# SYNTHESIS AND CHARACTERIZATION OF NEW CHALCONE DERIVATIVES AS ACETYLCHOLINESTERASE INHIBITOR

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*With lots of love and gratitude, I dedicate this thesis to my beloved parents, my husband, my lovely Children Shalya and Ahmad and closest friend.*

*Each of you always makes me feel special and thank you for believing in me.*

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## ABSTRACT

Chalcones are open-chain flavonoids and considered to be precursors of isoflavonoids and flavonoids which consist of two aromatic rings that linked by a three carbon consist of α, β-unsaturated carbonyl system. Besides, chalcones display a wide range of biological activities such as antibacterial, anticancer, antioxidant including AChE inhibition activities. Super-activation of cholinesterase (acetylcholinesterase) is linked to various neurological problems most precisely Alzheimer's disease (AD), which leads to senile dementia. Therefore, cholinesterase (AChE) inhibition is considered as a promising strategy for the treatment of Alzheimer's disease. For this purpose, this study focused on the synthesis of a series of new chalcone derivatives with anti-cholinesterase potential. In the first step of this study 1-(4-(benzyloxy)phenyl)ethan-1-one **(51)** was successfully synthesized by benzylation of 4-hydroxy acetophenone with a yield of 88.49% as a precursor to synthesize a series of chalcone derivatives. Then, the precursor was reacted with benzaldehyde derivatives **(52a-f)** with different substituent groups on its para position (4-H, 4-Br, 4-$NO_2$, 4-isopropyl, 4-$OCH_3$, and 4-Cl), respectively, by base-catalyzed Claisen-Schmidt condensation reaction to produce a series of new chalcone derivatives **(53a-f)**. The yield of synthesized compounds were (50-58%), and their molecular structures were confirmed using IR, $^{1}$H NMR and $^{13}$C NMR analysis. The synthesized chalcone derivatives **(53a-f)** were tested against AChE. All compounds showed good activity in AChE inhibition. Moreover, compounds with the presence of electron-withdrawing groups **(53b, 53c and 53f)** showed excellent activity in AChE inhibition, Among them, compound **(53c)** showed the most potent activity (89.44%) in acetylcholinesterase inhibition which quite near from the result of the standard Galantamine (94.11%).

# ABSTRAK

Kalkon adalah flavonoid rantai terbuka dan dianggap sebagai prekursor isoflavonoid dan flavonoid yang terdiri daripada dua gelang aromatik yang dihubungkan oleh tiga karbon terdiri daripada sistem karbonil α, β-tidak tepu. Selain itu, kalkon menunjukkan pelbagai aktiviti biologi seperti antibakteria, antikanser, antioksidan termasuk perencatan AChE. Pengaktifan lampau kolinesterase (asetilkolinesterase) dikaitkan dengan pelbagai masalah neurologi, terutamanya penyakit Alzheimer (AD), yang menyebabkan demensia senil. Oleh itu, perencatan kolinesterase (AChE) dianggap sebagai strategi yang berpotensi untuk rawatan penyakit Alzheimer. Untuk tujuan ini, kajian ini memfokuskan kepada sintesis terbitan kalkon baru dengan potensi anti-kolinesterase. Pada langkah pertama kajian ini 1-(4-(benziloksi)fenil)etan-1-one **(51)** berjaya disintesis melavi pembenzilan 4-hidroksiasetofenon dengan hasil 88.49% sebagai bahan permula untuk mensintesis satu siri terbitan kalkon. Kemudian bahan permula tersebut ditindak balas dengan terbitan benzaldehid **(52a-f)** dengan kumpulan penukar ganti yang berbeza pada kedudukan para (4-H, 4-Br, 4-$NO_2$, 4-isopropil, 4-$CH_3O$, dan 4-Cl) masing-masing, oleh tindak balas pemeluwapan Claisen-Schmidt bermangkinkan bes untuk menghasilkan satu siri terbitan kalkon yang baru **(53a-f)**. Sebatian yang disintesis diperoleh dengan hasil sederhana (50-58%) dan struktur molekulnya disahkan menggunakan analisis IR, $^{1}H$ NMR, $^{13}C$ NMR. Terbitan kalkon tersebut yang disintesis **(53a-f)** diuji terhadap AchE. Semua sebatian menunjukkan aktiviti yang baik dalam perencatan AchE. Tambahan lagi, sebatian dengan kumpulan penarik elektron **(53b, 53c dan 53f)** menunjukkan aktiviti yang sangat baik dalam perencatan AChE. Di kalangan sebatian tersebut, sebatian **(53c)** adalah yang paling berpotensi (89.44%) dalam perencatan asetilkolinesterase yang hampir sama dengan keputusan piawai Galantamine (94.11%).

