Use of the NEO strategy (Nucleophilic addition/Epoxide Opening) for the synthesis of a new C-galactoside ester analogue of KRN 7000

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Our goal in the search for potentially bioactive analogues of KRN 7000 was to design an easy synthetic approach to a library of analogues using a strategy recently developed in our laboratory based on a Nucleophilic addition followed by an Epoxide Opening (the NEO strategy). Through the use of a common pivotal structure, a new C-galactoside ester analogue (23) was synthesized which showed an encouraging TH2 biased response during preliminary biological tests.

KRN 7000 (1) is a synthetic glycolipid resulting from structure-activity studies based on compounds isolated from the Japanese marine sponge, Agelas mauritianus (Fig. 1). It has shown promising bioactivity against diverse pathologies. When associated with the protein CD1d, this α-Galactosyl/Ceramide (α-GalCer) interacts with the invariant Natural Killer T (iNKT) cells of the immune system, stimulating the production of signalling molecules involved in cellular communication called cytokines. According to the nature of the produced cytokines, a TH1/TH2 immune response profile is established and involves the activation of other immune cells (B cells, T cells ...), to fight cancer (TH1) or autoimmune diseases (TH2).

Biological tests have shown that certain parts of KRN 7000 must not be modified for an efficient stimulation of the iNKT cells. The configuration of the amide function, that of the 3′-OH and the α-glycoside bond are all important. Certain structural modifications are possible in position 6 of the sugar moiety with no loss of activity. Finally, the presence of lipid side chains is required to allow good contact with the CD1d protein. Various efforts have been made toward the synthesis of simple and more functionalized analogues (2–5 for example) in order to selectively induce TH1 or TH2 – type cytokine production. Among these compounds, few

Figure 1. KRN 7000, several analogues, and the envisaged α-C-GalCer ester analogue 6.