UNIVERSITI PUTRA MALAYSIA

SYNTHESIS AND CHARACTERIZATION OF PYRROLYLATED-CHALCONES AS ANTI METHICILLIN-RESISTANT *Staphylococcus aureus* AGENTS

MOHANAPRIYA GUNASEKHARAN

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By

MOHANAPRIYA GUNASEKHARAN

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

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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October 2020

Chairman : Siti Munirah binti Mohd. Faudzi, PhD
Faculty : Science

A bacterial infection is well recognized as one of the leading causes of fatal morbidity and death in patients infected with diseases, hence are immune compromised. Although some molecules including vancomycin and linezolid, the standard drugs used for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA), have been successfully developed over the years, the ability of microorganisms to develop resistance to these drugs during treatments has evoked the need for a continuous search for new drugs with better efficacies. Chalcone has been one of the most studied class of molecules possessing variety of remarkable bioactivities, including anti-bacterial, anti-parasitic and anti-inflammatory. Due to the ease of preparation and numerous pharmacological activities involving the chalcone motifs, therefore, it is worth to further study the anti-bacteria activity, specifically related to the multidrug-resistant methicillin-resistant *Staphylococcus aureus* (MDR-MRSA) on the new analogs of the pyrrolylated-chalcones.

In this study, a series of pyrrolylated-chalcone analogs (compounds **1-15**) were synthesized by treating 2-acetylpyrrole with respectively substituted benzaldehydes *via* a base-catalyzed Claisen-Schmidt condensation reaction. The purified final compounds were subjected for confirmatory structural elucidation by established spectroscopic techniques comprising of ^{1}H, ^{19}F- and ^{13}C- high field nuclear magnetic resonance (NMR), direct injection-mass spectroscopy (DI-MS), and Fourier transform infrared (FTIR) spectroscopy. The purified pyrrolylated-chalcones were then assayed for anti-MRSA activity through the disk diffusion (DDA, for a preliminary screening), *in vitro* minimal inhibitory concentration (MIC), minimum bactericidal concentration (MBC), and killing time curve assays. Based on the results, the hydroxyl-containing compounds (**8**, **9**, and **10**) showed the most significant anti-MRSA property, with range of inhibition zone diameters between

7.5 to 10 mm and the MIC and MBC values ranged of 0.08 to 0.70 mg/ml and 0.16 to 1.88 mg/ml, respectively. In comparison, the inhibition zone for the standard drug, chlorhexidine (CHX) was 14 to 15 mm in diameter with a respective MIC and MBC values of 0.03 to 0.12 mg/ml and 0.07 to 0.23 mg/ml. The time-kill curve plots showed that MRSA strains to a concentration of 4× MIC for four hours resulted in the death of all cells. Furthermore, ligand **9** was chosen for docking analyses with penicillin-binding protein 2a (PBP2a, PDB ID: 6Q9N) and the results showed a similar bonding interaction to the specific docking of the CHX with the respective binding affinity scores of -7.0 kcal/ mol and -8.2 kcal/mol. Following that, the morphology of compound **9** was further confirmed by the scanning electron microscopy (SEM) technique. Overall results suggested that the pyrrolylated-chalcones, particularly compound **9** may be considered as potential inhibitor in the design of new anti-MRSA agents.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

SINTESIS DAN PENCIRIAN PIROLILASI-KALKON SEBAGAI EJEN ANTI TAHAN METISILIN *Staphylococcus aureus*

