SYNTHESIS OF HYDROXYLATED AND PRENYLATED CHALCONES

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This dissertation is dedicated with affection and gratitude to the memory

of my respected Father

HAMEED HASAN

AND

To my respected Mother

BARWEEN ABDULKAREEM

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ABSTRACT

Prenylated chalcones are among the compounds found in local *Artocarpus* species which reported to have interesting biological activities. Moreover, prenylated chalcones are used as traditional folk medicine for the treatment of inflammation, malarial fever and to treat the ulcers and diarrhea. In this study, 2,4-dihydroxy-3-*C*-prenylacetophenone and 2,4-dihydroxy-5-*C*-prenylacetophenone were successfully synthesized by treating resacetophenone with 2-methylbut-3-en-2-ol in the presence of $BF_3.Et_2O$ as the catalyst. Meanwhile 2,4,6-trihydroxy-3-*C*-prenylacetophenone was synthesized using K_2CO_3 as the catalyst in dry acetone in the reaction of prenyl bromide with 2,4,6-trihydroxyacetophenone . In addition, two hydroxylated chalcone namely 2′,4′,4-trihydroxychalcone , 4′,4-dihydroxychalcone) together with 2′,4′,4,6′-tetrahydroxy-3′-prenylchalcone were synthesized by Claisen-Schmidt condensation of various hydroxyacetophenone and 2,4,6-trihydroxy-3-*C*-prenylacetophenone for prenylated chalcone with 4-hydroxybenzaldyhe using $BF_3.Et_2O$. The structures of all compounds were characterized using spectroscopic methods (NMR and IR).

ABSTRAK

Prenil kalkon adalah antara sebatian yang terdapat dalam spesies *Artocarpus* tempatan yang dilaporkan mempunyai aktiviti biologi yang menarik. Tambahan pula, prenil kalkon digunakan sebagai ubat tradisional untuk merawat keradangan, demam malaria, ulser, dan cirit-birit. Dalam kajian ini, 2,4-dihidroksi-3-*C*-prenilasetofenon dan 2,4-dihidroksi-5-C-prenilasetofenon telah berjaya disediakan dengan mencampurkan resasetofenon dan 2-metilbut-3-en-2-ol dengan kehadiran $BF_3.Et_2O$ sebagai pemangkin. Sementara itu, 2,4,6-trihidroksi-3-*C*-prenilasetofenon telah disintesiskan daripada 2,4,6-trihidroksiasetofenon dan prenil bromida dengan kehadiran K_2CO_3 sebagai pemangkin di dalam aseton kering. Tambahan pula, dua kalkon terhidroksil yang dinamakan 2′,4′,4-trihidroksikalkon dan 4′,4-dihidroksikalkon bersama dengan prenil kalkon, 2′,4′,4,6′-tetrahidroksi-3′-*C*-prenilkalkon telah disintesiskan menggunakan kondensasi Claisen-Schmidt dengan kehadiran $BF_3.Et_2O$. Struktur kesemua sebatian telah dianalisis dengan menggunakan kaedah spektroskopi (RMN dan IM).

TABLE OF CONTENTS

LIST OF SCHEMES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND SYMBOLS

CC	Column Chromatography
$CDCl_3$	Deuterated Chloroform
$BF_3.Et_2O$	Boron Trifloride-etherat
$SOCl_2$	Thionyl Chloride
CD_3COCD_3	Deuterated Acetone
DPPH	2,2-Diphenyl-1-picrylhydrazyl
d	doublet
dd	doublet of doublets
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
EtOH	Ethanol
^1H	Proton
Hz	Hertz
HCl	Hydrochloric acid
IR	Infrared
IC_{50}	Inhibition Concentration at 50%
J	coupling constant
KBr	Potassium bromide
MeOH	Methanol
$MgSO_4$	Magnesium sulphate
MHz	Megahertz
NMR	Nuclear Magnetic Resonance
nm	nanometer
ppm	parts per million
hr	hour
hrs	hours
R_f	retention factor

s	singlet
t	triplet
TLC	Thin Layer Chromatography
δ	chemical shift

LIST OF APPENDICES

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Organic synthesis is the most important branches of organic chemistry. It is common part of chemical synthesis which is concerned with the building of organic compounds *via* organic reactions [1]. Recently, the number of organic compounds that have been synthesized is far greater than the number of isolated from natural resources. Also, it might be important to synthesize a natural product in the laboratory in order to make the compound more widely available at lower cost than it would be if the compound had to be extracted from the natural products. There are some compounds that isolated from natural source but now produced by chemical reaction for commercial purpose such as vitamins, amino acids, the dye indigo and the antibiotic penicillin [2].

