SYNTHESIS AND BIOLOGICAL ACTIVITIES OF *O*- AND *C*-PRENYLATED FLAVONOID DERIVATIVES

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With lots of love,

Parents and Grandparents

The siblings,
Siti Umairah
Fairuz Wirdani
Muhammad Abbas
Muhammad Umar

Wonderful husband,
Muhammad Shahrul bin Po'at

For always standing by my side through ups and downs

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ABSTRACT

Chalcones scaffolds have attracted many researchers to investigate their synthetic routes, potential biological activities and their roles as intermediates for naturally occurring flavanoid skeletons. This study focused on the synthesis of chalcones bearing the *O*-, *C*-prenyl and chromane as substituents. The target compounds were purified by chromatographic methods and the structures of these compounds were determined by using infrared (IR), nuclear magnetic resonance (NMR) and mass spectrometry (MS) spectroscopies. The prenylated precursors were synthesized starting from 2,4-dihydroxyacetophenone **(65)** and 2,4,6-trihydroxyacetophenone **(93)**. Prenylation of 2,4-dihydroxyacetophenone using prenyl bromide has been successfully accomplished to produce 2-hydroxy-4-*O*-prenylacetophenone **(101)**. A reaction of 2,4,6-trihydroxyacetophenone with prenyl bromide in the presence of base resulted in a mixture and the chromatographic purification gave 2,4,6-trihydroxy-3-*C*-prenylacetophenone **(132)** and 2,4-dihydroxy-5,6-chromanacetophenone **(133)**. Compound **(133)** was prenylated into 2-hydroxy-4-*O*-prenyl-5,6-chromanacetophenone **(136)**. *C*-prenylated acetophenone **(132)** was then converted to 2-hydroxy-3-*C*-prenyl-4,6-dimethoxyacetophenone **(137)** using methyl iodide in the presence of potassium carbonate. Claisen-Schmidt condensation of *O*- and *C*-prenylated acetophenone with individual benzaldehydes, namely 4-(*N*,*N*-dimethyl)aminobenzaldehyde **(61)**, 2-methoxybenzaldehyde **(126)**, 4-isopropylbenzaldehyde **(127)**, 3,4-dimethoxybenzaldehyde **(128)** and 4-chlorobenzaldehyde **(129)** resulted in the formation of two series of chalcones, each consisting of five chalcones. These two series differ in the existence of prenyl substituents on ring A of the chalcone structure. Five chalcones bear *O*-prenyl and five others bear *C*-prenyl substituent with both series having the same substituents on ring B consisting of 4-*(N,N*-dimethyl)amino, 2-methoxy, 4-isopropyl, 3,4-dimethoxy and 4-chloro substituents. Chromanochalcone **(152)** was the sole compound successfully synthesized with the aid of prenylation of free hydroxyl group of the chromanacetophenone **(133)** precursor. All the synthetic compounds were screened for antibacterial activity by the micro dilution method against two bacteria strains, namely Gram positive (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram negative (*Pseudomonas aeruginosa* and *Escherichia coli*). The compounds were also tested for 15-LOX assay using Lipoxygenase inhibitory screening assay kit (Item No. 760700). All the synthetic compounds did not show activity against the bacteria tested, while compound **(138)** and **(145)** showed moderate lypoxygenase activity at 100 μM concentration with 53.9% and 50.9% inhibition, respectively.

ABSTRAK

Rangka kalkon telah menarik ramai penyelidik untuk mengkaji laluan sintesis, keupayaan aktiviti biologi dan peranannya sebagai bahan perantara untuk rangka flavanoid semulajadi. Kajian ini memfokuskan kepada sintesis kalkon yang mempunyai penukarganti *O*-, *C*-prenil dan kromano. Sebatian sasaran ditulenkan dengan kaedah kromatografi dan struktur semua sebatian ditentukan dengan menggunakan kaedah spektroskopi inframerah (IM), resonans magnetik nuklear (RMN) dan spektrometri jisim (SJ). Prekursor terprenil telah disintesiskan bermula daripada 2,4-dihidroksiasetofenon **(65)** dan 2,4,6-trihidroksiasetofenon **(93)**. Pemprenilan 2,4-dihidroksiasetofenon menggunakan prenil bromida telah dilaksanakan dengan jayanya bagi menghasilkan 2-hidroksi-4-*O*-prenilasetofenon **(101)**. Tindak balas 2,4,6-trihidroksiasetofenon dengan prenil bromida dengan kehadiran bes telah menghasilkan satu campuran, dan penulenan kromatografi memberikan 2,4,6-trihidroksi-3-*C*-prenilasetofenon **(132)** dan 2,4-dihidroksi-5,6-kromanasetofenon **(133)**. Sebatian **(133)** telah diprenilkan kepada 2-hidroksi-4-*O*-prenil-5,6-kromanasetofenon **(136)**. *C*-prenilasetofenon **(132)** kemudian diubah kepada 2-hidroksi-3-*C*-prenil-4,6-dimetoksiasetofenon **(137)** menggunakan metil iodida dengan kehadiran kalium karbonat. Kondensasi Claisen-Schmidt *O*- dan *C*-prenilasetofenon dengan benzaldehid individu, iaitu 4-(*N*,*N*-dimetil)aminobenzaldehid **(61)**, 2-metoksibenzaldehid **(126)**, 4-isopropilbenzaldehid **(127)**, 3,4-dimetoksibenzaldehid **(128)** dan 4-klorobenzaldehid **(129)** telah menghasilkan dua siri kalkon, tiap-tiap satu terdiri daripada lima kalkon. Dua siri ini berbeza dari segi kewujudan prenil pada gelang A struktur kalkon. Lima kalkon mempunyai *O*-prenil dan lima kalkon yang lain mempunyai penukar ganti *C*-prenil dengan kedua-dua siri mempunyai penukar ganti yang sama pada gelang B yang terdiri daripada penukar ganti 4-*(N,N*-dimetil)amino, 2-metoksi, 4-isopropil, 3,4-dimetoksi and 4-kloro. Kromanokalkon **(152)** adalah sebatian tunggal yang berjaya disintesis dengan bantuan pemprenilan kumpulan hidroksil bebas pada prekursor kromanasetofenon **(133)**. Semua sebatian sintetik telah disaring untuk aktiviti antibakteria menggunakan kaedah pencairan mikro terhadap dua jujukan bakteria iaitu Gram positif (*Staphylococcus aureus* dan *Bacillus subtilis*) dan Gram negatif (*Pseudomonas aeruginosa* dan *Escherichia coli*). Sebatian juga telah diuji untuk cerakin 15-LOX menggunakan kit cerakin saringan perencatan lipoksigenase (Item No. 760700). Semua sebatian sintetik tidak menunjukkan aktiviti terhadap bakteria yang diuji, manakala sebatian **(138)** dan **(145)** menunjukkan aktiviti lipoksigenase sederhana pada kepekatan 100 μM dengan masing-masing mempunyai nilai perencatan sebanyak 53.9% dan 50.9%.

