UNIVERSITI PUTRA MALAYSIA

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF NEW SYMMETRICAL 1,3-BENZOXAZINE COMPOUNDS

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By

CHIYA OTHMAN HASSAN

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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DEDICATION

*To my beloved **Father** & **Mother***

who have always loved me unconditionally and whose good examples have taught me to work hard for the things that I aspire to achieve

*To **DANA**,*

my wonderful husband,

who has been a constant source of support and encouragement during the challenges of study and life. I am truly thankful for having you in my life. Love you more than my heart

*To **NOOR** & **NIVEEN**,*

my dear daughters, who are really a present from Allah

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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Chairman: Professor Mansor B Hj Ahmad, PhD
Faculty: Science

l,3-Benzoxazine compounds constitute an important class among a wide variety of heterocyclic compounds that have been explored for developing pharmaceutically important molecules, due to their interesting biological activities. It is well known, that 1,3-benzoxazines have antimicrobial activity, or the ability to inhibit the growth of microorganisms such as bacteria, fungi or protozoans. Therefore, in this work, a series of new symmetrical 1,3-benzoxazine derivatives have been synthesized to study their antibacterial and antifungal activities in comparison with the standard drugs streptomycin and nystatin respectively. The synthesis of a series of new 1,3-benzoxazine compounds was achieved in high yield in two steps. In the first step, 1,1'-bis(4-hydroxyphenyl)cyclohexane was prepared from phenol and cyclohexanone via Friedel-Craft reaction. Subsequently, the bisphenol was treated with a variety of primary amines; including aliphatic, aromatic and heteroaromatic, in the presence of formaldehyde to produce new symmetrical 1,3-benzoxazine derivatives. The structures of all the newly synthesized compounds (nine compounds: including eight unknown compounds and one known intermediate) have been elucidated and confirmed by TLC and spectroscopic methods such as FTIR, ^{1}H NMR, ^{13}C NMR, GCMS and CHNS analysis. Following that, the in vitro bioactivity (antibacterial and antifungal) evaluation were performed for all new symmetrical 1,3-benzoxazine derivatives and 1,1'-bis(4-hydroxyphenyl)cyclohexane (bisphenol-C) against a panel of human pathogenic microorganisms: two gram positive bacteria (*Bacillus Subtitles B29, Staphylococcus aureus S276)* and two gram negative bacteria (*Pseudomonas aeruginosa ATCC 15442, Escherichia coli E266)* were used for the antibacterial assay, while (*Aspergillus brasilliensis ATCC 16404*) was used for the antifungal assay. Furthermore, the investigation of antimicrobial screening data clearly evident that most of the newly synthesized compounds exhibited excellent to moderate antibacterial activity against tested microorganisms as compared to that of the standard drugs. Among the newly prepared compounds, compounds 3,4-dihydro-2*H*-1,3-benzoxazine containing 5-methylisoxazole group was more potent than standard

streptomycin against all the tested bacteria strains as well as equally potent against the tested fungus compared to nystatin drug. In addition, compound 3,4-dihydro-2-*H*-1,3-benzoxazine containing 2-aminothiazole group demonstrated similar effect against all tested microorganisms as compared to the standard drug streptomycin. Generally, newly synthesized compounds were active towards all bacteria strains and showed greater activity than initial parent which showed significant activity.

In brief, a series of the new symmetrical 1,3-benzoxazine compounds were synthesized successfully in high yield and investigated for their antimicrobial activities for above-mentioned assays. The results showed that a number of 1,3-benzoxazines assayed inhibition the growth of certain bacteria and fungi which may help for drug development in the future.

