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3-nitroacridine derivatives arrest cell cycle at G0/G1 phase and induce apoptosis in human breast cancer cells may act as DNA-target anticancer agents

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Abstract

DNA is considered to be one of the most promising targets for anticancer agents. Acridine analogues have anticancer activity based on DNA binding and topoisomerases inhibition. However, due to the side effects, resistance and low bioavailability, a few have entered into clinical usage and the mechanisms of action are not fully understood. Novel acridine derivatives are needed for effective cancer therapy. A series of novel 3-nitroacridine-based derivatives were synthesized, their DNA binding and anticancer activities were evaluated. The chemical modifications at position 9 of the 3-nitroacridine were crucial for DNA affinity, thus optimizing anticancer activity. UV-Vis and circular dichroism (CD) spectroscopy indicated interaction of compounds with DNA, and the binding modes were intercalation and groove binding. MTT assay and clonogenic assay showed that compounds **1, 2** and **3** had obvious cell growth inhibition effect. They induced cell apoptosis in human breast cancer cells in a dose-dependent manner, and exhibited anticancer effect *via* DNA damage as well as cell cycle arrest at G0/G1 phage. Using confocal fluorescent microscope, the apoptotic features were observed. The results suggested that compounds **1-3** with high DNA binding affintiy and good inhibitory effect of cancer cell proliferation can be developed as prime candidates for further chemical optimization.

Keywords: acridine derivatives; synthesis; DNA binding; anticancer activity; structure-activity relationship (SAR); apoptosis.

1. Introduction

Cancer is a deadly disease in the world[1], great efforts have been made to understand the cancer biology and develop the potential anticancer drugs[2-6]. Among the current strategies for cancer treatment, chemotherapy remains the most mature and effective approach[7].

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