UNIVERSITI PUTRA MALAYSIA

DEVELOPMENT AND STRUCTURE ACTIVITY RELATIONSHIP OF DIARYLPENTADIENONE AND CHALCONE ANALOGUES AS POTENTIAL ANTI-INFLAMMATORY AGENT

SITI MUNIRAH MOHD FAUDZI

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By

SITI MUNIRAH MOHD FAUDZI

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

March 2015

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In the name of Allah, The Most Merciful and the Most Beneficent.

This thesis is especially dedicated to my beloved late mother,

Allahyarhamah Norshimah binti Md Nor,

My parent and parents in law,

Darling husband and precious son.

Without whom none of my task accomplishments would be impossible.

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

DEVELOPMENT AND STRUCTURE ACTIVITY RELATIONSHIP OF DIARYLPENTADIENONE AND CHALCONE ANALOGUES AS POTENTIAL ANTI-INFLAMMATORY AGENT

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March 2015

Chairman : Associate Professor Faridah Binti Abas, PhD

Institute : Bioscience

The main adverse effects of current non-steroidal anti-inflammatory drugs (NSAIDs), involved the gastroinstestinal tract, kidney and blood clotting has lead to the discovery of new drugs with improved safety profile today. Curcumin could be serves as potential NSAID candidate based on its strong anti-inflammatory property and low toxicity. However, its utilization in clinical trials was restricted due to poor pharmacokinetic properties. Thus far, several modifications of curcumin structure have been conducted, and reports have shown that diarylpentanoid scaffold without the β-diketone moiety influenced their anti-inflammatory properties via nitric oxide (NO) production suppression activity and inhibition on pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6).

In this study, a series of forty-five curcumin like compounds, the 1,5-diphenylpenta-2,4-dien-1-ones and five pyrazoline-diarylpentadienone analogues were synthesized following the Lipinski rule, and evaluated for nitric oxide (NO) suppression activity on interferon gamma (IFN-γ)/ lipopolysaccharides (LPS)-activated RAW 264.7 cells. Among these, compounds **3h**, **7a**, **7d**, and **7e** exhibited comparable or significantly enhancing anti-inflammatory property compared to curcumin (IC_{50} = 14.69 ± 0.24 μM), of which compound **7d** (5-methyl-thiophene bearing) displayed the most promising NO inhibitory activity with IC_{50} value of 10.2 ± 0.6 μM. In order to understand the structure-activity relationship (SAR) to the bioactivity, two-dimensional (2D) and three-dimensional (3D) quantitative structure activity relationship (QSAR) studies were carried out. The structure activity relationship (SAR) study revealed that *para*-hydroxyl group on ring B, and either *meta*-hydroxy or *para*-hydroxy moieties on ring A are crucial for a remarkable anti-inflammatory activity. Based on absorption, distribution, metabolism, excretion and toxicity (ADMET) and toxicity prediction by computer assisted technology (TOPKAT)

analyses, compounds **1c** (IC_{50} = 26.1 ± 0.1 µM) is predicted to have a good solubility and absorption, non-mutagenic and to exhibit high blood−brain barrier (BBB) penetration, which indicates a potential as an effective drug candidates for treating the central nervous system (CNS) related disorders.

Due to impressive array of biological profiles of pyrrole and chalcone, we therefore adopted the pyrrole structure and fused it into chalcone scaffold by replacing one of the aromatic rings, in an attempt to develop a new series of chalcone analogues with higher anti-inflammatory potential. All nine synthesized compounds displayed nitric oxide (NO) production suppression effect with IC_{50} values ranging from 21.5 to 62.9 µM. Among them, compounds **9c** (2,5-dimethoxy containing compound) and **9h** (2-methoxy bearing compound) exhibited highest nitric oxide (NO) inhibition effect with IC_{50} values of 21.5 ± 0.6 µM and 21.6 ± 1.1 µM, respectively.