Oleh

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Oktober 2020

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Jangkitan bakteria dikenali sebagai salah satu faktor penyebab penyakit berjangkit yang berbahaya serta membawa maut kepada pesakit yang dijangkiti. Walaupun ubat- ubatan yang digunakan dalam rawatan *Staphylococcus aureus* tahan metisilin (MRSA) seperti vancomycin dan linezolid telah dihasilkan, namun keupayaan mikroorganisma untuk mengadaptasi pertahanan terhadap ubat tersebut menyebabkan keperluan untuk pengajian berterusan bagi menghasilkan ubat yang lebih efektif. Kalkon merupakan salah satu kelas molekul yang mempunyai bioaktiviti yang luar biasa termasuk sifat anti-bakteria, antiparasit dan anti-radang. Oleh kerana kemudahan penyediaan dan banyak aktiviti farmakologi yang melibatkan kalkon, adalah wajar untuk kajian lebih lanjut mengenai aktiviti anti-bakteria dijalankan, khususnya yang berkaitan dengan *Staphylococcus aureus* tahan methicillin tahan pelbagai ubat (MDR-MRSA) ke atas analog baru pirol-kalkon.

Dalam kajian ini, satu siri analog pirol-kalkon (sebatian **1**-**15**) disintesis melalui pengolahan 2-asetilpirol dengan pelbagai benzaldehid melalui tindak balas pemeluwapan Claisen-Schmidt yang bermangkinkan bes. Sebatian tulen akhir disubjek bagi pengesahan strukturnya melalui teknik-teknik spektroskopi yang merangkumi ^{1}H-, ^{19}F- and ^{13}C- resonans nuklear magnetik (NMR) bermedan tinggi, spektroskopi jisim-suntikan terus (DI-MS), dan spektroskopi inframerah-penjelmaan Fourier (FTIR). Analog pirol-kalkon yang tulen kemudian disaring bagi menyiasat ciri-ciri potensi anti-MRSA melalui ujian penyebaran cakera, nilai kepekatan perencatan minimum (MIC) dan kepekatan bakterisidal minimum (MBC) dan ujian perencatan masa. Berdasarkan keputusan, sebatian yang mengandungi hidroksi (**8**, **9**, and **10**) menunjukkan aktiviti anti-MRSA paling tinggi dengan pembentukan zon perencatan sebanyak 7.5 hingga 10 mm, nilai MIC dan MBC ialah 0.08 hingga 0.70 mg/ml dan 0.16 hingga 1.88 mg/ml. Berbanding dengan standard, kloroheksidina (CHX) zon perencatan sebanyak 14 hingga 15 mm, nilai MIC dan

MBC adalah 0.03 hingga 0.12 mg/ml and 0.07 hingga 0.23 mg/ml. Ujian perenjatan masa menunjukkan bakteria MRSA boleh dibunuh pada kepekatan 4× MIC, iaitu pada jam ke-4. Sebatian **9** dipilih untuk analisis dok dengan penisilin-mengikat protein 2A (PBP2a, PDB ID: 6Q9N). Keputusan menunjukkan interaksi yang serupa dengan dok standard CHX dengan skor mengikat -7.0 kcal/mol dan -8.2 kcal/mol untuk ligan **9** dan CHX. Sehubungan dengan itu, sebatian **9** telah disahkan dengan mengunakan teknik pengimbasan mikroscopi (SEM). Secara keseluruhannya keputusan mencadangkan bahawa pirol-kalkon terutamanya sebatian **9** boleh dianggap calon yang berpotensi sebagai ejen anti-MRSA yang baru.

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Hereby, I would like to take this opportunity to thank every individual that has helped me directly and indirectly throughout the complete process of this thesis of mine. First and foremost, I would like to admit that all praises to the Lord for His abundant blessing upon me in completing this endeavour. My journey would not be as smooth as it was without His blessings.

