DESIGN, SYNTHESIS AND ANTI-ACETYLCHOLINESTERASE EVALUATION OF NEW COUMARIN HYBRIDS AS POTENTIAL AGENTS FOR THE TREATMENT OF ALZHEIMER DISEASE

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A thesis submitted in fulfilment of the
requirements for the award of the degree of
Doctor of Philosophy

Faculty of Science
Universiti Teknologi Malaysia

SEPTEMBER 2021

ACKNOWLEDGEMENT

In the name of Allah, the Most Gracious and the Most Merciful. Alhamdulillah, all praises to Allah for the strengths and His blessings in finalizing this thesis.

I wish to express my sincere appreciation to my main thesis, Dr. Joazaizulfazli Jamalis, for all his kindness, supervision and endless assistance, critics and friendship. I am also very thankful to my co-supervisors, Dr. Syazwani Itri Amran, Dr. Razauden Mohamed Zulkifli and prof. Dr. Faiq Hama Saeed Hussain. Alhamdulillah I finally manage to complete this thesis.

My appreciation also goes to all the academic staff of Chemistry Department, all laboratory staff (Mr. Azmi, Mr. Subri, Mr. Rasyidi, Mr. Mohd Amin and Mdm. Ain) and fellow friends (Helmi and Fatima) willing to lend a helping hand.

ABSTRACT

Acetylcholinesterase (AChE) is the primary enzyme responsible for the hydrolytic metabolism of the neurotransmitter acetylcholine (ACh). Acetylcholinesterase inhibitors (AChEIs) are found in the main class of drugs currently used for the treatment of Alzheimer's disease (AD). However, most of approved drugs have adversed side effects. Therefore, many compounds containing a coumarin scaffold have been assessed for their anti-AChE activity and becoming potential candidates for new anti-AD drugs. For this purpose, this research focused on the design of two different series of coumarin hybrids as potential agents for the treatment of AD by using molecular docking. Two series of novel coumarin-chalcone **(201-214)** and coumarin-imine **(215-224)** hybrids have been synthesized. The first step in this study is the synthesis of coumarin **155** and **160** *via* Pechmann condensation. Then, 4'-hydroxychalcones **(162-175)** were synthesized by Claisen-Schmidt reaction of substituted benzaldehydes with 4-hydroxyacetophenone. Besides, imines **(176-185)** were synthesized from the reactions between substituted hydroxybenzaldehydes and substituted aniline. Chalcones **(162-175)** were converted to their *o*-alkylated derivatives **(187-200)**. Finally, the reaction between coumarin **155** and *o*-alkylated derivatives **(187-200)** yielded 38.5-86.6%of hybrids **(201-214)**, while hybrids **(215-224)** were produced from the reaction of coumarin **160** and imines **(176-185)** in 29.8-79.7% yields. The structures of the synthesized compounds were confirmed by spectroscopic techniques which include the IR and NMR (^{1}H and ^{13}C) analyses. The synthesized products were evaluated for their potential inhibitory effect on acetylcholinesterase (AChE) using Ellman's protocol. All of them exhibited excellent inhibitory activity against AChE. In coumarin-chalcone series, the IC_{50} values are in the range of 105.71-483.05 μg/mL. Hybrid **204** which carrying chloro group on ring-B of the chalcone scaffold was found as the most active compound having IC_{50} value of 105.71 ± 0.95 μg/mL. Nevertheless, in coumarin-imine series, the IC_{50} values were reported in 87.84-515.59 μg/mL, hybrid **218** having chloro on the ring-B and methoxy on the ring-A of the imine moiety with IC_{50} value of 87.84 ± 0.29 μg/mL showed the most potent as AChEIs. The reference drug, Galantamine yielded the IC_{50} of 496.18 ± 0.57 μg/mL. Furthermore, the molecular docking studies on both series were also performed to predict the binding modes of the compounds. Results exhibited that most of the designed compounds could bind to the peripheral anionic site (PAS) and catalytic active site (CAS) of the AChE.

