NURUL HAZWANI BINTI CHE ABDUL RAHIM MASTER OF SCIENCE 2018

# SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITIES OF EUGENOL AND THYMOL DERIVATIVES

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**NURUL HAZWANI BINTI CHE ABDUL RAHIM**

**Thesis Submitted in Fulfillment of the Requirement for the Degree of Master of Science in the School of Fundamental Science**

**Universiti Malaysia Terengganu**

**2018**

# DEDICATION

*Dedicated to:*
*My Prime Love, Allah the Almighty*
*My initiator, His Messenger*
*My endless love, parent and siblings*
*My precursor, Cikgu Noraini, Dr Asnu and Dr Azna*
*My support system, relatives and friends*

*"My success can only come from Allah.*
*In Him I trust, and unto Him I look"*
*[Hud:88]*

Abstract of thesis presented to the Senate of Universiti Malaysia Terengganu in fulfillment of the requirement for the degree of Master of Science

**SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITIES OF EUGENOL AND THYMOL DERIVATIVES**

**NURUL HAZWANI BINTI CHE ABDUL RAHIM**

**2018**

**Main Supervisor : Asnuzilawati binti Asaari, Ph.D**

**Co-Supervisor : Associate Professor Noraznawati binti Ismail, Ph.D**

**School : School of Fundamental Science**

Drug development based on natural product especially on monoterpene and phenylpropanoid becomes a subject of interest due to their simple skeletal structures. Therefore, 18 derivatives were synthesized which comprise of 14 eugenol derivatives and five thymol derivatives with seven of them were considered new. These derivatives were synthesized *via* structural modification at hydroxyl group furnishing ether and ester derivatives in the presence of base. Each derivative was characterized by normal spectroscopic techniques of FTIR, UV-Vis, NMR and MS. The spectroscopic data of FTIR showed few significance peaks which corresponds to *v*(=CH), *v*(C-H), $v(C=C)_{aromatic}$ and *v*(C-O) stretches appeared for both derivatives at the range of 3092-2960 $cm^{-1}$, 1600 $cm^{-1}$ and 1455-1256 $cm^{-1}$; and additional stretch of *v*(C=O) around 1700 $cm^{-1}$ for ester derivatives. The absorption band in the UV-Vis spectra for aromatic moiety as $\pi \rightarrow \pi^*$ electronic transition was observed in both ether and ester derivatives. Meanwhile, additional band was observed in UV-Vis spectra for ester derivatives indicating the presence of $n \rightarrow \pi^*$ transition depicts the C=O moiety. In the NMR spectra analysis, the presence of methylene protons around $\delta_H$ 5.00 ppm in $^1H$ NMR spectra and the appearance of C=O peak at $\delta_C$ 160 ppm in $^{13}C$ NMR confirmed the ether and ester linkages. The structures of the derivatives were also confirmed by MS analysis where peaks in the form of ion $[M]^+$ obtained in *m/z* values were in agreement with the expected molecular weight of the synthesized compound.

All compounds were further investigated for biological assays of anti-bacterial activity and cytotoxicity. The anti-bacterial activities were tested *via* well-diffusion method against test strains of Gram-positive (*Bacillus subtilis, Staphylococcus aureus* and *S. epidermidis*) and Gram-negative *(Escherichia coli* and *S. typhimurium*) bacteria. Among all synthesized compounds, **H13** emerged as the potential anti-bacterial agent since it was susceptible for both Gram-positive and negative bacterial strains. The *in vitro* cytotoxicity was assayed against hepatocellular carcinoma, human cells line using MTS Cell Proliferation Assay Kit (Calorimetric) for selected derivatives (**H1, H6** and **H13)**. Among three tested compounds, **H1** exhibited cytotoxicity with $IC_{50}$ 12.5 µg/ml, whereas another two compounds displayed whether non-cytotoxic and no activity toward cell.

