UNIVERSITI TEKNOLOGI MARA

AN APPROACH TOWARDS THE SYNTHESIS OF CODINAEOPSIN DERIVATIVES AS UNIQUES TRYPTOPHAN-POLYKETIDE ANTI-MALARIAL COMPOUNDS

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ABSTRACT

In this study, codinaeopsin was chosen as our synthetic target compound due to its unique tryptophan-tetramic acid, pyrrolidinone structure. Codinaeopsin was isolated from biological source which is white yemeri trees and obtaining the continuous supply of codinaeopsin is problematic due to the scarcity of product origin. Over the decade, there is only one successful total synthesis of codinaeopsin was reported involving a lengthy step. Thus, a new synthetic route had been developed to overcome the problem. A series of successive functional group modifications was performed which began with esterification of *L*-tryptophan by using methanol and thionyl chloride (100%), followed by condensation of the methyl ester utilizing the methyl malonyl chloride to furnish an intermediate diester. This diester is then reacted with sodium methoxide to furnish β,β-diketo pyrrolidinone, a crucial diketo pyrrolidinone ring template via Dieckmann cyclization reaction. Lastly, the tetramic acid type compound is achieved by decarboxylation of the β,β-diketo pyrrolidinone employing acetonitrile. All compounds were synthesized in moderate to good yield in 4 steps with an overall yield of 34.05%. Nevertheless, different pyrrolidinone-type compounds from different hydrazine salts were synthesized via hydrazination and all the compounds were produced in low to good yields. In brief, this research was designed to provide intriguing new pathways to prepare tetramic acid carbon skeleton of codinaeopsin and minimize the cost and shorten the route for synthesizing tetramic acid.

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CHAPTER 1
INTRODUCTION

1.1 Research Background

In the past century, different classes of natural products have been isolated, and their structures were successfully characterized from living organisms such as animals, plants, and microorganisms. Natural products have a diverse range of multidimensional chemical structures; additionally, the utility of natural products as biological function modifiers has received considerable attention (Amit Koparde et al., 2019). Organic and medicinal chemists have centered their work around these discoveries and their biological and biochemical mechanisms for the therapeutic action.

These natural resources have been used as a major source for drug discovery. An important example is the analgesic activity of aspirin, which is by far the most well-known and widely used medicinal agent on the planet (Amit Koparde et al., 2019). It is related to salicin and derives from the plant genera *Salix* spp. and *Populus* spp. Many other examples demonstrate the value and significance of natural products derived from plants and microorganisms in modern times. Paclitaxel (Taxol) which was discovered in the bark of the Pacific yew tree *Taxus brevifolia* (Taxaceae), is the most recent example of a significant natural product that has made an impact in medicine (Littleton, 2017).

However, the scope for making chemical modifications to optimize their therapeutic use is limited due to the fact that most of the natural products have complex structures. Furthermore, the problem also arises in obtaining a renewable supply of active from biological sources. Hence, to control the scarcity of the sources of the natural products, the preliminary step to be undertaken is to study the synthesis of natural products. Natural products are mostly used as binding proteins and have become a source for the synthesis of compound collections (Kumar & Waldmann, 2009). Natural products can be divided into two major classes which are primary metabolites and secondary metabolites. A primary metabolite is one that directly contributes to healthy growth, development, and reproduction. Examples include cell components like lipids, vitamins, and polysaccharides, as well as fermentation products like ethanol, acetic acid, citric acid, and lactic acid. In contrast, secondary metabolites are not