UNIVERSITI PUTRA MALAYSIA

SYNTHESIS AND BIOLOGICAL EVALUATION OF A SERIES OF ANALOGUES OF 2,4,6-TRIHYDROXY-3-GERANYLACETOPHENONE, AN ANTI-INFLAMMATORY NATURAL PRODUCT COMPOUND

NG CHEAN HUI

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By

NG CHEAN HUI

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

January 2017

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DEDICATION

This thesis is dedicated to my beloved family, Professor and friends

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

SYNTHESIS AND BIOLOGICAL EVALUATION OF A SERIES OF ANALOGUES OF 2,4,6-TRIHYDROXY-3-GERANYLACETOPHENONE, AN ANTI-INFLAMMATORY NATURAL PRODUCT COMPOUND

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January 2017

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Faculty : Institute of Bioscience

The natural product molecule 2,4,6-trihydroxy-3-geranylacetophenone (tHGA) isolated from the medicinal plant *Melicope ptelefolia* was shown to exhibit potent lipoxygenase (LOX) inhibitory activity. It is known that LOX plays an important role in inflammatory response as it catalyzes the oxidation of unsaturated fatty acids, such as linoleic acid to form hydroperoxides that are potent proinflammatory mediators. The search for selective LOX inhibitors may provide new therapeutic approach for inflammatory diseases. Previous studies reported that tHGA was an effective LOX inhibitor and was able to control airway-hyper-responsiveness in an acute model of murine asthma. However, the structure-activity relationship (SAR) of this group of compounds is still unknown. Herein, we report the synthesis of tHGA analogues using simple Friedel-Craft acylation, direct *C*-alkylation and methylation reactions with the objective of obtaining a better insight into the structure-activity relationships of the compounds.

A total of seventeen synthetic analogues of tHGA were synthesized and evaluated for their soybean 15-LOX inhibitory activity, while three of them are new compounds. Modifications were made on the acyl moiety, alkyl moiety, and also the important hydroxyl group of phloroglucinol structural core. The combination of both electrophilic substitution on the phloroglucinol compound and nucleophilic substitution on the acylphloroglucinol derivatives gave tHGA analogues. *In vitro* soybean 15-LOX inhibiting activity was measured using spectrophotometric method. All the synthesized analogues showed potent to moderate soybean 15-LOX inhibitory activity in a dose-dependent manner (IC_{50} = 10.31–95.38 μM), the most active being compound **18e** (IC_{50} value of 10.31 μM ± 1.5) with the longest aliphatic chain on the acyl substituent. Interestingly, four target compounds **18c** (IC_{50} value of

12.32 μM ± 0.6), **18d** (IC_{50} value of 15.26 μM ± 0.5), **18e** (IC_{50} value of 10.31 μM ± 1.5) and **18g** (IC_{50} value of 15.20 μM ± 1.2) exhibited better 15-LOX inhibition than tHGA **(8)** where improvement in activities range from approximately 30-50%. The SAR study revealed that the presence of a short, branched acyl substituent and the introduction of a cyclohexyl ring were less favourable for LOX inhibitory activity when compared to aliphatic acyl substituent. On the other hand, the introduction of a planar aromatic ring in the acyl substituent was found to improve the inhibitory activity. The results of the simple SAR study suggest that a longer, aliphatic and aromatic acyl substituent is favourable for better inhibitory action.

Kinetic inhibition assay showed that both of the most active compound **18e** and tHGA **(8)** are competitive inhibitors. Molecular docking studies (cDOCKER) and molecular dynamic (MD) simulation (GROMACs) revealed that hydrophobic interactions were the main driving force for the binding interactions of the active analogues with the target protein. Analogues with the larger lipophilic nature had better binding affinity as compared to others. Besides, the binding interaction with one crucial amino acid residue (His499) involved in iron chelation for the target enzyme correlates well with the kinetic assay's result. Therefore, our findings support that these geranylated acylphloroglucinol compounds have promising potential as lead compounds for the design of new anti-inflammatory drugs or Non-Steroidal Anti-inflammatory Drugs (NSAIDs). The combination of both the bioassay results and *in silico* studies has reinforced the crucial structural features that are involved in the inhibitory activity which is important information for structure-based drug design.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

