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MICROWAVE AND CONVENTIONAL SYNTHESIS OF NEW DIHYDROBENZIMIDAZOQUINAZOLINE DERIVATIVES AND THEIR BIOLOGICAL ACTIVITIES

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By

HIBA ALI HASAN

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

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DEDICATION

To whom bears me through weakness upon weakness…
To whom her prayer lightened my path…
To the source of tenderness…
To my first teacher "**mom**"

To the most supportive man…
To the character of sacrifice and loyalty…
To whom taught me meaning of preciseness "**Dad**"

To the apple of my eye…
To my smile and absolute hope…
To whom has that kind of patience despite of her young age…
To "**Shams**", my daughter…

To the best friends in my life
To "**Huda** and **Dhuha**", my sisters and "**Al-hasan**" my lonely brother...

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

MICROWAVE AND CONVENTIONAL SYNTHESIS OF NEW DIHYDROBENZIMIDAZOQUINAZOLINE DERIVATIVES AND THEIR BIOLOGICAL ACTIVITIES

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HIBA ALI HASAN

April 2018

Chairman : Emilia binti Abd Malek, PhD
Faculty : Science

Inspired by the biological prominence of benzimidazoquinazoline, and trying to solve bacterial resistance problem as well as imbalance of antioxidant mechanisms inside our bodies, in this study, two series of eighteen dihydro-benzimidazoquinazoline derivatives (fifteen new derivatives except **39**, **45**, and **47**) were synthesised. These two series were synthesised from the reaction of 2-(2-aminophenyl)-1*H*-benzimidazole with two different series of aliphatic and aromatic aldehydes in a single step to investigate the activites of aliphatic as well as aromatic derivatives.

The compounds were synthesized using two different techniques of traditional heating by reflux and microwave-assisted organic synthesis (MAOS). A comparative study was used to compare the efficiency of these two protocols to synthesise the same target compounds regarding the reaction time, percentage yield, purity of the compounds, and benignity towards the environment. Furthermore, the structures of eighteen compounds were confirmed by applying TLC, spectrometric analysis (1D and 2D NMR, FTIR, and GCMS), elemental analysis (CHN) and photoluminescence properties (PL). Accordingly, single crystal analysis was performed for five crystal samples for further confirmation. The *in vitro* antimicrobial and antifungal activity was assessed against a panel of bacteria and fungi: two Gram-positive (*Staphylococcus aureus* ATCC 43300 and *Bacillus subtilis* UPMC 1175), two Gram-negative (*Pseudomonas aeruginosa* ATCC 15542 and *Salmonella choleraesuis* ATCC 10708), and one fungus (*Aspergillus brasiliensis ATCC 16404*) to test their biological activity against new microorganisms. Furthermore, ABTS and DPPH antioxidant activities of these analogues were performed to investigate their scavenging activities.

The microwave-enhanced synthesis method revealed superiority over its comparable method to synthesize the same type of compounds. The investigation of the antibacterial activity for both compound series (aliphatic and aromatic) revealed that some compounds gave moderate to good ability to inhibit Gram-positive bacterial growth, while only one compound in the aromatic family resulted in excellent inhibitory activity compared to tetracyclin standard drug. Neither of the two series displayed any inhibitory activity against the Gram-negative bacteria nor fungus. The ABTS scavenging activity for both series disclosed more powerful efficiency than for DPPH, as well as some of the derivatives displayed excellent antioxidant activity for both tests.

Fifteen new compounds together with another three known derivatives were synthesized to test their biological activates. The study found that the dihydro-benzimidazoquinazolines were synthesised within minutes by only one step to produce ultra-pure fluorescent compounds with very good to excellent yields (82-98%) in a more benign method towards the environment. The antimicrobial and antioxidant activities were investigated for these derivatives whereby, some of the compounds disclosed powerful activity that may help for future drug candidate development.

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

SINTESIS BERGELOMBANG MIKRO DAN KONVENSIONAL DERIVATIF BARU DIHIDROBENZIMIDAZOKUINAZOLIN DAN AKTIVITI BIOLOGI MEREKA

Oleh

HIBA ALI HASAN

April 2018

Pengerusi : Emilia binti Abd Malek, PhD
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Diilhamkan oleh kepentingan biologi benzimidazokuinazolin, dan cubaan untuk menyelesaikan masalah rintangan bakteria dan juga ketidak seimbangan mekanisme antioksidan di dalam badan kita, dalam kajian ini, dua siri bagi lapan belas bahan terbitan dihidro- benzimidazokuinazolin (lima belas bahan terbitan baru kecuali **39**, **45**, dan **47**) telah disintesiskan. Dua daripada bahan terbitan ini disintesis dalam tindak balas antara 2-(2-aminofenil)-1*H*-benzimidazole dengan dua siri alifatik dan aromatik aldehid yang berlainan dalam satu langkah untuk menyiasat aktiviti-aktiviti bahan terbitan alifatik dan juga aromatik.

