UNIVERSITI TEKNOLOGI MARA

SYNTHESIS AND BIOLOGICAL EVALUATION OF PYRROLIDINE-BASED IMINOSUGARS AS POTENTIAL ALPHA GLUCOSIDASE INHIBITORS

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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.

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ABSTRACT

In this study, pyrrolidine-based iminosugars is the target molecule due to its unique structure and its ability to be biological activity against diabetes. This thesis has been divided into five main sections. Chapter one is the introduction of this study that explains diabetes mellitus as the factor to the synthesis of iminosugars. Chapter two consists of reviews of iminosugars type, alpha glucosidase inhibitors, and synthetic approach of pyrrolidine-based iminosugars by different research groups. Chapter three consists of method of synthesis and biological evaluation of pyrrolidine-based iminosugars. Results and discussions are all provided in chapter four, and finally conclusion and recommendations for future works are given in chapter five. The target molecule **233-242** was synthesized with minimum three steps and maximum four steps. These steps are facile and multifaceted approach to the synthesis of pyrrolidine-based iminosugars comprising of MCR (multicomponent reaction), amination, and stereoselective reduction reactions. The key step of this strategy involved the construction of a highly functionalised pyrrolidine ring core **194-206** through MCR approach. This approach involved dissolving primary amines, aldehyde, and diethyl sodium salt in ethanol. The pyrrolidine core was successfully synthesized and existed in a more stable enolic form. In the next step, the MCR product that was treated with aromatic amines in neutral ethanolic medium and acidic ethanolic medium had given poor enamine **207** product yield. The problem was overcame with having protected *N*-pyrrolidine and substituent at the C-5 *via* MCR followed by the amination steps. The process was proceeded with stereoselective reduction of carbon carbon double bond of enolic ester **194-196** & **201** and enamino ester **207-209**. The enolic ester that was reduced via hydrogenation whereby the enolic ester (MCR product) reacted with palladium carbon in neutral and acidic ethanol afforded *cis* product. The enaminoester that was also reduced via hydrogenation whereby the enaminoester (amination product) reacted with palladium carbon in neutral and acidic ethanol afforded *cis* product. The enolic ester **197-201** that was reduced using sodium borohydride and acetic acid in dichloromethane produced *trans* saturated product **228-232**. Finally, in the last step, carbonyl ester and carbonyl amide from previous steps that were reduced with $LiAlH_4$ in dry THF gave pyrrolidine-based iminosugars **233-242**. In this project, ten iminosugar derivatives were synthesized and these synthesized antiglucosidase enzyme were tested against alpha glucosidase enzyme in which one compound, ((3*S*,4*S*)-4-((4-methoxyphenyl) amino)pyrrolidin-3-yl)methanol **237**, was found to be the most potent at low dosage (1.0 mM) compared to the standard reference (deoxynojirimycin). This study demonstrated that the newly synthesized azasugars have promising effects over alpha glucosidase enzyme. Hence, further structural variations of these *N*-pyrrolidine core position could improve the inhibition values.

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