Abstrak tesis yang dikemukakan kepada Senat Universiti Malaysia Terengganu sebagai memenuhi keperluan untuk Ijazah Sarjana Sains

**SINTESIS, PENCIRIAN DAN AKTIVITI BIOLOGI TERBITAN EUGENOL DAN THYMOL**

**NURUL HAZWANI BINTI CHE ABDUL RAHIM**

**2018**

**Penyelia Utama : Asnuzilawati binti Asari, Ph.D**

**Penyelia Bersama : Profesor Madya Noraznawati binti Ismail, Ph.D**

**Pusat Pengajian : Pusat Pengajian Sains Asas**

Perkembangan ubat-ubatan berasaskan produk semulajadi terutamanya pada monoterpina dan fenilpropanoid telah menjadi subjek yang menarik kerana struktur rangkanya yang ringkas. Untuk itu, 18 terbitan telah disintesis terdiri daripada14 terbitan eugenol dan lima terbitan thymol dengan tujuh daripada terbitan itu adalah dianggap sebatian baru. Terbitan-terbitan ini telah disintesis menerusi pengubahsuian struktur pada kumpulan hidroksil yang menghasilkan terbitan eter dan ester dengan kehadiran bes. Setiap terbitan telah dicirikan dengan teknik spektroskopi biasa seperti FTIR, UV-Vis, NMR dan MS. Data spektroskopi FTIR menunjukkan beberapa puncak penting yang bersamaan dengan regangan *v*(=CH), *v*(CH), $v(C=C)_{aromatik}$ dan *v*(C-O) muncul pada kedua-dua terbitan pada julat 3092-2960 $cm^{-1}$, 1600 $cm^{-1}$ dan 1455-1256 $cm^{-1}$ dan regangan tambahan untuk *v*(C=O) sekitar 1700 $cm^{-1}$. Jalur penyerapan dalam spektrum UV-Vis untuk moieti aromatik iaitu transisi elektronik $\pi \rightarrow \pi*$ telah diperhatikan dalam kedua-dua terbitan eter dan ester. Sementara itu, jalur tambahan telah diperhatikan dalam spektrum UV-Vis untuk terbitan ester yang menunjukkan transisi $n \rightarrow \pi*$ yang menggambarkan moieti C=O. Dalam analisis spektrum NMR, kehadiran proton metilina sekitar $\delta_H$ 5.00 ppm dalam spektrum $^1H$ NMR dan kemunculan puncak C=O pada $\delta_C$ 160 ppm dalam $^{13}C$ NMR mengesahkan ikatan eter dan ester. Struktur-struktur terbitan juga telah disahkan melalui analisis MS dimana puncak-puncak dalam bentuk ion $[M]^+$ diperolehi dalam nilai *m/z* didapati

bersesuaian dengan jangkaan berat molekul sebatian yang disintesis. Semua sebatian yang diperolehi terus disiasat untuk ujian biologi anktiviti anti-bakteria dan kesan kesitotoksian. Aktiviti anti-bakteria diuji melalui kaedah resapan-telaga terhadap bakteria strain ujian Gram-positif (*Bacillus subtilis, Staphylococcus aureus* dan *S. epidermidis*) dan Gram-negatif (*Escherichia coli* dan *S. typhimurium*). Di antara kesemua terbitan yang disintesis, **H13** muncul sebagai agen anti-bakteria yang berpotensi kerana ianya rentan kepada kedua-dua strain bakteria. Kesitotoksikan secara *in vitro* telah diuji terhadap sel manusia, karsinoma hepatoselular, menggunakan Kit Ujian MTS Proliferasi Sel (Kalorimetrik) untuk terbitan terpilih (**H1, H6** dan **H13**). Di antara tiga sebatian yang diuji, **H1** menunjukkan kesitotoksikan dengan nilai $IC_{50}$ 12.5 µg/ml manakala, dua sebatian lain memaparkan samada tidak sitotoksik dan tiada aktiviti terhadap sel.