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Synthesis and cytotoxic evaluation of novel indenoisoquinoline-propan-2-ol hybrids

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Abstract

The synthesis of *N*-substituted indenoisoquinolines was performed by applying a two-step condensation between 2-carboxybenzaldehyde and phthalide, followed by treatment with various primary amines. *N*-Allylindenoisoquinoline was subsequently selected as a substrate for hydroxybromination, providing 6-(3-bromo-2-hydroxy)indenoisoquinoline as a key intermediate for derivatization in the lactam side chain. In this way, a series of 6-(2-hydroxypropyl)indenoisoquinolines bearing various functional groups at the 3'-position were prepared, which can be considered as novel indenoisoquinoline-propan-2-ol hybrid molecules. Subsequent cytotoxic evaluation of 28 indenoisoquinolines against two human cancer cell lines (Hep-G2 and KB) demonstrated a moderate to high antiproliferative activity displayed by 11 indenoisoquinolines thus synthesized. In particular, the introduction of the 2-hydroxypropyl side chain was shown to be beneficial for the overall cytotoxic activity, pointing to the potential relevance of these novel indenoisoquinoline-propan-2-ol hybrids.

Keywords

Indenoisoquinolines; β-Amino alcohols; 2-Carboxybenzaldehyde; Phthalide; Cytotoxicity

Indenoisoquinolines represent a versatile class of compounds, known for their anticancer activity resulting from the inhibition of DNA topoisomerase I (Top1), a universal and essential enzyme for the relaxation of supercoiled DNA during important cellular processes.[1] Top1 had previously emerged as a valuable molecular target for the development of anticancer agents,[1e,1f,2] such as the pentacyclic alkaloid camptothecin **1** (Figure 1) and its semisynthetic analogues.[1f,1k,3] However, in spite of the established anticancer activity, the application and efficiency of the camptothecins was hampered by several pharmacological and clinical limitations, moving forward the class of the indenoisoquinolines