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Synthesis and characterization of quinazoline-cinnamic acid hybrid as Alzheimer's drug candidate

By

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A Thesis

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COMMITTEE DECISION

This Thesis (Synthesis and characterization of quinazoline-cinnamic acid hybrid as Alzheimer's drug candidate) was Successfully Defended and Approved on ----------

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Dedication

This work dedicated to my parents, family, friends and lovely people. To my father and my first supervisor, Muhsin Al-Dhalemi, for his love, caring and sacrifices for educating and preparing me for my future. He always being my supporter and a source of light in life. To my mother, for her prayers, love and kindness, for being in my side in all circumstances, for listening to me, for her patience while I was abroad and for being my friend around my life. To my lonely sister, for her lovely heart, for being my pressure release with her pure soul and for her support through it all. To my lovely brothers, Ahmed and Redha, for their emotional support. To my close friend, Fatima, for sharing me all the years past with difficulties and joys. She, for months past, has encouraged me attentively with her fullest and truest attention to accomplish my work with truthful self-confidence.

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Abbreviations or symbols	Definition
AD	Alzheimer's disease
ACh	Acetylcholine
AChEI	Acetyl cholinesterase inhibitors
AChEs	Acetyl cholinesterase
Aβ	Beta – amyloid
BChEs	Buteryl cholinesterases
$CDCl_3$	Deuterated chloroform
DCM	Dichloromethane
DHED	Dehydroevodiamine hydrochlorid
DPPH	2,2-diphenyl-1-picrylhydrazyl
eq	Equivalent
FDA	Food and Drug Administration
FID	Flame ionization detection

GC-MS	Gas chromatography-mass spectroscopy
H_2O	Water
H_2O_2	Hydrogen peroxide
Hr	Hour
IR	Infra-red spectroscopy
$LiAlH_4$	Lithium Aluminum hydride
N_2O_3	Di-nitrogen trioxide
Na_2SO_4	Sodium Sulfate
NaOH	Sodium hydroxide
NMR	Nuclear magnatic resonance spectroscopy
p-TSA	Toluene-4-sulfonic acid monohydrate
RF	Retardation Factor
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SAR	Structure Activity relationships

$SOCl_2$	Thionyl chloride
TEA	Triethyl amine
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMSCl	Trimethylsilyl chloride
t_R	Retention time
EtOAc	Ethyl acetate
UV	Ultra- Violet

Synthesis and characterization of quinazoline-cinnamic acid hybrid as Alzheimer's drug candidate

By

Dhuha Muhsin Al-Dhalemi

Supervisor

Dr. Zead Abudayeh

Abstract

Alzheimer's disease (AD) has been one of the most important cause of death for elderly people around the world. It's characterized by cognitive impairment and memory loss, mainly because of damage of cholinergic neurons in the fore-brain and hippocampus and reducing amount of Acetylcholine as well, the second main cause is the oxidative stress by reactive oxygen species (ROS) and reactive nitrogen species (RNS) in many brain region. Current treatment available for this neurodegenerative disease was mainly symptomatic and they were not affected on disease progression. Quinazoline moiety as promising structure in many research has the ability to inhibit acetylcholine esterase (AChE) enzyme and the ability of free radical scavenging. We decided to design and synthesize a novel hybrid compound **5** (quinazoline- cinnamic acid) that supposed to have a dual biological activity to delay the progression of AD. Synthesis of final hybrid compound was done through several reaction starting from N-methylisatoic anhydride which reacted with aqueous ammonia to form compound **2** with 90% yield. Second step involved synthesis of spiro compound (**3**) with 90% yeild by reacted compound **2** with cyclopentanone. Compound **4** was

synthesized with 94% yield by reduction of compound **3** using LiAlH4 and compound **5** was synthesized in 46% of yield. All reactions involved was monitored using TLC and GC-MS and characterized their final product by H-NMR and C-NMR. In future, the hybrid compound **5** as potential drug candidate for AD could be biologically evaluated for its ability to inhibit AChE enzyme and its antioxidant activity.