ABSTRAK

Asetilkolinesterase (AChE) adalah enzim utama yang bertanggungjawab bagi metabolisme hidrolisis asetilkolina neurotransmiter (ACh). Perencat asetilkolinesterase (AChEIs) ditemui dalam kelas utama ubat-ubatan yang kini digunakan bagi rawatan penyakit Alzheimer (AD). Walau bagaimanapun, kebanyakan ubat-ubatan yang telah diluluskan mempunyai kesan sampingan. Oleh itu, banyak sebatian yang mengandungi perancah kumarin telah dinilai bagi aktiviti anti-AChE dan berpotensi sebagai ubat anti-AD yang baharu. Bagi tujuan ini, penyelidikan ini memberi tumpuan kepada reka bentuk dua siri hibrid kumarin yang berbeza sebagai agen yang berpotensi bagi rawatan AD dengan menggunakan dok molekul. Dua siri hibrid kumarin-kalkon **(201-214)** dan kumarin-imina **(215-224)** yang baharu telah disintesis. Langkah pertama dalam kajian ini ialah sintesis kumarin **155** dan **160** melalui kondensasi Pechmann. Kemudian, 4'-hidroksikalkon **(162-175)** telah disintesis dengan tindak balas Claisen-Schmidt benzaldehid tertukar ganti dengan 4'-hidroksikalkon. Selain itu, imina **(176-185)** telah disintesis daripada tindak balas antara hidrokdibenzaldehid tertukar ganti dan aniline tertukar ganti. Kalkon **(162-175**) telah ditukar kepada terbitan *o*-alkilnya **(187-200)**. Akhirnya, tindak balas antara kumarin **155** dan terbitan *o*-alkil **(187-200)** menghasilkan 38.5-86.6% hibrid **(201-214)**, manakala hibrid **(215-224)** dihasilkan daripada tindak balas kumarin **160** dan imina **(176-185)** dengan hasil 29.8-79.7%. Struktur sebatian yang disintesis itu telah disahkan oleh teknik spektroskopi termasuk analisis inframerah (IR) dan resonans magnet nukleus (NMR) (^{1}H dan ^{13}C). Produk yang disintesis telah dinilai potensinya untuk memberi kesan perencatan terhadap AChE menggunakan protokol Ellman. Kesemua sebatian tersebut menunjukkan aktiviti perencatan yang sangat baik terhadap AChE. Dalam siri kumarin-kalkon, nilai IC_{50} adalah dalam julat 105.71-483.05 μg/mL. Hibrid **204** yang mempunyai kumpulan kloro pada gelang B peracah kalkon didapati sebagai sebatian yang paling aktif dengan nilai IC_{50} 105.71 ± 0.95 μg/mL. Namun, dalam siri kumarin-imina, nilai IC_{50} telah dilaporkan dalam julat 87.84-515.59 μg/mL, dengan hibrid **218** yang mempunyai kumpulan kloro pada gelang B dan metoksi pada gelang A moieti imina dengan nilai IC_{50} 87.84 ± 0.29 μg/mL menunjukkan sebagai AChEIs yang paling berpotensi. Ubat rujukan, Galantamine menghasilkan nilai IC_{50} 496.18 ± 0.57 μg/mL. Selanjutnya, kajian dok molekul pada kedua-dua siri ini telah juga disiasat untuk meramalkan mod pengikatan sebatian tersebut. Keputusan mempamerkan bahawa kebanyakan sebatian yang telah direka bentuk dapat terikat kepada tapak anion persisian (PAS) dan tapak aktif pemangkinan (CAS) AChE.

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LIST OF ABBREVIATIONS

ACh	Acetylcholine
AChE	Acetylcholinesterase
AChEIs	Acetylcholinesterase Inhibitors
AD	Alzheimer Disease
Å	Angstrom
ATR	Attenuated Total Reflection
BuChE	Butyrylcholinesterase
C	Carbon
^{13}C	Carbon-13
CAS	Catalytic Active Site
δ	Chemical Shift
$CHCl_3$	Chloroform
J	Coupling Constant
$CDCl_3$	Deuterated Chloroform
DCM	Dicholoromethane
DMSO	Dimethyl Sulfoxide
d	Doublet
dd	Doublet of Doublets
EtOH	Ethanol
EtOAc	Ethyl Acetate
Et_3N	Triethylamine
FTIR	Fourier Transform Infrared Spectroscopy
H	Hydrogen
*h*AChE	Human Acetylcholinesterase
*h*BuChE	Human Butyrylcholinesterase
*h*MAOs	Human Monoamine Oxidases
^{1}H	Proton
HCl	Hydrochloric Acid
H_2SO_4	Sulphuric Acid
IR	Infrared

IC_{50}	Half-Maximal Inhibition Concentration
KBr	Potassium Bromide
KOH	Potassium Hydroxide
ν_{max}	Maximum Absorbance
m.p	Melting Point
MeOH	Methanol
mg	Milligram
mL	Millilitre
µL	Microlitre
µg/mL	Microgram Per Mililitre
m	Multiplet
nM	Nanomolar
NaOH	Sodium Hydroxide
NaOAc	Sodium Acetate
$NaHCO_3$	Sodium Bicarbonate
Na_2SO_4	Sodium Sulphate
NMR	Nuclear Magnetic Resonance
ppm	Part Per Million
π	Pi
PAS	Peripheral Anionic Site
q	Quartet
R_f	Retention Factor
RMN	Resonans Magnet Nukleus
s	Singlet
SAR	Structure Activity Relationship
TLC	Thin Layer Chromatography
THF	Tetrahydrofuran
UV	Ultraviolet

