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It is certified that the work contained in the thesis titled "**DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF FERULIC ACID TEMPLATE BASED NATURALLY INSPIRED NOVEL NEUROPROTECTIVE MULTIFUNCTIONAL MOLECULES FOR THE TREATMENT OF ALZHEIMER'S DISEASE**" by **YASH PAL SINGH** has been carried out under my supervision and that this work has been not submitted elsewhere for a degree.

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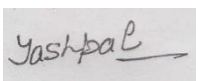

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List of Abbreviations

Abbreviations	Full forms
AD	Alzheimer's disease
ACh	Acetylcholine
*h*ACh	Human acetylcholine
AChE	Acetylcholinesterase
ADME	Absorption, Distribution, Metabolism, and Excretion
AFM	Atomic force microscopy
ATCI	Acetylthiocholine iodide
BTCI	Butyrylthiocholine iodide
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-(dimethyamino)-propyl]-3-ethylcarbodiimide hydrochloride
FA	Ferulic acid
HBA	Hydrogen bond acceptor
HBD	Hydrogen bond donor
HRMS	High-resolution mass spectrometry
HOBt	*N*-hydroxybenzotriazole
IC_{50}	Inhibitory concentration required to kill 50% of the population
MW	Molecular weight
MTT	3- (4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium
PAS	Peripheral anionic site
ROS	Reactive oxygen species
TMS	Tetramethylsilane

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
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, which accounts for more than 80% of dementia cases worldwide in older people. It is characterized by the deposition of Aβ plaque and neurofibrillary tangles. The disease leads to progressive loss of memory, functional ability to learn and is primarily characterized by the progressive loss of memory associated with other cognitive deficits.

Despite decades of study on the etiology of disease and also significant efforts by the pharmaceutical industry to develop therapies, there is no effective treatment available to cure AD or inhibit its progression significantly. However, there are four drugs *viz.* donepezil, galantamine, and rivastigmine, approved by USFDA, acting on cholinergic pathway and memantine acting on NMDA receptor. Given the complex and multifactorial nature of the disease, the development of multifunctional ligands was considered a better option.

The present study is being divided into six chapters:

Chapter 1 deals with Alzheimer's disease (AD), pathophysiology, and current treatments for AD.

Chapter 2 provides insight into the literature reports related to the relevant work.

Chapter 3 includes the hypothesis, rationale, and plan of the work.

Chapter 4 deals with the rationale for synthesizing and evaluating novel ferulic acid glycine/piperazine amide/benzylpiperazine/tryptamine derivatives. The designed molecules were promoted to synthesis and *in-vitro* enzyme inhibition studies. The potent molecules obtained from the *in-vitro* study were further investigated for enzyme kinetics, antioxidant, metal chelation, Aβ modulation, and neuroprotection study. Furthermore, lead compounds were selected for *in-vivo* studies in AD animal models to evaluate the working memory and learning response.

Chapter 5 includes the general synthetic procedure involved in the synthesis of targeted compounds and their biological evaluation.

Chapter 6 deals with the conclusion and final summary.