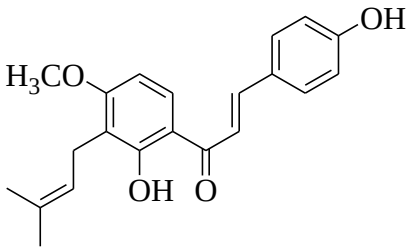
Nowadays, organic synthesis is still attracting the attention of researchers especially in the field of drug discovery due to the development method and also improvement involving new catalysts. The synthesis of different compounds offers the advantage of increasing percentage yield of some potentially active compounds with diverse structures and functionalities hence improving medicinal chemistry of these compounds as potential pharmacological compounds [3]. Moreover, research in the field of organic synthesis is still increasing as naturally occurring compounds are found to poss bioactive properties. As such, synthetic approach is carried out to produce these compounds with appreciable percentage yield [4].

Additionally, development in chemical instruments becomes one of the factors for many research undergone their research more effectively [5]. Advanced technology able to produce instruments with higher accuracy with less time needed to produce high quality products such as NMR, HPLC, IR and UV. The inventions of such scientific instruments promote the organic synthesis sector to widen up the study of interest [1].

The development of science and technology offers assistance in many fields especially in drug discovery. This development introduced the importance of naturally occurring compounds in plants and research have been done significantly to synthesize these natural compounds artificially [5]. In this case, it can be concluded that organic synthesis is as highly developed, versatile and interdisciplinary branch of complex molecules and new materials with unexpected properties [2].

The flavonoids are natural compounds that are found in all vascular plants, and they are especially prominent in seeds, citrus fruits, olive oil, tea and cocoa. Certain plants and spices containing flavonoids have long been recognized for their beneficial effects on human health [6]. The flavonoids appear to have played a major role in the successful medical treatments of ancient times, and their use has persevered up to now [7].

Chalcones are classified under flavonoids type and they participate in the biosynthetic pathway of flavonoids and isoflavonoids [8]. 4-Hydroxyderricin **(1)**, a prenylated chalcone was synthesized by Claisen-Schmidt condensation of 2-hydroxy-4-methoxy-2-prenylacetophenone with 4-methoxymethoxybenzaldehyde [9]. Moreover, 2-hydroxy-3-(3,3-dimethylallyl)-4,6-dimethoxymethoxychalcone **(2)** synthesized by condensation of 2-hydroxy-3-(3,3-dimethylallyl)-4,6-dimethoxymethoxyacetophenone and benzaldehyde in a basic medium [10].



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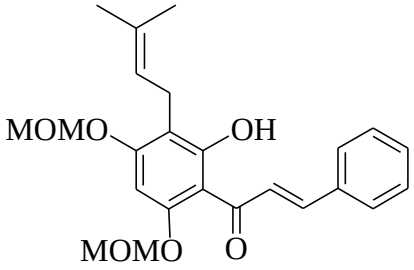

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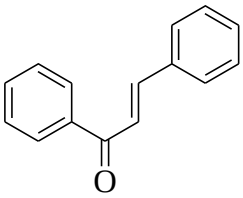
1.2 Natural Flavonoids

The flavonoids are phenolic compounds found in natural products that recently have been the subject of considerable scientific and therapeutic interest. Flavonoids are ubiquitous in green plant cells and therefore, they are found in fruit, vegetables, nuts, seeds, stems and flowers as well as tea, wine [11], propolis and honey [12], and represent a common constituent of the human diet [13]. They possibly participate in the photosynthetic process [7]. Since flavonoids are capable of protecting unsaturated fatty acids (FAs) in membranes as well as ascorbate against oxidation [14].

1.3 Classification of Flavonoids

Flavonoids can be classified according to biosynthetic origin. Some classes, for example chalcones **(3)** and flavanones **(4)**, are both intermediates in biosynthesis as well as end products that can accumulate in plant tissues. Other classes are only known as end products of biosynthesis, for example flavones **(5)** and flavonols **(6)**. Two additional classes of flavonoid are those in which the 2-phenyl side chain of flavanone isomerises to the C-3 position **(7)**, giving rise to isoflavones and related isoflavonoids. The neoflavonoid is formed through further isomerisation to the C-4 position **(8)** [13].



