SYNTHESIS OF CHALCONES AND DERIVATIVES

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"To my beloved dad, mum, brother and Vishnu....."

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ABSTRACT

In the present study, we undertook the total synthesis of several chalcones and derivatives namely chalcone, 2'-hydroxychalcone, 2',4-dihydroxychalcone, 2'-hydroxy -3,4-dimethoxychalcone, 1,3-diphenylprop-2-en-1-ol, 2,3-dibromochalcone, 1-(1,3-diphenylallylidene)-1-phenylhidrazine, 3-hydroxy-2-phenyl-4-chromen-4-one and 2-phenylchromen-4-one. These target compounds were synthesized *via* Claisen-Schmidt condensation of the respective ketones and benzaldehydes under basic condition to give the corresponding chalcone, 2'-hydroxychalcone, and 2'-hydroxy -3,4-dimethoxychalcone. At the same time, 2',4-dihydroxychalcone was synthesized by Boron-trifluoride etherate method. 2'-Hydroxychalcone was converted to flavone by treatment with iodine in dimethylsulfoxide and to 3-hydroxy-2-phenyl-4-chromen-4-one by treating with hydrogen peroxide and NaOH. 1,3-Diphenylprop-2-en-1-ol was synthesized from chalcone through reduction process using $NaBH_4$ while 1-(1,3-diphenylallylidene)-1-phenylhidrazine was prepared from chalcone and phenylhydrazine in ethanol. Structures were confirmed spectroscopically by IR, NMR (^{1}H and ^{13}C), DEPT and GC-MS. The antibacterial and toxicity activities of the synthesized compounds were evaluated by disc diffusion method and brine shrimps lethality test, respectively. All the synthesized compounds were inactive towards the tested bacteria. Chalcone and 2'-hydroxychalcone were found to be the most toxic compounds against brine shrimp (*Artemia salina)* both with LD_{50} 1.7 ppm.

ABSTRAK

Dalam kajian ini, kalkon dan beberapa terbitannya iaitu kalkon, 2'-hidroksikalkon, 2',4-dihidroksikalkon, 2'-hidroksi -3,4-dimetoksikalkon, 1,3-difenilprop-2-en-1-ol, 2,3-dibromokalkon, 1-(1,3-difenilalliliden)-1-fenil-hidrazin, 2-fenilkromen-4-on dan 3-hidroksi-2-fenil-4-kromen-4-on telah disintesis. Sebatian kalkon yang disintesis melalui tindak balas kondensasi Claisen-Schmidt adalah kalkon, 2'-hidroksikalkon, dan 2'-hidroksi-3,4-dimetoksikalkon. Manakala 2',4-dihidroksikalkon dihasilkan melalui kaedah Boron-trifluorid etherat. 2'-Hidroksikalkon telah diubah secara kimia kepada 2-fenilkromen-4-on melalui tindakbalas dengan iodin dalam dimetilsulfoksida. Manakala, 3-hidroksi-2-fenil-4-kromen-4-on dihasilkan melalui tindakbalas antara hidrogen peroksida dan NaOH dengan 2'-hidroksikalkon. 1,3-Difenilprop-2-en-1-ol telah disintesis daripada kalkon melalui kaedah penurunan menggunakan $NaBH_4$ manakala 1-(1,3-difenilalliliden)-1-fenilhidrazin dihasilkan melalui tindakbalas antara kalkon dan fenil hidrazin dalam etanol. Struktur semua sebatian dikenalpasti secara spektroskopi menggunakan IR, RMN (^1H dan ^{13}C), DEPT dan KGSJ. Aktiviti antibakteria dan ketoksikan bagi semua kalkon dan terbitannya telah dijalankan dengan kaedah pembauran cakera serta ketoksikan ke atas anak udang. Semua sebatian yang disintesis didapati tidak aktif terhadap semua bakteria yang diuji. Kalkon dan 2'-hidroksikalkon merupakan sebatian yang paling toksik terhadap anak udang (*Artemia salina*) dengan nilai LD_{50} 1.7 ppm.