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CHAPTER 1

INTRODUCTION

1.1 Background of Research

Alzheimer's disease (AD) is a deadly neurodegenerative disease that commonly attacks elderly people around the world. Alzheimer's disease is the major form of dementia and degenerative disorder of the brain that is progressive in nature. It can be determined by dementia, cognitive impairment, memory loss, language deterioration, and severe behavioural abnormalities. Factors such as cholinergic dysfunction, oxidative stress, the inflammation of neurons and β-amyloid (Aβ) deposits are considered to play a significant role in the disease [1-7]. The cholinergic dysfunction is caused by insufficient neurotransmission due to low level of acetylcholine (ACh) or downregulation of the receptors. Acetylcholine (ACh), the primary neurotransmitter helps carry nerve impulses across a nerve synapse. In AD, ACh level is altered and impulse transmission is terminated by the action of acetylcholinesterase enzyme (AChE) which catalyzes the breakdown of ACh [8-13].

There are two cholinesterases (ChEs) enzymes were caused to the degradation of ACh, which named as acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) [14]. Currently, based on inhibition of ChE, the disease therapy is establishing in order to maintain or increase of ACh levels in the cholinergic synapses [15]. For this reason, inhibitors targeting AChE have become the principal treatment for AD management approved by the FDA for treatment of the cholinergic deficit several approaches have been reported. Hence, up to date the approved drugs are [16]; rivastigmine **1** [17, 18], donepezil **2** [19, 20], galantamine **3** [21-23], tacrine **4** [24] and memantine **5** (*N*-methyl-D-aspartate (NMDA) antagonist) [25] (**Figure 1.1**).

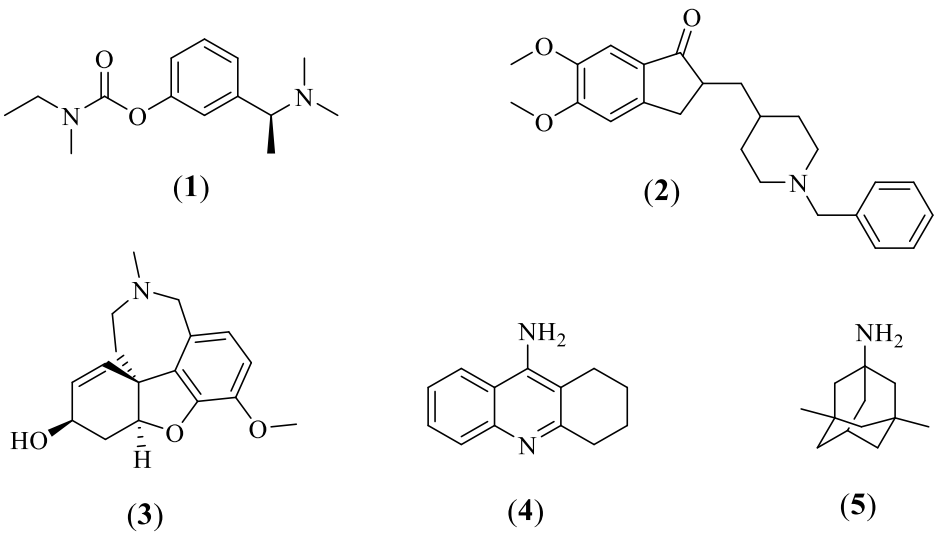

Figure 1.1: Structure of Approved Drugs for Alzheimer's Disease

Most of the approved drugs have a heterocyclic system; this is evidence for activity of a heterocyclic based compounds to inhibit the ChEs [26]. Moreover, compounds with heterocyclic system such as coumarins, were able to interact with each of the catalytic anionic site (CAS) and peripheral anionic site PAS of the ChEs through hydrophobic interactions and π-stacking with the aryl group of amino acids of the enzyme gorge in AChE [27-29]. Coumarins (2*H*-chromen-2-one or 2*H*-1-benzopyran-2-one) **(6)** are secondary heterocyclic metabolites, belonging to benzopyrones family which composed of fused benzene and α-pyrone rings and they occur widely in different parts of plants, such as roots, seeds, nuts, flowers, and fruits [30].