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BF_3-Et_2O	boron trifluoride etherate
^{13}C	carbon-13
CD_3COCD_3	deuterated acetone
$CDCl_3$	deuterated chloroform
$CHCl_3$	chloroform
d	doublet
DBU	1,8-diazobicyclo [5.4.0] undec-7-ene
dd	doublet of doublets
DEPT	Distortionless Enhancement by Polarization Transfer
EIMS	Electron Impact Mass Spectrometry
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
^1H	proton
HCl	hydrochloric acid
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum coherence
Hz	hertz
iNOS	inducible nitric oxide synthase
IR	infrared
IM	inframerah
J	coupling constant
K_2CO_3	potassium carbonate
KBr	potassium bromide
KOH	potassium hydroxide
lit.	Literature
LOX	Lipooxygenase

m/z	mass to charge ratio
m	multiplet
M	molar
MBC	minimum bactericidal concentration
Me_2SO_4	dimethyl sulphate
MeOH	methanol
$MgSO_4$	magnesium sulphate
MHz	megahertz
MIC	minimum inhibition concentration
MOM	methoxylmethyl ether
m.p	melting point
MS	mass spectrometry
NaOH	sodium hydroxide
NMR	nuclear magnetic resonance
ppm	parts per million
R_f	retention factor
RMN	resonans magnetik nuklear
SD	standard deviation
s	singlet
sept	septet
SM	spectrum jisim
t	triplet
THP	tetrahydropyranyl acetal
TLC	thin layer chromatography
δ	chemical shift
λ	lambda

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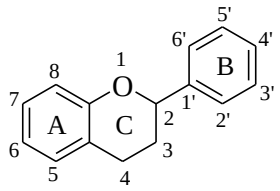
CHAPTER 1

INTRODUCTION

1.1 General Introduction

Flavonoids are abundance group of polyphenolic substances which can be extracted in most plants and sometimes presence as glycosides [1]. Multiple combination of substituent such as hydroxyl, oxygen, methyl groups and sugars attached to these structures create the various classes of flavonoids **(1)**, flavonols **(2)**, flavanones **(3)**, flavones **(4)**, flavan-3-ols **(5)**, anthocyanidins **(6)** and isoflavones **(7)**. Flavonoids have shown capability as potential antitumor, antineoplastics activities, antimicrobial and antimalarial agents [1].



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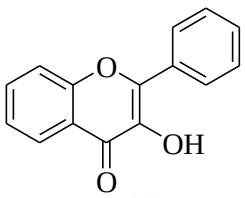

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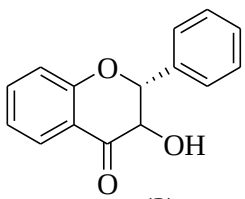

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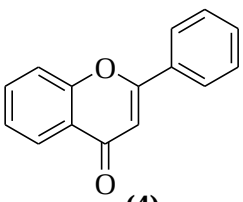

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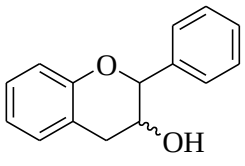

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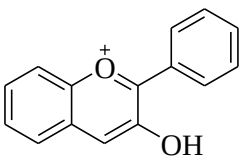

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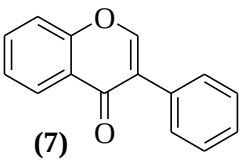
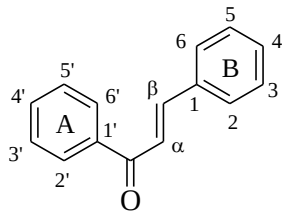


(7)

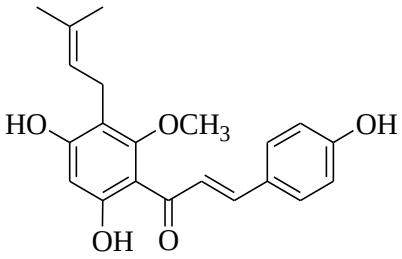
Chalcone is the simplest flavonoid with a fifteen-carbon skeleton (C6-C3-C6) **(8)** which possessed two phenyl rings connected by three carbon bridges [2]. The synthesized chalcones were obtained *via* Claisen-Schmidt condensation with

association of cross aldol condensation of appropriate aldehydes and ketones, catalysed by base or acid and enclosed by dehydration [3].