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

PERKEMBANGAN DAN HUBUNGAN STRUKTUR-AKTIVITI ANALOG DIARILPENTADIENON DAN KALKON SEBAGAI AGEN ANTI-RADANG YANG BERPOTENSI

Oleh

SITI MUNIRAH BINTI MOHD FAUDZI

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Kesan-kesan negatif utama yang dikaitkan dengan penggunaan ubat anti radang bukan steroid (NSAIDs) di pasaran kini melibatkan saluran usus gastro, buah pinggang dan masalah pembekuan darah. Kesan-kesan ini telah memacu penemuan ubat-ubatan baru yang lebih selamat digunakan. Dalam mencapai objektif tersebut, kurkumin dilihat sebagai satu alternatif ubat anti radang bukan steroid yang berpotensi memandangkan ianya mempunyai ciri anti radang yang kuat dan bertoksik rendah. Walau bagaimanapun, penggunaan kurkumin dalam ujian klinikal terbatas kerana ciri farmakokinetiknya yang agak lemah. Setakat ini, terdapat beberapa pengubahsuaian yang dilakukan terhadap struktur kurkumin, dan terdapat laporan menunjukkan rangka diarilpentadienon tanpa kumpulan β-diketon, mempengaruhi sifat anti-radang mereka melalui aktiviti perencatan terhadap produksi nitrik oksida (NO) dan perencatan ke atas sitokin-sitokin pro-radang seperti tumor nekrosis alfa (TNF-α) dan interleukin 6 (IL-6).

Di dalam kajian ini, empat puluh lima sebatian menyerupai kurkumin, 1,5-difenilpenta-2,4-dien-1-on dan lima analog pirazolina-diarilpentadienon telah disintesis dan dikaji untuk aktiviti perencatan nitrik oksida (NO) ke atas sel RAW264.7 yang diaktifkan oleh interferon gamma (IFN-γ) dan lipopolisakarida (LPS). Di antara semua, sebatian **3h**, **7a**, **7d**, dan **7e** mempamerkan sifat anti-radang yang setara atau peningkatan yang ketara berbanding kurkumin (IC_{50} = 14.7 ± 0.2 μM), di mana sebatian **7d** (mempunyai 5-metil-thiofin) memberikan aktiviti perencatan nitrik oksida (NO) yang paling tinggi dengan nilai IC_{50} 10.2 ± 0.6 μM. Dalam usaha untuk memahami hubungan struktur-aktiviti (SAR) dengan bioaktiviti, kajian dua dimesi (2D) dan tiga dimensi (3D) hubungan struktur-aktiviti secara kuantitaif (QSAR) telah dijalankan. Kajian hubungan struktur-aktiviti (SAR) mendedahkan kumpulan hidroksil di kedudukan *para* di gelang B, dan sama ada

kumpulan hidroksil di kedudukan *meta* atau *para* di gelang A adalah penting untuk sifat anti-radang yang tinggi. Berdasarkan analisis penyerapan, pengedaran, metabolisma, penyingkiran dan keracunan (ADMET) dan ramalan keracunan oleh bantuan berteknologi komputer (TOPKAT), sebatian **1c** (IC_{50} = 26.1 ± 0.1 μM) diramalkan mempunyai kadar kelarutan dan penyerapan yang tinggi, tidak mutagen dan mempamerkan penembusan halangan otak-darah (BBB) yang tinggi, menunjukkan sebatian berkenaan berpotensi sebagai ubat yang berkesan untuk merawat penyakit berkaitan dengan gangguan sistem saraf pusat.

Berdasarkan profil biologikal yang sangat menarik yang ditunjukkan oleh kalkon dan pirol, kami telah menggabungkan struktur pirol ke bahagian kalkon dengan menggantikannya dengan salah satu gelang aromatik, dalam usaha untuk membangunkan siri baharu bagi analog kalkon dengan potensi anti-radang yang lebih tinggi. Kesemua sembilan sebatian yang disintesis merencat produksi nitrik oksida (NO) dengan julat IC_{50} antara 21.5 ke 62.9 μM. Di antara mereka, sebatian **9c** (mempunyai kumpulan 2,5-dimetoksi) dan sebatian **9h** (mempunyai kumpulan 2-metoksi) menunjukkan kesan perencatan nitrik oksida (NO) yang paling tinggi dengan masing-masing mencatat nilai IC_{50} 21.5 ± 0.6 μM dan 21.6 ± 1.1 μM.