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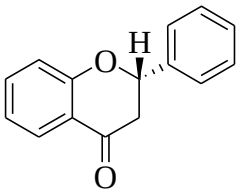

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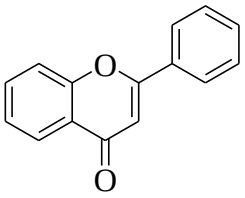

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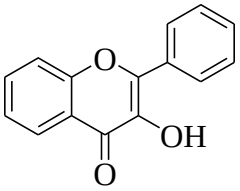

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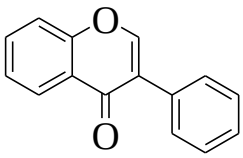

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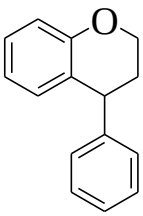

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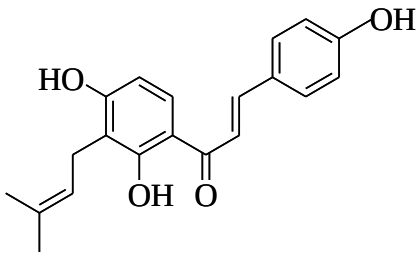
Chalcones **(3)** are known as benzalacetophenone or benzylidene acetophenone. In chalcones, two aromatic rings are linked by an aliphatic three carbon chain. Chalcone bears very well functional groups so that variety of novel heterocyclic with good pharmaceutical profile can be designed [15].

Chalcones are α, β-unsaturated ketone containing the reactive ketoethylenic group –CO-CH=CH-. They are coloured compounds due to the presence of the ketoethylenic group, which depend on the presence of other auxochromes [15].

Chalcones **(3)** exist naturally such as prenylated chalcone, isobavachalcone **(9)**, xanthohumol **(10)**.



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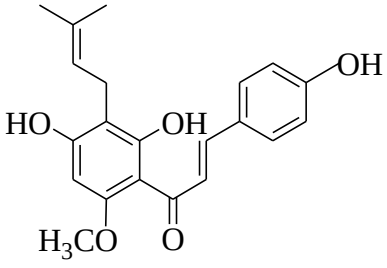

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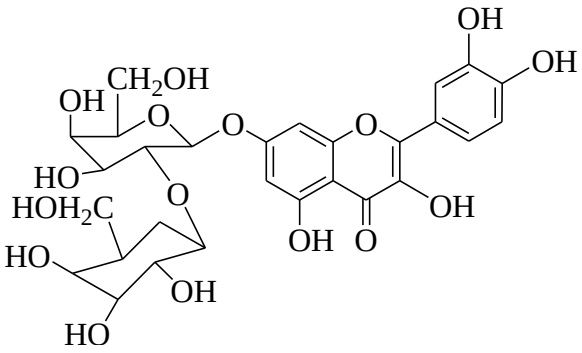
1.4 Biological Activities of Natural Flavonoids

Generally all flavonoids contain hydroxyl group and two aromatic groups. Flavonoids are becoming the subject of medical researchers. They have been reported to possess many useful biological properties, such as anti-inflammatory, estrogenic, enzyme inhibition, antimicrobial, antiallergic, antioxidant, vascular and cytotoxic activities [13, 16-18]. For a group of compounds of relatively homogenous structure, the flavonoids inhibit a perplexing number and variety of eukaryotic enzymes and have extremely wide range of activities. In the case of enzyme inhibition, this has been postulated to be due to the interaction of enzymes with different parts of the flavonoid molecule, e.g. carbohydrate, phenyl ring and phenol and benzopyrone ring [16].

In Argentine folk medicine the quercetagetin-7-arabinosyl-galactoside **(11)** was used to treatment infectious disease which it consists in the plant of *Tagetesminuta* [19]. *Scutellaria baicalensis* is yet another example. This herbal medicine has been used systemically and topically for thousands of years in China for the treatment of periodontal abscesses and infected oral wounds. The flavone baicalein **(12)** is reported to be largely responsible for this plant's antimicrobial effect [20].



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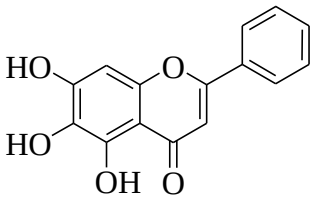

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Isobavachalcones **(9)** i.e 2,4,4′-trihydroxy-3-*C*-prenylchalcone is a prenylated chalcone, with good biological activities. This compound can be isolated from many plants, including *Psoralea corylifolia* [21], *Dorstenia kameruniana* [22], *Artocarpus lowii* [23], *Anthyllis hermanniae* [24] and *Glycyrrhiza glabra* [25]. Isobavachalcone **(9)** has been isolated from plants of the Fabaceae and Moraceae families as summarized in **Table 1.1**.

