To

maa, PAPA, THUNU

"Thank you for everything"

TEZPUR UNIVERSITY
(A Central University established by an Act of Parliament)
Napaam-784028, Tezpur, Sonitpur, Assam, India

DECLARATION BY THE CANDIDATE

I, **Ms. Dikshita Dowerah,** hereby, declare that the thesis entitled **"Studies on Structure and Dynamics of Bridged Nucleic Acid based ASOs Using Density Functional Theory and Molecular Dynamics Approach for Targeted RNA Therapeutics"** has been submitted to the Department of Chemical Sciences under the School of Sciences of Tezpur University, in partial fulfilment of the requirements for the award of the degree of **Doctor of Philosophy in Chemical Sciences**. This thesis is a record of original research work carried out by me under the guidance of **Prof. Ramesh Ch. Deka** and the contents of the thesis, in full or in part, has not been previously considered for the award of any degree, diploma, associateship, fellowship or any other similar title or recognition from any University, Institute or other Organization.

I further declare that; I have duly acknowledged all sources of assistance and any text, figures, results or design that are not of my own are appropriately referenced in order to give credit to the original author(s).

Date: 28/12/2023
Place: Tezpur University

Dikshita Dowerah
(Dikshita Dowerah)
Department of Chemical Sciences
Tezpur University

Dr. Ramesh Ch. Deka, FRSC
Professor, Department of Chemical Sciences
School of Sciences, Tezpur University
Napaam-784028, Tezpur, Assam, India
Mobile: 9435380221
Email: ramesh@tezu.ernet.in, rcdekatu@gmail.com

NAAC Grade A+

CERTIFICATE FROM THE SUPERVISOR

This is to certify that the thesis entitled **"Studies on Structure and Dynamics of Bridged Nucleic Acid based ASOs Using Density Functional Theory and Molecular Dynamics Approach for Targeted RNA Therapeutics"** has been submitted by **Ms. Dikshita Dowerah** to the Department of Chemical Sciences under the School of Sciences of Tezpur University, in partial fulfilment of the requirements for the award of the degree of **Doctor of Philosophy in Chemical Sciences**. This thesis is a record of bona fide research work carried out by her under my supervision and guidance. She has been registered, completed her PhD course work and the thesis presented is worthy of consideration for the award of PhD degree.

All help received by her from various sources have been duly acknowledged.

The contents of this thesis, in full or in part, have not been submitted for the award of any degree, diploma, associateship, fellowship or any other similar title or recognition from any University, Institute or other Organization.

Ramesh Ch. Deka

Date: 28.12.2023.

Place: Tezpur University

(Ramesh Ch. Deka)
Department of Chemical Sciences
Tezpur University, Assam

“Acknowledgement is the only way to keep love alive”

- Barry Long

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"জীৱনত একোহৰে অভাৱ হবলৈ নিদি, আমাৰ সপোনবোৰক দিঠকত পৰিণত কৰিবলৈ আৰু জীৱনবাটত আগবাঢ়িবলৈ দিয়া সকলোখিনি স্বাধীনতাৰ বাবে তোমালোকৰ ওচৰত মই চিৰঋণী" – ধুনু।

Dikshita Dowerah (দীক্ষিতা দুৱৰা)

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ABBREVIATIONS AND SYMBOLS

ALT	Alanine Transaminase
AMBER	Assisted Model Building with Energy Refinement
ASO	Antisense Oligonucleotide
AST	Aspartate Transferase
BNA	Bridged Nucleic Acid
CADD	Computer-Aided Drug Design
CeNA	Cyclohexene Nucleic Acids
cEt	Constrained Ethyl
CG	Coarse-Grained
CHARMM	Chemistry at Harvard Macromolecular Mechanics
CML	Chronic Myeloid Leukaemia
cMOE	Constrained Methoxyethyl
CPCM	Conductor-like Polarizable Continuum Model
CPP	Cell Penetrating Peptides
DFT	Density Functional Theory
DMD	Duchenne Muscular Dystrophy
DNA	Deoxyribonucleic Acid
ED_{50}	Effective Dose 50
ENA	Ethylene Nucleic Acid
FANA	2'-Fluoro-Arabino Nucleic Acid
FDA	Food and Drug Administration
FF	Force-field
GGA	Generalized Gradient Approximations
GPU	Graphics Processing Unit
GROMACS	GROningen MAchine for Chemical Simulation
HF	Hartree-Fock
HIV	Human Immunodeficiency Virus
HOMO	Highest Occupied Molecular Orbital
HPC	High Performance Computers
KS	Kohn Sham

LDA	Local Density Approximations
LJ	Lennard-Jones
LNA	Locked Nucleic Acid
LUMO	Lowest Unoccupied Molecular Orbital
MC	Monte Carlo
MD	Molecular Dynamics
MM	Molecular Mechanics
MM-GBSA	Molecular Mechanics with Generalised Born and Surface Area Solvation
MO	Molecular Orbital
MP	Møller-Plesset
mRNA	Messenger RNA
NBO	Natural Bond Orbital
NIH	National Institutes of Health
NMR	Nuclear Magnetic Resonance
NP	N3'-P5' phosphoroamidates
NPT	Isobaric-Isothermal Ensemble
NVE	Microcanonical Ensemble
NVT	Canonical Ensemble
ODN	Oligodeoxynucleotide
ON	Oligonucleotide
ONIOM	Our own N-layered Integrated molecular Orbital and Molecular Mechanics
OPLS-AA	All-Atom Optimized Potentials for Liquid Simulations
PBC	Periodic Boundary Condition
PCA	Principal Component Analysis
PDB	Protein Data Bank
PES	Potential Energy Surface
PME	Particle Mesh Ewald
PMO	Phosphoramidate Morpholino Oligomer
PNA	Peptide Nucleic Acid
PS	Phosphothioate

PTEN	Phosphatase and Tensin homolog
QM	Quantum Mechanics
QM/MM	Quantum Mechanics/Molecular Mechanics
QSAR	Quantitative Structure-Activity Relationship
RCSB	Research Collaboratory for Structural Bioinformatics
RESP	Restrained electrostatic potential
RMSD	Root Mean Square Deviation
RMSF	Root Mean Square Fluctuation
RNA	Ribonucleic Acid
RNase H	Ribonucleases H
RoG	Radius of Gyration
RSV	Rous Sarcoma Virus
SASA	Solvent Accessible Surface Area
siRNA	Small-interfering RNA
SMA	Spinal Muscular Atrophy
ssRNA	Single-stranded RNA
tcDNA	Tricyclo-DNA
tRNA	Transfer RNA
vdW	van der Waals
VMD	Visual Molecular Dynamics
WC	Watson-Crick