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

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A	Alpha
B	Beta
Δ	Chemical shift
AA	Arachidonic acid
AB	Aerobic biodegradability
ACHN	Human renal cell carcinoma
ADMET	Absorption, distribution, metabolism, excretion and toxicity prediction
AM	Ames mutagenicity
AMPK	Adenosine monophosphate-activated protein kinase
AS	Aqueous solubility
ATCC	American Type Culture Collection
BAECs	Bovine aortic endothelial cells
BBB	Blood brain barrier
BBr_3	Boron tribromide
Bcl-2	B-cell lymphoma 2
BDMC	Bisdemethoxycurcumin
BF_3-Et_2O	Boron trifluoride-etherate
BHC	benzoylhydrazinocurcumin
br	Broad
^{13}C	Carbon-13
$^{\circ}C$	Degree in Celcius
Calu 1	Human non-small cell lung carcinoma
CC	Column chromatography
CCK-8	Cell-counting Kit 8
$CDCl_3$	Deuterated chloroform
CH_2Cl_2	Dichloromethane
CHARMm	Chemistry at Harvard Macromolecular Mechanics
CNE2	Human nasopharyngeal carcinoma cell lines
CNS	Central nervous system
CO_2	Carbon dioxide
CoMFA	Comparative Molecular Field Analysis
COX	Cyclooxygenase
Cu	Copper
CYP2D6	Cytochrome P450 2D6
CYP450	Cytochrome P450
d	Doublet
dd	Doublet of doublet
DHC	dihydrocurcumin
DIMS	Direct infusion mass spectrometry
DMC	Demethoxycurcumin
DMEM	Dulbecco's Modified Eagle's Medium
DMSO	dimethylsulfoxide
DNA	Deoxyribonucleic acid
DR4	Death receptor pathway-4

EI	Electron impact
EIMS	Electron ionization mass spectroscopy
eNOS	Endothelial nitric oxide synthase
EPFP_6	Daylight-style path-based fingerprints
ERK	Extracellular signal receptor-activated kinase
EtOAc	Ethyl acetate
eV	Electron-volt
FBS	Fetal bovine serum
g	gram
GC-MS	Gas Chromatography-Mass Spectroscopy
GFA	Genetic Function Approximation
^{1}H	Proton
H460	Human non-cell lung carcinoma
H_2SO_4	Sulphuric acid
HC	hydrazinocurcumin
HCl	Hydrochloric acid
HCT 116	Human colon carcinoma
HepG2	Human hepatoma cell lines
HHC	hexahydrocurcumin
HIA	Human intestinal absorption
HIV	Human immunodeficiency virus
hMAO-B	Human monoamine oxidase-B
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HPLC	High performance liquid chromatography
HSQC	Heteronuclear single-quantum correlation spectroscopy
HT	hepatotoxicity
Hz	Hertz
IC_{50}	Half maximal inhibitory concentration
IFN-γ	Interferon-gamma
IκBα	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
IKK	IκB-kinase
IL	interleukin
iNOS	Inducible nitric oxide synthase
J	Coupling constant in Hz
JNK	c-Jun NH_2 terminal kinase
kg	Kilogram
KF-Al_2O_3	Potassium fluoride on alumina
KOH	Potassium hydroxide
LOF	Lock-of-fit
LOX	Lipoxygenase
LPS	lipopolysaccharides
m	Multiplet
µg	Microgram
µl	Microlitre
µM	Micromolar
M	Molarity
mg	Miligram

ml	Millilitre
mmol	Milimole
mm	Milimeter
mM	Milimolar
m/z	Mass to charge ratio
MAPK	Mitogen-activated protein kinase
MCF-7	Human breast adenocarcinoma cell lines
MCP	Methylenecyclopropanes
MFPSA	Molecular Fractional Polar Surface Area
$MgSO_4$	Magnesium sulphate
MHz	Mega hertz
MIC	Minimum inhibitory concentration
MS	Mass spectroscopy
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NaOH	Sodium hydroxide
$NaHCO_3$	Sodium bicarbonate
ND	Not determined
NF-κB	Nuclear factor kappa beta
ng	Nanogram
nm	Nanometre
nM	Nanomolar
NO	Nitric oxide
NOS	Nitric oxide synthase
nNOS	Neuronal nitric oxide synthase
NK	Natural killer
NMR	Nuclear Magnetic Resonance
NSAIDs	Non-steroidal anti-inflammatory drugs
OHC	Octahydrocurcumin
OI	Ocular irritancy
$ONOO^-$	Peroxynitrite
P53	Tumor protein 53
Panc1	Human pancreatic carcinoma
PBS	Phosphate-buffered saline
Pd	Palladium
$Pd(OAc)_2$	Palladium (II) acetate
PG	Prostaglandin
Ph_3P	Triphenylphosphine
pIC_{50}	-log IC_{50}
PLS	Partial least square
PPB	Plasma protein binding
ppm	Part per million
q^2	Cross-validation correlation coefficient
QSAR	Quantitative structure-activity relationship
r^2	Conventional non-cross validation coefficient
RAW 264.7	Macrophage cell lines
RC	Rodent carcinogenicity
R_f	Retention factor
RMS	Root mean square

