

UNIVERSITI TEKNOLOGI MARA

**SCREENING OF SCHIFF BASE
LIGANDS DERIVED FROM
PHENYLENEDIAMINE AND
ITS METAL COMPLEXES AS A
POTENTIAL EFFLUX PUMP
INHIBITOR AGAINST
*Klebsiella pneumoniae***

NORSHAHIDA BINTI MAT JAYA

MSc

November 2020

AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the results of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

Name of Student : Norshahida binti Mat Jaya

Student I.D. No. : 2018627346

Programme : Master of Science (Applied Microbiology) – AS724

Faculty : Applied Sciences

Thesis Title : Screening of Schiff Base Ligands Derived from
Phenylenediamine and Its Metal Complexes as a
Potential Efflux Pump Inhibitor against *Klebsiella
pneumoniae*

Signature of Student :

Date : November 2020

ABSTRACT

A newly synthesized complexes known as Schiff base has become an interesting strategy in the development an alternative treatment against the diseases of multi-drug resistance (MDR) bacteria that are highly resistant to most available antibiotics. Schiff base was produced from a condensation reactions between primary amines and active carbonyl complexes and considered as “privileged ligands” because of their facile preparation and capability to combine and coordinate to other metal and strengthen the combination in different states of condition. These Schiff base metal complexes have attracted interest of many researchers and have been pointed as promising antibiotics and possess so many antibacterial activities. Despite of its versatility, there is still limited research on the screening potential of chemical synthesized of Schiff base ligand and its metal complexes that were derived from phenylenediamine as efflux pump inhibitor in bacterial resistance mechanism. This study focus on the screening of 40 Schiff base complexes that consist of ligands Salicylaldehyde *Ortho*-phenylenediamine (SalOPD), *Ortho*-Vanillin *Ortho*-phenylenediamine (OVanOPD), *Ortho*-Vanillin *Meta*-phenylenediamine (OVanMPD), *Ortho*-Vanillin 2,4,6-trimethyl-*m*-phenylenediamine [OVan(Me)MPD] and *Ortho*-Vanillin 4-chloro-1,3-diaminobenzene [OVanMPD(Cl)] and their mono-, di- and tetra- metal of copper, nickel, cobalt and zinc for their antibacterial activity and eventually as efflux pump inhibitor against *Klebsiella pneumoniae* by resazurin microtiter based assay. The highest antibacterial activity was demonstrated by Cu₄[OVan(Me)MPD] that showed 64.2% inhibition against *K. pneumoniae*. In the other hand, screening for efflux pump inhibitor found that, Co₄[OVan(Me)MPD] displayed the highest inhibition percentage of 86.5% when Schiff base complexes and *K. pneumoniae* ATCC 700603 were treated with the Sub-MIC chloramphenicol (20 µg/mL). Metal complex of copper exhibits highest antibacterial activity among others metal complexes as this due to steadiness of the metal ion which produces a great and strong bond between N and O ions effects from the overlapping of the ligand orbital and partial sharing of positive charge between metal ions of these ligands has decreased the polarity of the ions thus enhances the lipophilicity and improves the cell permeability of the complexes. This situation agree with theory of Overton’s and Tweedy’s theory, where a chemical synthesized of Schiff base metal complexes exhibited better potential as antibiotics as compared to their parent ligands. As a conclusion, unique tetranuclear complexes possess potential for future development of antibacterial agents as well as efflux pump inhibitors.

ACKNOWLEDGEMENT

Firstly, I wish to thank ALLAH for giving me the opportunity to embark on my MSc and for completing this challenging journey successfully. My gratitude and thanks go to my supervisor Assoc. Prof. Dr. Sharifah Aminah Syed Mohamad for her excellent supervision, continuous encouragement, valuable advice and guidance throughout my research work. I wish ALLAH reward you with goodness Dunya and Akhirah.

I would also like to thanks my co-supervisor, Prof. Dr. Hadariah Bahron and Dr Anis Low Mohamad Low for their willingness to share the knowledge in coordination chemistry and I have learned a great deal of chemistry. The assistance of Dr Anis Low from AuRins in guiding the antibacterial activity and efflux pump inhibitor screening is gratefully acknowledged.

My appreciation goes to the lab assistance and science officer of Faculty of Applied Sciences who provided the facilities and assistance during completing the research work. I also wish to thank Universiti Teknologi MARA for the research facilities. Special thanks to my colleagues and friends for helping me with this project. I am particularly indebted to Siti Solihah Khaidir who synthesized the Schiff base complexes.

Finally, this thesis is dedicated to my dearest mother and father, Aminah Bakar and Mat Jaya Shukri for the vision and determination to educate me and i am grateful to my husband, Muhd Amirul Nizam Mohd Zahari who has provided me through moral and emotional support in my life. This piece of victory is dedicated to all of you. Alhamdulillah.

TABLE OF CONTENTS

	Page
CONFIRMATION BY PANEL OF EXAMINERS	ii
AUTHOR'S DECLARATION	iii
ABSTRACT	iv
ACKNOWLEDGEMENT	v
TABLE OF CONTENTS	vi
LIST OF TABLES	ix
LIST OF FIGURES	x
LIST OF ABBREVIATIONS	xii
CHAPTER ONE: INTRODUCTION	1
1.1 Background of study	1
1.2 Problem Statement	7
1.3 Objectives of the Study	8
1.4 Significance of Study	8
1.5 Scope and Limitation of the Study	8
CHAPTER TWO: LITERATURE REVIEW	9
2.1 Schiff Bases and Its Mono-, Di-, and Polynuclear Metal Complexes: A Review of Schiff Bases and Its Metal Complexes Antibacterial Activity	9
2.2 Multi-Drug Resistance (MDR) Bacterial Strains	12
2.2.1 The Evolutionary	12
2.2.2 Mechanisms of Multidrug Resistance (MDR) and Its Impacts	14
2.3 Biology of <i>Klebsiella pneumoniae</i>	16
2.3.1 Characteristics of <i>K. pneumoniae</i>	16
2.3.2 Pathogenesis of <i>K. pneumoniae</i>	16
2.4 Efflux Pumps and <i>Klebsiella pneumoniae</i>	17
2.4.1 The First Line of Resistance mechanisms	17
2.4.2 <i>Klebsiella pneumoniae</i> Efflux Pumps and It's EPIs	20