Sebatian-sebatian ini disintesis menggunakan dua teknik yang berbeza iaitu pemanasan tradisional menggunakan refluks dan sintesis organik berbantu-mikrogelombang. Kajian perbandingan digunakan untuk membandingkan kecekapan di antara dua protokol ini untuk mengsintesiskan sebatian sasaran yang sama mengenai tempoh tindak balas, peratusan hasil, ketulenan sebatian, dan kebajikan terhadap alam sekitar. Tambahan pula, struktur-struktur untuk lapan belas sebatian tersebut telah disahkan dengan menggunakan TLC, analisis spektrometri (1D dan 2D NMR, FTIR, dan GCMS), analisis unsur (CHN) dan sifat fotopendarcahayaan (PL). Sewajarnya, analisis hablur tunggal telah dijalankan untuk lima sampel hablur untuk pengesahan yang lebih lanjut. Aktiviti *in vitro* anti-mikrob dan anti-kulat telah dinilai terhadap satu panel bakteria dan kulat: dua (2) Gram-positif (*Staphylococcus aureus* ATCC 43300 dan *Bacillus subtilis* UPMC 1175), dua (2) Gram-negatif (*Pseudomonas aeruginosa* ATCC 15542 dan *Salmonella choleraesuis* ATCC 10708), dan satu (1) kulat (*Aspergillus brasiliensis ATCC 16404*) untuk menguji aktiviti biologi mereka terhadap mikroorganisma yang baru. Tambahan lagi, aktiviti antioksidan ABTS dan

DPPH untuk analog-anolog tersebut telah dijalankan untuk menyiasat aktivit penipisan mereka.

Kaedah sintesis yang dipertingkatkan dengan ketuhar gelombang mikro menunjukkan kelebihannya ke atas kaedah yang setandingnya untuk mensintesis jenis sebatian yang sama. Penyelidikan terhadap aktiviti antibakteria untuk kedua-dua siri sebatian (alifatik dan aromatik) menunjukkan yang beberapa sebatian memberi keupayaan yang sederhana baik untuk membantutkan pertumbuhan bakteria Gram-positif, sementara hanya satu sebatian dalam keluarga aromatik menunjukkan aktiviti pembantutan yang sangat baik berbanding dengan –tetrasiklin dadah piawai. Kedua-dua siri tidak menunjukkan apa-apa aktiviti pembantutan terhadap bakteria atau kulat Gram-negatif. Aktiviti penipisan ABTS untuk kedua-dua siri menunjukkan kecekapan yang lebih hebat daripada DPPH, dan juga beberapa analog yang lain menunjukkan aktiviti antioksidan yang sangat baik untuk kedua-dua uji kaji.

Lima belas sebatian baru bersama-sama dengan tiga analog yang diketahui disintesis untuk diuji aktiviti biologinya. Kajian mendapati bahawa dihidro-benzimidazokuinazolin disintesis dalam masa beberapa minit dengan menggunakan satu langkah sahaja untuk menghasilkan sebatian pendarfluor yang sangat tulen dengan peratusan hasil yang sangat baik (82-98%) menggunakan kaedah yang lebih mesra alam. Aktiviti-aktiviti antimikrob dan antioksidan dikaji untuk analog-analog tersebut, di mana beberapa sebatian mendedahkan aktiviti yang sangat kuat yang boleh membantu perkembangan calon ubatan pada masa hadapan.

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Hiba.