RNS	Reactive nitrogen species
ROS	Reactive oxygen species
RT	Room temperature
RT-PCR	Reverse-transcriptase-polymerase chain reaction
s	Singlet
SAR	Structure-activity relationship
S.E.M	Standard error of the mean
SI	Skin irritancy
SS	Skin sensitization
SW480	Human colon carcinoma cell lines
t	triplet
THC	tetrahydrocurcumin
TLC	Thin layer chromatography
TMS	tetramethylsilane
TMSCl	Tetramethylsilyl chloride
TNF-α	Tumor necrosis factor alpha
TOPKAT	Toxicity Prediction by Komputer Assisted Technology
$Yb(OPf)_3$	Ytterdium perfluorooctane sulfonate

CHAPTER 1

INTRODUCTION

1.1 General

Natural products are structurally diverse and are not commonly found in synthetic compounds. Of the 1184 new chemical entities reported, 60.0% were derived from natural products (Gautam and Jachak, 2009). Based on this, it can be stated that natural products play a dominant role in contributing to the diversity of chemical entities, which in turn enhanced the discovery and development efforts of drugs in combating human diseases. In addition, traditional medicine and natural products offer great opportunities for the identification and discovery of biologically active compounds. These compounds may be further developed into agents that can be used in the treatment of human diseases, especially triggered by inflammatory process.

Since ancient times, humans suffering from inflammatory reactions and diseases were treated with phytochemicals such as myrtle and willow tree bark, which were used in the treatment of stiff and painful joints (Vonkeman et al., 2010). Plants contain various complex mixtures of bioactive molecules, some of which may possess beneficial effects that can improve body resistance to cellular stress or exogenous factors, while also preventing the cytotoxicity of various agents.

The biologically active compounds that have shown significant anti-inflammatory properties exhibit a wide range of structural diversity and can be classified as alkaloids, steroids, flavonoids, terpenoids, polyphenolics, phenylpropanoids, fatty acids and lipids, and various miscellaneous products (Gautam and Jachak, 2009).

In recent years, the use of natural products has attracted scientific and public attention for its use in the prevention or treatment of chronic diseases. It has been shown that the consumption of natural products helps reduce the risk of developing pathological conditions such as cancer, cardiovascular illnesses, nervous system disorders, as well as genetic and inflammatory diseases (Jurenka, 2009; Newman and Cragg, 2007).

1.2 Inflammation

Inflammation is a complex component of an organism's response to a variety of stimuli including both biological and chemical stimuli, physical damage, ultra irradiation, immune reactions, and microbial invasions (Ferrero-Miliani et al., 2007). The features of inflammation are warmth, swelling, pain, redness, and loss of function. Further looks into the processes that occur in response to an injury reveal that the immune system's cells, such as leukocytes migrate via chemotaxis to the injury site in an orchestrated sequence. This movement is mediated by various cytokines and acute phase proteins to remove foreign materials through phagocytosis, subsequently initiating the healing process (Figure 1.1). It has also been found that prolonged exposure to a stimulus can lead to the onset of a chronic phase (Lin and Karin, 2007).

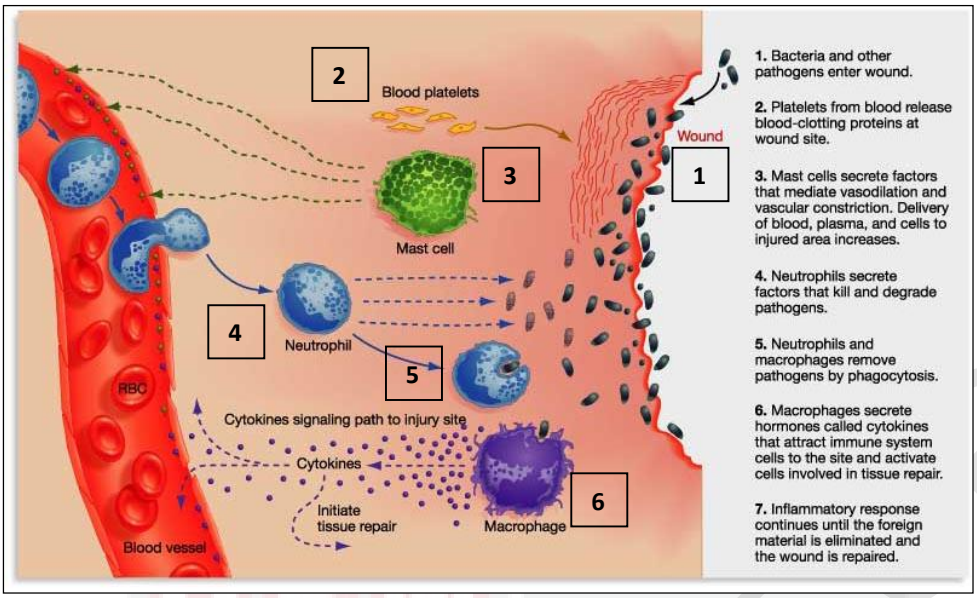


Figure 1.1 The flow of inflammatory cascade (uic.edu, 2011)

