Tetrahedron Letters 54 (2013) 6660–6664

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis and bioactivity of α-galactosylceramide analogues bearing an aryl group within the fatty amide chain

Dong Jae Baek [a], Jun-Seok Park [b], Joo-Youn Lee [b], Chaemin Lim [b], Chang-Yuil Kang [b], Robert Bittman [a,*]

[a] Department of Chemistry and Biochemistry, Queens College, The City University of New York, Flushing, NY 11367-1597, United States
[b] College of Pharmacy, Seoul National University, Seoul 151-742, South Korea

ARTICLE INFO

Article history:
Received 12 September 2013
Revised 26 September 2013
Accepted 28 September 2013
Available online 5 October 2013

Keywords:
Glycosphingolipids
Sonogashira reaction
Lipid antigen
KRN7000

ABSTRACT

We describe the synthesis and bioactivity of analogues of α-galactosylceramide (**1**) bearing a long-chain alkyl group substituted at the *meta* or *para* position of an aryl group embedded within the amide chain. We compared the ability of these compounds and of **1** and C6Ph (**2**, which has a phenyl group at the amide chain terminus) to stimulate murine invariant Natural Killer T cells and to dock with human CD1d.
© 2013 Elsevier Ltd. All rights reserved.

KRN7000 (α-galactosylceramide; α-GalCer, **1**) is a synthetic analogue of agelasphins, which was obtained from the marine sponge *Agelas* mauritianus,[1] and is a ligand for CD1d of antigen-presenting cells.[2] The KRN7000/CD1d complex binds to T cell receptors on the surface of invariant Natural Killer T (iNKT) cells.[3,4] On activation in vivo, iNKT cells rapidly secrete large amounts of both T helper 1 (Th1) and T helper 2 (Th2) cytokines, such as interferon-γ (IFN-γ) and interleukins-4, -10, and -13 (IL-4, IL-10, IL-13), respectively, which play critical roles in the regulation of innate and adaptive immune responses.[5,6] Unfortunately, the results of early human clinical trials of α-GalCer have been disappointing probably because (i) the simultaneous secretion of Th1 and Th2 cytokines can antagonize the biological functions of each type alone, and (ii) an anergic state of iNKT cells is induced by α-GalCer.[7] Therefore, analogues of α-GalCer have been sought that can modulate the iNKT cell response by increasing the selectivity toward either Th1 or Th2 cytokines responses, with a retention of activity to stimulate iNKT cells. A wealth of structure–activity relationships have been established by introducing modifications in the D-galactosyl moiety, the α-anomeric glycosidic linkage, the linker region between the sugar and the sphingolipid chain, and in the structures of both lipid chains. Some of these modifications were guided by the crystal structures of the mouse and human CD1d/α-GalCer complex, which were first reported in 2005.[8,9] The X-ray studies revealed how the two lipid chains of **1** fit into the two CD1d binding pockets and how hydrogen bonding interactions orient **1** in the CD1d groove. In the fatty amide chain, up to 26 carbons can be accommodated in the A′ pocket of CD1d, and up to 18 carbons in the phytosphingosine can fit into the F′ pocket.[8,9] Decreasing the length of the phytosphingosine chain results in an incomplete filling of the F′ hydrophobic channel, resulting in multiple conformations of human CD1d, whereas decreasing the amide chain length and resultant incomplete filling of the A′ channel did not influence the orientation of the α-GalCer head group.[10] More recently, the structures of NKT TCR/CD1d/glycolipid complexes have been determined, showing the interactions that affect the recognition of the α-galactosyl head group of **1** by the iNKT TCR.[11,12] The TCR affinity and stability of the CD1d/glycolipid complexes affect the cytokine response, and a prolonged stimulation of NKT cells enhances IFN-γ production by NK and dendritic cells.

Since the molecular basis for the promotion of Th1- versus Th2-biased responses by **1** and its analogues is still unclear, many recent investigations have focused on glycosphingolipids with modified lipid chain structures. For example, previous studies showed that installation of an aryl group at the terminus of the amide chain, such as in **C6Ph** (**2**) and **C8Ph**,[13] **7DW8–5**,[14] **7b** (which is an α-*C*-GalCer analogue),[15] and **C34**[16] (see Fig. 1), generally yielded analogues that induce human iNKT cells in vitro to secrete more IFN-γ than α-GalCer.[13,14,17–19] Only a limited number of analogues of **1** with an aryl-substituted amide chain have been prepared to date, all of which bear the aryl group at the chain terminus. Therefore, we decided to prepare and evaluate the bioactivity of new analogues of **1** bearing an aryl group within the fatty amide chain. Figure 2 shows the structures of α-GalCer

* Corresponding author.
E-mail address: robert.bittman@qc.cuny.edu (R. Bittman).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.09.134

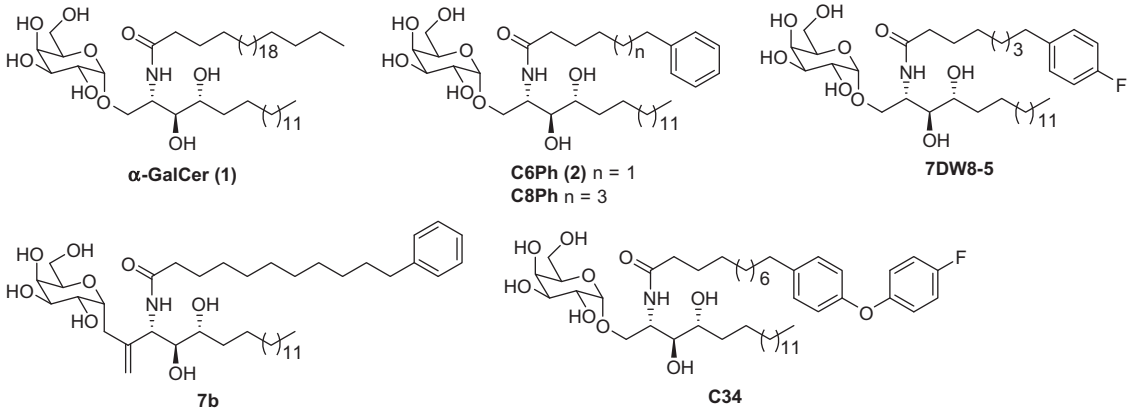


Figure 1. Structures of **1** and of its known analogues bearing a terminal aryl group.

