Bioorganic & Medicinal Chemistry 19 (2011) 1816–1822

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Antitumor agents 283. Further elaboration of Desmosdumotin C analogs as potent antitumor agents: Activation of spindle assembly checkpoint as possible mode of action

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ARTICLE INFO

Article history:
Received 15 November 2010
Revised 23 December 2010
Accepted 1 January 2011
Available online 15 January 2011

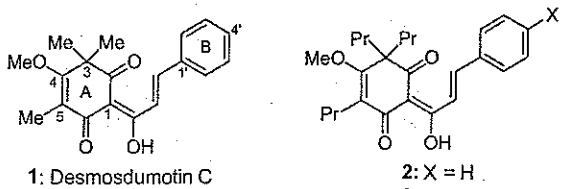
Keywords:
Desmosdumotin C
Antiproliferative activity
Human tumor cell lines
Microarray

ABSTRACT

In our ongoing study of the desmosdumotin C (**1**) series, twelve new analogues, **21**–**32**, mainly with structural modifications in ring-A, were prepared and evaluated for in vitro antiproliferative activity against several human tumor cell lines. Among them, the 4′-iodo-3,3,5-tripropyl-4-methoxy analogue (**31**) showed significant antiproliferative activity against multiple human tumor cell lines with ED_{50} values of 1.1–2.8 μM. Elongation of the C-3 and C-5 carbon chains reduced activity relative to propyl substituted analogues; however, activity was still better than that of natural compound **1**. Among analogues with various ether groups on C-4, compounds with methyl (**2**) and propyl (**26**) ethers inhibited cell growth of multiple tumor cells lines, while **28** with an isobutyl ether showed selective antiproliferative activity against lung cancer A549 cells (ED_{50} 1.7 μM). The gene expression profiles showed that **3** may modulate the spindle assembly checkpoint (SAC) and chromosome separation, and thus, arrest cells at the G2/M-phase.

1. Introduction

Desmosdumotin C (**1**), isolated from the roots of *Desmos dumosus*,[1] has a distinctive chalcone skeleton with an unusual non-aromatic A-ring possessing a *gem*-dimethyl group on C-3 and methyl group on C-5 (Fig. 1). This compound showed significant and selective antiproliferative activity against 1A9 (ovarian cancer) and A549 (human lung carcinoma) cell lines with ED_{50} values of 3.5 μg/mL (11.2 μM).[1] In addition, it was more active against KB-VIN [vincristine-resistant KB, overexpressing P-glycoprotein (P-gp)] cells than against the parent KB (epidermoid nasopharyngeal carcinoma) cell line. We previously established the first total synthesis of **1**.[2] Based on our synthetic methodology, the A-ring was modified with triethyl and tripropyl groups at C-3 and -5 positions and various substituted aromatic B-rings were also incorporated.[3] From the preliminary data, analogues with tripropyl substitution at the C-3 and C-5 positions (i.e., **2**) showed better activity than analogues with triethyl and trimethyl groups. Furthermore, addition of a bromophenyl B-ring (bromide at C-4′) enhanced cell growth inhibition against all tested tumor cell lines.



1: Desmosdumotin C

2: X = H
3: X = Br

Figure 1. Desmosdumotin C and its analogs.

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doi:10.1016/j.bmc.2011.01.001