SINTESIS DAN PENILAIAN AKTIVITI BIOLOGI BAGI SATU SIRI ANALOG 2,4,6-TRIHIDROKSI-3-GERANILASETOFENON, SATU SEBATIAN SEMULA JADI BAGI ANTI-RADANG

Oleh

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2,4,6-trihidroksi-3-geranil-asetofenon (tHGA) merupakan molekul semula jadi yang dipencilkan daripada tumbuhan ubatan *Melicope ptelefolia* dan telah menpamerkan aktiviti perencatan enzim lipoksigenas (LOX) yang poten. Enzim LOX dikenali memainkan peranan penting dalam tindak balas keradangan kerana ia memangkinkan pengoksidaaan asid lemak tak tepu, seperti asid linoleik, untuk membentuk hidroperoksida yang merupakan perantara pro-radang yang poten. Pencarian perencat LOX terpilih dapat memberikan pendekatan terapeutik baru untuk penyakit radang. Pengajian sebelum ini melaporkan bahawa tHGA adalah perencat LOX yang berkesan dan dapat mengawal hiper-responsif bagi saluran udara dalam model tikus asma yang runcing. Namun begitu, hubungkait struktur-aktiviti (SAR) bagi kumpulan sebatian ini masih tidak diketahui. Di sini, kita melaporkan sintesis untuk beberapa sebatian analog tHGA dengan menggunakan tindak balas pengasilan Friedel-Craft yang mudah, diikuti dengan tindakbalas pengalkilan-C dan pemetilan dengan tujuan untuk mendapatkan gambaran yang lebih baik mengenai SAR sebatian.

Sebanyak tujuh belas analog tHGA telah disintesis dan diuji dengan aktiviti perencatan 15-LOX kacang soya, manakala tiga daripada mereka adalah sebatian baru. Pengubahsuaian telah dibuat pada kumpulan asil, alkil, dan juga hidroksil pada teras struktur sebatian floroglusinol. Penggabungan kedua-dua gantian elektrofilik pada sebatian floroglusinol dan gantian nukleofilik pada terbitan asilfloroglusinol menghasilkan analog tHGA. Aktiviti perencatan 15-LOX kacang soya *in vitro* diukur dengan menggunakan cara spektrofotometrik. Semua analog yang disintesis menunjukkan aktiviti yang poten dan sederhana dalam aktiviti perencatan 15-LOX kacang soya secara bersandarkan dos (IC_{50} = 10.31-95.38 μM). Sebatian **18e** (nilai IC_{50} 10.31 μM ± 1.5) merupakan sebatian yang paling aktif dengan rantai alifatik

terpanjang di gantian asil. Secara menariknya, empat sebatian sasaran iaitu **18c** (nilai IC_{50} 12.32 μM ± 0.6), **18d** (nilai IC_{50} 15.26 μM ± 0.5), **18e** (nilai IC_{50} 10.31 μM ± 1,5) dan **18g** (nilai IC_{50} 15.20 μM ± 1.2) menunjukkan perencatan 15-LOX yang lebih baik daripada tHGA **(8)** di mana penambahbaikan aktiviti adalah sekitar 30-50%. Kajian SAR mendedahkan bahawa penggantian dengan kumpulan asil yang pendek, yang bercabang dan mempunyai kumpulan sikloheksil adalah kurang baik untuk aktiviti perencatan LOX berbanding dengan penggantian dengan kumpulan asil alifatik. Manakala, penggantian kumpulan asil dengan kumpulan aromatik yang satar didapati dapat mempertingkatkan aktiviti perencatan. Secara amnya, kajian SAR ini menunjukkan bahawa kumpulan asil yang panjang, alifatik dan aromatik memberikan aktiviti perencatan yang lebih baik.

