SYNTHESIS AND BIOACTIVITY STUDIES OF FLAVONOID AND ITS DERIVATIVES

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With lots of love,

Ayahanda & Bonda
Hj. Hashim Sarnap & Hjh. Juriah Jamin

The siblings,
Muhammad Raqib
Muhammad Diauddin
Muhammad Amilin
Muhammad Akmal
Haziqah

Wonderful companions,
Nor Hasbullah Ibrahim & family

For always standing by my side through ups and downs without even a slightest sigh

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PREFACE

This thesis is the result of my work carried out at the Department of Chemistry, Universiti Teknologi Malaysia between December 2009 and December 2011 under the supervision of Assoc Prof. Dr. Farediah Ahmad and Dr. Norazah Basar. Parts of my works described in this thesis have been reported in the following publications:

1. Farediah Ahmad, Nur Athirah Hashim, Norazah Basar, Khalijah Awang and Seik Weng Ng. (E)-3-(2H-1,3-Benzodioxol-5-yl)-1-(7-hydroxy-5-methoxy-2,2-dimethylchroman-8-yl)prop-2-en-1-one. (2011). *Acta Crystallographica Section E* (Structure Reports Online).**E67**: o2301. ISSN 1600-5368

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ABSTRACT

Flavonoids are the most widespread class of plants constituents. Most flavonoids are produced in biosynthetic pathways of secondary metabolites in plants and chalcones constituent as the important intermediate in flavonoid biosynthesis. In this study, eleven flavonoid derivatives were synthesized namely 2′,3,4-trihydroxy-4′,6′-dimethoxychalcone (**110**), 2′,4′,6′-trihydroxy-4,6-dimethoxychalcone (**120**), along with new compounds of 4′,5,7-trimethoxy-3′-*O*-prenylflavanone (**123**), 4′,5,7-trimethoxy-3′-*O*-6-*C*-diprenylflavanone (**126**), 2′-hydroxy- 4′,6′- dimethoxy-3,4-methylenedioxy -3′-*C*-prenylchalcone (**127**), 5,6- chroman- 7-methoxy- 3′,4′-methylenedioxyflavone (**130**), 5,6,7,8- dichroman- 3′,4′- methylenedioxyflavone (**132**), 5′,6′- chroman-2′,3,4- trihydroxy- 4′-methoxychalcone (**134**), 3′,4′,5′,6′-dichroman- 2′,3,4-trihydroxychalcone (**137**), 3′,4′,5′,6′-dichroman-3,4-dimethoxy-2′-hydroxychalcone (**138**) and 5′,6′- chroman-2′- hydroxy-4′- methoxy-3,4-*O*-diprenylchalcone (**139**). The initial step in the synthesis was to prepare various derivatives of 2,4,6-trihydroxyacetophenone and 3,4-dihydroxybenzaldehyde by methylation, methylenation, protection and prenylation of the phenolic hydroxyl groups. The derivatives of both ketone and aldehyde were coupled and reacted using Claisen-Schmidt condensation to obtain the desired 2′-hydroxychalcone. 2′-Hydroxy-4,4′,6′-trimethoxy-3-*O*-prenylchalcone (**122**) and 4,4′,6′-trimethoxy-3-*O*-5′-*C*-diprenylchalcone (**125**) underwent an acid hydrolysis to yield flavanones (**123**) and (**126**), respectively. In addition, 2′-hydroxy- 4-methoxy- 5,6-chroman- 3,4-methylenedioxychalcone (**129**) and 2′- hydroxy- 3′,4′,5′,6′- dichroman- 3,4-methylenedioxychalcone (**131**) were converted to flavones (**130**) and (**132**) using iodine in dimethylsulfoxide as an oxidative agent The structures of all compounds were confirmed spectroscopically by UV, IR, NMR and MS analysis. The biological studies of all the synthetic compounds were tested towards antioxidant, anti-inflammatory and antibacterial properties. The hydroxylated flavonoids with 3,4-dihydroxyl substituents were tested positive in 2,2-diphenyl-1-dipicrylhydrazyl (DPPH) assay and the highest antioxidant activity was exhibited by chalcone (**110**) with IC_{50} 19.3 μg/mL. Two assays were used to evaluate the potential of the compounds as anti-inflammation agents. The results showed that chalcones (**110**) (IC_{50} 2.4 μg/mL), (**134**) (IC_{50} 1.94 μg/mL) and (**137**) (IC_{50} 20.8 μg/mL) which possessed 3,4-dihydroxyl substituents exhibited good activity in the 13-lipooxygenase (LOX) assay. For xanthine oxidase assay, chalcone (**120**) with 4′,6′-dihydroxyl showed a significant activity with IC_{50} 6.83 μg/mL. All the synthesized flavonoids were found inactive towards the tested bacteria in the antibacterial assay.