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LIST OF ABBREVIATIONS

br	-	broad
^{13}C	-	carbon-13
C_6H_{12}	-	Hexane
$CaCO_3$	-	calcium carbonate
CC	-	Column Chromatography
$CHCl_3$	-	Chloroform
CH_2Cl_2	-	dichloromethane
d	-	doublet
dd	-	doublet of doublets
DEPT	-	distortionless enhancement of polarization transfer
DMSO	-	dimethylsulfoxide
EtOAc	-	Ethyl Acetate
EtOH	-	Ethanol
FTIR	-	Fourier Transform Infrared Spectrometer
GCMS	-	Gas Chromatography- Mass Spectrometer
^{1}H	-	proton
HCl	-	hydrochloric acid
H_2O_2	-	hydrogen peroxide
IR	-	Infrared
J	-	coupling constant
KOH	-	potassium hydroxide
m	-	multiplet
$MgSO_4$	-	magnesium sulphate
MS	-	Mass spectrum
MeOH	-	Methanol
m/z	-	mass-to-charge ratio

m.p	-	melting point
NaCl	-	sodium chloride
$NaBH_4$	-	sodium borohydride
NaOH	-	sodium hydroxide
NaOAc	-	sodium acetate
Na_2SO_4	-	sodium sulphate
NMR	-	Nuclear Magnetic Resonance
PE	-	petroleum ether
ppm	-	part per million
R_f	-	Retention factor
rt	-	room temperature
s	-	singlet
t	-	triplet
TBATB	-	tetrabutylammonium tribromide
THF	-	tetrahydrofuran
TLC	-	Thin Layer Chromatography
UV	-	Ultraviolet
δ	-	chemical shift
λ	-	lambda

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CHAPTER 1

INTRODUCTION

1.1 Background of Study

Organic synthesis is one of a special branch in chemical synthesis and is concerned with the construction of organic compounds by reactions. It is believed to be one of the most vital in organic chemistry because the organic molecules used to contain higher level of complexity compared to pure inorganic compounds. Organic synthesis specifically becomes centre of attraction for many scientists because the ability to produce beneficial products artificially for human goods. So far, organic synthesis plays a very important role in many sectors such as pharmaceuticals, agricultural and others.

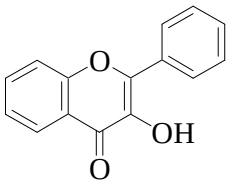
On the other hand, development in chemical instruments becomes one of the factors for many researches undergone their research more effectively. Advanced technology able to produce instruments with higher accuracy with less time needed to produce high quality products such as NMR, HPLC and others. The inventions of such scientific instruments promote the organic synthesis sector to widen up the study of interest. The development of science and technology offers assistance in many fields especially in medical field. This development introduced the importance of naturally occurring compounds in plants and researches have been done significantly to synthesize these natural compounds artificially. 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.

Flavonoids with 1,3-diarylpropane skeleton can be classified as an outstanding class of naturally occurring compounds (Avila *et al.,* 2008). Chalcones or 1,3-diphenyl-2-propen-1-one derivatives are open chain unsaturated carbonyl system in which two aromatic rings are joined by three carbons of having α, β-unsaturated system (Avila *et al.,* 2008). Chalcones can be considered as the precursors of flavonoids and isoflavonoids (Tomar *et al*., 2007) and are secondary metabolites of terrestrial plants that exhibit various biological activities (Narender and Reddy, 2007).

1.2 Classification of Flavonoids

The flavonoids are members of a class of natural compounds that recently has been the subject of considerable scientific and therapeutic interest. The flavonoids are ubiquitous to green plant cells and therefore, could be expected to participate in the photosynthetic process (Havstee, 2002). Flavonoids are compounds found in fruits, vegetables and certain beverages (tea, coffee, beer, wine and fruit drinks) that have diverse beneficial biochemical and antioxidant effects. Their dietary intake is quiet high compared to other dietary antioxidants like vitamin C and E.

Flavonoids are polyphenolic compounds and are categorized according to chemical structure such as flavonol **(1)**, flavone **(2)**, flavanone **(3)**, isoflavone **(4)**, catechin **(5)**, anthocyanidin and chalcone **(6)** (Geissman, 1969). The flavonoids have aroused considerable interest recently because of their potential beneficial effects on human health.