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## LIST OF SYMBOLS

| | |
|---|---|
| % | Percentage |
| B | Beta |
| Cm | Centimetre |
| A | Alfa |
| G | Gram |
| H | Hour |
| Min | Minute |
| ml | Mili Litre |
| mol/L | Mole per litre |
| mW | Milliwatt |
| nm | Nanometer |
| C | Degree Celcius |
| μm | Micrometre |
| MW | Molecular weight |

## LIST OF ABBREVIATION

| | |
|---|---|
| AD | Alzheimer's disease |
| Aβ | Beta-amyloid |
| ACh | Acetylcholine |
| AChE | Acetylcholinesterase |
| AChEIs | Acetylcholinesterase inhibitors |
| IR | Infrared spectroscopy |
| NMR | Nuclear magnetic resonance |
| MAO-B | Monoamine oxidase-B |
| BuChE | Butyrylcholinesterase |
| KOH | Potassium hydroxide |
| NaOH | Sodium hydroxide |
| PAS | Peripheral anionic site |
| CAS | Catalytic active site |
| LCA | Licochalcone |
| TCM | Traditional Chinese Medicine |
| XN | Xanthohumol |
| COX-2 | Cyclooxygenase 2 |
| COX-1 | Cyclooxygenase 1 |
| iNOS | Inducible nitric oxide synthase |
| PGE2 | Prostaglandin-E2 |
| NF-kB | Nuclear factor-Kb |
| BIG3 | Brefeldin A-inhibited guanine nucleotide-exchange protein 3 |
| PHB2 | Prohibitin 2 |
| DNA | Deoxyribonucleic acid |
| CYP19 | Aromatase |
| Cyp | Cytochrome |
| NaH | Sodium hydride |
| $BF_3$ | Boron trifluoride |
| $Et_2O$ | Diethyl ether |

| | |
|---|---|
| KOEt | Potassium ethoxide |
| EtOH | Ethanol |
| $K_2CO_3$ | Potassium carbonate |
| $MIC_{80}$ | Minimal inhibitory concentration |
| FICI | Fractional inhibitory concentration index |
| $NRF_2$ | Nuclear factor erythroid 2 |
| MAO | Monoamine oxidase |
| FA | Ferulic acid |

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# CHAPTER 1

# INTRODUCTION

## 1.1 Introduction

Chalcone is defined as a chemical compound that contains two aromatic rings joined by an unsaturated α, β–ketone, i.e., 1,3-diphenyl-2-propen-1-one derivative which has different substituents on its rings. Chalcone scaffold in collaboration with benzoxazepine, pyrazole, benzothiazepine, pyrimidine, isoxazole, pyrazoline, thiadiazole, and benzodiazepine serves as a promising basis for the manufacture of pharmacologically efficient compounds for drug discovery [1].

Moreover, it is recognized as a natural product because of its existence in nature in diverse forms such as free, complexed, and hybrid. The term ' chalcone ' was first coined in the 19$^{th}$ century by Kostanecki and Tambor, who first synthesized a series of natural chromophoric products. Furthermore, chalcone is a natural pigment that can be found easily in most plants and is a crucial intermediate precursor of isoflavonoids and flavonoids, an isomeric key step in the skeletal alteration of chalcones [2]. The isomers of chalcones and flavanones are readily interconverted in the presence of acid or base, where the former serves as a catalyst for the formation of chalcones, and the latter helps to form flavanones, respectively [3].