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

SINTESIS, PENCIRIAN DAN AKTIVITI BIOLOGI SEBATIAN SIMETRIKAL BARU 1,3-BENZOXAZINE

Oleh

CHIYA OTHMAN HASSAN

Januari 2017

Pengerusi: Profesor Mansor B Hj Ahmad, PhD
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Sebatian l,3-benzoxazine membentuk satu kelas penting di kalangan pelbagai jenis sebahan heterosiklik yang diteroka dalam membangunkan molekul-molekul yang penting, dari sudut farmaseutikalnya, disebabkan oleh kegiatan biologinya yang menarik. Ramai telah sedia maklum bahawa 1,3-benzoxazines mempunyai kegiatan anti-mikrobial, atau kebolehan merencat pertumbuhan mikroorganisma seperti bakteria, kulat atau protozoa. Oleh itu, dalam kajian ini, satu siri derivatif simetrikal baru 1,3-benzoxazine telah disintesis untuk mengkaji aktiviti anti-bakteria dan anti-kulat berbanding dengan ubat piawai iaitu streptomycin dan nystatin. Sintesis satu siri sebatian baru 1,3-benzoxazine telah dicapai dengan baik dalam dua langkah. Dalam langkah yang pertama, 1,1'-bis(4-hidroksifenil)sikloheksana telah disediakan dari fenol dan sikloheksanon melalui gerakbalas Friedel-Craft. Seterusnya, bisfenol telah dirawat menggunakan beberapa jenis amin primer; termasuk alifatik, aromatik and heteroaromatik, dengan kehadiran formaldehid untuk menghasilkan derivatif baru simetrikal 1,3-benzoxazine. Struktur kesemua sebatian yang baru disintesis (sembilan sebatian: termasuk lapan sebatian yang tidak diketahui dan satu perantara yang diketahui) telah dikenalpasti dan disahkan oleh TLC dan kaedah spetroskopik seperti analisis FTIR, ^{1}H NMR, ^{13}C NMR, GCMS dan CHNS. Seterusnya, penilaian bio-aktiviti in-vitro (anti-bakteria dan anti-kulat) telah dijalankan untuk semua simetrikal baru derivatif 1,3-benzoxazine dan 1,1'-bis (4-hidroksi fenil) sikloheksana (bisfenol-C) ke atas satu panel mikroorganisme patogenik manusia: dua gram bakteria positif (*Bacillus Subtitles B29, Staphylococcus aureus S276)* dan dua gram negatif bakteria (*Pseudomonas aeruginosa ATCC 15442, Escherichia coli E266)* digunakan untuk cerakinan anti-bakteria, sementara (*Aspergillus brasilliensis ATCC 16404*) digunakan untuk cerakinan anti-kulat. Tambahan lagi, pengkajian data penapisan anti-mikrobial membuktikan bahawa kebanyakan sebatian yang baru dicerakinkan menunjukkan kegiatan anti-mikrobial yang sederhana ke aktif ke atas mikroorganisme yang diuji berbanding dengan ubat-ubatan piawai. Di antara sebatian yang baru disediakan, sebatian 3,4-dihidro-2*H*-1,3-benzoxazine mengandungi kumpulan 5-metilisoxazole lebih kuat dari streptomisin piawai ke atas semua tapisan bakteria yang diuji dan sama kuatnya

ke atas kulat yang diuji berbanding dengan ubat nistatin. Tambahan pula, sebatian 3,4-dihidro-2-*H*-1,3-benzoxazine mengandungi kumpulan 2-aminothiazole group menunjukkan kesan yang serupa ke atas semua mikroorganisme yang diuji berbanding dengan ubat piawai iaitu streptomisin. Amnya, sebatian yang baru dicerakinkan adalah aktif terhadap semua bakteria yang diaji dan menunjukkan aktiviti lebih hebat dari induk asal yang menunjukkan aktiviti yang signifikan.

Ringkasnya, satu siri sebatian baru 1,3-benzoxazine yang simetrikal telah dicerakinkan dengan baik dengan pengeluaran yang tinggi dan dikaji untuk memeriksa aktiviti anti-mikrobial untuk cerakinan yang disebutkan tadi. Keputusan menunjukkan bahawa sebilangan 1,3-benzoxazines yang dicerakinkan merencat pertumbuhan bakteria dan kulat yang boleh membantu memajukan lagi dunia perubatan pada masa akan datang.

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January 2017

Chiya Othman
Chemist

I certify that a Thesis Examination Committee has met on 26 January 2017 to conduct the final examination of Chiya Othman Hassan on her thesis entitled "Synthesis, Characterization and Biological Activity of New Symmetrical 1,3-Benzoxazine Compounds" 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 Master of Science.

