UNIVERSITI TEKNOLOGI MARA

CHEMICAL STUDIES TOWARDS THE TOTAL SYNTHESIS OF PACHYDERMIN AND BIOACTIVE METABOLITES DERIVED FROM *Chamonixia pachydermis*

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Thesis submitted in fullfillment
of the requirements for the degree of
Doctor of Philosophy
(Science)

Faculty of Applied Sciences

January 2019

ABSTRACT

Pachydermin **1**, an oxylated tetramic acid with 3-chloro-4-hydroxyphenyl substituent, was isolated from the New Zealand basidiomycete *Chamonixia pachydermis* and was chosen as an attractive target for synthesis. Its degradation product was found to exhibit mild antibacterial activity against *Bacillus subtilis*, thus its derivatives are anticipated to have similar biological potentials. In this study, the main synthetic strategy was divided into three parts. The first part was to develop the synthesis of pachydermin utilizing *N*-benzylated β,β-diketoester **11** as the key structural moiety. The β,β-diketoester **11** was initially synthesized *via* nucleophilic substitution of ethyl iodoacetate with benzylamine to yield a benzylated glycine ethyl ester which accordingly, underwent condensation with methyl malonyl chloride followed by Dieckmann cyclisation to give the desired β,β-diketoester **11** with an overall yield of 71%. In the second part, insertion of an oxalyl subunit using ethyl chlorooxoacetate as well as other acyl or alkyl subunits at the C-3 position of the pyrrolidinedione ring *via* acylation or alkylation reactions furnished the required intermediates of pachydermin and its derivatives. Alkene functionalities at the C-5 position were subsequently introduced using different alkyl or aryl aldehydes with different non-nucleophilic bases which include diisopropylamine and lithium bis(trimethylsilyl)amide (LHMDS) in anhydrous tetrahydrofuran. Selective demethoxycarbonylation using lithium iodide in DMF was also performed on a precursor of pachydermin, **139**, to successfully give a mixture of decarboxylated product **143** which is an essential intermediate of pachydermin and **144**, in 30% yield. Unlike **143**, product **144** has an additional methyl substituent at the C-3 position of the ring moiety. Nevertheless, synthesis of **143** was achieved in six steps with an overall yield of 2%. An effort to synthesize pachydermin derivatives *via* an alternative route was attempted using a series of 3-acyltetramic acids, which were generated from *O*-acylations of *N*-protected pyrrolidine-2,4-dione with different acyl halides. Employing different bases on the acylation reactions which include trimethylamine (Et_3N), sodium hydride (NaH), potassium *tert*-butoxide (*t*-BuOK), tetrabutylammonium fluoride (TBAF), dicyclohexylcarbodiimde (DCC) and some ionic liquids ($BmimBF_4$ and $BmimBF_6$), gave all *O*-acylated products which are the enol esters of the tetramic acids. The subsequent step which is the key and optimum step to furnish the required *C*-acylated compounds towards pachydermin was the acyl migration of the respective enol esters using potassium cyanide and DMAP. Formation of another significant intermediate of pachydermin, *C*-acylated *N*-benzylpyrrolidine-2,4-dione **126** *via* this acyl migration protocol was successfully achieved in seven steps in an overall yield of 3%. The third part of this study was to perform biological investigation of synthesized intermediates and derivatives of pachydermin using disk diffusion method (Gram-positive and Gram-negative) and anti-quorum sensing method. The biological activities have shown that compounds **109** and **112** exhibit mild inhibition zone on antibacterial against *S.haemolyticus*. In conclusion, two advanced intermediates of pachydermin as well as more than 41 new derivatives were successfully synthesized *via* different synthetic approaches. Structural conformations of all synthesized compounds were analysed by mass spectroscopy (MS) and nuclear magnetic resonance spectroscopy (NMR) techniques.

ACKNOWLEDGEMENT

First of all, I would like to express my special thanks to my supervisor Assoc. Prof. Dr. Zurina Shaameri and co-supervisor Assoc. Prof. Dr. Noorhana Hussain. I am greatly indebted to them for their continuous support throughout my study, as well as for their patience, motivation and immense knowledge. Their guidance in conducting research and writing this thesis, and also their advice on both research and career have been very invaluable.

I would also like to extend my deepest respect and appreciation to Prof. Dr. Ahmad Sazali Hamzah who provided me the opportunity to join the Organic Synthesis Research team and to use the research facilities. Without his support it would not be easy to conduct this research. I thank him for all insightful comments and encouragement, but most of all for the difficult questions which incented me to widen my research in different perspectives.

I would like to thank all the staff of Institute of Science especially Dr. Mohd. Fazli Mohammat, Dr. Agustono Wibowo, Pn. Zaleha Afandi and Pn. Irmaizatussyehdany Buniyamin as well as the staff of Microbiology Laboratory for providing facilities and assistance.

Special thanks to my colleagues and friends for helping me with this project especially Syafiqah, Ain, Aishah, Fatin, Za, Faezuan, Siddiq, Puteri and Azra for their assistance whenever and wherever it was needed.

Finally, this thesis is dedicated to my dear husband Mohamad Hafiz Sudin, daughters, and not to forget to all my family members for their constant prayers, patience and support. I could not thank them enough for encouraging me throughout this experience.

I would like to acknowledge the Ministry of Higher Education as well as Universiti Teknologi MARA for the financial support and opportunity for me to pursue my PhD dream. Most of all, I am very grateful to Allah for giving me strength and patience to overcome all difficulties and challenges.

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