In the 21$^{st}$ century, the chemistry of chalcones has left attraction among researchers because of its ease of preparation and the presence of several of replaceable hydrogen to produce lots of chalcone derivatives. The scaffold is generally prepared by Claisen- Schmidt reaction. In addition to the Claisen-Schmidt reaction, several reactions have been reported to achieve a high yield of this compound, such as Suzuki-Miyaura reaction, Friedel-Crafts reaction, Julia-Kocienski reaction, Sonogashira isomerization coupling, Carbonylated Heck coupling reaction

and direct cross-coupling reaction. Moreover, green fabrication techniques such as solvent-free technique, one-pot synthesis method, microwave-assisted technique, and solid acid catalyst mediated technique are also utilized in synthesizing benzylideneacetophenone scaffold [4].

Chalcone derivatives exhibit a wide range of therapeutic activities as reported in Figure 1.1, such as anticancer, antioxidants [5], anti-inflammatory [6], antihypertensive [7], antimalarial [8], antiulcer [9], antiviral [10], antiprotozoal [11], cardiovascular activity [12] and anti-alzheimer [13].

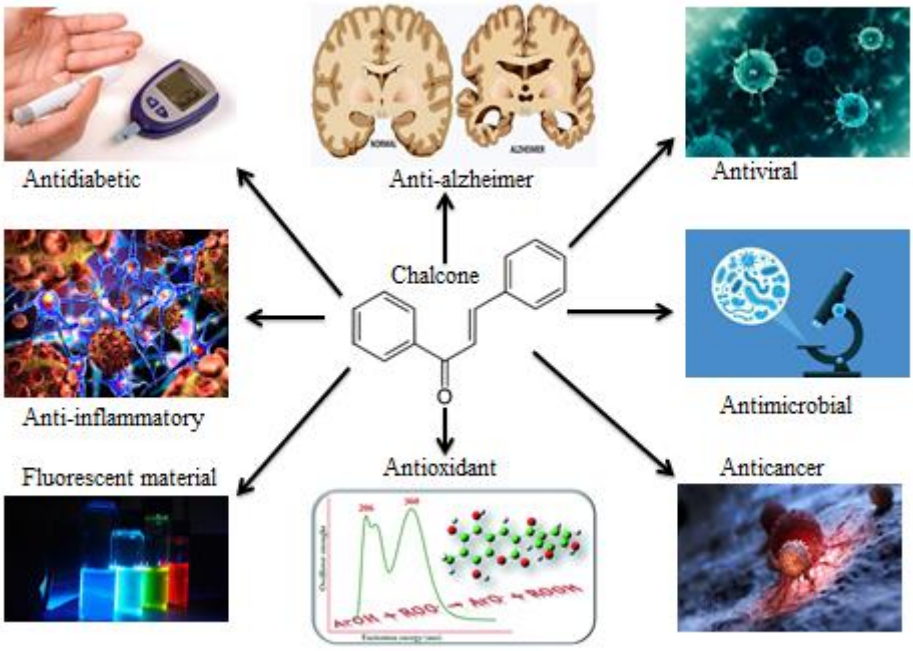


**Figure 1.1**: Bioactivity of natural and synthesized chalcone derivatives.

Alzheimer's disease (AD) is characterized by memory loss, language regression and other cognitive impairments in elderly people [14]. To date, AD is diagnosed with more than 46.8 million people worldwide, and this number will continue to grow [15]. Moreover, this disease leads to nerve cell death and tissue loss throughout the brain. Over time, the brain shrinks dramatically and affects nearly all its functions. This attracts researchers' attention to find new potent drugs to treat the Alzheimer disease (AD) more efficiently.

The current drugs such as donepezil, rivastigmine, memantine and galantamine only modulate a single target to improve the symptoms but not halting or curing the neurodegeneration of AD. These drugs are cholinesterase inhibitors which prevent the breakdown of acetylcholine, a chemical messenger important for learning and memory [16]. This supports communication among nerve cells by keeping acetylcholine high. However, these drugs can cause side effect to patients such as nausea, vomiting, loss of appetite and increased frequency of bowel movements [17].

There were many previous research studies on chalcone derivatives to develop possible biological agents for anti-Alzheimer but, more significant researches focus on the study the possibility of the synthesized compounds from chalcone derivatives that are able to treat Alzheimer diseases. Based on the aforementioned reasons, the present research is intended to fabricate a series of novel chalcone derivatives as potent cholinesterase inhibitors.

