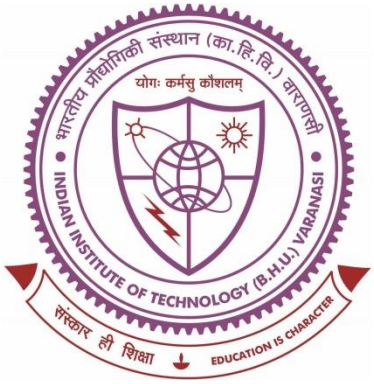
Structure Activity Relationship Studies on Ferulic Acid Template-Based Novel Molecules to Improve Upon Multifunctional Properties for The Management of Alzheimer's Disease



Thesis submitted in partial fulfilment for the Award of Degree

Doctor of Philosophy

By

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CERTIFICATE

It is certified that the work contained in the thesis titled "***Structure Activity Relationship Studies on Ferulic Acid Template-Based Novel Molecules to Improve Upon Multifunctional Properties for The Management of Alzheimer's Disease***" by ***Gourav Singh*** has been carried out under my supervision and that this work has been not submitted elsewhere for a degree.

It is further certified that the student has fulfilled all the requirements of Course work, Comprehensive, Candidacy, SOTA and Pre-submission seminar.

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DECLARATION BY THE CANDIDATE

I, ***Gourav Singh***, certify that the work embodied in this Ph.D. thesis is my own bonafide work and carried out by me under the supervision of ***Dr. Gyan Prakash Modi*** from **January, *2019 to July, 2024*** at the ***Department of Pharmaceutical Engineering & Technology***, Indian Institute of Technology (B.H.U.), Varanasi. The matter embodied in this thesis has not been submitted for the award of any other degree/diploma.

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It is certified that the above statement made by the student is correct to the best of my/our knowledge.

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List of Schemes

List of Abbreviations

Abbreviations	Full forms
AD	Alzheimer's disease
ACh	Acetylcholine
*h*ACh	Human acetylcholine
MW	Molecular weight
MTT	3- (4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium
PAS	Peripheral anionic site
ROS	Reactive oxygen species
TMS	Tetramethylsilane
BChE	Butyrylcholinesterase
BBB	Blood-Brain Barrier
CAS	Catalytic active site
$CDCl_3$	Deuterated chloroform
DMSO-d_6	Deuterated dimethyl sulfoxide-d_6
DPZ	Donepezil
DTNB	5,5'-dithiobis-2-nitrobenzoic acid
DPPH	2,2-diphenyl-1-picrylhydrazyl
EDCI.HCl	1-[3-(dimethylamino)-propyl]-3-ethyl carbodiimide hydrochloride
FA	Ferulic acid
MABs	Monoclonal antibodies
JNK	Janus kinase
HRMS	High-resolution mass spectrometry
HOBt	*N*-hydroxybenzotriazole
IC_{50}	The inhibitory concentration required to kill 50% of the population
IL-6	Interleukin-6
IL-β	Interleukin-beta
MMP	Mitochondrial membrane potential
TLR4	Toll-like receptor 4
NLRP3	Nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3
CAT	Catalase
MDA	Malondialdehyde
SOD	Superoxide dismutase

List of Symbols

Symbols	Meaning
α	Alpha
β	Beta
δ	Delta
ºC	Degree Celsius
Å	Angstrom
mg	Milligram
μg	Micro gram
μM	Micromole
mmol	Millimole
mL	Milliliter
μL	Microliter
h	Hour
s	Singlet
nm	Nanometer
µm	Micrometer
mm	Millimeter
cm	Centimeter
ppm	Parts per million
rpm	Revolutions per minute
Kcal	Kilocalories
Hz	Hertz
MHz	Megahertz
J	Coupling constant
d	Doublet
t	Triplet
q	Quartret
m	Multiplet
dd	Doublet of doublet
m/z	Mass-to-charge ratio
%	Percent
pH	Potential of hydrogen
≤	Less than or equal
<	Less than
>	More than
±	Plus or minus

Preface

Alzheimer's Disease (AD) is an age-related neurodegenerative disorder that accounts for over 80% of dementia cases in older adults worldwide. It is characterized by low level of acetylcholine (Ach), Incease of oxidative stress, accumulation of metals, deposition of amyloid-beta (Aβ) plaques and neurofibrillary tangles, leading to the progressive loss of memory and cognitive functions. Despite decades of research on the etiology of the disease and substantial efforts by the pharmaceutical industry to develop effective therapies, no treatment has been found to cure AD or significantly inhibit its progression. Currently, four drugs—donepezil, galantamine, rivastigmine (acting on the cholinergic pathway), and memantine (acting on the NMDA receptor) and are approved by the USFDA. Aducanumab and Lecanemab are monoclonal antibodies (MABs) recently approved for the treatment of AD. These drugs target amyloid-beta (Aβ) plaques, which are believed to play a central role in the pathophysiology of AD. Given the complex and multifactorial nature of AD, developing multifunctional ligands is a more promising approach.

The present study is divided into six chapters:

Chapter 1: This chapter overviews Alzheimer's disease, including its pathophysiology and the current treatments.

Chapter 2: This chapter presents a comprehensive review of the existing literature related to the relevant research.

Chapter 3: This chapter outlines the research work's hypothesis, rationale, and detailed plan.

Chapter 4: This chapter discusses the rationale for synthesizing and evaluating novel ferulic acid derivatives, specifically glycine/piperazine amide/benzylpiperazine/tryptamine derivatives. The designed molecules were synthesized and subjected to *in-vitro* enzyme inhibition studies. The potent molecules identified from these studies were further investigated for enzyme kinetics, antioxidant activity, metal chelation, Aβ modulation, and neuroprotection. Lead compounds were then selected for *in-vivo* studies in AD animal models to evaluate their effects on working memory and learning.

Chapter 5: This chapter details the general synthetic procedures used for the targeted compounds and their subsequent biological evaluation.

Chapter 6: This chapter provides the final summary and conclusions drawn from the research.

Introduction