It has been reported that chronic inflammation may lead to the development of numerous diseases including cancer (Yamamoto and Gaynor, 2001), chronic asthma (Murdoch and Lloyd, 2010), cardiovascular diseases (Libby, 2006), diabetes (Lobner and Fuchtenbusch, 2004), autoimmune diseases (Ishihara and Hirano, 2002), atherosclerosis (Hansson et al,. 2006), allergies (Fan et al., 2005), rheumatoid arthritis (Choy and Panayi, 2001), inflammatory bowel disease (Itzkowitz and Yio, 2004), psoriasis (Dowlatshahi et al., 2013), multiple sclerosis (Kidd, 2001), and may also contribute to aging (Chung et al., 2001).

To block the inflammatory cascade, the source of molecular targets must be antagonized. The anti-inflammatory targets of anti-inflammatory drugs are cyclooxygenase (COX-1, COX-2) (Dinarello, 2010), cytokines and cytokine receptors, tumour necrosis factor (TNF)-α (Popa et al., 2007), interleukin (IL)- 1β (Dinarello et al., 2012), and interferon (IFN)- γ (Muhl and Pfeilschifter, 2003), as well as G-protein-coupled receptors (Sun and Ye, 2012) histamine 1 (MacGlashan, 2003) and cysteinyl leukotriene 1 (Holgate et al., 2003). In addition, the transcription factor, nuclear factor (NF)-κB (Lawrence, 2009), mitogen-activated protein kinases (MAPKs) (Kaminska, 2005), c-Jun-N-terminal kinase (JNK) (Waetzig et al., 2005), and p38 kinases (Schieven, 2005) have also been described as potential anti-inflammatory targets. Several reviews have described natural anti-inflammatory products that are restricted to a particular molecular target, such as lipoxygenases (LOXs) (Martel-Pelletier et al., 2003), arachidonic acid (AA) cascade (Ferrandiz and Alcaraz, 1991), nitric oxide (NO) (Cirino et al., 2006), and NF-κB, or TNF-α. There have also been reports showing that inhibitor of prostaglandin (PG) biosynthesis and NO production were considered as potential anti-inflammatory and cancer chemopreventive agents (Gautam and Jachak, 2009).

NO is a short-lived key molecular signalling involved in host defences and immune responses. NO is produced through oxidative deamination of L-arginine to L-citrulline, catalyzed by NO synthase (NOS) family, in NADPH and oxygen-dependent process (Ma et al., 2015). Three major isoforms of NOS are neuronal NOS (nNOS), endothelial NOS (eNOS) and inducible NOS (iNOS). In chronic inflammation, the activated pro-

inflammatory cytokines or lipopolysaccharide (LPS) induce iNOS to produces a high level of NO in response to inflammatory signals.

NO aggressively react with superoxide to produce peroxynitrite ($ONOO^-$), a member of reactive nitrogen species (RNS), which also form another extremely reactive oxygen species (ROS), hydroxyl radicals. Hence, uncontrollable production of NO will lead to elevated level of RNS and ROS, which contributed towards various DNA modifications, cellular injuries, genotoxicity and carcinogenesis (Surh et al., 2001).

Therefore, overproduction of NO is one of the important factor involved in a variety of diseases including cancer (Ridnour et al., 2008), cardiovascular disorder (Naseem, 2005), asthma (Fitzpatric et al., 2009) and rheumatoid arthritis (Hensley et al., 1997). Based on this reason, pharmacological reduction of NO production is a promising strategy in developing effective drugs for inflammation-related diseases. To name a few, ibuprofen, indomethacin, diclofenac, and piroxicam are common analgesic NSAIDs used in treatment of arthritis which possess strong anti-inflammatory characters due to their capability in inhibit various pro-inflammatory enzymes including COX-1, COX-2 and iNOS (Berg et al., 1999).