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

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Name of Chairman of Supervisory Committee: Dr. Siti Munirah binti Mohd. Faudzi

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Signature: _____
Name of Member of Supervisory Committee: Dr. Thiruventhan a/l Karunakaran

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α	Alpha
β	Beta
δ	Chemical shift in ppm
µl	Microliter
µM	Micromolar
%	Percentage
˚ C	Degree Celsius
µg	Microgram
^{13}C	Carbon 13
^{19}F	Fluorine 19
^{1}H NMR	^{1}H-Nuclear Magnetic Resonance spectroscopy
^{1}H	Proton
br	Broad
br. d	Broad doublet
br. s	Broad singlet
CFU	Colony forming unit
CLSI	Clinical and Laboratory Standards Institute
d	Doublet
dd	Doublet of doublets
DMSO	Dimethyl sulfoxide
EtOH	Ethanol
EtOAc	Ethyl acetate
FT-IR	Fourier Transform-Infrared spectroscopy
g	Gram
GC-MS	Gas Chromatograph-Mass Spectrometry
HCl	Hydrochloric acid
HPLC	High Performance Liquid Chromatography
hrs / hr	Hours/Hour
Hz	Hertz
IC_{50}	Half maximal inhibitory concentration

Log	Logarithm
lit.mp	Literature melting point
M	Molar
m	Multiplet
m/z	Mass-to-charge ratio
mg	Miligram
MHA	Mueller Hinton agar
MHB	Mueller Hinton broth
min	Minute
ml	Milliliter
MP	Melting point
NaOH	Sodium hydroxide
nm	Nanometer
NMR	Nuclear Magnetic Resonance
p	Para
PDB	Protein data bank
Ph	Phenyl
ppm	Parts per million
rt	Room Temperature
s	Singlet
SAR	Structure-activity relationship
t	Triplet
td	Triplet of doublets
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
tt	Triplet of triplets
UV	Ultraviolet

CHAPTER 1

INTRODUCTION

1.1 General

Bacterial infections are one of the threats to the global health problem, mainly owing to the resistance of microorganisms towards antibiotics (Zaki *et al*., 2019). Bacterial infections may lead to the occurrence of diseases including diarrhea, meningitis, respiratory tract infections, and hospital-acquired infections (nosocomial infections). If not treated properly, it may be causing mortality and hence, are immune compromised (Sivakumar *et al*., 2010). According to the Centre for Disease Control and Prevention (CDC) in year 2017, more than 2 million diseases and 23,000 deaths occur annually due to antibiotic resistance in the United States. Moreover, patients will be facing a financial burden owing to continuous hospitalization with regards to the failure treatment caused by the antibiotic resistance. The inadequacy of treatment for antibiotic resistance worldwide has led to the growing needs for the development of new drug with less resistance.

For the past 15 to 20 years, the development of new antimicrobials for the treatment of gram-positive bacterial infections has become significant (Macvane, 2017). *Staphylococcus aureus* (*S. aureus*) is a gram-positive bacterium that seizes in human skin, bone joints through the bloodstream, respiratory system, and endovascular tissues (Prabhoo *et al*., 2019; Zaki *et al*., 2019). Patients with chronic disease i.e. adolescents, elder people, and patients on treatment have a higher tendency to be infected by methicillin-resistant *Staphylococcus aureus* (MRSA). Insufficient diagnosis of MRSA has led to patients having to stay in the hospital longer which increases the hospital cost and mortality rate. *S. aureus* is also categorized as a death-dealing pathogen. In the year 1950, methicillin was found to be the treatment agent for *S. aureus*-caused infections (Shamsuddin & Basri, 2018). Unfortunately, *S. aureus* was found to be resistant to methicillin in the year 1961 in England. Hospital-acquired (HA) and community-acquired (CA) methicillin-resistant *S. aureus* (MRSA) have infected and increased the number of deaths almost similar to the number of deaths of AIDS and tuberculosis at that time (Negi *et al*., 2016).

Although many antibacterial drugs are available, the resistance of bacteria to these drugs is also gradually increasing becoming a worldwide concern (Okwu *et al*., 2019). To circumvent this, it is important to develop a new prototype of drugs to treat infections apart from the currently available drugs which are limited in treatment efficiency to a certain pathogen, particularly MRSA.

