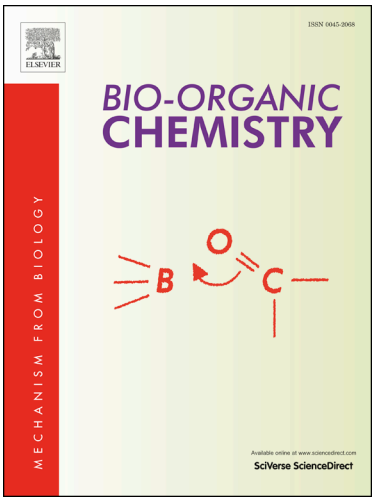

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Bioorganic Chemistry- Regular Articles

Synthesis, antiproliferative activity and molecular docking of thiocolchicine urethanes

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Abstract

A number of naturally occurring compounds such as paclitaxel, vinblastine, combretastatin, and colchicine exert their therapeutic effect by changing the dynamics of tubulin and its polymer form, microtubules. The identification of tubulin as a potential target for anticancer drugs has led to extensive research followed by clinical development of numerous compounds from several families. In this paper we report on the design, synthesis and *in vitro* evaluation of a group of thiocolchicine derivatives, modified at ring-B, labelled here compounds **4-14**. These compounds have been obtained in a simple reaction of 7-deacetyl-10-thiocolchicine **3** with eleven different alcohols in the presence of triphosgene. These novel agents have been checked for anti-proliferative activity against four human cancer cell lines and their mode of action has been confirmed as colchicine binding site inhibition (CBSI) using molecular docking. Molecular simulations provided rational tubulin binding models for the tested compounds. On the basis of *in vitro* tests, derivatives **4-8** and **14** demonstrated the highest potency against MCF-7, LoVo and A549 tumor cell lines (IC_{50} values = 0.009-0.014 μM). They were more potent and characterized by a higher selectivity index than several standard chemotherapeutics including cisplatin and doxorubicin as well as unmodified colchicine. Further, studies revealed that colchicine and its several derivatives arrested MCF-7 cells in mitosis, while its selected derivatives caused microtubule depolymerization.