Bioasai perencatan aktiviti kinetik menunjukkan bahawa kedua-dua sebatian iaitu **18e** yang merupakan sebatian yang paling aktif dan tHGA **(8)** adalah perencat kompetitif. Kajian dok molekul (cDOCKER) dan simulasi dinamik molekul (MD) (GROMACs) menunjukkan bahawa interaksi hidrofobik adalah penyebab utama yang mendorong interaksi yang mengikat analog aktif dengan protein sasaran. Analog dengan sifat yang lebih lipofilik mempunyai potensi mengikat yang lebih tinngi berbanding dengan yang lain. Selain itu, interaksi mengikat dengan satu baki asid amino penting (His499) yang terlibat dalam kelatan besi untuk enzim sasaran berhubung kait dengan keputusan asai kinetik. Oleh itu, penemuan kajian ini menyokong bahawa sebatian geranil asilfloroglusinol mempunyai potensi yang menggalakkan sebagai sebatian utama untuk reka bentuk ubat-ubatan anti-radang baru atau ubat anti-radang bukan steroid (NSAIDs). Penggabungan kedua-dua keputusan bioasai dan pengajian *in silico* telah memperkuatkan ciri-ciri struktur yang penting dalam melibatkan aktiviti perencatan di mana ia merupakan informasi yang penting bagi reka bentuk ubat berdasarkan struktur.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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AA	Arachidonic acid
AB	Aerobic biodegradability
ADMET	Absorption, distribution, metabolism, excretion, and toxicity prediction
AlogP	Estimated lipophilicity
AM	Ames mutagenicity
AS	Aqueous solubility
A	Alpha
Å	Angstrom
BALF	Bronchoalveolar lavage fluid
BBB	Blood brain barrier
B	Beta
$CDCl_3$	Deuterated chloroform
CD_3OD	Deuterated methanol
CHARMm	Chemistry at HARvard Macromolecular Mechanics
cLogP	Estimated hydrophilicity
COX	Cyclooxygenase
CYP2D6	Cytochrome $P_{450}2D6$
cysLTs	Cysteinyl leukotriene
^{13}C	Carbon-13
Δ	Chemical shift
°C	Degree in Celsius
DIP	Direct Inlet Probe
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
D	Doublet
Dd	Doublet of doublets
ddd	Doublet of doublet of doublets
Dq	Doublet of quartets
EIMS	Electron Ionization Mass Spectrometry
ΔE_{MM}	Molecular Mechanic Energy
FLAP	Five-Lipoxigenase-Activating Protein
GC-MS	Gas-chromatogrpahy-mass-spectrometer
GROMACs	GROningen MAchine for Chemical Simulations
G	Gram
ΔG_{bind}	Free binding interaction energy
ΔG_{PB}	Polar solvation energy
ΔG_{SA}	Non-polar solvation energy
5-HETE	5-hydroxyeicosatetraenoic acid
HIA	Human Intestinal Absorption
HMBC	Heteronuclear Multiple Bond Correlation

13-HPOD	13-Hydroperoxide
5-HpETE	5-hydroperoxyeicosatetraenoic acid
HPODEs	Hydroperoxyoctadecadienoic acid
HSQC	Heteronuclear Single Quantum Coherence
^{1}H	Ptoron-1
IC_{50}	Half maximal inhibitory concentration
IgE	Immunoglobulin E
IL	Interleukin
J	*J*-coupling constant
kcal/mol	Kilocalorie per mole
kDa	Kilo Dalton
K_i	Michaelis constant
K_m	Michaelis concentration
LOX	Lipoxygenase
LTC_4	Leukotriene C_4
l	Litre
MD	Molecular dynamic
MM-GBSA	Molecular Mechanics- Generalized Born
MHz	Megahertz
mmLOX	Mackerel muscle LOX
MM-PBSA	Molecular Mechanics-Poisson-Boltzmann
m	Multiplet
mg	Milligram
mL	Microliters
µg	Microgram
µM	Micro molar
NCE	New Chemical Entities
NDGA	Nordihydroguaiaretic
NMR	Nuclear Magnetic Resonance
NSAIDs	Non-Steroidal-Anti-Inflmmatory-Drugs
ns	Nanosecond
OI	Ocular Irritancy
PAMPs	Pathogen-Associated Molecular Patterns
PBML	Peripheral Blood Mononuclear Leukocytes
PDB	Protein Data Bank
PG	Prostaglandin
PGE_2	Prostaglandin E_2
PPB	Plasma Protein Binding
PSA	Polar Surface Area
π	Pi
PUFAs	Poly-Unsaturated Fatty Acid
QSAR	Quantitative Structure Activity Relationship
RC	Rodent carcinogenicity