Chalcone (1, 3-diaryl-2-propenone) (Figure 1.1) is an acyclic compound containing α, β-unsaturated carbonyl group appended by the two aromatic rings (A and B), which is commonly synthesized via acid- or base-catalyzed aldol or Claisen-Schmidt condensation reaction in the laboratory (Makarand *et al*., 2010). Naturally, chalcone

could also be an initial intermediate structure used in the biosynthesis of all flavonoids.

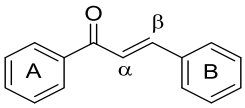


Figure 1.1 : Molecular structure of chalcone (1, 3-di-aryl-2-propenone)

Some studies have reported on chalcones with possible antimicrobial prospects against fungi, bacteria, and even resistant to bacteria (Özdemir *et al*., 2017). Chalcones and its derivatives have displayed a wide range of biological activities including antibacterial, antifungal, antioxidant (Sivakumar *et al*., 2010), anti-inflammatory, antimalarial, anticancer, antiviral, anti-tubercular, and anti-hyperglycemic (Makarand *et al*., 2010). These activities render chalcone as targeting compounds for pioneering and developing new anti-MRSA agents.

In this study, a series of pyrrolylated-chalcones (Figure 1.2) were designed and synthesized as potential anti-MRSA agents. These analogues (**1-15**) were prepared by reacting 2-acetylpyrrole with respective hydroxyl-, nitro-, and fluoro-containing benzaldehydes via base-catalyzed Claisen-Schmidt condensation reaction as shown in Scheme 1.1, while the structures of all fifteen compounds are depicted in Table 1.1.

Pyrrole is a *N*-containing heterocyclic ring with multiple pharmacophores, serve as intermediate towards the generation of enormous lead molecules with numbers of reported pharmacological activities such as anti-fungal, antibacterial, anti-inflammatory and anti-cancer. These pyrrole-based compounds are being consolidated either as a substituent or with different replacements on the ring itself. Several medications containing pyrrole moiety are now accessible in market while rest are under clinical preliminaries (Kaur *et* al., 2017). In this study, the electron-donating (OH), electron-withdrawing (F and NO_2) groups were selectively chosen as substituents in optimizing the interaction of the respective chalcones with its target to produce the desired anti-MRSA property. Fluorine has recently become a significant in medication disclosure, as it allows simultaneous modulations of electronic, lipophilic, and steric parameters, all of which can critically influence both the pharmacokinetics and pharmacodynamics properties of drugs (Xu *et al*., 2019).