I certify that a Thesis Examination Committee has met on 20 April 2018 to conduct the final examination of Hiba Ali Hasan on her thesis entitled "Microwave and Conventional Synthesis of New Dihydrobenzimidazoquinazoline Derivatives and their Biological Activities" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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This thesis submitted to the Senate of Universiti Putra Malaysia has been accepted as fulfillment for the degree of Doctor of Philosophy. The members of the Supervisory committee were as follows:

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Name of Member of Supervisory Committee: Professor Dr. Mohd Basyaruddin Abd Rahman

Signature: 
Name of Member of Supervisory Committee: Professor Dr. Khozirah Shaari

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Å	Angstrom
δ	Chemical shift
CHN	Carbon, Hydrogen, and Nitrogen
DIMS	Direct Injection Mass Spectroscopy
DMF	Dimethylformamide
DMSO	Dimethyl Sulfoxide
eV	Electron Volt
FTIR	Fourier Transform Infrared
GCMS	Gas Chromatography Mass Spectroscopy
GHz	Giga Hertz
Hz	Hertz
IC_{50}	Half Inhibitory Concentration
J	NMR Coupling Constant
M	Molar concentration
MHz	Mega Hertz
MIC	Minimum Inhibitory Concentration
mp	Melting Point
MS	Mass Spectroscopy
MW	Microwave
m/z	Mass to Charge ratio
NMP	N-methyl-2-pyrrolidone
SD	Standard Deviation
R_f	Retention factor
RSD	Relative Standard Deviation
THF	Tetrahydrofuran
TLC	Thin layer Chromatography
NMR	Nuclear Magnetic Resonance
Uv-Vis	Ultraviolet Visible

CHAPTER 1

INTRODUCTION

Heterocyclic compounds occupy a central position in medicinal and organic chemistry, with considerable attention concentrating on their syntheses. Nitrogen-containing heterocycles are ubiquitous backbones found in natural products, medicine and organic materials. They exhibit diverse biological and pharmacological activities partially due to their similarities to many natural and synthetic molecules with known biological activities (Pang *et al*., 2015; Rohini *et al*., 2010). Fused-ring heterocyclic compounds containing nitrogen are frequently studied owing to their diverse biological and pharmaceutical properties. Indeed, designing novel heterocyclic motifs has rapidly become an increasingly urgent mission for chemists. (Chen *et al*., 2016).

Quinazoline derivatives, which belong to the *N*-containing heterocyclic compounds, have likewise caused universal interest due to their broad and distinct biopharmaceutical activities. Researchers have already determined many therapeutic activities of quinazoline derivatives, including anti-cancer, anti-inflammation, anti-bacterial, analgesia, anti-viral, anticytotoxin, anti-spasm, anti-tuberculosis, anti-oxidant, antimalarial, anti-hypertension, anti-obesity, anti-psychosis, and anti-diabetic, etc., (Shen *et al*., 2016; Zayed and Hassan, 2014; Asif, 2014; Wang and Gao, 2013; Desai *et al*, 2013; Kaur *et al*., 2011; Aly *et al*., 2010).

Accordingly, medicinal chemists have synthesised a variety of quinazoline compounds with different biological activities by introducing various active groups to the quinazoline moiety using progressive synthetic methods. The potential applications of the quinazoline derivatives in the fields of biology, pesticides and medicine have also been investigated (Wang and Gao, 2013).

In turn, benzimidazole derivatives are important nitrogen-comprising heterocycles which constitute useful intermediates in organic synthesis, and over the past few years, there has been a growing interest towards the examination of these compounds as it can be considered an interesting tool for the development of compounds exerting biological properties (Davoodnia *et al*., 2007; Via *et al*., 2001). Benzimidazole containing compounds display a broad range of therapeutic activities, including antimicrobial, antitumor, and antibacterial activities and are also used as inhibitors of PI3-kinase 6 and the potent antistaphylococcal agents with dual inhibitory mechanisms against DNA gyrase (Li *et al*., 2014; Gurvinder *et al*., 2013; Singh *et al*., 2012). Many clinically used drugs contain quinazoline and benzimidazole moieties. **Figure 1.1** displays those important clinical drugs (Mahire *et al*., 2016; Li, *et al*., 2014; Saha *et al*., 2007).