(8)

Chalcone **(8)** are intermediates in the biosynthesis of flavonoids that widespread in plants and with an array of bioactivities [2]. Derivatives of chalcone are physiologically active compounds and become the substrates for the valuation of various organic syntheses [2]. Lipophilic prenyl side-chain attached to a chalcone moiety has been attracting the attention of the scientific community because of their myriad biological activities [4] which include *O*-prenylation, *C*-prenylation and chroman group [5]. Natural prenylated chalcones such as xanthohumol **(9)** exhibit numerous pharmacological properties such as antibacterial [6], antitumor [7], antihistaminic [8], antioxidant [9], and antiplasmodial activity [10].



(9)

1.2 Problem Statement

Owing to their simple structures and ease of preparation, chalcones intermediates for the synthesis of large number of derivatives of flavonoids. Besides prenylation, the pharmacological properties of chalcones also related to the presence, number and position of hydroxyl and methoxyl groups in both A and B ring. Hence,

the synthesis of prenylated derivatives which include *O*-prenyl, *C*-prenyl, and chromane chalcones bearing hydroxyl and methoxyl substituents is undertaken. The previous mentioned structural moieties are expected to display significant biological activities.

1.3 Objectives of Study

The objectives of this study are:

1. To synthesis, purify and elucidate the acetophenone derivatives with *O*-prenyl, *C*-prenyl and chromane as the side chains.
2. To synthesis, purify, elucidate the series of *O*-prenyl, *C*-prenyl and chromanochalcones.
3. To screen the antibacterial and anti-inflammatory activities (LOX) of the synthesized chalcones.

1.4 Scope of Study

The initial reactions were carried out by synthesizing *O*-prenyl, *C*-prenylacetophenone and chromanacetophenone from 2,4-dihydroxyacetophenone and 2,4,6-trihydroxyacetophenone using prenyl bromide in the presence of either 1,8-diazabicycloundec-7-ene (DBU) or K_2CO_3 as base without the use of protecting group. Mixtures of compounds were purified by recrystallization techniques or silica gel column chromatography (CC). Structures of *O*-prenyl, *C*-prenyl and chromanacetophenone were determined using IR and NMR (1D and 2D). Acetophenone derivatives were subjected to methylation using methyl iodide in K_2CO_3 followed by purification and structural elucidation. All characterized acetophenone derivatives were subjected to Claisen-Schmidt reaction with benzaldehyde derivatives which include benzaldehyde bearing substituents 4-(*N*,*N*-dimethyl)amino, 2-methoxyl, 4-isopropyl, 3,4-dimethoxyl, and 4-chloro to form

chalcones. The reaction mixtures were purified by CC and the pure compounds were elucidated spectroscopically by IR, NMR and MS. The synthesized chalcones were screened for antibacterial and anti-inflammatory activities. Minimum inhibition concentration (MIC) using microdilution method was used as the tool to determine the antibacterial activity of the synthesized compounds against the Gram-positive and Gram-negative bacteria. Lipoxygenase assay (LOX) was used to screen the anti-inflammatory activity of the synthesized chalcones.

REFERENCES

1. Kumar, N., Kumar, S., Gupta, H., and Sharma, P. K. (2012). 3-Hydroxy-2-(substituted phenyl)-4h-chromen-4-one derivatives-synthesis, spectral characterization and pharmacological screening. *World research Journal of Biochemistry*. 1, 3–7.

2. Narender, T., Khaliq, T., Shweta, Nishi, Goyal, N., Guota, Suman. (2005). Synthesis of chromenochalcones and evaluation of their *in vitro* antileishmanial activity. *Bioorganic and Medicinal Chemistry*. 13, 6543–50.

3. Ahmad, M. R., Sastry, V. G., Bano, N., and Anwar, S. (2011). Synthesis of novel chalcone derivatives by conventional and microwave irradiation methods and their pharmacological activities. *Arabian Journal of Chemistry*. 1–5.

4. Botta, B., Vitali, A., Menendez, P., Misiti, D., and Monache, D. G. (2005). Prenylated flavonoids: pharmacology and biotechnology. *Current Medicinal Chemistry*. 12, 717–739.

5. Grealis, J. P., Muller-Bunz, H., Casey, M., and McGlinchey, M. J. (2013). Synthesis of isobavachalcone and some organometallic derivatives. *European Journal of Organic Chemistry*. 332-347.

6. Karabin, M., Hudcova, T., Jelinek, L., and Dostalek, P. (2015). Biotransformations and biological activities of hop flavonoids. *Biotechnology Advances*. 33, 1063–1090.

7. Zhang, E. H., Wang, R. F., Guo, S. Z., and Liu, B. (2013). An update on antitumor activity of naturally occurring chalcones. *Evidence Based Complementary and Alternative Medicine*. 2013, 815621.