ABSTRAK

Flavonoid adalah kelas sebatian paling banyak dijumpai dalam tumbuhan. Kebanyakan flavonoid adalah terhasil melalui laluan biosintesis bagi metabolisma sekunder tumbuhan dengan kalkon adalah perantara utama dalam biosintesis flavonoid tersebut. Dalam kajian ini, sebelas terbitan flavonoid telah disintesis iaitu 2′,3,4- trihidroksi-4′,6′- dimetoksikalkon (**110**), 2′,4′,6′- trihidroksi- 4,6-dimetoksikalkon (**120**), termasuk sebatian baru iaitu 4′,5,7- trimetoksi-3′-*O*-prenilflavanon (**123**), 4′,5,7-trimetoksi-3′-*O*-6-*C*-diprenilflavanon (**126**), 2′-hidroksi-4′,6′-dimetoksi-3,4-metilenadioksi-3′-*C*-prenilkalkon (**127**), 5,6-kroman-7-metoksi-3′,4′-metilenadioksiflavon (**130**), 5,6,7,8-dikroman-3′,4′-metilenadioksiflavon (**132**), 5′,6′-kroman-2′,3,4-trihidroksi-4′-metoksikalkon (**134**), 3′,4′,5′,6′-dikroman-2′,3,4-trihidroksikalkon (**137**), 3′,4′,5′,6′-dikroman-3,4-dimetoksi-2′-hidroksikalkon (**138**) dan 5′,6′-kroman-2′-hidroksi-4′-metoksi-3,4-*O*-diprenilkalkon (**139**). Langkah pertama dalam sintesis ini adalah untuk menyediakan pelbagai sebatian terbitan dari 2,4,6-trihidroksiasetofenon dan 3,4-dihidroksibenzaldehid melalui tindak balas pemetilan, pemetilenan, perlindungan dan pemprenilan kumpulan hidroksil. Sebatian terbitan keton dan aldehida ditindakbalas melalui kondensasi Claisen-Schmidt untuk menghasilkan 2′-hidroksikalkon. 2′-Hidroksi-4,4′,6′-trimetoksi-3-*O*-prenilkalkon (**122**) dan 4,4′,6′-trimetoksi-3-*O*-5′-*C*-diprenilkalkon (**125**) melalui proses hidrolisis berasid untuk menghasilkan masing-masing flavanon (**123**) dan (**126**). Iodin dalam dimetilsulfoksida telah digunakan sebagai agen pengoksidaan untuk menukar 2′-hidroksi-4-metoksi-5,6-kroman-3,4-metilenadioksikalkon (**129**) dan 2′-hidroksi-3′,4′,5′,6′-dikroman-3,4-metilenadioksikalkon (**131**) kepada flavon (**130**) dan (**132**). Struktur kesemua sebatian dikenal pasti secara spektroskopi menggunakan analisa UL, IM, RMN dan SJ. Kajian biologi semua sebatian sintetik dijalankan melibatkan aktiviti antioksida, anti-radang dan antibakteria diuji bagi semua sebatian sintetik. Hidroksi flavonoid dengan 3,4-dihidroksil sebagai penukarganti telah menunjukkan aktiviti positif dalam cerakinan 2,2-difenil -1-pikrilhidrazil (DPPH) dan aktiviti antioksidan paling tinggi ditunjukkan oleh kalkon (**110**) dengan IC_{50} 19.3 μg/mL. Dua cerakinan telah digunakan untuk menilai potensi sebatian sebagai ejen anti-radang. Keputusan cerakinan kalkon (**110**) (IC_{50} 2.4 μg/mL), (**134**) (IC_{50} 1.94 μg/mL) dan (**137**) (IC_{50} 20.8 μg/mL) yang mempunyai kumpulan penukarganti 3,4-dihidroksi menunjukkan aktiviti yang baik dalam cerakinan 13-lipooksigenase (LOX). Untuk cerakinan xantina oksidase, kalkon (**120**) dengan 4′,6′-dihidroksi menunjukkan aktiviti yang baik dengan IC_{50} 6.83 μg/mL. Manakala, semua sebatian flavonoid sintetik didapati tidak aktif terhadap kesemua bakteria dalam cerakinan antibakteria.

