*A*

*Thesis*

*On*

# *Exploring In silico Structure based and Ligand based Approaches for the Development of Neurodegenerative Agents*

Submitted for Partial Fulfillment of the Requirement for the Award of Degree of

**Master of Pharmacy**

**(Pharmaceutical Chemistry)**

*By*

**NISHA LAKRA**

Enrollment No. GGV/20/06326

Roll No. 20703004

*Under the Supervision of*

**Dr. PARTHA PRATIM ROY**

Assistant Professor (Pharmaceutical Chemistry)

**SESSION 2021-2022**

**DEPARTMENT OF PHARMACY**

**GURU GHASIDAS VISHWAVIDYALAYA (A Central University)**

**BILASPUR (C.G.)**

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# FORWARDING CERTIFICATE

This is to certify that **NISHA LAKRA** student of M. Pham 4th semester has submitted her thesis entitled "**Exploring *In silico* Structure based and Ligand based approaches for the development of Neurodegenerative agents**" for the partial fulfillment of the requirement for the Degree of **Master of Pharmacy (Pharmaceutical Chemistry)** at Department of Pharmacy, GGV Bilaspur (C.G.). She has completed her thesis under the supervision of **Dr. PARTHA PRATIM ROY** (Asst. Prof.). Her work is Original, Satisfactory and is not submitted anywhere else for the award of any degree.

I hereby forward her project work in M. Pharm. (Pharmaceutical Chemistry) during the academic session 2021-2022.

**Forwarded by**

28/10/22

**Date:** 28/10/2022

**Dr. BHARTI AHIRWAR**
**Associate Professor and**
**Head of Department**
**Department of Pharmacy, G.G.V.**
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# CERTIFICATE

This is to certify that **NISHA LAKRA** student of M. Pharm. 4th Semester, Department of Pharmacy (GGV) has submitted her thesis entitled "**Exploring *In silico* Structure based and Ligand based approaches for the development of Neurodegenerative agents"** for the partial fulfillment of the requirement for the Degree of **Master of Pharmacy (Pharmaceutical Chemistry)**. She has completed her project under my supervision.

I hereby recommend to forward her thesis for the award of degree of M. Pharm. (Pharmaceutical Chemistry) during the academic session 2021-2022.

**Supervised By**

**Date:** 28/10/2022

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**Asst. Professor (Pharm. Chem.)**
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# DECLARATION

I hereby declare that the thesis entitled "**Exploring *In silico* Structure based and Ligand based approaches for the development of Neurodegenerative agents"** was done by me and the entire work was done with the guidance and suggestion received from my supervisor **Dr. PARTHA PRATIM ROY** (Asst. Prof.) for the submission of thesis for the partial fulfillment of the requirement for the Degree of Master of Pharmacy (Pharmaceutical Chemistry).

I further declare that I have not submitted this thesis previously for award of any degree or diploma anywhere else.

**Date:** 28/10/2022

**NISHA LAKRA**

**Master of Pharmacy**

**Enroll. No. GGV/20/06326**

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*My Sincere thanks to all...!!*

**NISHA LAKRA**

# PREFACE

The work presented in this dissertation was done throughout nearly one year of the M. Pharm. curriculum, as required. It has only looked at a small portion of the wide range of theoretical work.

Neurodegenerative disease is the progressive loss of structure or function of neurons and the process is known as neurodegeneration. Neurons are the building blocks of the central nervous system. It connects with each other in order to send and receive messages in the brain and spinal cord. Neuronal injury may ultimately lead to cell death. Neurodegenerative disease represent a serious threat to human health aspeople live longer, these diseases are becoming more prevalent. Alzheimer disease, Parkinson disease, Huntington disease, Prions disease, Multiple sclerosis and Amyotrophic lateral sclerosis are the different types of neurodegenerative disease. From all these disease, my main focus is on Alzheimer disease for my detailed studybecause Alzheimer disease is one of the typical medical and social problems most widely prevalent in older people. Additionally, if we see the statistic of Alzheimer disease, it is reported that 13% of the individual over the age of 65 in growing countries have Alzheimer disease and also reported that these age-dependent disorders are becoming increasingly prevalent, in part because the elderly population has increased in recent years. So, as the rate of Alzheimer disease cases is increasing continuously there is a need develop new, more potent and effective therapeutic strategies to combat these devastating disease.Cholinesterase are the primary promising targets which is mainly involved in Alzheimer diseaseand the inhibitors of these targets are the choice for the anti-alzheimer agents. The US FDA approved drugsare Donepezil, Galantamine, Rivastigmine, Memantine and Tacrine these are all cholinesterase inhibitors for the management of Alzheimer disease, but it only alleviate some symptoms and also have side-effects.

In silico refers to the computational modelling techniques in the process of finding new drugs. In silico tools are currently used in the drug discovery process to identify and develop a potential lead/hit.Nowadays, computational techniques are becoming popular in the academic as well as in pharmaceutical industries. Structure-based and ligand-based modelling techniques are the two broad categories of modelling methodology. The

structure-based approach consists of using the 3D structure of the target (enzyme/receptor) for the generation or screening of potential ligands followed by synthesis, biological testing, and optimization. In contrast, the ligand-based approach entails using computational modelling techniques to create theoretical predictive models using a collection of compounds with various structures and known potency.These models are then employed for structural optimization to increase potency and for the virtual screening of a huge chemical library in order to discover new chemical entities. In this context we use coumarin derivatives as coumarin are the natural compounds with lots of biological activities such as anti-inflamatory, anti-allergy, anti-alzheimer, anti-hypertension, anti-epileptic, anti-convulsant, anti-fungal, anti-cancer, anti-tumor, anti-viral and so on. The possible chemical substitution in the basicnucleus of coumarin structure makes them interesting molecules in drug discovery. Moreover, according to literature survey HDAC inhibitors also play a key role in neurodegenerative disease. HDAC inhibitors are responsible for homeostasis of protein acetylation and transcriptional dysfunction. A wide range of brain disorders are associated with protein acetylation levels and transcriptional dysfunction. Treatment with various HDAC inhibitors can correct these deficiencies and has emerged as a promising new strategy for therapeutic intervention in neurodegenerative disease acting through multiple targets.

In this framework we have tried to study the potential of Pharmacophore screening in search of new and novel analogues as anti Alzheimer agents. In addition we have also focused our study in polypharmacological approach for HDAC inhibitors for possible contribution in Alzheimer disease acting through multiple targets in structure based Pharmacophore and docking approach

In this context the following studies were carried out:

1. Pharmacophore Based Virtual Screening of Cholinesterase Inhibitors: Search of New Potential Drug Candidates as Antialzheimer Agents.

2. Structure based pharmacophore for screening of HDAC inhibitors.

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