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SYNTHESIS OF ACETYLCHOLINESTRASE INHIBITOR AS POTENTIAL DRUG FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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COMMITTEE DESSION

This Thesis / Dissertation (Synthesis of Acetylcholinesterase Inhibitor as Potential Drug for the Treatment of Alzheimer's Disease) **was successfully defend and approved.**

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List of Content

List of Tables

List of Figures

List of Abbreviations

AD	Alzheimer's disease
APOE4	Apolipoprotein gene E4 alleles
ADAMS	Aging, Demographics, and Memory Study
Aβ	Amyloid beta
BBB	Blood brain barrier
ROS	Reactive oxygen species
PD	Parkinson's disease
mRNA	Messenger ribonucleic acid
NBM	Nucleus basalis of Meynert
ACh	Acetylcholine
ChAT	Choline acetyltransferase
AChE	Acetylcholinestrase enzyme
BuChE	Butyrylcholinesterase
Ac CoA	Acetyl coenzyme A
CAS	Acylation site
PAS	Peripheral anionic site

NMDA	*N*-methyl-D-aspartate
nAChRs	Nicotinic cholinergic receptors
mAChRs	Muscarinic cholinergic receptors
α7 receptors	Alpha-7 nicotinic acetylcholine receptors
anti-TMV	Anti-tobacco mosaic virus
anti-HIV	Anti human immunodeficiency virus
LDL	Low density lipoprotein
GC-MS	Gas Chromatography-Mass Spetroscopy
FID	Flame ionisation detection
TLC	Thin layer chromatography
Rf	Retention factor
Hsp	Heat shock protein
SAR	Structure activity relationships
TEA	Triethylamine
NMR	Nuclear magnetic resonance
TMS	Tetramethylsilane
$LiAlH_4$	Lithium aluminum hydride

TMSCl	Trimethylsilyl chloride
DCM	Dichloromethane
THF	Tetrahydrofurane
NaOH	Sodium hydroxide
Ppm	Parts per million
$CDCl_3$	Deuterated chloroform
Na_2SO_4	Sodium sulfate
HCl	Hydrochloric acid

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disorder in which the death of brain cells causes memory loss and cognitive decline. The disease starts with mild symptoms and gradually becomes severe. AD is one of the leading causes of mortality worldwide. Several different hallmarks of the disease have been reported such as low levels of acetylcholine, deposits of β-amyloid around neurons, hyperphosphorylated tau protein, oxidative stress, etc. Strategies for prevention of AD through non pharmacological treatments are associated with lifestyle interventions such as exercise, mental challenges, and socialization as well as caloric restriction and a healthy diet. Pharmacotherapy for AD currently depends on using acetylcholinesterase inhibitors (AChEIs) and *N*-methyl-D-aspartate (NMDA) receptor antagonists. They provide only symptomatic relief and mostly targets cognitive revival.

Quinazoline ring scaffold represents a privileged structure that has been utilized to design therapeutic agents for a wide number of diseases. In this research novel quinazoline derivatives **3** and **4** were synthesized starting from 1-*N*-Methylisatoic anhydride (**1**) and different analytical methods were utilized for monitoring synthesis and characterization of the target products as TLC, GC-MS and NMR (H^1 and C^{13}).

Ammonia aqueous solution was reacted with compound **1** to produce compound **2** giving (85.71%) yield, this product has been used to synthesize novel compound **3** through the reaction with cycloheptanone catalyzed by toluene-4-sulfonic acid monohydrate afforded the desired compound (97%) yield.

The second novel compound **4** was formed through activation of carbonyl carbon in the amide group of **3** with trimethylsilyl chloride (TMSCl) followed by reduction with lithium aluminium hydride ($LiAlH_4$) giving (73.1%) yield.

In this work, the reaction conditions were optimized for the synthesis of **3** and **4** allowing to get them in an excellent yield.