8. Mahapatra, D. K., Asati, V., and Bharti, S. K. (2015). Chalcones and their therapeutic targets for the management of diabetes: Structural and pharmacological perspectives. *European Journal of Medicinal Chemistry*. 92, 839–865.

9. Miranda, C. L., Stevens, J. F., Ivanov, V., McCall, M., Frei, B., Deinzer, M. L., and Buhler, D. R. (2000). Antioxidant and prooxidant actions of prenylated and nonprenylated chalcones and flavanones in vitro. *Journal of Agriculture and Food Chemistry*. 48, 3876–84.

10. Frolich, S., Schubert, C., Bienzle, U., and Jenett-Siems, K. (2005). In vitro antiplasmodial activity of prenylated chalcone derivatives of hops (Humulus lupulus) and their interaction with haemin. *Journal of Antimicrobial Chemotherapy*. 55, 883–887.

11. Terao, J., and Mukai, R. (2014). Prenylation modulates the bioavailability and bioaccumulation of dietary flavonoids. *Archives of Biochemistry Biophysics*. 559, 12–16.

12. Dixon, R. A., and Pasinetti, G. M. (2010). Flavonoids and isoflavonoids: from plant biology to agriculture and neuroscience. *Plant Physiology*. 154, 453–457.

13. Yang, D. S., Li, Z. L., Peng, W. B., Yang, Y. P., Wang, X., Liu, K., Li, X., Xioa, W. (2015). Three new prenylated flavonoids from *Macaranga denticulata* and their anticancer effects. *Fitoterapia*. 103, 165–170.

14. Masuoka, N., Matsuda, M., and Kubo, I. (2012). Characterisation of the antioxidant activity of flavonoids. *Food Chemistry*. 131, 541–545.

15. Garritano, S., Pinto, B., Giachi, I., Pistelli, L., and Reali, D. (2005). Assessment of estrogenic activity of flavonoids from Mediterranean plants using an in vitro short-term test. *Phytomedicine*. 12, 143–7.

16. Selepe, M. A., Van Heerden, F.R. (2013). Application of the Suzuki-Miyaura reaction in the synthesis of flavonoids. *Molecules*. 18, 4739–65.

17. Stevenson, D. E., and Hurst, R. D. (2007). Polyphenolic phytochemicals–just antioxidants or much more?. *Cellullar and Molecular Life Sciences*. 64, 2900–2916.

18. Putignani, L., Massa, O., and Alisi, A. (2013). Engineered *Escherichia coli* as new source of flavonoids and terpenoids. *Food Research Intstitute.* 54, 1084–1095.

19. Rahman, M. A. (2011). Chalcone: A Valuable Insight into the Recent Advances and Potential Pharmacological Activities. *Chemical Sciences Journal*. 2011, 1–16.

20. Bohm, B. A. (1998). *Introduction to Flavonoids* (2nd ed.). Vancouver, Canada. Harwood Academic Publisher.

21. Abe, I., Morita, H., Nomura, A., and Noguchi, H. (2000). Substrate Specificity of Chalcone Synthase: Enzymatic Formation of Unnatural Polyketides from Synthetic Cinnamoyl-CoA Analogues. *Journal of American Chemical Society*. 122, 11242–11243.

22. Jez, J. M., Ferrer, J. L., Bowman, M. E., Dixon, R. A., and Noel, J. P. (2000). Dissection of malonyl-coenzyme A decarboxylation from polyketide formation in the reaction mechanism of a plant polyketide synthase. *Biochemistry*. 39, 890–902.

23. Sasaki, Y., Nagano, Y. (2004). Plant acetyl-CoA carboxylase: structure, biosynthesis, regulation, and gene manipulation for plant breeding. *Bioscience, Biotechnology and Biochemistry*. 68, 1175–1184.

24. Stafford, H.A. *Flavonoid Metabolism*. Florida, United States: CRS Press Incorporated. 1990.

25. Harbone, J. B. *The Flavonoids.* vol. 53. Drodretch: Chapman and Hall Publisher. 1989.

26. Chuankui Song (2015). *Biosynthesis of Acylphloroglucinol Glucosides in Strawberry Fruit*. Doctor Philosophy, Technische Universitat Munchen.

27. Blangetti, M., Rosso, H., Prandi, C., Deagostino, A., and Venturello, P. (2013). Suzuki-miyaura cross-coupling in acylation reactions, scope and recent developments. *Molecules*. 18, 1188–1213.

28. Heide, L. (2009). Prenyl transfer to aromatic substrates: genetics and enzymology. *Current Opinion in Chemical Biology*. 13, 171–179.

29. Haslam, E. *The Shikimate Pathway*. London: Butterworth and Co (Publishers) Ltd. 1974.

30. Smejkal, K. (2014). Cytotoxic potential of *C*-prenylated flavonoids. *Phytochemistry*. 13, 2014.

31. Crozier, A., Clifford, M. N., and Ashihara, H. (2006). *Plant Secondary Metabolites Occurrence, Structure and Role in the Human Diet*. Oxford, UK. Blackwell Publishing Ltd.

32. Stevens, J. F., and Page, J. E. (2004). Xanthohumol and related prenylflavonoids from hops and beer: to your good health. *Phytochemistry*. 65, 1317–30.