Some coumarin compounds are well-known as cholinesterase inhibitors [31, 32]. Hamulakova *et al.* reported that mono- and bis-coumarin hybrids displayed excellent acetylcholinesterase inhibitory activity [32]. Besides, Asadipour and co-workers demonstrated that coumarin-3-carboxamides, which bearing *N*-benzylpiperidine moiety are the most active against both AChE and BuChE [33]. On the other hand, ensaculin, a coumarin hybrid that combines a benzopyran with a substituted of piperazine core, was found to improve memory and cognitive function [34, 35]. Therefore, coumarin could be considered as the leading scaffolds to design and evaluate for anti-Alzheimer drugs in searching for AD management. Coumarin compounds have been broadly categorized as simple coumarins **(6)**, furanocoumarins

or furocoumarins **(7)**, pyranocoumarins **(8)**, biscoumarins (ex. Edgeworoside C) **(9)**, triscoumarins (ex. Edgeworoside B) **(10)** and coumarinolignans (ex. Cleomiscosin B) **(11)** [36] **(Figure 1.2)**.

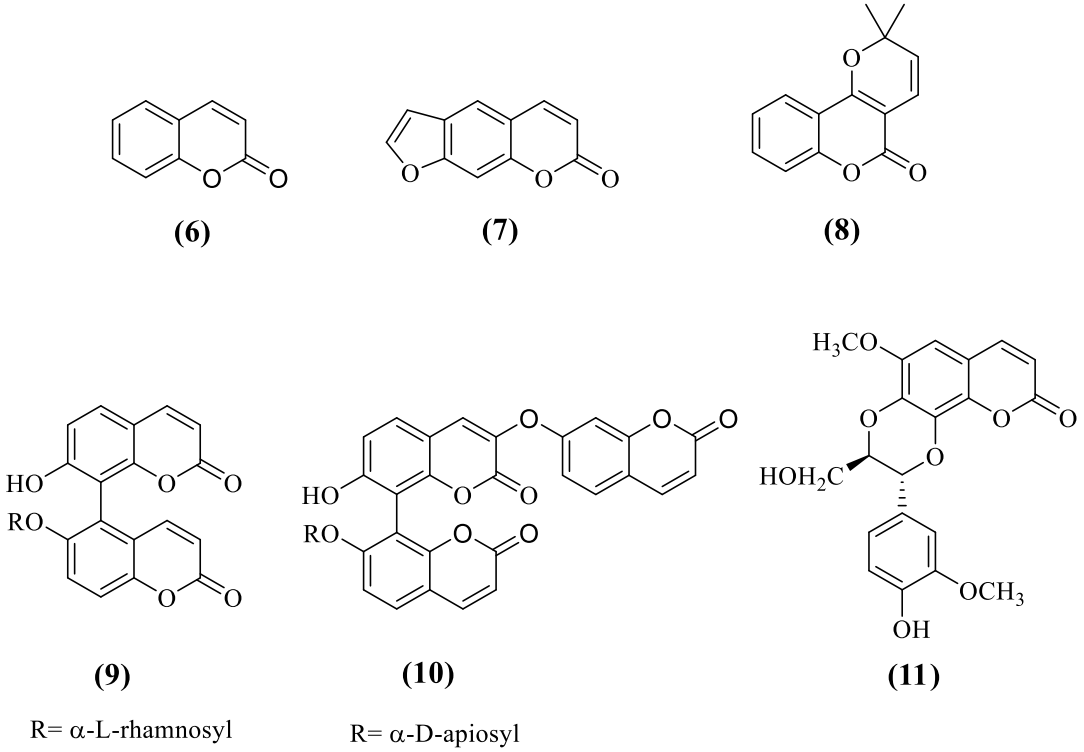

Figure 1.2: Structure of Coumarins

Nowadays, many designs to synthesize of new AChE inhibitors have been attempted *via* computational approches. Molecular docking is the most common computational simulation approach of a candidate ligand (compound) binding to a receptor such as protein and enzyme and predicts the preferred orientation of binding of compound to the active site of receptor to form a stable complex. Therefore, docking studies play an important role in the rational design of compound toward a particular receptor. The sensitivity of docking calculations regarding the geometry of the input ligand illustrations that even small changes in the ligand conformation can lead to large differences in the geometries and scores of the resulting docked poses [37-39]. Some computational tools are performing the docking studies; one of them is AutoDock package. AutoDock is a program that docks a ligand to its target protein, while performs with accurate and fast. Moreover, it is used to predict the affinity and activity of binding of the small molecule to their protein targets by using scoring functions. This package can be used to screen a variety of possible

compounds, searching for new compounds with specific binding properties or testing a range of modifications of an existing compound [40]. Kryger *et al*. (1999), reported molecular docking study of donepezil with the AChE, results displayed several interactions such as π–π stacking, cation–π, hydrogen bond with amino acid residues. TRP84, TRP279, PHE330 and TYR121, respectively. These interactions resulted in the binding energy of -10.60 kcal/mol [41, 42].

