identification and Molecular visualization. Also, I am familiar with molecular dynamics using Molecular Operating Environment (MOE), used to study protein motions. Similarly, I am also interested in XXXXXXX. His lab based its research on AI-driven drug discovery, using artificial intelligence (AI) methods that enable the design of chemical libraries with the desired physicochemical and biological properties. Joining his lab will help me use a mechanistic-driven approach to identify novel molecules and molecular-level understandings to discover novel drug candidates to address unmet human health and disease needs, which are essential in drug design and discovery. Joining either of these esteemed research groups would provide an avenue for expanding my knowledge and skills and also align with my ambition to contribute meaningfully to XXXXX research. As a doctoral candidate, I aspire to contribute to the ongoing research at the University of XXXXXX by developing integrated methodologies that bridge the gaps between computational, theoretical, and XXXXXX. My background and research experience, coupled with the collaborative and supportive research environment at the University of XXXXX, will empower me to make meaningful contributions to the XXXXXX field.

My ultimate career goal after my Ph.D. is to apply for a Post-doctoral role in protein-ligand interactions research at a research-intensive University; this role will also improve my knowledge and skills in XXXXX by working with different experts in this field. After my Post-doctoral role, I plan to head a research laboratory studying XXXXX with the application of Computational tools to work on mechanisms of different diseases affecting humans. I plan to collaborate with different research institutes for a novel research

project. I seek to become a professor at a research-intensive university, which will allow me to serve as a mentor and train the next generation of scientists in XXXXX. Earning a doctoral degree from the University of XXXX is the ideal preparation for the advanced research I hope to accomplish. I am excited by the prospect of joining the university. The University of XXXX is the right place for my doctoral degree because of its excellent learning environment and opportunities for collaborative research offered by the university, which will build my career goal.