Activation of Human Telomerase Reverse Transcriptase Expression by Some New Symmetrical Bis-Substituted Derivatives of the Anthraquinone

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摘要

Abstract

As a part of our program aimed at exploring the biological activity of symmetrical substitution of side chains into the anthracene-9,10-dione chromophore, we have synthesized a series of 1,5-bisthioanthraquinones 2 and 1,5-bisacyloxyanthraquinones 3 that are related to the antitumor agent mitoxantrone. Since the telomerase enzyme is a novel target for potential anticancer therapy and stem cell expansion, we explore the biological effects of these compounds by evaluating their effects on telomerase activity and telomerase expression. Telomerase is required for telomere maintenance and is active in most human cancers and in germinal cells but not in most of the normal human somatic tissues. We found that most of the 1,5-disubstituted anthraquinones did not exhibit inhibitory activity at the concentration ranging from 20 to 30 microM. To facilitate the analysis of the expression of telomerase, we used cancer and normal cell lines that carry secreted alkaline phosphatase (SEAP) gene under the control of human telomerase reverse transcriptase (hTERT). The effects of these compounds on the expression of telomerease were analyzed using the cell-based reporter systems. While most of these compounds did not appear to selectively repress the expression of hTERT in cancer cells, compounds 3a, 3d, and 3i activated hTERT expression in normal cells. The effects of these three compounds on hTERT expression appear to be specific because they did not increase the expression of a CMV promoter-driven SEAP. Thus, in addition to anticancer functions, our finding raises the possibility that these compounds might also have a role in cell immortalization. The application of these anthraquinone derivatives in stem cell research and tissue engineering is also discussed