## 1.2 Problem statement

Alzheimer's disease (AD), which is typically identified by loss of memory, behavioural irregularities, and cognitive impairment is one of the most healthcare challenges of the 21$^{st}$ century. It is believed that more than 100 million people will suffer from AD by 2050 [18]. Although the exact aetiology for AD development is not fully explored, certain pathophysiological factors such as β-amyloid (Aβ) deposits, π-protein aggregation, oxidative stress, neuroinflammation, biometal dyshomeostasis, and low acetylcholine (ACh) levels are assumed to play a vital role in this disease development [19, 20]. Based on these factors, different theories were suggested to illustrate the mechanism of the development of AD. Among these, the cholinergic hypothesis has been early recognized by researchers. This traditional hypothesis argues that it is the low level of ACh in the brain that contributes to AD patients ' memory and cognitive deficits and that ACh hydrolysis by inhibiting acetylcholinesterase (AChE) will relieve these symptoms [21]. Based on this theory, a few medicines such as donepezil, rivastigmine, and galantamine have been

authorized or recommended to act as temporary systematic relief for AD patients [22, 23]. However, existing drugs are only effective against the mild form of AD [24]. This attracts researchers' attention to find new potent drugs to treat the Alzheimer disease (AD) more efficiently.

Several study revealed that natural and synthetic analogues of chalcones display diverse biological activities, due to versatile structures and characteristics of Michael acceptors [25]. In particular, some chalcone derivatives had strong potency to hinder AChE [26], $\beta$-amyloid aggregation [27] and MAO-B [28, 29], which are important for treating AD. Based on the aforementioned factors, the present work is intended to synthesize a series of chalcone derivatives as acetylcholinesterase inhibitor.

## 1.3 Research Objectives

The main goal of this research is to investigate a series of novel chalcone derivatives as active cholinesterase inhibitors. Hence, the objectives of this research are:

1. To synthesize 1-(4-(benzyloxy)phenyl)ethan-1-one by benzylation of 4-hydroxy acetophenone as a starting material.
2. To synthesize a series of new chalcone derivatives by Claisen-Schmidt condensation.
3. To characterize the synthesized chalcone derivatives using various spectroscopic methods.
4. To evaluate acetylcholinesterase inhibitor activity of the synthesized chalcone derivatives.

## 1.4 Scope of Study

The current research is divided into three parts. The first part focuses on the preparation of 1-(4-(benzyloxy)phenyl)ethan-1-one by benzylation of 4-hydroxy acetophenone in the presence of potassium carbonate, as a precursor for the fabrication of different chalcone derivatives that possess bioactive properties through base catalyzed Claisen-Schmidt condensation reaction using a acetophenone and various aldehydes (benzaldehyde, 4-bromo benzaldehyde, 4-nitrobenzaldehyde, 4-methoxybenzaldehyde, 4-isopropyl benzaldehyde and 4-chlorobenzaldehyde) with different substituent groups in para position (4-H, 4-Br, 4-$NO_2$, 4-isopropyl, 4-$OCH_3$ and 4-Cl), respectively. Second, the synthesized chalcone derivatives were characterized using various characterization methods such as Nuclear Magnetic Resonance (NMR) and Infrared Spectroscopy (IR). Finally, the bioactivity inhibiting effects of new synthesized chalcone derivatives compounds in the present study against AChE were evaluated by the modified Ellman method, using galantamine as the positive control.

## 1.5 Significance of Research

The current AD drugs in the market are purely symptomatic, with little or no effect on the disease progression. Moreover, the recent failure in development of disease-modifying therapies for AD justifies the importance of a shift towards alternative novel drug targets. So, this study is conducted to synthesize a series of novel chalcone derivatives which have potency to inhibit AChE, which is valuable for the treatment of AD. Moreover, the synthesized chalcone derivatives are expected to demonstrate significant cholinesterase inhibitor properties. Hence, discovering new selective compound that could be developed as anti-AD drugs is considered as a significant breakthrough in AD treatment.

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