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Synthesis and Antiproliferative Activity of Simplified Lactone Analogues of Mycalin A, a Polybrominated Metabolite of Marine Origin

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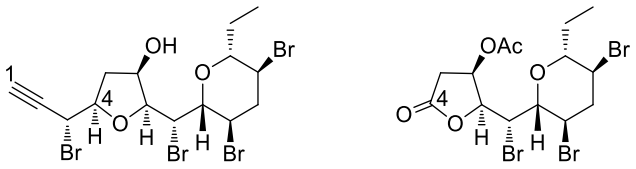
Mycalin A (**1**, Figure 1) is an antiproliferative metabolite isolated from the marine sponge *Mycale rotalis*[1] that induces cell death by an apoptotic mechanism. Recent studies[2] conducted in our group have shown that a degraded lactone analogue (**2**, Figure 1) of mycalin A retains the cytotoxic activity of the original substance while displaying a limited killing effect on human dermal fibroblasts (HDF) healthy cells used as control. Preparation of several synthetic analogues of mycalin A, including **2**, has shown that their anti-tumour activity is mostly associated with the presence in the molecule of the THF or a THF-mimicking left-hand portion.

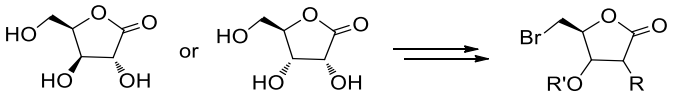
Based on these observations, we have synthesised[3] some simplified lactone analogues of **2** (Figure 2), including C-3 epimeric analogues, starting from D-ribonolactone and D-xylonolactone. Preliminary results on their cytotoxic activity have shown that some of them possess good antiproliferative activity on the same human tumour cell lines used for assays on mycalin A and on its lactone derivative **2**.

The identification of the biological target through the Drug Affinity Responsive Target Stability (DARTS) technique[4,5] is currently under investigation and will also be discussed.



Mycalin A (1) Mycalin A lactone (2)

Figure 1: Mycalin A and a degraded lactone analogue thereof.



D-xylonolactone D-ribonolactone R =H, αBr, βBr
R'= H, Ac

Figure 2: Simplified lactone analogues of **2**.

References:

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