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LIST OF ABBREVIATIONS

δ	Chemical Shift
Ar	Aryl Group
BC	1,1'-bis(4-hydroxyphenyl)cyclohexane
CHNS	Carbon, Hydrogen, Nitrogen, and Sulfur
DMSO	Dimethyl Sulfoxide
FTIR	Fourier Transformation Infrared
GCMS	Gas Chromatography Mass Spectroscopy
hr	Hours
IC_{50}	Cytotoxic dose at 50%
J	NMR Coupling Constant
LC_{50}	Lethal dose
m	meta
M	Molar
MCF-7	Michigan Cancer Foundation-7
M.F	Molecular Formula
MHz	Megahertz
m.p	Melting Point
M.W	Molecular Weight
m/z	Mass to Charge Ratio
NMR	Nuclear Magnetic Resonance
o	Ortho
p	Para
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
UV	Ultraviolet Light

CHAPTER 1

INTRODUCTION

Heterocyclic compounds have always been one of the most popular structures in almost every discipline in chemistry (Dawood *et al.*, 2010; Jin *et al.*, 2011). Most of them have diverse biological or medical activities and are very common in natural and non-natural compounds (Jakopin & Dolenc, 2010; Rahman *et al.*, 2010). The synthesis of them has drawn the attention of many organic chemists for over a century and it is still a challenging subject today both in the total synthesis of natural products and organic synthetic methodologies (Alonso *et al.*, 2004; McReynolds *et al.*, 2004).

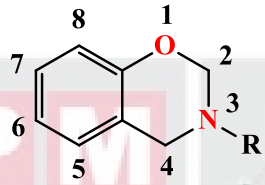
Among the large numbers of heterocyclic compounds, fused heterocycles are a family of the most important ones, which are considered as "privileged structures" and contribute greatly to both the pharmaceutical and agrochemical industries (Clement & Cavell, 2004; Evano *et al.*, 2008). Therefore, great efforts have been made in order to develop efficient approaches for the preparations of various fused heterocyclic compounds (Bender *et al.*, 2009; Murata *et al.*, 2009). Heterocyclic compounds are one that containing a ring made up of more than one kind of atom, most commonly nitrogen, oxygen or sulphur. Heterocyclic intermediates are being used more and more in synthesis as protecting groups, readily generated, and readily removed. In the biological world, heterocyclic compounds are everywhere. Heterocycles formed the sites of reactions in many enzymes and co-enzymes. Among a wide variety of heterocycles that have been explored for developing pharmaceutically important molecules, l,3-benzoxazines constitute an important group due to their wide variety of biological activities such as antibacterial (Manikannan & Muthusubramanian, 2010; Prasad *et al.*, 2012), fungicidal (Tang *et al.*, 2015; Tang *et al.*, 2011; Tang *et al.*, 2012), antitubercular (Kalra *et al.*, 2013; Shakil *et al.*, 2003), anticancer (Bharathkumar *et al.*, 2015; Garg *et al.*, 2013) and anti-inflammatory activities (Akhter *et al.*, 2011b; Kumar *et al.*, 2014).

Many substituted l,3-benzoxazines have shown to possess antimicrobial activity (Didwagh & Piste, 2013b; Kategaonkar *et al.*, 2010; Mathew *et al.*, 2010; Mayekar *et al.*, 2011). Moreover, 1,3-benzoxazine derivatives with 2-pyridine-l-oxide group at C4 act as potassium channel openers (Mizufune *et al.*, 2001; Yamamoto *et al.*, 1996). l,3-benzoxazinediones have been reported to possess antimycobacterial activity especially having a 3-aryl substitution (Kamble *et al.*, 2015). Similarly, a number of dihydro-1,3-pyridobenzoxazines are reported to possess antimalarial activity (March *et al.*, 1973).

Owing to the biological significance of 1,3-benzoxazine compounds and continuation of our ongoing study on antimicrobial activities, we planned to synthesize a series of new symmetrical 1,3-benzoxazine compounds **21-28** and to evaluate their *in vitro* antibacterial and antifungal activities.

1.1 1,3-Benzoxazines

1,3-Benzoxazines are heterocyclic compounds which contain a benzene ring fused to another six-membered ring containing the heteroatom oxygen and nitrogen at positions 1 and 3 respectively as shown in **Figure 1.1**. The numbering is based on general heterocycle naming rule, which starts at the oxygen and proceeds consecutively around the oxazine six-membered ring and around the aromatic ring (Pritchard *et al.*, 2005). 3,4-Dihydro-2*H*-1,3-benzoxazine is a kind of hydrogenated derivatives of benzoxazine (Liu, 1995; Sainsbury, 1984). When the benzene ring replaced by naphthalene, the corresponding oxazine becomes naphthoxazine.



