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Synthesis of 3-*O*-propargylated betulinic acid and its 1,2,3-triazoles as potential apoptotic agents

Rabiya Majeed [a,b], Payare L. Sangwan [a,*], Praveen K. Chinthakindi [a], Imran Khan [a], Nisar A. Dangroo [a], Niranjan Thota [a], Abid Hamid [b,*], Parduman R. Sharma [b], Ajit K. Saxena [b], Surrinder Koul [a,*]

[a] Bioorganic Chemistry Division, CSIR-Indian Institute of Integrative Medicine, Canal Road Jammu, Jammu and Kashmir 180001, India
[b] Cancer Pharmacology Division, CSIR-Indian Institute of Integrative Medicine, Canal Road Jammu, Jammu and Kashmir 180001, India

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ABSTRACT

Cytotoxic agents from nature are presently the mainstay of anticancer chemotherapy, and the need to reinforce the arsenal of anticancer agents is highly desired. Chemical transformation studies carried out on betulinic acid, through concise 1,2,3-triazole synthesis via click chemistry approach at C-3position in ring A have been evaluated for their cytotoxic potentiation against nine human cancer cell lines. Most of the derivatives have shown higher cytotoxic profiles than the parent molecule. Two compounds i.e. 3{1*N*(2-cyanophenyl)-1*H*-1,2,3-triazol-4yl}methyloxy betulinic acid (**7**) and 3{1*N*(5-hydroxy-naphth-1yl)-1*H*-1,2,3-triazol-4yl}methyloxy betulinic acid (**13**) displayed impressive IC_{50} values (2.5 and 3.5 μM respectively) against leukemia cell line HL-60 (5–7-fold higher potency than betulinic acid). As evident from various biological end points, inhibition of cell migration and colony formation, mitochondrial membrane disruption followed by DNA fragmentation and apoptosis, is demonstrated.

1. Introduction

Natural products (NPs) and the molecules based on NP scaffolds being the proven source of therapeutic agents have increasingly attracted the interests of researchers involved in the area of cancer therapy. In fact, the majority of anticancer and anti-infectious agents are of natural origin [1]. Pentacyclic triterpenoid class of compounds is found pharmacologically active scaffold, and provides privileged motifs for further modifications and structure activity relationship (SAR) analyses [2,3]. To date several reports are available wherein simple or advanced modifications have been performed for the desired biological properties [4–7]. Betulinic acid, a naturally occurring lupane triterpenoid is reported to exhibit anti-cancer, antibacterial and anti-HIV activities [7,8]. The induction of cytotoxicity involves modulation of Bcl-2 family, cell cycle regulatory proteins, regulation of the nuclear factor kappa B (NFκB), as well as inhibition of aminopeptidase N, and growth factor-induced angiogenesis [9,10]. The NP has been extensively studied in xenograft mouse models for its cytotoxic effect against primary cancer cells isolated tumor specimens obtained from glioblastoma and leukemia [10] and the molecule is currently undergoing clinical study at national cancer institute (NCI) [11].

In continuation of our interest involving structural modification of natural products [12,13] for better efficacy, lesser toxicity, betulinic acid was chosen for chemical modification targeting position-3 of ring A, one of the hot spots of the molecule (Fig. 1) in a bid to arrive at a more potent analog having some possible clinical utility and application. Triazole compounds in biological system show binding ability with a variety of enzymes and receptors via diverse non-covalent interactions and display versatile biological activities and many of them have been identified as clinical drugs or candidates for the treatment of various types of diseases [14–16]. These have shown their large development value and wide potential as therapeutic agents such as anti-infective, anticancer, antiviral, and anti-hypertensive agents. In the present paper, the preparation of C_3-aryl substituted 1,2,3-triazoles of betulinic acid and their cytotoxic profiles is described.

2. Result and discussion

Betulinic acid (**1**) is reported as cytotoxic against several human cancer cell lines with $IC_{50} > 40$ baring one or two cell lines where

* Corresponding authors. Tel.: +91 191 2569021; +91 191 2569001 to 11x232/371; fax: +91 191 2569333.
E-mail addresses: plsangwan@iiim.ac.in (P.L. Sangwan), ahdar@iiim.ac.in (A. Hamid), skoul@iiim.ac.in (S. Koul).

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