FAST AND EFFECTIVE PREPARATION OF HIGHLY CYTOTOXIC HYBRID MOLECULES OF SCHWEINFURTHIN E AND OSW-1

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We present the first synthesis of hybrid molecules combining two biologically active compounds: Schweinfurthin E (SW-E) and OSW-1, both exhibiting very powerful antiproliferative properties. Schweinfurthins (SWs) are a family of natural prenylated stilbenes isolated from Macaranga. Some of them contain a hexahydroxanthene (HHX) moiety, which is essential for their biological properties [1]. SW's pharmacological profile is distinct from traditional chemotherapy agents, suggesting it targets a novel biological pathway, specifically the OSBP protein [2], which regulates cholesterol transport between the endoplasmic reticulum and the Golgi apparatus. OSW-1, on the other hand, is a steroid with a disaccharide moiety crucial for its cytotoxicity. The integrity of this disaccharide unit is essential for maintaining its activity, and it likely contributes to hydrophobic clustering that enhances the compound's potency [3]. The preparation of these hybrids was achieved through a CuAAC reaction involving a polyfunctionalized alkyne derived from SW-E and various azido sugars. Additionally, we developed a novel and efficient method for preparing the disaccharide of OSW-1 through sequential functionalization of L-arabinose, facilitated by a boronic ester as a switchable protective/activating group [4]. This study allowed us to improve the existing synthesis routes of OSW-1 disaccharide by reducing the number of steps and purifications, thereby saving time and simplifying manipulation. The cytotoxicity of the hybrids was also evaluated, with some being much more cytotoxic than SW-E on a glioblastoma cancer cell line [5]. Finally, a molecular modeling study was carried out to rationalize the biological results obtained.

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