Bioorganic & Medicinal Chemistry Letters 21 (2011) 1926–1928

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis and proteasome inhibition of lithocholic acid derivatives

Zhao Dang[a], Andrew Lin[a], Phong Ho[a], Dominique Soroka[a], Kuo-Hsiung Lee[b,c], Li Huang[a,*], Chin-Ho Chen[a,*]

[a] Surgical Science, Department of Surgery, Duke University Medical Center, Durham, NC 27710, USA
[b] Natural Products Research Laboratories, Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599, USA
[c] Chinese Medicine Research and Development Center, China Medical University and Hospital, Taichung 401, Taiwan

ARTICLE INFO

Article history:
Received 14 January 2011
Revised 8 February 2011
Accepted 14 February 2011
Available online 17 February 2011

Keywords:
Lithocholic acid
Proteasome
Proteasome inhibitor

ABSTRACT

A new class of proteasome inhibitors was synthesized using lithocholic acid as a scaffold. Modification at the C-3 position of lithocholic acid with a series of acid acyl groups yielded compounds with a range of potency on proteasome inhibition. Among them, the phenylene diacetic acid hemiester derivative (**13**) displayed the most potent proteasome inhibition with IC_{50} = 1.9 μM. Enzyme kinetic analysis indicates that these lithocholic acid derivatives are noncompetitive inhibitors of the proteasome.

The proteasome is an important protein complex that plays a critical role in maintaining cellular homeostasis.[1–3] The main function of the proteasome is intracellular degradation of damaged, unwanted, and misfolded proteins. The 20S proteasome has a cylindrical structure containing four rings stacked on top of each other. The two outer rings each contain seven structural α-subunits that do not have enzymatic activity. The two inner rings, each with seven β-subunits, contain three major proteolytic activities: a chymotrypsin-like (β5), a trypsin-like (β2), and a caspase-like (β1) activity. These proteolytic activities allow the proteasome to cleave unwanted proteins into 8–12 amino acid peptides. The chymotrypsin-like activity is believed to be the most important activity in protein degradation and is thus the primary target of most proteasome inhibitors.[2,3]

By regulating cellular protein levels, the proteasome is critical for maintaining many important cellular functions, such as the cell cycle, apoptosis, and immune response. Targeting proteasomal proteolysis may lead to new treatments for a variety of clinical conditions, such as cancers, inflammation, and neurodegenerative diseases. One successful example is the proteasome inhibitor peptide boronate, PS341 (Bortezomib), which was developed into an anti-cancer drug for the treatment of multiple myeloma.[4]

In addition to bortezomib, a number of other proteasome inhibitors have been developed either as experimental tools or as potential drug candidates for clinical usage, especially for anti-cancer therapy. Originating from both chemical synthesis and natural sources, the majority of these proteasome inhibitors have peptide-related structures, interacting with the proteasome at the catalytic site to competitively inhibit the proteolysis of substrate. Examples of these compounds include MG132, CEP1612, PS341, lactacystin, TMC-89A, and argyrin A.[5] On the other hand, non-peptide proteasome inhibitors are less common than the peptide-related proteasome inhibitors. Two triterpene derivatives, celastrol and withaferin A, and some green tea polyphenols, have been reported with proteasome-inhibitory effects.[6–9] We recently reported that a series of triterpene 18β-glycyrrhetinic acid derivatives had potent inhibitory activity on the 20S proteasome.[10] Although the competitive proteasome inhibitors targeting the catalytic sites are well documented, noncompetitive inhibitors are less common and have generally not been well characterized[11] though some quinolines were reported to be noncompetitive inhibitors.[12,13] In this paper, we report a class of novel proteasome inhibitors that inhibit the proteasome in a noncompetitive manner.

Our previous study indicated that glycyrrhetinic acid can be used as a scaffold to synthesize proteasome inhibitors through esterification of its C-3 hydroxyl group.[10] In an effort to search for new scaffolds for the synthesis of proteasome inhibitors, several natural products, including moronic acid, ursolic acid, oleanolic acid, and lithocholic acid (LA), were evaluated as potential scaffolds.[10,14] Among these natural products, only LA inhibited the chymotrypsin-like activity of the 20S proteasome with an IC_{50} of 18.1 μM (Table 1). Therefore, LA was used as a new scaffold to further increase the potency of the proteasome inhibition. The usage of LA as the scaffold is advantageous in that it is readily available and less expensive than other triterpene natural products. The molecular size of LA is also smaller than other triterpenes.

* Corresponding author. Tel.: +1 919 684 2952; fax: +1 919 684 3878 (L.H.); tel.: +1 919 684 3819; fax: +1 919 684 3878 (C.-H.C.).
E-mail addresses: lihuang@duke.edu (L. Huang), chc@duke.edu (C.-H. Chen).

0960-894X/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2011.02.041