Synthesis and Biological Activity of a New Class of Antitumor Cyclopeptides based on the Solomonamides

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Solomonamides A (**1**) and B (**2**) are novel natural products recently isolated from the marine sponge *Theonella swinhoei* [1]. Preliminary structural studies revealed an unprecedented cyclic peptide type structure. Interestingly, solomonamide A exhibits anti-inflammatory activity, showing potent reduction (60%) of inflammation at a very low concentration of 100 µg/kg in animal models. However, the scarcity of these compounds from their natural sources has been a drawback for further pharmacological assays. In fact, the anti-inflammatory activity of solomonamide B was not evaluated due to the limited amounts. This difficulty to access large amounts of these compounds makes quite difficult to gain insight into their biological profiles and mechanism of action and justifies the chemical synthesis of this new class of cyclic peptides. As a consequence, the solomonamides have been the subject of several synthetic efforts [2] notably by the Reddy group who has recently reported the first total synthesis of solomonamide B based on a intramolecular Heck reaction, which led to a revision of the initially proposed structure for **2** [3].

With the aim of establishing a flexible and divergent synthetic strategy capable of providing not only the natural compounds, but also provide analogues for biological studies, we have explored the ring-closing metathesis reaction as the key step for construction of the macrocycle. This cyclisation step would be followed by an oxidation phase, which would include the final functional groups contained in the natural products. Interestingly, this synthetic study generated several solomonamide precursors whose biological activities were evaluated, showing anti-tumor activity in various cell lines, including endothelial cells, which may indicate antiangiogenic effect. These preliminary biological evaluations of simple solomonamide analogues indicate promising antitumor properties for the natural products and qualify them as new scaffolds of biological and medicinal interest.

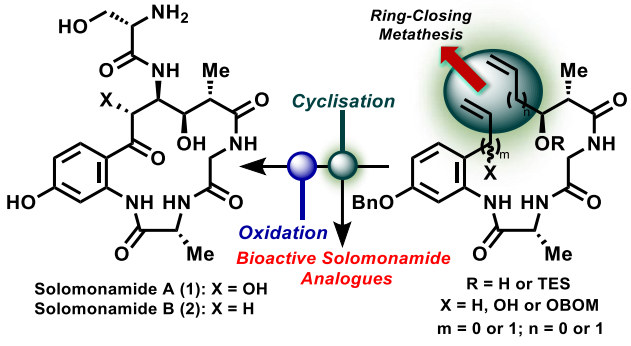

Figure 1. Molecular Structures and Synthetic Plan of the Solomonamides

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