33. Yazaki, K., Sasaki, K., and Tsurumaru, Y. (2009). Prenylation of aromatic compounds, a key diversification of plant secondary metabolites. *Phytochemistry*. 70, 1739–1745.

34. Dong, X., Liu, Y., Yan, J., Jiang, C., Chen, J., Liu, T., and Hu, Y. (2008). Identification of SVM-based classification model, synthesis and evaluation of prenylated flavonoids as vasorelaxant agents. *Bioorganic and Medicinal Chemistry*. 16, 8151–60.

35. Shah, B. N., Panchal, M. A., Gohil, N., Nayak, B. S., and Modi, D. C. (2010). Phyto-pharmacological profile of *Humulus lupulus*. *Pharmacologyonline Newsletter*. 736, 719–736.

36. Dat, N. T., Binh, P. T. X., Quynh, L. T. P., Minh, C. V., Huong, H. T., and Lee, J. J. (2010). Cytotoxic prenylated flavonoids from *Morus alba*. *Fitoterapia.* 81, 1224–7.

37. Stevens, J. F., Taylor, A. W., Nickerson, G. B., Ivancic, M., Henning, J., Haunold, A., and Deinzer, M. L. (2000). Prenylflavonoid variation in *Humulus lupulus*: Distribution and taxonomic significance of xanthogalenol and 4'-*O*-methylxanthohumol. *Phytochemistry*. 53, 759–775.

38. Vogel, S., Ohmayer, S., Brunner, G., and Heilmann, J. (2008). Natural and non-natural prenylated chalcones: synthesis, cytotoxicity and anti-oxidative activity. *Bioorganic and Medicinal Chemistry.* 16, 4286–93.

39. Ugwu, D. I., Ezema, B. E., Eze, F. U., Onoabedje, E. A., Ezema, C. G., Ekoh, O. C., and Ayogu, J. I. (2014). Synthesis and antimalarial activities of chalcone derivatives. *International Journal of ChemTech Research.* 7 (4), 1966–1984.

40. Li, Y. P., Yang, Y. C., Li, Y. K., Jiang, Z. Y., Huang, X. Z., Wang, W. G., Gao, X. M., and Hu, Q. F. (2014). Five new prenylated chalcones from *Desmodium renifolium*. *Fitoterapia.* 9, 41–45.

41. Kathiravan, M. K., Salake, A. B., Chothe, A. S., Dudhe, P. B., Watode, R. P., Mukta, M. S., and Gadhwe, S. (2012). The biology and chemistry of antifungal agents: a review. *Bioorganic of Medicinal Chemistry.* 20, 5678–98.

42. Rial, E., Rodríguez-Sánchez, L., Aller, P., Guisado, A., Gonzalez-Barroso, M., Gallardo-Vara, E., Redondo-Horcajo, M., Castellanos, E., Pradilla, R. F., and Viso, A. (2011). Development of chromanes as novel inhibitors of the uncoupling proteins. *Chemistry and Biology.* 18, 264–274.

43. Macone, A., Lendaro, E., Comandini, A., Rovardi, I., Matarese, R. M., Carraturo, A., and Bonamore, A. (2009). Chromane derivatives of small aromatic molecules: Chemoenzymatic synthesis and growth inhibitory activity on human tumor cell line LoVo WT. *Bioorganic and Medicinal Chemistry.* 17, 6003–7.

44. Lourens, A. C. U., Viljoen, A. M., and Heerden, F. R. V. (2008). South African *Helichrysum* species: A review of the traditional uses, biological activity and phytochemistry. *Journal of Ethnopharmacology.* 119, 630–652.

45. Su, X. H., Li, C. Y., Zhong, Y. J., Yuan, Z. P., Fang, L. Y. and Bing, L. (2012). A new prenylated chalcone from the seeds of *Millettia pachycarpa*. *Chinese Journal of Natural Medicine.* 10, 222–225.

46. Lee, Y. R., Wang, X., and Xia, L. (2007). An efficient and rapid synthetic route to biologically interesting pyranochalcone natural products. *Molecules.* 12, 1420–9.

47. Wang, G., Peng, F., Cao, D., Yang, Z., Han, X., Liu, J., Wu, W., He, L., Ma, L., Chen, J., Sang, Y., Xiang, M., Peng, A., Wei, Y., and Chen, L. (2013). Design, synthesis and biological evaluation of millepachine derivatives as a new class of tubulin polymerization inhibitors. *Bioorganic and Medicinal Chemistry.* 21, 6844–6854.

48. Guida, A., Lhouty, M. H., Tichit, D., Figueras, F., and Geneste, P. (1997). Hydrotalcites as base catalysts. Kinetics of Claisen-schmidt condensation, intramolecular condensation of acetonylacetone and synthesis of chalcone. *Applied Catalysis.* 164, 251–264.

49. Sashidhara, K. V., Kumar, M., and Kumar, A. (2012). A novel route to synthesis of flavones from salicylaldehyde and acetophenone derivatives. *Tetrahedron Letters.* 53, 2355–2359.

50. Dev, S., and Dhaneshwar, S. R. (2013). A solvent-free protocol for the green synthesis of heterocyclic chalcones. *Der Pharmacia Lettre.* 5, 219–223.

51. Jarag, K. J., Pinjari, D. V., Pandit, A. B., and Shankarling, G. S. (2011). Synthesis of chalcone (3-(4-fluorophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one): advantage of sonochemical method over conventional method. *Ultrasonics Sonochemistry*. 18, 617–623.