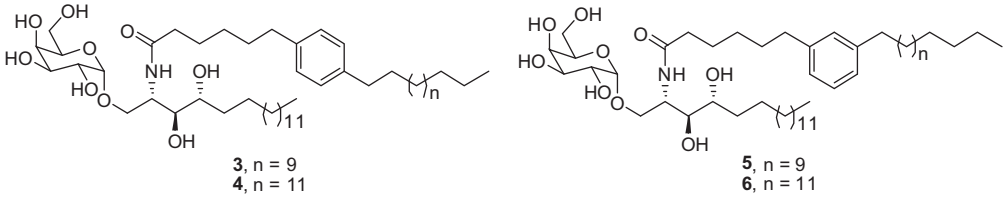
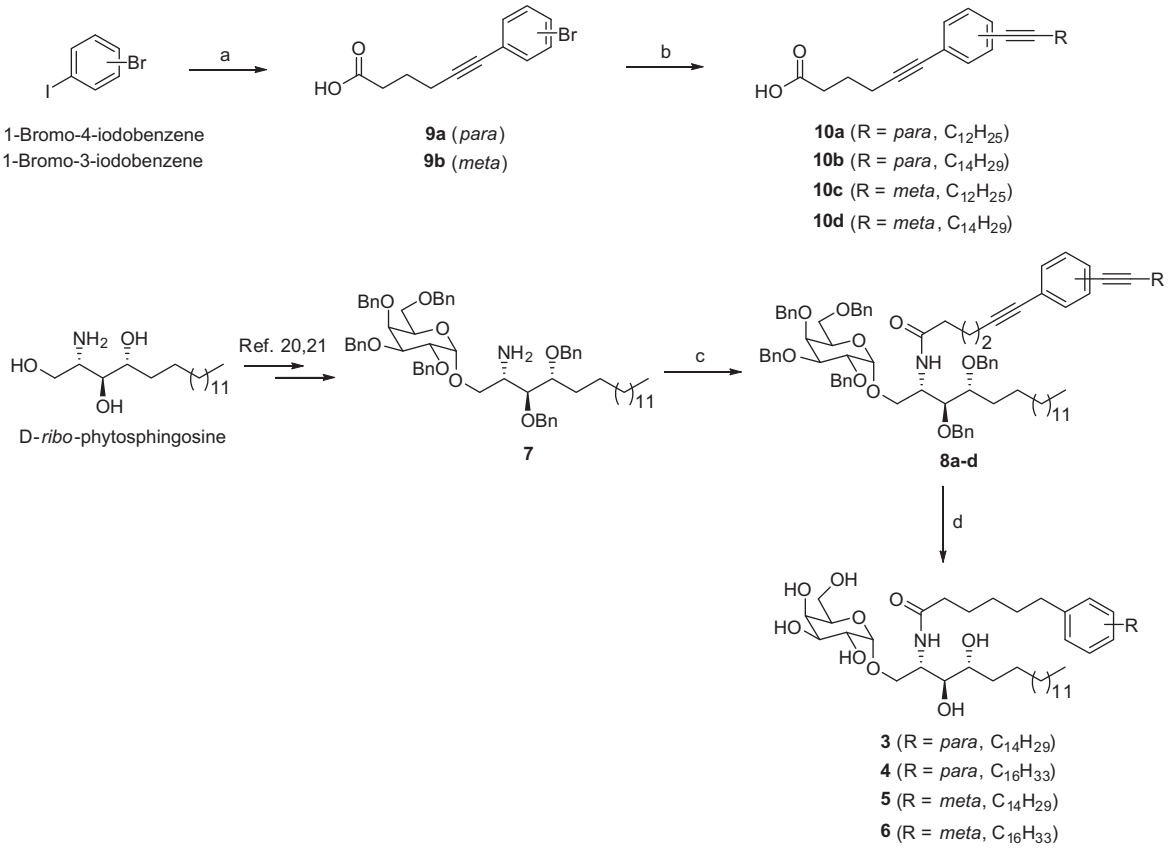


Figure 2. Structures of analogues **3**–**6**.



Scheme 1. Synthesis of analogues **3**–**6**. (a) 5-hexynoic acid, $Pd(PPh_3)_4$, CuI, NEt_3, 60 °C, 12 h; (b) 1-tetradecyne (for **10a** and **10b**), 1-hexadecyne (for **10c** and **10d**), $Pd(PPh_3)_4$, CuI, NEt_3, 60 °C, 24 h; (c) EDCI, DMAP, **10a**–**d**, CH_2Cl_2, rt, 12 h; (d) H_2, $Pd(OH)_2$/C, EtOH/CH_2Cl_2 (3:1), rt, 12 h.

Download English Version:

https://daneshyari.com/en/article/5262969

Download Persian Version:

https://daneshyari.com/article/5262969

Daneshyari.com