RMSD	Root-mean square derivation
s	Singlet
SAR	Structure Activity Relationship
SI	Skin Irritancy
SS	Skin Sensitization
T	Triplet
tHGA	2,4,6-trihydroxy-3-geranylacetophenone
Th_2	T-helper 2
TLC	Thin Layer Chromatography
TLRs	Toll-Like Receptors
TOPKAT	TOxicity Prediction by Komputer Assisted Technology
UV	Ultraviolet
V_{max}	Maximal Velocity
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 General Introduction

Drug discovery and development is an important activity to combat diseases especially those of unmet clinical needs. Furthermore, for some diseases the drugs in clinical use have been found to have serious side effects or the drugs have been rendered ineffective due to development of resistance of the causative agent. Therefore, the task of discovering and developing safe and more effective drugs become more pressing. The World Health Organization (WHO) identified that 11% of the 252 drugs discovered in the twenty-first century and considered as basic or essential were exclusively of flowering plant origin (Veeresham, 2012). In many areas of drug discovery research, the influence of natural products is very clear as can be seen from the high number of 'natural product mimics' approved as drugs for many diseases (Newman and Cragg, 2007). The drug discovery process involves the identification of lead and its target, synthesis, characterization, screening and assay for therapeutic efficacy. The average time required to bring a drug to the market ranges from 10-15 years at an average cost of U$$ 897 million to U$$ 1.9 billion (Giersiefen *et al*., 2003). Figure 1 shows the schematic flow of a drug discovery pipeline.

Figure 1: Schematic flow of the drug discovery pipeline (Prakash and Devangi, 2010)

Rational drug design efficiently guided medicinal chemists in lead identification to rapidly synthesize a large number of potential pharmacologically active compounds. Lead identification combines the knowledge and skills from the field of cheminformatics, molecular modeling and structural bioinformatics and understanding of the physicochemical properties of the three-dimensional molecule. Meanwhile, lead optimization aims to improve the effectiveness, diminish toxicity, or increase absorption for enhancing the most promising compounds (Adam, 2005). Although lead optimization is a time-consuming and costly step which often becomes a tight bottleneck in the drug discovery process, it is a key step in turning a biologically active chemical into an effective and safe drug. Thus, lead optimization is an essential step in the drug discovery process (Prakash and Devangi, 2010).

Structure-Activity-Relationship (SAR) is the relationship between the biological activity of a molecule and its chemical or three-dimensional structural features. The physiological action of a molecule is a function of its chemical constitution, thus the analysis of SAR enables the determination of the chemical groups that are responsible for inducing a target pharmacological activity. This allows the medicinal chemist to modify the potency of a bioactive compound (typically a drug) by inserting or substituting new chemical groups into the bioactive compound and test the modification for their biological effects (Kalyani *et al*., 2013). Further refinement of the method enabled mathematical relationships between the chemical structure and the biological activity, known as quantitative structure-activity relationship (QSAR), to be built. QSAR can be considered as the method of trying to build a model to understand why some compound interacts and others do not (Prakash and Devangi, 2010).