52. Neves, M. P., Lima, R. T., Choosang, K., Pakkong, P., Nasciment, M., Vasconcelos, M. H., Pinto, Madalena., Silva, A. M. S. and Cidade, H. (2012). Synthesis of a natural chalcone and its prenyl analogs--evaluation of tumor cell growth-inhibitory activities, and effects on cell cycle and apoptosis. *Chemistry and Biodiversity*. 9, 1133–43.

53. Narender, T., Venkateswarlu, K., Nayak, B. V., and Sarkar, S. (2011). A new chemical access for 3'-acetyl-4'-hydroxychalcones using borontrifluoride-etherate *via* a regioselective Claisen-Schmidt condensation and its application in the synthesis of chalcone hybrids. *Tetrahedron Letters*. 52, 5794–5798.

54. Jung, D. H., Lee, Y. R., and Kim, S. H. (2010). New synthetic routes to biologically interesting geranylated flavanones and geranylated chalcones: first total synthesis of (±)-prostratol f, xanthoangelol, and (±)-lespeol. *Helvetica Chimica Acta.* 93, 635–647.

55. Raj, G. (2004). *Organic Name Reactions and Molecular Rearrangements* Meerut. Gurdeep Raj, Krishna Prakashan Media (P) Ltd.

56. Fox, M. A., and Whitesell, J. K. *Organic Chemistry*. Sudbury, Massachusetts: Jones and Bartlett Publishers International. 2004.

57. Narender, T., and Reddy, K. P. (2007). $BF_3.Et_2O$ mediated biogenetic type synthesis of chromanochalcones from prenylated chalcones via a regioselective cyclization reaction. *Tetrahedron Letters.* 48, 7628–7632.

58. Boyer, J., Krum, J., Myers, M., Fazal, A. N., and Wigal, C. (2000). Synthetic utility and mechanistic implications of the Fries rearrangement of hydroquinone diesters in boron trifluoride complexes. *Journal of Organic Chemistry.* 65, 4712–4.

59. Narender, T., and Reddy, P. K. (2007). A simple and highly efficient method for the synthesis of chalcones by using borontrifluoride-etherate. *Tetrahedron Letters*. 48, 3177–3180.

60. Sugamoto, K., Matsusita, Y., Matsui, K., Kurogi, C., and Matsui, T. (2011).

Synthesis and antibacterial activity of chalcones bearing prenyl or geranyl groups from *Angelica keiskei*. *Tetrahedron*. 67, 5346–5359.

61. Xin, Y., Jiang, H., Zhao, J., and Zhu, S. (2008) BF_3-promoted cyclization reaction of imines and salicylaldehyde with silyl enol ethers: unexpected formation of dioxaspiro compounds. *Tetrahedron*. 64, 9315–9319.

62. Pandurangan, N., Bose, C., Banerji, A. (2011). Synthesis and antioxygenic activities of seabuckthorn flavone-3-ols and analogs. *Bioorganic of Medicinal Chemistry Letters*. 21, 5328–5330.

63. Rullah, K., Mohd Aluwi, M. F. F., Yamin, B. M., Bahari, A. M. N., Wei, L. S., Ahmad, S., Abas, F., Ismail, N. H., Jantan, I., and Wai, K. (2014). Inhibition of prostaglandin E_2 production by synthetic minor prenylated chalcones and flavonoids: Synthesis, biological activity, crystal structure, and in silico evaluation. *Bioorganic of Medicinal Chemistry Letters*. 24, 3826–3834.

64. Arai, M. A., and Kittaka, A. (2006). Novel 2-alkyl-1α,25-dihydroxy-19-norvitamin D_3: efficient synthesis with Julia olefination, evaluation of biological activity and development of new analyzing system for co-activator recruitment. *Anticancer Research.* 26, 2621–31.

65. Sundberg, R. J., and Francis, A. C. (2007). *Advance Organic Chemistry. Part B: Reactions and Synthesis*. Charlottesville, Virginia. Springer.

66. Bonifait, L., Marquis, A., Genovese, S., Epifano, F., and Grenier, D. (2012) Synthesis and antimicrobial activity of geranyloxy- and farnesyloxy-acetophenone derivatives against oral pathogens. *Fitoterapia.* 83, 996–999.

67. Gavara, L., Petit, C., and Montchamp, J. L. (2012). DBU-promoted alkylation of alkyl phosphinates and H-phosphonates. *Tetrahedron Letter*. 53, 5000–5003.

68. Pan, Y., Chen, Y., Li, Q., Yu, X., Wang, J., and Zheng, J. (2013). The synthesis and evaluation of novel hydroxyl substituted chalcone analogs with

in vitro anti-free radicals pharmacological activity and in vivo anti-oxidation activity in a free radical-injury Alzheimer's model. *Molecules*. 18, 1693–1703.

69. Kumar, D., Kumar, N. M., Akamatsu, K., Kusaka, E., Harada, H., and Ito, T. (2010). Synthesis and biological evaluation of indolyl chalcones as antitumor agents. *Bioorganic of Medicinal Chemistry Letters*. 20, 3916–3919.

