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Potent Inhibition of Human Telomerase by Small Chemical Compounds

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Telomerase activity is expressed in most types of cancer cells but not in normal somatic cells, suggesting that telomerase may be an important target for cancer chemotherapy. Inhibition of telomerase results in telomere erosion leading to the subsequent growth-arrest of cancer cells followed by senescence or cell death. In this study, we screened a chemical library for inhibition of human telomerase, identifying two groups of inhibitors. One group contained a common nitrostyrene moiety conjugated to different side chains. One of these compounds, DPNS, showed the most potent inhibitory effect with 50% inhibition at ~0.4 μM and did not inhibit DNA and RNA polymerases including retroviral reverse trancriptase. A series of enzyme kinetic experiments suggest that DPNS is a mixed-type noncompetitive inhibitor, with an inhibitor-binding site distinct from the binding sites for the TS primer and the dNTPs. Extensive propagation of cancer cell line in the presence of DPNS resulted in progressive telomere erosion followed by the induction of senescence phenotype. Second group of inhibitors include TNQX which showed potent inhibitory effect with 50% inhibition at ~1.4 μM and did not inhibit DNA and RNA polymerases including retroviral reverse trancriptase. Long-term cultivation of MCF7 cell line with non-acute cytotoxic drug concentration resulted in progressive telomere erosion followed by increased chromosome abnormalities and induction of senescence phenotype. The results presented here indicate that DPNS and TNQX are highly potent and selective antitelomerase agents with good potential for further development as a promising anticancer agent.