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The ocean as a source of new anti-inflammatory and anti-pruritic molecules

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Abstract

Background: Pruritus, the most common symptom of skin diseases, is considered a chronic condition when experienced for more than six weeks. Although the etiology of the symptom remains elusive, chronic pruritus has been associated with neurokinin 1 receptor (NK1R) and its agonist substance P [1]. Since pruritus and inflammation often go together, the development of compounds with dual activity, specifically anti-inflammatory and anti-pruritic, is an upcoming strategy [1,2]. **Objective:** The present work aimed the discovery of new molecules inspired in models from the sea, a source of unique chemical structures with anti-pruritic and anti-inflammatory activities. **Methods:** Seventy marine-inspired compounds were tested *in silico* regarding their binding affinity to NK1R and their pharmacokinetic properties evaluated using SwissADME software. *In vitro* molecules' cytotoxicity was evaluated in cells representative of the skin constitution, namely keratinocytes (HaCaT), macrophages (Raw 264.7), and fibroblasts (3T3). The anti-inflammatory properties were investigated in macrophages, by evaluating nitric oxide synthase (iNOS) protein levels (Western blot analysis), nitric oxide (NO) production (Griess assay) and NO scavenging potential using an *in chimico* assay. **Results:** The tested compounds demonstrated a high binding affinity for NK1R *in silico* and no relevant cytotoxicity *in vitro*. Some compounds were able to reduce inflammation through the decrease of the pro-inflammatory mediator NO, not because of their NO scavenging potential, but by decreasing iNOS protein levels, thus suggesting the blockade of pro-inflammatory signaling pathways upstream iNOS synthesis, namely the transcription factor NF-kB. Importantly, most tested marine-inspired compounds presented MW up to 500 and log P in the range 2.40-5.76 which favours good skin permeation. **Conclusions:** The ocean is a potential source of anti-inflammatory compounds and NK1R antagonists for the treatment of skin conditions associated with pruritus and inflame mation.

Keywords: chronic pruritus; inflammation; neurokinin 1 receptor; marine natural products; skin diseases

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