70. Ning, J. J., Wang, J. F., Ren, Z. G., Young, D. J., and Lang, J. P. (2015). Versatile palladium(II)-catalyzed Suzuki–Miyaura coupling in ethanol with a novel, stabilizing ligand. *Tetrahedron*. 71, 4000–4006.

71. Rateb, N. M., and Zohdi, H. F. (2009). Atom-Efficient, Solvent-Free, Green Synthesis of Chalcones by Grinding. *Synthetic Communication*. 39, 2789–2794.

72. Sarda, S. R., Jadhav, W. N., Bhusare, S. R., Wasmatkar, S. K., Dake, S. A., and Pawar, R. P. (2009). Solvent-free NaOH-Al_2O_3 supported synthesis of 1,3-diaryl-2-propene-1-ones. *International Journal of Chemtech Research*. 1, 265–269.

73. Epifano, F., Genovese, S., Menghini, L., and Curini, M. (2007). Chemistry and pharmacology of oxyprenylated secondary plant metabolites. *Phytochemistry*. 68, 939–953.

74. Feldman, M., Tanabe, S., Epifano, F., Genovese, S., Curini, M., and Grenier, D. (2011). Antibacterial and Anti-inflammatory Activities of 4-Hydroxycordoin: Potential Therapeutic Benefits. *Journal of Natural Product.* 26–31.

75. Reddy, N. P., Aparoy, P., Reddy, T. C. M., Achari, C., Sridhar, P. R., and Reddanna, P. (2010). Design, synthesis, and biological evaluation of prenylated chalcones as 5-LOX inhibitors. *Bioorganic and Medicinal Chemistry*. 18, 5807–15.

76. Basabe, P., De Roman, M., Marcos, I.S., Diez, D., Blanco, A., Bodero, O,

Mollinedo, F., Sierra, B. G., and Urones, J. G. (2010). Prenylflavonoids and prenyl/alkyl-phloroacetophenones: Synthesis and antitumour biological evaluation. *European Journal of Medicinal Chemistry*. 45, 4258–4269.

77. Chinthala, Y., Thakur, S., Tirunagari, S., Chinde, S., Kumar, K., Khan, F., Tiwari, A., and Grover, P. (2015). European Journal of Medicinal Chemistry Synthesis, docking and ADMET studies of novel chalcone triazoles for anti-cancer and anti-diabetic activity. *European Journal of Medicinal Chemistry*. 93, 564–573.

78. Lee, Y. R., Li, X., Lee, S. W., Yong, C. S., Hwang, M., and Lyoo, W. S. (2008). Concise Total Synthesis of Biologically Interesting Prenylated Chalcone Natural Products: 4'-*O*-Methylxanthohumol, Xanthohumol E, and Sericone. *Bulletin Korean Chemical Society*. 29, 1205–1210.

79. Parker, A. J. (1981) The effects of solvation on the properties of anions in dipolar aprotic solvents. *Quarterly Review of the Chemical Society*. 16, 163-187.

80. Furniss, B. S., Hannaford, A. J., Smith, P. W. G., and Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*. New York: John Wiley & Sons, Inc. 1979.

81. Ramirez, R. E., Garcia-Martinez, C., and Mendez, F. (2013). Understanding the nucleophilic character and stability of the carbanions and alkoxides of 1-(9-anthryl)ethanol and derivatives. *Molecules*. 18, 10254-10265.

82. Orlikova, B., Tasdemir, D., Golais, F., Dicato, M., and Diederich, M. (2011). Dietary chalcones with chemopreventive and chemotherapeutic potential. *Genes and Nutrition*. 6, 125–147.

83. Patil, C. B., Mahajan, S. K., and Katti, S. A. (2009). Chalcone: A versatile molecule. *Journal of Pharmaceutical Sciences and Research*. 1, 11–22.

84. Bhasker, N., and Reddy, M. K. (2011). Synthesis and characterization of new series of prenyloxy chalcones, prenyloxy aurones and screening for anti-

bacterial activity. *International Journal of Research in Pharmaceutical and Biomedical Sciences*. 2, 1266–1272.

85. Field, L. D., Sternhell, S., and Kalman, J. R.. *Organic Structures from Spectra*. West Sussex, UK. A John Wiley & Sons, Ltd, Publication. 2013.

86. Yadav, L. D. S. *Organic Spectroscopy*. New Delhi: Kluwer Academic Publisher. 2005.

87. Wu, J., Wheeldon, I., Guo, Y., Lu, T., Yanan, D., Wang, B., He, J., Hu, Y., and Khademhosseini, A. (2010). A sandwiched microarray platform for benchtop cell-based high throughput screening. *Biomaterials*. 32, 841–848.

88. Howard, J. A. K., Slovokhotov, Y. L., and Batsanov, A.S. (2007). Molecular van der Waals symmetry affecting bulk properties of condensed phases: melting and boiling points. *Structural Chemistry*. 18, 477–491.

89. Daley, R. F., and Daley, S. J. *Organic Chemistry* (1st ed.). Daley Publication. 2013.

90. Wade, L. G. *Organic Chemistry* (6th ed.). Walla Walla, Washington: Prentice Hall Publication. 2009.

91. Vh, E. S., Matsjeh, S., and Wahyuningsih, T. D. (2014) Improved synthesis of 2',6'-dihydroxy-3,4-dimethoxychalcone by grinding technique to synthesize 5-hydroxy-3', 4'-dimethoxyflavone. *Indonesian Journal of Chemistry*. 14 (2), 174–178.