Structure of 3-alkyl-3,4-dihydro-2*H*-1,3-benzoxazine

Figure 1.1: General nomenclature of benzoxazine

1.2 Synthesis Pathways of Benzoxazine

There are many synthesis pathways for benzoxazines. These depend not only on the specific type of benzoxazine desired but also on starting materials available. The first synthesis of benzoxazines was reported in 1944 when it was observed that synthesis can be modelled as the Mannich type reaction (Holly & Cope, 1944). Followed by other benzoxazines reaction schemes were also found to follow the Mannich reaction model (Burke, 1949; Burke *et al.*, 1964a).

Most of the 3-substituted-3,4-dihydro-2*H*-1,3-benzoxazines resulted from the reaction of *p*-substituted phenols with formaldehyde and primary amines in a molar ratio of 1:2:1, respectively (Burke, 1949). The reaction may be considered as a variant of the Mannich reaction. The reaction is best carried out by the first condensation of the primary amine with formaldehyde to form the *N,N*-dihydroxymethylamine derivatives, which is then allowed to react with the phenol. Alternatively, Mannich base was formed when a *p*-substituted phenol, formaldehyde, and a primary amine were allowed to react in a molar ratio of 1:1:1, *p*-aminomethylphenols. These compounds further condensed with formaldehyde in the presence of a base to yield the 3,4-dihydro-2*H*-1,3,-benzoxazine. In a similar way, difunctional benzoxazines were prepared from various combinations of difunctional primary amines and monofunctional phenols (Burke *et al.*, 1964b; Wiberley *et al.*, 1990) or difunctional. When naphthols were used instead of phenols, 3,4-dihydro-2*H*-1,3-naphthoxazines were obtained.

1.3 Problem Statement

Infectious diseases such as HIV, H5N2, H1N1, EVD (Ebola), TB, etc., are the leading cause of illness and death throughout the world. Along with globalization, many new diseases are arising in the world and the search for remedies combat it is perhaps equally old. The sincere attempt by man control and cure diseases has lead to search for new drugs or suitable derivatives of existing drugs. The synthesis of derivatives has been an important part and is aimed at modifying the action of drugs, particularly to reduce the side effects and to potentiate the drug action. Today more than 60% of drugs used in practice are synthesized derivatives and day by day the scope of the synthetic medical chemistry is broadening. Drugs are chemicals that prevent diseases or assist in restoring health to the diseased individuals as such they play an indispensable role in modern medicine.

Recently, It was found that bacteria are mutating and developing new strains that are resistant to known antibiotics continuously (Belz *et al.*, 2013). However, infections due to such bacterial strains are infrequent although potentially fatal (Foucault & Brouqui, 2007; Neu, 1992; Wise *et al.*, 1998). Therefore, the search for new antibacterial compounds is a challenging task. This ongoing problem has resulted in the search for newer, more effective antibacterial compounds (Foucault & Brouqui, 2007; Neu, 1992; Wise *et al.*, 1998). It is well known, those 1,3-benzoxazines have antimicrobial activity, or the ability to inhibit the growth of microorganisms such as bacteria, fungi or protozoans. Therefore, in this current work, we have synthesized a series of new symmetrical 1,3-benzoxazine derivatives to study some biological activities including antibacterial and antifungal activities in comparison with the standard drugs.

1.4 Goals and Objectives

Since the literature review revealed enormous reports on the synthesis, characterization and pharmacological activity of 1,3-benzoxazine derivatives. The chemistry of these linked heterocycles has been a fascinating field of investigation in medicinal chemistry as they have been found to exhibit enhanced biological profile. Encouraged by those interesting reports, the objectives of the research were set as follows:

1. To synthesize new symmetrical 1,3-benzoxazine compounds via Mannich type reaction based on 1,1'-bis(4-hydroxyphenyl)cyclohexane.

2. To characterize the newly synthesized 1,3-benzoxazine compounds by using the spectroscopic methods.

3. To evaluate the in *vitro* bioactivities of the newly synthesized 1,3-benzoxazine compounds including antibacterial and antifungal activity in comparison with the standard drugs.

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