1.3 Curcumin

Curcumin, 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (Figure 1.2), generally known as diferuloyl methane, is a hydrophobic polyphenol, yellow compound, isolated from the rhizome of the herb *Curcuma longa* Linn. The three major curcuminoids isolated from turmeric are curcumin (**1**, 94%), demethoxycurcumin (**2**, 6%), and bisdemethoxycurcumin (**3**, 0.3%) (Chattopadhyay et al., 2004).

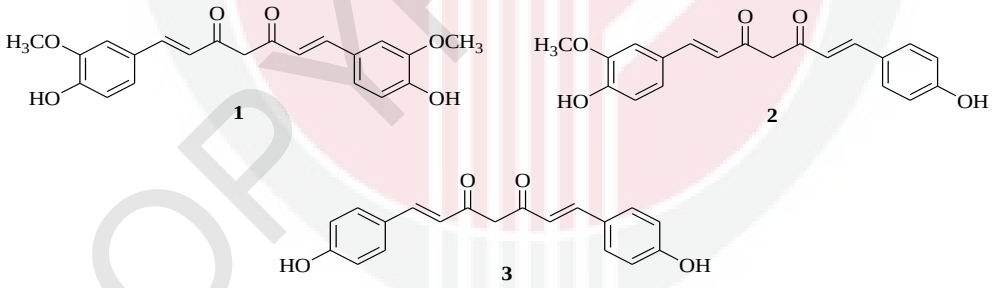


Figure 1.2 Chemical structures of curcuminoids.

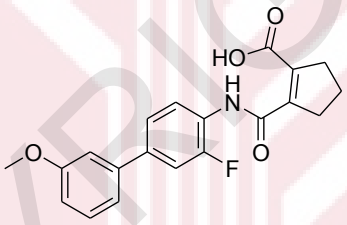
Curcumin and its analogues have been found to exhibit various biological and pharmacological properties including anti-inflammatory, antioxidant, antiviral, antimicrobial, chemo-preventive, antiangiogenic, antiandrogenic, and anticancer properties (Bisht et al., 2010). Anti-inflammatory properties of curcumin are manifested by suppressing the activation and production of nuclear factor kappa-beta (NF-κβ) (Singh and Aggarwal, 1995), cyclooxygenase-2 (COX-2) and other pro-inflammatory mediators, such as tumor-necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) (Maheshwari et al., 2006). However, poor bioavailability has limited the practical use of curcumin.

Several approaches have been developed to improve the bioavailability of curcumin, including nanoparticle-encapsulation (Mulik et al., 2010), liposomal formulations (Anand et al., 2007) and structure modifications (Aggarwal and Mishra, 2010).

1.4 Drug design

Once a target and testing system are identified, the next stage is to find and develop a good lead compound that may exhibits the desired pharmacological activity. Today's marketed medicines are either obtained directly from a natural source or were developed from a lead compound originally obtained from natural products. The lead compounds can be discovered through various ways, including screening of natural products, particularly from the plant kingdom. Clinically useful drug, paclitaxel (Taxol) have recently been isolated from pacific yew tree. Various studies have reported Paclitaxel as an effective anticancer agent against lung, ovarian, breast and liver cancer (Priyadarshini and Keerthi Aparajitha, 2012).

The alternative approach in finding a lead compounds is through virtual screening, which libraries of available small molecules were docked into the target of interest *in silico* and scored based on their interaction with the site (Anderson, 2003). Virtual screening is generally divided into two methods, the structure-based and ligand-based. The structure-based method is very useful when the target is available, led to the detailed investigation of target-ligand interaction mode, thus the rational design of novel chemical structures with improved properties was carried out. Equally, the ligand-based technique that uses the predictive compound activity models based on previous experimental data is also attractive. The potential of virtual screening has been demonstrated by the identification and development of patented drug candidate SC12267 as a rheumatoid arthritis agent (Clark, 2006).



SC12267

Once a small molecule has been identified, it must be evaluated before proceed to the next stages. Leads are first evaluated visually through computer analysis and often been optimized at this step for affinity enhancement (Anderson, 2003). Leads also been evaluated for their orally bioavailability properties using the Lipinski rules (Lipinski et al., 1997), which stated 'lead-like' compounds generally have MW < 500, HBA <10, HBD < 5 and log P < 5. Veber et al., (2002) also stated that number of rotatable bond should be less than 10 to increase the oral bioavailability. Finally, the lead compounds were tested for their biological activities. The promising lead compounds often re-enter the structural determination process in finding the exact binding mode and further structurally optimized until becomes evident.