92. Niazi, S. K. *Handbook of Preformulation: Chemical, Biological and Botanical Drugs*. Illinois, US: CRC Press. 2007.

93. Pessini, G. L., Filho, B. P. D., Nakamura, C. V., and Cortez, D. A. G. (2003). Antibacterial activity of extracts and neolignans from *piper*. *Memorias do Instituto Oswaldo Cruz*. 98 (8), 1115–1120.

94. Kromann, H., Larsen, M., Boesen, T., Schonning, K., and Nielsen, S. F. (2004) Synthesis of prenylated benzaldehydes and their use in the synthesis

of analogues of licochalcone A. *European Journal of Medicinal Chemistry*. 39, 993–1000.

95. Yamaguchi, N., Satoh-Yamaguchi, K., and Ono, M. (2009). In vitro evaluation of antibacterial, anticollagenase, and antioxidant activities of hop components (*Humulus lupulus*) addressing acne vulgaris. *Phytomedicine*. 16, 369–376.

96. Aparoy, P., Reddy, K. K., and Reddanna, P. (2012). Structure and ligand based drug design strategies in the development of novel 5- LOX inhibitors. *Current Medicinal Chemistry*. 19, 3763–3778.

97. Sharma, V., and Kumar, V. (2015). Pharmacophore mapping studies on indolizine derivatives as 15-LOX inhibitors. *Bulletin Faculty of Pharmacy, Cairo University*. 53, 63–68.

98. Sogawa, S., Nihro, Y., Ueda, H., and Izumi, A. (1993). 3,4-Dihydroxychalcones as potent 5-lipoxygenase and cyclooxygenase inhibitors. *Journal of Medicinal Chemistry*. 36, 3904–3909.

99. Armstrong, M. M., Freedman, C. J., Eun, J., Zheng, Y., Kalyanaraman, C., Jacobson, M. P., Simeonov, A., Maloney, D. J., Leyen, K. V., Jadhav, A., and Holman, T. R. (2016). Bioorganic & medicinal chemistry a potent and selective inhibitor targeting human and murine. *Bioorganic and Medicinal Chemistry*. 24, 1183–1190.

100. Kim, Y. P., Ban, H. S., Lim, S. S., Kimura, N., Jung, S. H., Ji, J., Lee, S., Ryu, N., Keum, S. R., Shin, K. H., and Ohuchi, K. (2001). Inhibition of prostaglandin E_2 production by 2'-hydroxychalcone derivatives and the mechanism of action. *Journal of Pharmacy and Pharmacology*. 53, 1295–1302.

101. Keese, R., Brandle, M. P., and Toube, T. P. *Practical Organic Synthesis: A Student's Guide* (6^{th} ed.). West Sussex, US: John Wiley & Sons, Ltd. 2006.

102. Helesbeux, J. J., Duval, O., Guilet, D., Seraphin, D., Rondeau, D., and

Richomme, P. (2003). Regioselectivity in the ene reaction of singlet oxygen with ortho-prenylphenol derivatives. *Tetrahedron*. 59, 5091–5104.

103. Narender, T., and Reddy, K. P. (2009). $BF_3.Et_2O$-Mediated One-Pot Synthesis of Acetylchromans from polyhydroxyacetophenones and isoprene/allyl alcohol. *Synthetic Communications*. 39, 384–394.

104. Hossain, M. A., and Islam, A. (1993). Claisen rearrangement of 2'-hydroxy-4'-benzyloxy-4'-prenyloxychalcone and 2'-hydroxy-3,4-dimethoxy-4'-prenyloxychalcone. *Indian Journal of Chemistry*. 32.

105. Bhasker, N., Prashanthi, Y., and Subba, R. B. V. (2015). Piperidine mediated synthesis of new series of prenyloxy chalcones, flavanones and comparative cytotoxic study. *Der Pharmacia Lettre*. 7 (1), 8–13.

106. Kitawat, B. S., and Singh, M. (2014). Synthesis, characterization, antibacterial, antioxidant, DNA binding and SAR study of a novel pyrazine moiety bearing 2-pyrazoline derivatives. *New Journal of Chemistry*. 38, 4290–4299.

107. Islam, M. M., Masum, S. M., and Mahbub, K. R. (2011). *In vitro* antibacterial activity of shrimp chitosan against *Salmonela paratyphi* and *Staphylococcus aureus*. *Journal of Bangladesh Chemical Society*. 24 (2), 185–190.

108. Odeyemi, O. A., and Ahmad, A. (2015). Antibiotic resistance profiling and phenotyping of Aeromonas species isolated from aquatic sources. *Saudi Journal of Biological Sciences*. 1319-562X.

109. Detsi, A., Majdalani, M., Kontogiorgis, C. A., Hadjipavlou-Litina, D., and Kefalas, P. (2009). Natural and synthetic 2'-hydroxy-chalcones and aurones: Synthesis, characterization and evaluation of the antioxidant and soybean lipoxygenase inhibitory activity. *Bioorganic and Medicinal Chemistry*. 17, 8073–8085.

110. Shaveta, Singh, A., Kaur, M., Sharma, S., Bhatti, R., and Singh, P. (2014). Rational design, synthesis and evaluation of chromone-indole and chromone-

pyrazole based conjugates: identification of a lead for anti-inflammatory drug. *European Journal of Medicinal Chemistry*. 77, 185–92.