Natural products containing a phloroglucinol core have been reported to have interesting biological properties (Chung, 1995). In an earlier study on the anti-inflammatory properties of the medicinal plant *Melicope ptelefolia*, a simple compound containing the phloroglucinol structural-core, 2,4,6-trihydroxy-3 geranylacetophenone (tHGA), was identified as one of the bioactive principles of the plant (Suryati, 2005; Khozirah *et al*., 2006). Initially, this compound was found to exert a dose-dependent inhibition against soybean 15-lipoxygenase (15-LOX) with an IC_{50} value of 20 μM. Subsequently, this compound was shown to exert a dose-dependent inhibition of cysteinyl leukotriene secretion from activated macrophage cells. Further exploration of both the chemistry and pharmacology of tHGA revealed that tHGA inhibited human 5-lipoxygenase (5-LOX) and both cyclooxygenase isoforms (COX-1 and COX-2), albeit with greater selectivity towards COX-2 (Khozirah *et al*., 2006; Khozirah *et al*., 2011).

When used in an acute model of murine asthma, tHGA was found to be as effective as Zileuton, a clinically used 5-LOX inhibitor. The compound was able to control airway hyper-responsiveness to methacholine challenge, and reduce pulmonary cellular infiltration, goblet cell metaplasia, cytokine (IL-4, IL-5, IL-13) and cysteinyl leukotriene secretions as well as reduce systemic IgE concentrations (Khozirah *et al*., 2006; Khozirah *et al*., 2011; Ismail *et al*., 2012). These interesting biological activities of tHGA have prompted this study to synthesize several synthetic analogues of the compound by varying the substituents and to re-evaluate them for any improvement in their anti-inflammatory activity against LOX. In summary, tHGA is an effective LOX inhibitor and able to control airway hyper-responsiveness in acute model of murine asthma, however, the SARs for this groups of compounds is still unkown. A better insight into the SARs is important for designing a better drug.

1.2 Objectives of Research

On going effort to develop a better lead compound than tHGA, the studies of SARs of the compounds generated substantial interest because it is believed to be essential for a better drug design. With the assistance from the *in silico* studies, a better insight about the SARs of the compounds will help to identify important structural features that influence the ligand-protein interactions between the compounds and the enzyme. Our goal of present study is to synthesize several synthetic analogues of tHGA and to re-evaluate them for any improvement in their anti-inflammatory activity against LOX.

The specific objectives of the present study are:

1. To synthesize a series of analogues of tHGA.
2. To determine the 15-LOX inhibitory activity of the synthesized analogues.
3. To determine the structure-activity relationships of the synthetic analogues with regards to their 15-LOX inhibition.
4. To determine the ligand-receptor interactions of tHGA analogues with 15-LOX enzyme via *in silico* studies.
5. To predict the pharmacological effect of tHGA analogues by using ADMET and TOPKAT analysis.

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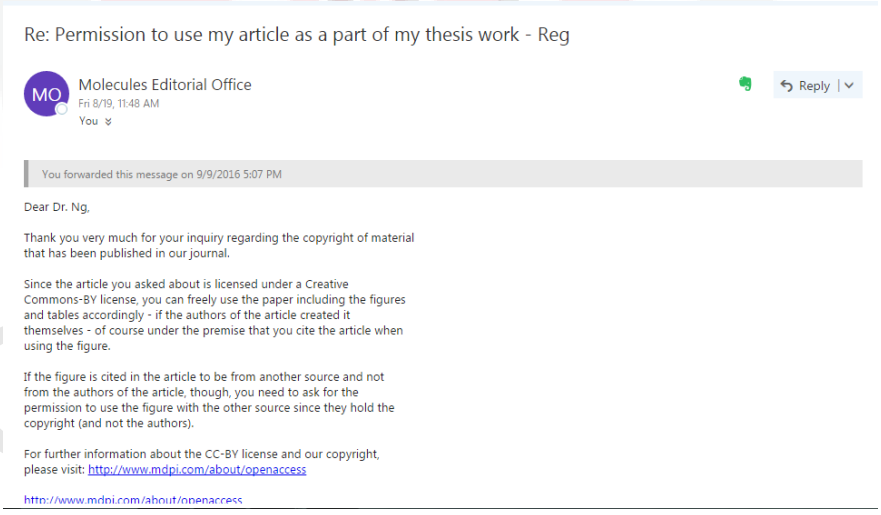

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