TOTAL SYNTHESIS AND BIOLOGICAL STUDIES OF A NEW ANTI-PROTEASOME DRUG, LACTACYSTIN AND ITS DERIVATIVES

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LAPORAN AKHIR PENYELIDIKAN "TOTAL SYNTHESIS AND BIOLOGICAL STUDIES OF A NEW ANTI-PROTEASOME DRUG, LACTACYSTIN AND ITS DERIVATIVES"

Merujuk kepada perkara di atas, bersama-sama ini disertakan 4 (empat) naskah Laporan Akhir Penyelidikan bertajuk "Total Synthesis and Biological Studies of a New Anti-Proteasome Drug, Lactacystin and its Derivatives".

Sekian, terima kasih.

Yang benar,

AHMAD SAZALI HAMZAH
Ketua
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ABSTRACT

Lactacystin is the first non-protein metabolite isolated from *Streptomyces* specie by Omura in 1991. It mimics the nerve growth factor because it inhibits cell growth and induces neurite outgrowth. Since nerve growth factor is essential for the survival and function of nerve cells or neurons, lactacystin can be a suitable alternative in the therapy of neurodegenerative diseases like Alzheimer's and Parkinson's.

Lactacystin possesses a common structural moiety, 3-hydroxy-4-methyl proline, which is also found in many biologically active natural products. This proline ring system, which derived from the basic pyrrolidine ring skeleton, can act as a versatile intermediate for synthesizing more complex medicinally important compounds such as piracetam, clausenamide, detoxine, tirandamycin and echinocandin. This work reports on the synthesis of a pyrrolidine-ring template, β,β-diketoester, and the use of it as a building block to synthesize lactacystin and some other biologically active compounds.

By means of various synthetic methods, over 40 compounds with the pyrrolidine ring system have been generated in fairly good yields. Some were found to exhibit neuroprotective ability *via* the hydrogen peroxide oxidative stress-induced model. Identification of important partial structures such as above can lead to the discovery of a new drug with potential medicinal values.

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1.0 INTRODUCTION

1.1 Lactacystin

Lactacystin, **1**, is a novel microbial natural product isolated by Omura *et al.* from *Streptomyces* species after screening several thousand microbial cultures.[1] Lactacystin inhibits cell growth or proliferation and also induces neurite outgrowth and differentiation in a mouse neuroblastoma cell line, Neuro 2A. In other words, lactacystin is considered to be an important mimic of the nerve growth factor.

Nerve growth factors (NGF) are valuable compounds that are responsible and essential for the survival and function of nerve cells or neurons.[2] Deficiency of these compounds is thought to cause various nerve related diseases which include Alzheimer's and Parkinson's. The findings of these investigations suggested that NGF-like compounds might be therapeutically useful for the treatment of these diseases.[3] Nerve growth factors are also important as therapeutic agents and as neuroscience research tools which are in great demand in many biological laboratories today.

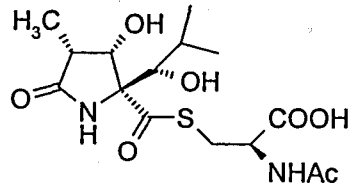

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Figure 1.1: Molecular structure of lactacystin