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Design and synthesis of a potential lead compound quinazoline-lipoic acid derivative for the treatment of Alzheimer's disease

By

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A Thesis

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Dedication

Making this thesis come alive was one of my biggest dream in life, even when I was experiencing hardship and depression due sudden detours in my life, I still managed to persevere and complete my work. It wasn't easy but somehow imade it through. I'd like to thank almighty God for giving me the patience and determination to make it happen. I've finally made it.

For my father, Mueen Fadhil al-khafaji, you work tirelessly all your life so I wouldn't go without. I've never said this to you but I'm indebted to you for everything you've done. I want you to know that your support mattered immensely to me. Your enthusiasm for my work release encouraged me to make it happen. I hope I've made you proud and that you're pleased with how far I've come despite the obstacles I've faced and criticisms levelled against me.

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LIST OF ABBREVIATIONS OR SYMBOLS

Abbreviation or symbols	Definition
Ach	Acetylcholine
AchEI	Acetylcholinesterase inhibitors
AchEs	Acetylcholinesterase
AD	Alzheimer's disease
Aβ	Beta – amyloid
BchEs	Buterylcholinesterases
$CDCl_3$	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
H2O	Water
H_2O_2	Hydrogen peroxide
Hr	Hour
IR	Infra-red spectroscopy
LA	Lipoic acid
$LiAlH_4$	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

R*f*	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
UV	Ultra- Violet

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Prepared by

Fatimah Mueen Fadhil Alhudaby

Supervised by

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Abstract

Alzheimer's disease (AD) is one of most common neurodegenerative disorder and irreversible form of dementia in elderly people and the available treatment for this disease is only symptomatic and doesn't delay the disease progression. Alzheimer's disease is multi-factorial disease involved several pathological hypothesis mainly cholinergic and oxidative stress hypothesis.

Quinazoline derivative moiety had been reported in many previous studies that had inhibition activity against acetylcholine esterase (AChE) the main enzyme in cholinergic hypothesis. In this work we designed and synthesized a novel hybrid compound of quinazoline-lipoic acid derivative (compound **5**) which supposed to have dual activity to delay the progression of AD. Compound **5** synthesis was started from N-methyl isatoic anhydride that react with aqueous ammonia to form compound **2** in 95% yield, compound **2** then reacted with cycloheptanone to form Spiro compound **3** in 94% yield. Compound **3** then reduced to form compound **4** with 95% yield, compound **4** then coupled with lipoic acid using thionyl chloride, the reactions monitored

with TLC and the final product characterized by GC-MS, H-NMR and C-NMR. Compound **5** was synthesized in 25% yield and could biologically evaluated for its ability to inhibit AChE and its anti-oxidant activity as future work.