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Dual Inhibitors of the Pro-Survival Proteins Bcl-2 and Mcl-1 Derived from Natural Compound Meiogynin A

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Abstract

Thirty analogues of natural meiogynin A, a pan-Bcl-2 inhibitor, were prepared in order to elaborate cytotoxic compounds on specific cancer cells overexpressing one or more proteins of the Bcl-2 family. The interaction of all the new analogues with Bcl-xL, Mcl-1 and Bcl-2 proteins was first evaluated by fluorescence polarization assay (FPA) and showed that modulation of the lateral chain has a dramatic impact as subtle changes significantly modify the activity on the target proteins. The acetoxymethyl prodrugs of the two most active compounds were then elaborated to determine their cytotoxicity on B cell lines. A strong cytotoxic effect on BL2, RS4;11 and H929 cells was observed with a triazole prodrug that induces apoptosis.

Keywords

Natural Compound – Apoptosis – Bcl-2 proteins – Protein-protein interactions – Cancer

1. Introduction

Apoptosis is a physiological form of programmed cell death that is essential for tissue homeostasis through the elimination of useless or potentially harmful cells [1]. Evasion of apoptosis is a hallmark of cancer. It is often correlated with the deregulation of the Bcl-2 family of proteins that control the intrinsic pathway of apoptosis [2]. All the proteins of this family share one or more of the four Bcl-2 homology (BH) domains, namely BH1, BH2, BH3 and BH4. This complex family comprises multi-domain-anti-apoptotic members such as Bcl-2, Bcl-xL or Mcl-1 and pro-apoptotic ones which are either multi-domain effector proteins (Bax and Bak) or BH3-only proteins such as Bim, Bid, Bad, and Noxa. The intrinsic pathway of apoptosis is initiated by cellular stress signals such as DNA damage that lead to the transcriptional upregulation and/or activation of pro-apoptotic BH3-only proteins. These proteins are able to bind to anti-apoptotic members of the family and inhibit their activity. In addition, direct activator BH3-only proteins (e.g., BID and BIM) also bind to and activate the multi-domain proteins BAK and BAX. Once activated, BAK and BAX oligomerize and form pores in the outer mitochondrial membrane, inducing its permeabilization (MOMP) and the release of two apoptogenic factors (CYT C and SMAC/DIABLO) which triggers caspase activation leading *in fine* to cell death [3].

Despite tremendous progress, many important questions concerning the mechanism of action of the Bcl-2 family proteins remain unanswered. Nevertheless, numerous studies have shown that anti-apoptotic Bcl-2, Bcl-xL or Mcl-1 proteins are overexpressed in many types of cancers [4,5]. Alongside being part of the oncogenesis process, their overexpression confers resistance to apoptosis that is induced by standard anticancer therapies. The anti-apoptotic proteins sequester and neutralize the BH3 death domain of the pro-apoptotic proteins within a binding groove formed by their BH1, BH2 and BH3 regions through protein-protein interactions, thus preventing