Table 1.1: Isobavachalcone in the Fabaceae and Moraceae families

Family	Species	Plant part	References
Fabaceae	*Psoralea corylifolia* L.	Seeds	21
	Anthyllis hermanniae L.	Aerial parts	24
	Erythrina burtti Balli.f.	Roots bark	26
	Erythrina fusca Lour	Bark	27
	Fructus Psoraleae L.	Fruits	28
	Glycyrrhiza glabra L.	Roots	25
	Glycyrrhiza uralensis	Tissue culture	29
	Sophora prostrata	Roots	30
Moraceae	*Artocarpus lowii*	Leaves	23
	Maclura tinctoria (L.)D. Don ex steud.	Leaves	31
	Dorstenia poinsettifolia var.angusta Engl.	Whole plant	32

Dorstenia turbinate	Twigs	33
Dorstenia barteri Bureau.	Twigs	34
Broussonetia papyrifera L 'Her.ex Vent.	Whole plant	35
Treculia acuminata	Twigs	36
Dorstenia kameruniana Engler	Leaves	22

1.5 Statement of Problem

Prenylated chalcone have many interesting bioactivities such as antioxidant and antiplatelet activating factor (PAF) properties which were studied during isolation of natural products from *A. lowii* [37]. Screening on the antiproliferative activity of several isolated chalcones from this species also showed promising results. Since isolation of these chalcones from natural resourses is in very limited amount, it is of great interest to attempt synthesize the prenylated chalcone using chemical methods.

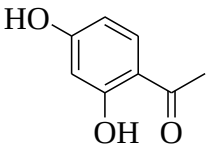
1.6 Objective of Study

The objectives of this study are as follows:-

- To synthesize prenylated 2,4-dihydroxyacetophenone and 2,4,5-trihydroxyacetophenone.
- To synthesize hydroxylated and prenylated chalcones using Claisen-Schmidt condensation.

1.7 Scope of Study

The first step in this synthesis work will involve prenylation of 2,4-dihydroxyacetophenone **(13)** using 2-methyl-3-buten-2-ol **(14)** in dry dioxane and $BF_3.Et_2O$ and 2,4,6-trihydroxyacetophenone **(15)** using 3,3-dimethylallyl bromide (prenyl bromide) **(16)** in the presence of K_2CO_3 as a catalyst to produce 2,4-dihydroxyprenylacetophenone (prenylated resacetophenone) and 2,4,6-trihydroxy-3-prenylacetophenone respectively. The second step is to react 2,4,6-trihydroxy-3-prenylacetophenone with 4-hydroxybenzaldehyde **(17)** in the presence of $BF_3.Et_2O$ *via* Claisen-Schmidt condensation to produce prenylated chalcone. Finally, the hydroxylated chalcones will be synthesized using 2,4-dihydroxyacetophenone **(13)** and 4-hydroxyacetophenone **(18)** with 4-hydroxybenzaldehyde **(17)** as the main precursor *via* Claisen-Schmidt condensation. The reaction products will be characterized using IR and ^{1}H NMR spectroscopies.



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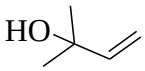

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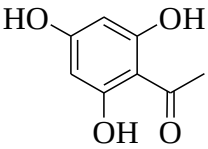

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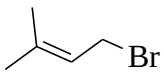

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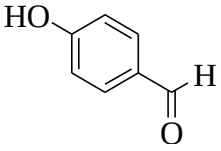

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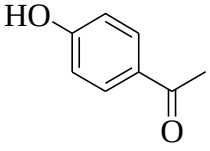

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1.8 Significance of Study

Natural flavonoids especially prenylated flavonoids are well known to have very interesting biological activities including antioxidant, anticancer, antiPAF, and anti-inflammatory. This study will produce hydroxylated and prenylated chalcones. These types of chalcones should have good antioxidant activity as reported by researchers during isolateion and bioactivity studies from natural resourses [37]. This study will use $BF_3.Et_2O$ as the catalyst which will lead to clean reaction with high yield. In addition, using $BF_3.Et_2O$ the hydroxyl groups of starting materials does not need to be protected as it is reported by Narender and Reddy (2007).

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