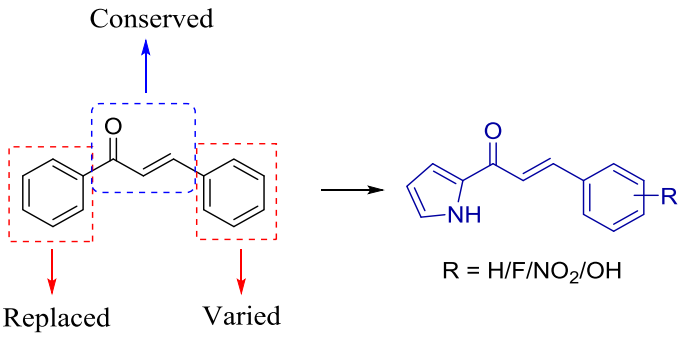
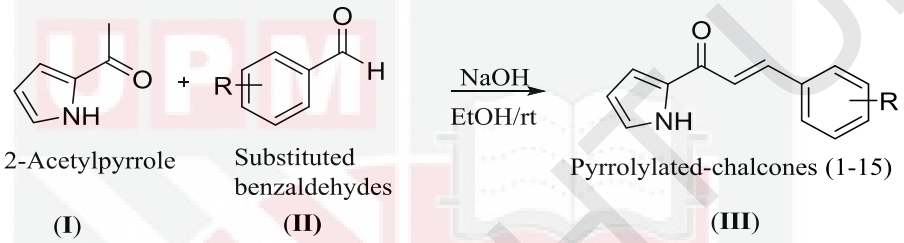
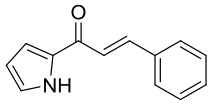
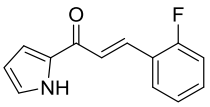
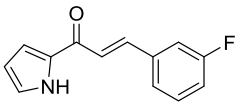
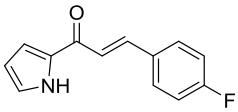
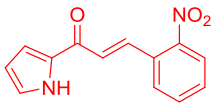
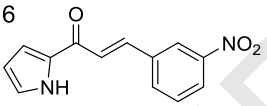
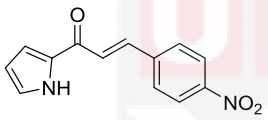
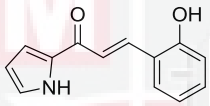
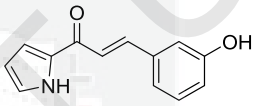
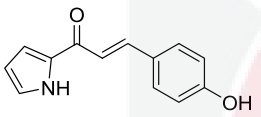
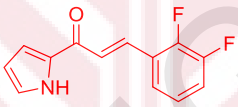
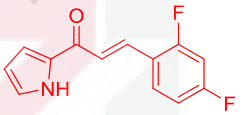
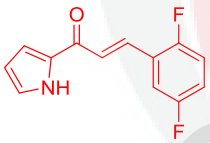
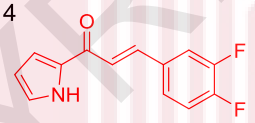
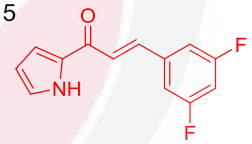


Figure 1.2 : General conversion of chalcone to pyrrolylated-chalcone



Scheme 1.1 : General structure and reaction scheme

Table 1.1 : List of synthesized pyrrolylated-chalcones (new compounds are coloured in red)

1  3-phenyl-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one	2  3-(2-fluorophenyl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one	3  3-(3-fluorophenyl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one
4  3-(4-fluorophenyl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one	5  3-(2-nitrophenyl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one	6  3-(3-nitrophenyl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one
7  3-(4-nitrophenyl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one	8  3-(2-hydroxyphenyl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one	9  3-(3-hydroxyphenyl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one
10  3-(4-hydroxyphenyl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one	11  3-(2,3-difluorophenyl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one	12  3-(2,4-difluorophenyl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one
13  3-(2,5-difluorophenyl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one	14  3-(3,4-difluorophenyl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one	15  3-(3,5-difluorophenyl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one

1.2 Problem statement

A bacterial infection caused by microorganisms includes *S. aureus*, *Enterococcus faecalis*, *Escherichia coli*, and *Klebsiella penumoniae*, and their increasing resistance towards antibiotics is one of the major problems to the present and future populations as these resistant bacteria are the culprits for respiratory tract infections and meningitis (Sivakumar *et al*., 2010). Although there are commercially designed antibiotics to treat bacterial infection-related diseases such as methicillin and vancomycin, these antibiotics are gradually losing their efficiency as these organisms constantly evolve in resistance development against antibiotics. Thus, the need for developing new useful drugs have drastically increased worldwide. With the recent discovery of chalcones possessing high anti-infective potentials and the therapeutic importance of nitrogen-containing marketed antibiotics, it has led to the synthesis of a new series of pyrrolylated-chalcone as potential antibacterial agents. The series are

hypothesized to possess anti-MRSA potential, which is comparable to the standard Chlorhexidine (CHX).

1.3 Objectives

The objectives of this research are as follows:

1) To synthesize and structurally characterize a series of pyrrolylated-chalcones.
2) To evaluate the *in vitro* antibacterial properties and mechanism of action of the newly synthesized compounds against methicillin-resistant *Staphylococcus aureus* (MRSA).
3) To predict the binding mode and binding affinity of the most active compound on the specific binding sites of the molecular targets using docking tools.

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