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LIST OF ABBREVIATIONS

BF_3-Et_2O	boron trifluoride etherate
BHT	butylated hydroxytoluene
br	broad
^{13}C	carbon-13
CD_3COCD_3	deuterated acetone
$CDCl_3$	deuterated chloroform
COSY	correlation spectroscopy
CuBr.DMS	dimethyl sulphide complex-copper bromide
d	doublet
DBU	1,8-diazobicyclo [5.4.0] undec-7-ene
DCM	dichloromethane
dd	doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azidocarboxylate
DEPT	Distortionless Enhancement by Polarization Transfer
DIAD	diisopropyl azidocarboxylate
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
DPPH	2,2-diphenyl-1-picrylhydrazyl
EIMS	Electron Impact Mass Spectrometry
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
hr	hour
^1H	proton
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum coherence

Hz	hertz
IC_{50}	inhibition concentration at 50%
IR	infrared
J	coupling constant
lit.	Literature
LOX	Lipooxygenase
m/z	mass to charge ratio
m	multiplet
M	molar
MBC	minimum bactericidal concentration
Me_2SO_4	dimethyl sulphate
MeI	iodomethane
MeOH	methanol
$MgSO_4$	magnesium sulphate
MHz	megahertz
MIC	minimum inhibition concentration
MOM	methoxymethyloxy
MOMCl	methoxymethyl chloride
m.p	melting point
MS	mass spectrometry
NaOAc	sodium acetate
NaOMe	sodium methoxide
NDGA	nordihydroguaiaretic acid
NMR	nuclear magnetic resonance
nm	nanometer
Ph	phenyl
Pet	petroleum ether
ppm	parts per million
R_f	retention factor
SD	standard deviation
s	singlet
t	triplet
TBAOH	tetrabutylammonium hydroxide
TBATB	tetrabutylammonium tribromide

TLC	thin layer chromatography
UV	ultraviolet
XO	xanthine oxidase
δ	chemical shift
λ	lambda

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CHAPTER 1

INTRODUCTION

1.1 General Introduction

Nature is always an innovative laboratory. This concept applied to the development of organic synthesis field to enhance the pharmacological activities of naturally isolated compounds. Moreover, potential bioactivities and medicinal used has long been the justification for research in natural products field. Hence, realization of this objective has indeed led to a better understanding of the structural requirements for a diversity of physiological activities, and subsequentially leading to the synthesis and modification of several target compounds and analogues.

In natural products, flavonoids are the most abundant plants compounds [1]. They were distributed numerously with more than 5000 different flavonoids having been described to date [2]. The flavonoids may be classified into seven groups according to the basic ring system namely flavones, flavonones, flavonols, anthocyanins, chalcones, isoflavones and also biflavones [3].

In general, naturally occurring flavonoids usually have free phenolic (-OH) group or methoxyl (-OCH_3) group [4]. The flavones, a subclass of flavonoids can be classified into several subgroups which are mainly indicated either by hydroxylation,

O-methylation, *C*-methylation, isoprenylation or methylenedioxy substitution [5]. In the previous researches, flavonoids have been shown to possess remarkable physiological activities in mammalian systems [6].