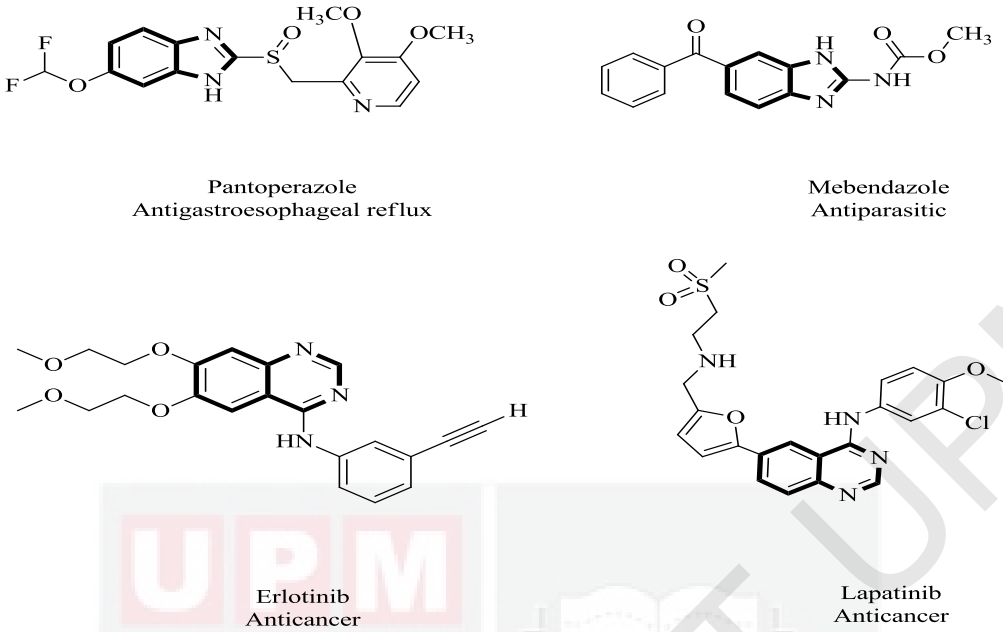
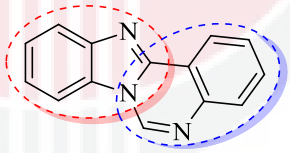


Figure 1.1 : Selected clinically useful benzimidazole and quinazoline-containing drugs.

Given the several interesting properties of these two moieties, it is postulated that introduction of benzimidazole group into the quinazoline system would be a useful strategy for designing a new class of drugs which appreciably, will influence the biological activity. Notwithstanding, many previous literature reported the pharmaceutical properties of quinazoline-fused benzimidazole skeleton. **Figure 1.2** illustrates the attractive fused scaffold consisting of both benzimidazole and quinazoline.



Benzimidazole Quinazoline

Figure 1.2 : Benzimidazoquinazoline scaffold.

Review of the previous literature that studied benzimidazoqunazolines has also revealed that those derivatives are fluorescent and emit light under ultraviolet source. The benzimdazoquinazoline derivatives were used as chemo-sensor and fluorescent probe for sequential recognition (Tang *et al*, 2013; Jeyanthi *et al*, 2013).

Recently, microwave-assisted reactions have attracted significant research interest because of the simplicity of operation and enhanced reaction rates (Davoodnia, 2010). Indeed, motivated by these results, along with interest in the utilisation of microwave irradiation for the synthesis of heterocyclic compounds, a rapid and efficient synthesis of some dihydro-benzimidazo[1,2-*c*]quinazolines through cyclocondensation of 2-(1H-benzimidazol-2-yl) aniline and different series of aldehydes with a catalytic amount of acetic acid under microwave irradiation is hence, investigated and reported in this stud

1.1 Problem Statement

There are innate defense mechanisms in human bodies to scavenge free radicals (generated in the body as a result of redox reactions) in order to sustain the homeostasis. However, the imbalance of such mechanisms leads to the progression of oxidative stress and numerous diseases, especially various chronic and age-related ones such as carcinogenesis, inflammation, and atherogenesis. As important supplements to the scavenging mechanisms, antioxidants (both naturally occurring and synthetic) have been widely applied in pharmaceuticals, foods, and cosmetics (Zhang *et al*., 2014). In addition, good antioxidant compounds are good potential leads for further physiological and biological activities. Therefore there is growing request to design and synthesise new antioxidants for pharmaceutical use.

On the other hand, the bacterial resistance to the available antibiotics have reached to the level of crisis. That has attributed to the overuse and misuse of these medications, as well as a lack of new drug development by the pharmaceutical industry due to reduced economic incentives and challenging regulatory requirements. This has led to fears of a "postantibiotic era" in which many bacterial infections will be untreatable (Ventola, 2015). Despite the large number of antibiotics available for medical use, design and synthesis of new potent antimicrobial agents is still in demand because of acquired resistance against old and new antibiotics.

1.2 Objectives of Study

This work aims to synthesise a library of new dihydro-benzimidazoquinazoline compounds with good biological activity that could be further possibly developed as drug candidates. The specific objectives were set as the following:

To synthesise two series dihydro-benzimidazoquinazoline derivatives using microwave and conventional methods.

To characterize the physicochemical properties of the synthesised compounds.

To investigate their antioxidant and antimicrobial activities.

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