1.5 Problem statement

The main adverse effects of current NSAIDs, involved the gastroinstestinal tract, kidney and blood clotting has lead to the discovery of new NSAIDs with improved safety profile. Curcumin could be serves as potential NSAID candidate based on its strong anti-inflammatory property and low toxicity. However, its utilization in clinical trials was restricted due to poor pharmacokinetic properties. Recent studies reported the mono carbonyl diarylpentanoid analogues possess enhanced stability *in vitro* and improved pharmacokinetic profiles *in vivo* particularly in anti-inflammatory activity (Liang et al., 2009). Hence, this has prompted us to design smaller and less complex diarylpentanoid-related compounds due to the fact that smaller molecules are more likely to bind readily to the binding sites of selected target, and thus improve the activity.

To the best of our knowledge, none of the studies incorporated the α,β,γ,δ-unsaturated ketone moiety in a diarylpentadienone scaffold in the evaluation of the anti-inflammatory properties, particularly with regards to NO inhibition activity. The general structures of the targeted compounds are shown in Figure 1.3. The design of new diarylpentadienone system was primarily based on steric and electronic properties of substituent. The selected functional groups were appended on different positions of both ring A and ring B to examine their important influence towards NO inhibitory activity. Also, by replacing an aromatic moiety of ring A with heteroaromatic ring able to introduce the possibility of hydrogen bonding interaction and improve the ligand-receptor interactions of diarylpentadienone system, resulted better activity.

In addition, we have designed a new series of diarylpentadienone derivatives by introducing pyrazoline ring into the system (Figure 1.3) which might increase their bioavailability through the better rigidity, thus give a positive effect on selected activity (Veber et al., 2002). Besides that, we also synthesized a series of pyrrolylated-chalcone analogues (Figure 1.3) with a shorter linker chain in comparison to diarylpentadienone analogues to observe their flexibility impact towards NO inhibition activity. Moreover, no computational analyses (2D and 3D QSAR, ADMET and TOPKAT) of these diarylpentadienone analogues and their NO inhibitory properties have previously been studied.

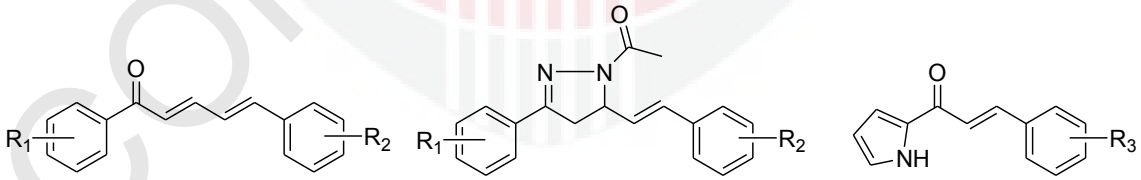


Figure 1.3 Structures of targeted compounds

1.6 Hypothesis

In this study, we are focusing on design strategies in optimizing the interaction of diarylpentadienone analogues with its target in order to produce the desired anti-inflammation property, by studying the effect of various functional groups at different positions of diarylpentadienone rings on NO inhibitory effects. Previous studies has been reported that introduction of polar group at *para*-position on phenyl ring of curcuminoid proven to be essential for anti-inflammatory activity (Orlikova et al., 2011). Based on this, we predicted that diarylpentadienone analogues with *para*-hydroxyl moiety will show a remarkable NO inhibition activity. Rigidification has been used to enhance the activity of drug or to reduce its adverse effects. Therefore, we are trying to study the effect of rigidity on the diarylpentadienone scaffold by incorporating the pyrazoline ring into the system. We expected that this pyrazoline-diarylpentadienone analogues will displayed a comparable NO inhibitory performance to curcumin. The shortening of five-carbon spacer to three-carbon chain length to forms the chalcone analogues will reduced flexibility and might improve the binding interactions with the active site, thus enhance the targeted anti-inflammatory activity.

1.7 Objectives of this study

1. To design and synthesize diarylpentadienone, and pyrrolylated chalcone analogues.
2. To evaluate the anti-inflammatory property of diarylpentadienone and pyrrolylated chalcone analogues using the NO inhibitory activity.
3. To identify active compounds of diarylpentadienone and pyrrolylated chalcone analogues based on SAR studies.
4. To analyse 2D and 3D QSAR, ADMET and TOPKAT of diarylpentadienone analogues.