1.2 Flavones in Nutrition and Health

Along with their important functions in the biochemistry, physiology and ecology of plants, flavones are conjointly important compounds for human nutrition and health [5]. Moreover, it has been reported that even a high intake of plant-based dietary flavonoids is at a halt safe and not associated with any adverse health effect [7]. For instance, flavonoids were well known antioxidants which act as scavengers of various oxidizing species [8]. Besides, flavones also played an important role in cancer prevention in plummeting cancer rates since these compounds were found abundantly in plants. Flavonoids and its subclass isoflavonoids have been prominent in assessing cancer anticipation in models of breast and colon cancer [9].

A subclass of flavonoids, chalcones and analogues, apart from having a good antioxidant activity, they also showed analgesic and anti-inflammatory activities [10, 11]. In fact, a research has done on the structure activity relationship of chalcones on their antibacterial activity against human pathogenic microorganisms which have the promising effect on certain substitutions patterns [12]. In addition, *C*-methylated chalcones which were isolated from the fruits of *Syzygium samarangense* displayed cytotoxic activity against the human colon cancer line [13].

Equally important, a common flavonol, kaempferol has been reported as tyrosinase inhibitor that catalyzes reactions of melanin synthesis [14]. Another group, flavone and its derivatives have demonstrated as a potent anti-HIV activity with therapeutic effects which will lead to a further anti-HIV drug development [15]. Naturally occurring prenylated flavones from *Artocarpus elasticus* showed to be a potent inhibitor of both T- and B-lymphocyte mitogen induced proliferation in human lymphocytes [16]. Besides, prenyl substituent at C-3 position of flavone

isolated from the wood of *Artocarpus heterophyllus* plays an important role for revealing tyrosinase inhibition on B16 melanoma cells [17]. Likewise, chalcone substitution also by prenylation has been reported in increasing their binding affinity to P-glycoprotein responsible for cancer cells chemoresistance [18]. On the other hand, the derivatives of flavone, flavanone bearing a C-8 hydrated prenyl showed extremely high inhibition activity for neuraminidase inhibition which most commonly known as a target for the prevention of influenza infection [19].

1.3 Problems Statements

In recent years, there has been a resurgence of scientific interest in flavonoids, which is due to the association of these compounds with a wide range of health promoting effects. Numerous natural flavonoids had been reported and screened for antibacterial and antioxidant activities. However, small amounts and hard to isolate, limit further studies of their pharmacological activities. Therefore, the symthesis of flavones and derivatives involving mainly the hydroxylated, *O*-methylated, *O*- and *C*- prenylated and chromane have to be synthesized. The synthetic routes and mechanism of reactions of the target compounds need to be developed.

1.4 Objectives of Study

The objectives of this study are:

1. To synthesize flavones and derivatives with hydroxylated, methoxylated, *O*- and *C*- prenylated and chromane substituents by multi-step reactions using established and newly develop methodologies.
2. To investigate the bioactivity of the derivatives on antioxidant, antibacterial and anti-inflammatory activites.

1.5 Scope of Study

The scope of this study covered the multi-step reactions which were protection, methylation and prenylation or *vice-versa* of 2,4,6-trihydroxyacetophenone and 3,4-dihydroxybenzaldehyde which then be subjected to condensation using Claisen-Schmidt reaction to form chalcones. The chalcones were cyclized to flavone derivatives and deprotection of the protecting groups were required to form hydroxylated flavones. Structure elucidation of the pure compounds were carried out using several spectroscopic methods, including UV, IR, 1D NMR (^{1}H, ^{13}C, DEPT), 2D NMR (COSY and HMQC), and MS. The selected synthetic flavones and derivatives were screened and tested for antioxidant activity by 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging assay, antibacterial activity by disc diffusion method (DDM), minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC), anti-inflammatory activity by lipooxygenase (13-LOX) and xanthine oxidase (XO) assays.

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