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Enhancement of anti-inflammatory drug activity by multivalent adamantane-based dendrons

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ABSTRACT

We have developed a straightforward method to prepare 1st and 2nd generation adamantane-based dendrons, previously called *HYDRAmers*, bearing at the periphery the anti-inflammatory drug, ibuprofen. The multivalency effect on the drug activity was studied, demonstrating that our multivalent ibuprofen-dendron conjugates exert an enhanced anti-inflammatory activity compared to free ibuprofen, *in vitro*. These results provide insights into the effect of *HYDRAmer* multivalency on biological interactions for therapeutic applications.

1. Introduction

Dendrimers and the so-called "dendrons" (wedge-shaped dendrimer sections) [1] have unique molecular architectures and properties that make them attractive candidates for several biomedical applications [2–5]. Indeed, by controlling the dendrimer synthesis it is possible to manipulate both their molecular weight and chemical composition, thereby allowing to solve problems of biocompatibility, toxicity, pharmacokinetics and organ specificity [6,7]. Moreover, these hyperbranched structures have the advantage that they can display at their periphery a desired motif in a multivalent manner [8], in order to give synergistic enhancement of a particular required function [9]. Multivalency, widely expressed in nature [10,11], has been shown to lead to a strongly increased activity (*e.g.* binding affinity or catalytic activity) compared to the corresponding monomeric interaction [12–14].

In this context, we have recently developed a straightforward strategy to synthesize different generation (G1 to G3) adamantane-based dendrons, called *HYDRAmers* [15]. We have chosen to build the arborescent structure on adamantane scaffolds because these rigid molecules with a 3D tripodal geometry can point the attached entities in a spatially well-defined way. On the other hand, the introduction of suitable linkers or spacers between the adamantane units confers certain flexibility and can modulate the solubility properties of the different higher generations. These factors play an important role in the biological interactions. Consequently, our dendrons can bring further advantages compared to other proposed dendritic structures for studies on multivalent ligand/receptor interactions [16,17]. Poly(amido amine)-based dendrimers have been already reported in the literature as efficient multivalent delivery systems of anti-inflammatory drugs [18,19].

In the present work we explored the multivalency effect of our *HYDRAmers* on the activity of the well-known anti-inflammatory drug, ibuprofen, on lipopolysaccharide (LPS)-stimulated murine macrophages. For this purpose we have functionalized the periphery of G1 and G2 adamantane-based dendrons with ibuprofen in order to obtain the corresponding conjugates bearing the drug in trimeric or nonameric arrangement, respectively. Out of several non steroidal anti-inflammatory drugs (NSAIDs), ibuprofen is one of the most commonly used due to its antipyretic, analgesic and antibacterial activity [20]. Furthermore, this drug has a wide therapeutic window and becomes toxic only at very high doses [21]. As other NSAIDs, ibuprofen mediates its anti-inflammatory effects by inhibiting the cyclooxygenase enzyme (COX) and consequently prostaglandin production, which are known to affect the formation of pro-inflammatory cytokines [22–24]. However, studies exploring the effects of ibuprofen on pro-inflammatory cytokines have generated contrasting results. In fact, even if ibuprofen treatments were shown to inhibit production of tumour necrosis factor alpha (TNFα) and interleukin 6 (IL6) *in vitro* and

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