UNIVERSITI TEKNOLOGI MARA

STUDIES TOWARDS THE SYNTHESIS OF 4-HYDROXYBENZYL 3-ACYLTETRAMIC ACID

NORHANIM BINTI MOHALID

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CONFIRMATION BY PANEL OF EXAMINERS

I certify that a Panel of Examiners has met on 21st May 2015 to conduct the final examination of Norhanim binti Mohalid on her Master of Science thesis entitled "Studies towards the Synthesis of 4-Hydroxybenzyl 3-Acyltetramic Acid" in accordance with Universiti Teknologi MARA Act 1976 (Akta 173). The Panel of Examiners recommends that the students be awarded the relevant degree. The Panel of Examiners was as follows:

Nor Hadiani Ismail, PhD
Professor
Faculty of Applied Sciences
Universiti Tekologi MARA
(Chairman)

Norizan Ahmat, PhD
Associate Professor
Faculty of Applied Sciences
Universiti Tekologi MARA
(Internal Examiner)

Zainab Ngaini, PhD
Associate Professor
Faculty of Resource Science and Technology
Universiti Malaysia Sarawak
(External Examiner)

DR MOHAMMAD NAWAWI
DATO' HAJI SEROJI
Dean
Institute of Graduate Studies
Universiti Teknologi MARA
Date : 7 June 2016

ABSTRACT

The tetramic acid (pyrrolidine-2,4-dione) ring system is present as a key structural unit in many natural products. In this project, a derivative of fuligorubin, namely 4-hydroxybenzylated 3-acyl tetramic acid from slime mold *Leocarpus fragilis* was chosen as the synthetic target not only due to its biological properties, but mainly due to the challenging structure of the hydroxybenzylated tetramic acid moiety. We were also synthesized fused ring (bicyclic) compounds and tetramic acid as the key structural unit. Our synthetic approach towards 4-hydroxybenzylated 3-acyltetramic acid started with the formation of key important tetramic acid ring system using two possible routes. The first route began with the benzylation of hydroxyl group of commercially available *L*-tyrosine, followed by *N*-Boc protection and a one-pot condensation and Dieckmann cyclisation. In this route, we managed to synthesize the required tetramic acid **3**, in three steps with an overall yield of 37%. The second route began with the esterification of *L*-tyrosine, followed by condensation, Dieckmann cyclisation and demethoxycarbonylation to furnish the required tetramic ring 7, in four steps with 36% overall yield. The synthesized tetramic acid **3** was then subjected to acylation reaction using different acyl chlorides and reaction conditions to give the acylated tetramic acids **117** and **118** in 8-14% overall yields. Apart from these acylated products highlighted, several pyrrolidinone type compounds have been successfully synthesized towards the formation of fused ring (bicyclic) compounds. Our accomplishment in performing these reactions confirmed the feasibility of our synthetic strategy towards exploring new drugs based on pyrrolidinone moiety. This study may as well be used to develop new scientific knowledge and remarkable findings.

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CHAPTER ONE
INTRODUCTION

1.1 NITROGEN HETEROCYCLIC COMPOUNDS

Known organic compounds commonly have an enormous diversity of structures, where most of which contain ring systems. These compounds can be classified as heterocyclic when the ring contains carbons and at least one other element, such as nitrogen, oxygen, and sulphur. Heterocyclic compounds have various applications. They are the types of compounds used in pharmaceuticals, agrochemicals, veterinary products, antioxidants, corrosion inhibitors and additives with a variety of other functions. Heterocyclic compounds are also widely distributed in nature, as a key component in biological processes. Nucleic acid bases, chlorophyll for photosynthesis and oxygen transport, essential diet ingredients such as vitamin B and C, contain heterocyclic ring moiety [1].

Organic compounds bearing a heterocyclic ring brought a great interest in organic synthesis. They are commonly used as intermediates because of the stability of the ring system prepared from a number of synthetic steps and cleaved at required stages in the synthesis. A lot of researches in the area of heterocyclic chemistry are concerned with discovering new synthetic pathways of the ring systems [1]. Many molecules with ring systems display interesting biological activities, which include antimicrobial and antihypertensive properties. Thus, the study of heterocyclic chemistry provides much impulse for the growth of organic synthesis field, and it remains today a fascinating area of research especially compounds possessing a five-membered ring such as the pyrrolidinone ring structure.

1.2 NATURALLY OCCURRING TETRAMIC ACID

Tetramic acid (Figure 1.1), or pyrrolidine-2,4-dione, is an important class of naturally occurring heterocyclic molecules. It has been known since the early twentieth century. However, its importance was realized in 1960s when it was discovered as a key structural unit in many natural products such as antiprotozoal malonomycin, terminal DNA transferase inhibitor streptolydigin and antibiotic