Structural Diversity and Selective Anticancer Activity of Marine-Derived Elastase Inhibitors: Key Features and Mechanisms Mediating the Antimetastatic Effects in Invasive Breast Cancer

Al-Awadhi, F.H. (Department of Medicinal Chemistry, Center for Natural Products, Drug Discovery and Development, University of Florida, Gainesville, USA), Paul, V.J. (Smithsonian Marine Station),Luesch, H. (Department of Medicinal Chemistry, University of Florida)

Introduction

The implication of dysregulated protease activity in cancer progression highlights the importance of proteases as therapeutic targets. Human neutrophil elastase (HNE) has been shown to play a role in tumor progression leading to metastasis and is associated with poor prognosis. 3-amino-6-hydroxy-2-piperidone-containing cyclodepsipeptides are among the most predominant HNE inhibitors isolated from marine cyanobacteria; However, there are no rigorous studies describing their cellular effects in cancer. Herein, we describe the discovery of new members of this family and report their effects on the migration of breast cancer cells.

Experimental

Floridian marine cyanobacterium was freeze dried, extracted and fractionated. Pure compounds were purified by HPLC. Structures were elucidated using NMR spectroscopy and mass spectrometry. The absolute configuration was established by enantioselective HPLC-MS. Molecular docking was performed using Autodock Vina. Biological evaluation involves protease inhibition assays, AlphaLisa, RT-qPCR, and migration assays.

Results and Discussion

Three new compounds named loggerpeptins A–C (**1**−**3**) along with molassamide (**4**) were discovered (Fig.1). The antiproteolytic activity of **1**−**4** was evaluated against the serine proteases elastase and chymotrypsin. Molassamide (**4**) was the most potent and selective analogue against HNE. Molassamide (**4**) inhibited the cleavage of the elastase substrate CD40 in biochemical assays and exhibited significant cellular activity. As CD40 processing culminates in NF_KB activation, we assessed the effects on the expression of target genes, including ICAM-1. Molassamide (**4**) attenuated both elastase-induced ICAM-1 gene expression and cleavage, revealing a potential dual effect on migration. Molassamide (**4**) also inhibited the elastase-mediated migration of highly invasive breast cancer cells.

Conclusions

The discovery of loggerpeptins A−C (**1**−**3**) and molassamide (**4**) add to the growing family of cyanobacterial elastase inhibitors. This class of compounds might be developed into probes to further investigate the biology of elastase mediated processes and serve as a starting point for the design and development of more potent and selective leads with therapeutic potential.

Acknowledgements

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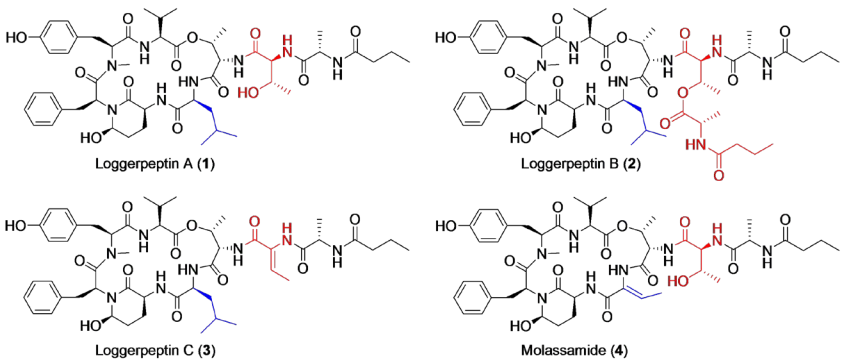

Fig.1 Structures of loggerpeptins A−C (**1**–**3**) and molassamide (**4**)