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LIST OF PUBLICATIONS

1. Sze Wei Leong, Siti Munirah Mohd Faudzi, Faridah Abas, Mohd Fadhlizil Fasihi Mohd Aluwi, Kamal Rullah, Lam KokWai, Mohd Nazri Abdul Bahari, Syahida Ahmad, Chau Ling Tham, Khozirah Shaari, Nordin H. Lajis.Synthesis and SAR study of curcuminoid analogues as new anti-inflammatory agents. *Molecules.*– **Published**

2. Siti Munirah Mohd Faudzi, Leong Sze Wei, Faridah Abas, Mohd Fadhlizil Fasihi Mohd Aluwi, Kamal Rullah, Lam KokWai, Mohd Nazri Abdul Bahari, Syahida Ahmad, Chau Ling Tham, Khozirah Shaari, Nordin H. Lajis. Synthesis, biological evaluation, QSAR studies of diarylpentanoid analogues as potential nitric oxide inhibitors. *Medicinal Chemistry Communication.***- Published**

3. Leong Sze Wei, Siti Munirah Mohd Faudzi, Faridah Abas, Mohd Fadhlizil Fasihi Mohd Aluwi, Kamal Rullah, Lam KokWai, Mohd Nazri Abdul Bahari, Syahida Ahmad, Chau Ling Tham, Khozirah Shaari, Nordin H. Lajis. Antioxidant and anti-inflammatory properties of asymmetrical diarylpentanoid derivatives. *Medicinal Chemistry Research.* **- Submitted**

4. Siti Munirah Mohd Faudzi, Leong Sze Wei, Faridah Abas, Mohd Fadhlizil Fasihi Mohd Aluwi, Kamal Rullah, Lam Kok Wai, Mohd Nazri Abdul Bahari, Syahida Ahmad, Chau Ling Tham, Khozirah Shaari, Nordin H. Lajis. Synthesis and anti-inflammatory evaluation of pyrazoline derivatives of diarylpentenedione analogues. *Medicinal Chemistry Research.* **- Under review**

5. Leong Sze Wei, Siti Munirah Mohd Faudzi, Faridah Abas, Mohd Fadhlizil Fasihi Mohd Aluwi, Kamal Rullah, Lam KokWai, Mohd Nazri Abdul Bahari, Syahida Ahmad, Chau Ling Tham, Khozirah Shaari, Nordin H. Lajis. Acetyl- and butyrylcholinesterase inhibitory effects of diarylpentanoid derivatives. *Bioorganic & Medicinal Chemistry Letters.* **– Under review**

LIST OF CONFERENCES ATTENDED

1. Siti Munirah Mohd Faudzi, Faridah Abas, Lam Kok Wai, Syahida Ahmad, Chau Ling Tham, Khozirah Shaari, Nordin H. Lajis. "Synthesis and Anti-tyrosinase activity of diarylprntanoid analogues". Poster presentation at 17th Malaysian Chemical Congress (17 MCC), Putra World Trade Centre, Kuala Lumpur, 15th-17th October 2012.

2. Siti Munirah Mohd Faudzi, Leong Sze Wei, Faridah Abas, Lam Kok Wai, Syahida Ahmad, Chau Ling Tham, Khozirah Shaari, Nordin H. Lajis. "Design, synthesis and biological evaluation of diarylpentanoid derivatives as new anti-inflammation agents". Poster presentation at 2nd Junior ICCEOCA (ACP), Universiti Malaya, Kuala Lumpur, 8th-11th December 2012.

3. Siti Munirah Mohd Faudzi, Leong Sze Wei, Faridah Abas, Mohd Fadhlizil Fasihi Mohd Aluwi, Kamal Rullah, Lam Kok Wai, Mohd Nazri Abdul Bahari, Syahida Ahmad, Chau Ling Tham, Khozirah Shaari, Nordin H. Lajis. "Design, synthesis, biological evaluation, and SAR studies of diarylpentanoid analogues as potential anti-inflammation agents". Oral presentation at International Conference on Natural Products (ICNP) 2014, Palm Garden Hotel, IOI Resort Putrajaya, 18th-19th March 2014.

4. Siti Munirah Mohd Faudzi, Leong Sze Wei, Faridah Abas, Mohd Fadhlizil Fasihi Mohd Aluwi, Kamal Rullah, Lam Kok Wai, Mohd Nazri Abdul Bahari, Syahida Ahmad, Chau Ling Tham, Khozirah Shaari, Nordin H. Lajis. "Design, synthesis and biological evaluation of diarylpentanoid analogues as potential NO inhibitor". Oral presentation at Medan International Conference on Advanced Pharmaceuticals Sciences (MICAPS) 2014, Garuda Plaza Hotel, Medan, Indonesia, 3rd-4th November 2014.