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Extended Abstract

Synthesis of Polyfluorinated KRN7000 Analogues and Biological Implications †

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KRN7000 is a synthetic glycosphingolipid developed as an anticancer drug candidate, which upon association with the CD1d protein activates NKT cells. This event leads to the release of different cytokines, which modulate a T_H1 response (antitumoral and antimicrobial functions) or a T_H2 response (against autoimmune diseases). Unfortunately, the simultaneous secretion of both cytokines limits the therapeutic potential of KRN7000, as they can antagonize the biological functions of each type alone. For that reason, the synthesis of new KRN7000 analogues with a more biased T_H1/T_H2 profile is an area of special interest [1].

It has been suggested that T_H1 response is certainly favoured by stabilization of the KRN7000–CD1d–NKT complex [2]. In this regard, it has been recently demonstrated that perfluorinated chains produce stronger interactions with hydrophobic cavities of proteins than its hydrocarbon counterparts [3].

In this communication, we will report the synthesis of set of KRN7000 analogues bearing different perfluoroalkyl chains at the ceramide moiety, with the aim of increasing the stability of the complex to obtain a selective T_H1 response. Biological implications based on binding affinity towards mouse CD1d protein as well as mouse and human iNKT cell stimulation experiments will also be discussed.

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