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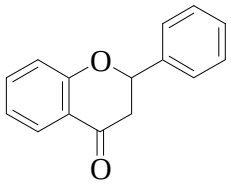

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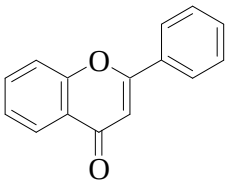

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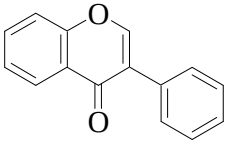

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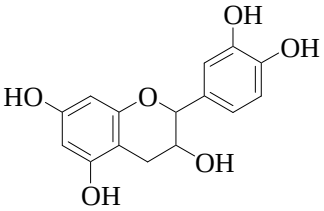

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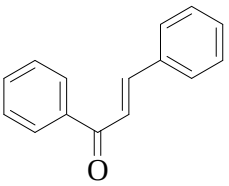

(6)

These groups usually share a common chalcone **(6)** precursor which is the basic skeleton, and therefore are biogenetically and structurally related. Flavonoids cannot be produced *via* human body cells and thus to be taken mainly through the daily diet (Joule, 1972). Flavonoids similar as chalcones composed of C_{15} of two aromatic rings linked through three carbon bridge with a carbonyl function located at one end of the bridge. Flavone **(2)** is the skeleton of a large class of flavonoids (Geissman, 1969). The interest in biological properties of the flavonoids has resulted intense synthetic efforts towards the synthesis of various flavonoids (Havstee, 2002). Some of the methods which used to synthesize flavonoids are Baker-Venkataraman, Von-Konstanecki, Allan-Robinson and others.

1.3 Chalcones as Drugs

Chalcones are popular intermediates for synthesizing various heterocyclic compounds (Rajendra Prasad *et al*., 2008). The compounds with the backbone of chalcones have been reported to possess various biological activities such as antimicrobial, anti-inflammatory, analgesic, antiplatelet, antiulcerative, antimalarial, anticancer, antiviral, antileishmanial, antioxidant, antitubercular, antihyperglycemic, immunomodulatory, inhibition of chemical mediators release, inhibition of leukotriene B_4, inhibition of tyrosinases and inhibition of aldose

reductase activities (Rajendra Prasad *et al.,* 2008). The presence of a reactive α,β-unsaturated keto function in chalcones is found to be responsible for their biological activities (Rajendra Prasad *et al.,* 2008).

1.4 Problem Statement

There are varieties of methods available for preparation of chalcones. The Claisen-Schmidt condensation and borontrifluoride-etherate methods were chosen to produce chalcones using substituted aldehydes and substituted ketones. Due to the reversible nature of Claisen-Schmidt reaction, the reactants were taken in excess of stoichiometric proportion in order to increase the α,β-unsaturated product (Dhar and Lal, 1958). Antimicrobial activity and toxicity test were examined to the synthesized compound to observe the pharmacologically effects of the synthetic compounds.

1.5 Objectives of Study

The objectives of the study are:-

i. To synthesize and characterized the chalcones and derivatives.
ii. To modify the functional groups of the selected chalcones.
iii. To screen the antimicrobial and toxicity activities of the chalcone and derivatives

1.6 Scope of Study

The respective chalcones are synthesized by Claisen-Schmidt condensation and BF_3-Et_2O catalyzed reaction. The crude products are purified by chromatographic methods and recystallization techniques. The pure compounds are characterized spectroscopically by NMR (^1H and ^{13}C), IR, MS and UV techniques.

The characterized compounds are subjected to simple chemical reactions (addition, reduction and cyclisation) to form derivatives. The pure chalcones and derivatives are screened for antimicrobial activity by disc diffusion method and toxicity test using brine shrimp larvae (*Artemia salina*).

1.7 Significance of Study

This study will produce characterized chalcones and their derivatives. In addition, the biological activity performed on the chalcones and derivatives will give compounds with antibacterial and toxicity activities.