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Contributed Paper

Topoisomerase I Inhibitory Activity and 3D QSAR Studies of Chromone Derivatives

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ABSTRACT

Topoisomerase I (Top I) is the molecular target for a diverse set of anticancer agents. This study was a continuation of previous work examining the Top I inhibitory activity of a series of chromone derivatives. Nine chromones were evaluated using eukaryotic DNA TOP I drug screening kit. The most potent inhibitor, chromone **20** showed greater inhibitory activity (IC_{50} = 0.83 μM) than the previously reported chromone compounds as well as the known Top I inhibitor, camptothecin. To develop the structure-Top I inhibitory activity relationship, the 3 dimensional quantitative structure-activity relationship (3D QSAR) were performed using comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA). The best CoMFA model gave cross-validated r^2 (q^2) = 0.578 and non cross-validated r^2 = 0.995 while CoMSIA gave q^2 = 0.632, r^2 = 0.996. The contour maps provide the fruitful structural features which are useful for designing new compounds with higher activity.

Keywords: chromone derivatives, topoisomerase I inhibitory activity, CoMFA, CoMSIA

1. INTRODUCTION

DNA topoisomerases are important targets of approved and experimental anticancer drugs. They are essential for a number of cellular processes those involve DNA unwinding including DNA replication, transcription, recombination, and chromatin remodeling [1]. Their functions have been reported to relieve the torsional stress in the DNA helix that is generated as a result of replication, transcription, and other nuclear processes [2-3]. Topoisomerases affect the supercoiling of closed circular DNA and long strands of double-stranded DNA by introducing transient breaks in the phosphodiester backbone and form a covalent phosphotyrosine intermediate with the DNA [4-6]. Based on the mechanism of cleaving DNA, topoisomerases are classified