1.2 Problem Statement

Alzheimer's disease (AD) is one of the leading causes of death among older people in the world [43, 44]. Nowadays, more than 46 million people worldwide are living with this disease, in this number as Alzheimer's Disease Foundation Malaysia in 2016 reported that around 50,000 individuals in Malaysia are affected. With its fast growth and morbidity, this number continues to overgrow in the coming years when the population of age 65 and older, it is expected to increase to 131.5 million by 2050, AD ranks second on the burden of illness in Asia Pacific Region [45, 46]. The current drugs in the market are unable to halt the progress of the disease, some of these drugs were found to have side effects, including nausea, vomiting, diarrhea, allergic reactions and loss of appetite [14, 47, 48]. In recent years, hybrid compounds have drawn a great deal of attention in drug discovery, and exhibited many biological activities. Therefore, reports showed that coumarins were coupled with another molecule having a wide range of pharmacological properties. The coupling process will enhance and provide the bioactivities of compounds [49-52]. Numerous natural and synthesized coumarins together with chalcones and imines have been reported as anti-Alzheimer agent [53-59]. However, no report on coumarin combined with chalcones or imines.

Hence, this research will focus on synthesis of a series of novel coumarin-chalcone and coumarin-imine hybrids and biological evaluation as potential agents against acetylcholinesterase (AChE) for Alzheimer’s disease.

1.3 Objectives of Research

The objectives of this study are:

1) To design target compounds by using molecular docking of a potential candidate for the treatment of Alzheimer disease.

2) To synthesize two series of coumarin hybrids using established methods and characterize the synthesized compounds by spectroscopic techniques.

3) To perform the test for acetylcholinesterase inhibitory activity for the proposed derivatives.

1.4 Scopes of Research

In the current research coumarins were used as a template to design novel therapeutic agents for the treatment of AD by using molecular docking. At the beginning of this research, molecular docking was performed to execute the possibility of the designed compounds as acetylcholinesterase inhibitor by determined their binding affinities. Therefore, two series of coumarin hybrids were designed. The proposed coumarins hybrids were synthesized by using retrosynthetic analysis. In this research, syntheses of various coumarin hybrids were involved Pechmann condensation of resorcinol with ethyl acetoacetate to give 7-hydroxy-4-methylcoumarin.

On the other hand, 4-hydroxychalcones were prepared from the reaction of 4-hydroxyacetophenone with various benzaldehyde derivatives. These chalcones were under *O*-alkylation by treatment with 1,3-dibromopropane. The last step was the formation of coumarin-chalcone derivatives from the reaction of 7-hydroxy-4-methylcoumarin and *O*-alkylation chalcones. In another series, 4-methoxy phenol was treated with ethyl 4-chloroacetoacetate *via* Peckmann condensation to form 4-(chloromethyl)-7-methoxy-2*H*-chromen-2-one. The second intermediates commonly

known as Schiff bases (imine) were prepared from the reaction of various benzaldehydes and different anilines. Finally, condensation of these two intermediates afforded coumarin-imine hybrids.

Then, all synthesized target compounds were characterized using spectroscopic methods such as nuclear magnetic resonance (^{1}H and ^{13}C), Fourier Transform Infrared (FTIR) or Attenuated Total Reflection (ATR). The synthesized compounds were evaluated for the inhibitory activity against acetylcholinesterase (AChE) by using Ellman's spectrophotometric protocol [60] and the results were compared with control drug such as galantamine. Finally, the molecular docking study was investigated to clarify the binding mode of the protein (AChE) with the proposed hybrids.

1.5 Significance of Research

Molecular docking simulation is more economic, time saving, and effective for efficacy of the designing and drug discovery. Therefore, the search for the good inhibitory agents with higher binding energy has become easier [40]. In this research, the molecular modelling method was employed to design the most active coumarin hybrids as anti-Alzheimer agents. Moreover, efficient methods (affordable starting materials, preparative simplicity with good yield) were proposed to synthesize the designed hybrids.

From the literature review aspect, some of the compounds with coumarin backbone were revealed better result than standard drugs. This research studied coumarin hybrids with different substituents to provide new discovery of knowledge and enhance inhibitory potency effect on AChE. Thus, the designed compounds may have the potential to be commercialized and introduced for the clinical use if show good result in bioassays with less side effects on patients.

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