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Analysis of Napthoquinone derivatives as Topoisomerase 1 inhibitors

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Various scaffolds of naphthoquinone Derivatives have been reported to show antitumor activity against Topoisomerase 1 (Topo 1) with unique features of structure activity relationship (SAR). This article focusses on characteristic features of naphthoquinones to exhibit specificity towards Topo 1. Comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) based on three-dimensional quantitative SAR (3D-QSAR) studies were conducted on a series of 90 naphthoquinone derivatives representing distinctive scaffolds which are potent inhibitors of the enzyme Topo 1. The best predictions were obtained with a CoMFA standard model (q^2=0.568, r^2=0.960) and with CoMSIA combined electrostatic and hydrophobic fields (q^2=0.663, r^2=0.940). Both models were validated by a test set of twenty seven compounds and gave satisfactory predictive r^2 values of 0.742 and 0.704, respectively. Contour maps were used to analyze the structural features of the ligands to account for the activity in terms of positively contributing physicochemical properties: steric, electrostatic and hydrophobic fields. The information obtained from 3-D contour maps can be used for further design of naphthoquinone analogs as anti-Tumor agents. The resulting contour maps were used to identify the structural features relevant to the biological activity in this series of analogs. Further analysis of these interaction-field contour maps also showed a high level of internal consistency. This study suggests that introduction of bulky and highly electronegative groups on the basic amino side chain along with decreasing steric bulk and electronegativity on the bulky long chains might be suitable for designing better antitumor agents. In addition to QSAR, docking studies were performed to analyze the mechanism of binding of naphthoquinones on Topo 1. It was seen most of the derivatives showed similar binding pattern as that of camptothecin derivatives indicating that they also bring about the cleavage of DNA at +1 and -1 position.

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