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Structure-Activity Relationship of 3-*o*-Acylated Betulinic Acid Derivatives Obtained by Enzymatic Synthesis as Anticancer Agents

Faujan Bin H. Ahmad[1], Mansour Ghaffari Moghaddam[2] and Nur Hana Faujan[3]

[1]Natural Product Laboratory, Faculty of Applied Science, Universiti Teknologi Mara, 40450 Shah Alam, Malaysia; [2]Department of Chemistry, Faculty of Science, University of Zabol, Zabol, Iran; [3]Department of Chemistry, University Putra Malaysia, 43400 UPM, Serdang, Selangor

Betulinic acid (1) is a naturally occurring pentacyclic lupane-type triterpenoid that possess multiple pharmacological activities including inhibition of human immunodeficiency virus (HIV), anti-bacterial, anti-malarial, anti-inflammatory, anthelmintic, antioxidant and anticancer properties [1]. The medical uses of betulinic acid in the pharmaceutical industry is strongly limited since it is insoluble in water, which causes a difficulty in preparation of injectable formulations for biological assays and decreases its bioavailability in the organism. The introduction of polar groups at the C-3 position such as phthalates in some cases, increases, its hydrosolubility and anticancer activity [2, 3]. In this study several 3-*O*-acyl-betulinic acid derivatives was prepared (Scheme 1) using various anhydrides and Novozym 435 as a biocatalyst. The cytotoxicity of betulinic acid derivatives was then evaluated on human lung carcinoma (A549) and human ovarian (CAOV3) cancer cell lines. On the basis of our *in vitro* cytotoxic results and the structure-activity relationship (SAR), we concluded that compounds (4), (6) and (8) were the most active compounds as compared to betulinic acid (1) against human lung carcinoma (A549). In an ovarian cancer cell line, all betulinic acid derivatives prepared showed weaker cytotoxicity than betulinic acid.

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