Biomedical Data Mining

Extended Abstract

Analysis of Napthoquinone derivatives as Topoisomerase 1 inhibitors

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Abstract

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 (q2=0.568, r2=0.960) and with CoMSIA combined electrostatic and hydrophobic fields (q2=0.663, r2=0.940). Both models were validated by a test set of twenty seven compounds and gave satisfactory predictive r2 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.

In this investigation an endeavor was made to comprehend the auxiliary prerequisites for Topoisomerase I (Topo I) restraint utilizing a novel Group based QSAR (GQSAR) or piece based QSAR strategy. Here we consolidated the GQSAR innovation with customary 2D and 3D QSAR to infer GQSAR models for different detailed naphthoquinone subordinates. Different relapse models, for example, Multiple Regression (MRA), Partial Least Square (PLS) and Principal Component Analysis (PCA) just as k-Nearest neighbor (k-NN) QSAR were utilized to build up a few joined 2D and 3D GQSAR models. The GQSAR examinations uncovered the significance of Geometrical topological files and Baumann's arrangement autonomous topological descriptors alongside dipole second and other general descriptors like HBonddonor and XYHydrophilic and so forth for overseeing the movement variety. Further the GQSAR demonstrated that concoction variety like nearness of subbed twofold reinforced C molecule isolated from oxygen by 6 securities and HBonddonor check are exceptionally compelling for accomplishing profoundly powerful Topo I inhibitors. The Naphthoquinone subordinates having 2-CH(OX)- (CH2CH=CMe2)- 5,8-dihydroxy-1,4-naphthoquinone replacements are most significant parts for the inhibitory action. Furthermore the k-closest neighbor grouping model brought about 3 significant descriptors like snapshot of idleness, quadrapole and hydrogen check. The created models are

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interpretable with acceptable factual and prescient criticalness and can be utilized for controlling ligand adjustment for advancement of potential new Topo I inhibitors. From the current examination it very well may be seen that the replacements made on 2-CH(OX)-(CH2CH=CMe2)- 5,8-dihydroxy-1,4-naphthoquinone position can bring about better Topo I inhibitors.

A progression of benz[f]indole-4,9-diones, in light of the antitumor action of 1,4-naphthoquinone, were blended and assessed for their cytotoxic movement in refined human disease cell lines A549 (lung malignancy), Col2 (colon malignancy), and SNU-638 (stomach disease), and furthermore for the restraint of human DNA topoisomerases I and II action in vitro. A few mixes including 2-amino-3-ethoxycarbonyl-N-methyl-benz[f]indole-4,9-dione demonstrated a potential cytotoxic action decided by IC50º20.0 mgWml in the board of disease cell lines. Particularly, 2-hydroxy-3-ethoxycarbonyl-N-(3,4-dimethylphenyl)-benz[f]indole-4,9-dione had possible specific cytotoxicity against lung malignant growth cells (IC50 ＝0.4 mgWml)) contrasted with colon (IC50À20.0 mgWml) and stomach (IC50À20.0 mgWml) disease cells. To additionally explore the cytotoxic component, the ešects of test mixes on DNA topoisomerase I and II exercises were utilized. In a topoisomerase I-interceded unwinding test utilizing human placenta DNA topoisomerase I and supercoiled pHOTI plasmid DNA, 2-amino-3-ethoxycarbonyl-N-(4-‰uorophenyl)- benz[f]indole-4,9-dione had the most intense inhibitory action among the mixes tried. Notwithstanding, the greater part of the mixes demonstrated just feeble restraint of the DNA topoisomerase II-interceded KDNA (Kinetoplast DNA) decatenation measure, aside from 2-amino-3-ethoxycarbonyl-N-(4-methylphenyl)- benz[f]indole-4,9-dione and 2-amino-3-ethoxycarbonyl-N-(2-bromoehtyl)- benz[f]indole-4,9-dione with a moderate inhibitory movement. These outcomes propose that few dynamic mixes had moderately specific inhibitory action against toposiomearse I contrasted with toposiomerase II. No conspicuous relationship was seen between the cytotoxicity of the individual compound and the inhibitory action of DNA unwinding and decatenation by topoisomerase I and II, separately, in vitro. Watchwords: topoisomerase I and II; benz[f]indole-4,9-diones; cytotoxicity 1,4-Naphthoquinone subsidiaries with an amino gathering at the 2-position have been accounted for to have great antineoplasmic,1,2) carcinostatic actions3) and bacterial development inhibition.4) Based on the cytotoxic capability of 1,4-naphthoquinone subordinates, in our proceeding ešorts to create novel antitumor specialists, we have been blended benz[f]indole-4,9-dione analogs,5) heterocyclic pyrrole ring subordinates connected to 1,4-naphthoquinone.6) In this investigation we assessed the cytotoxic capability of extra benz[f]indole-4,9-dione analogs in refined human strong tumor cell lines including human lung (A549), colon (Col2), and stomach (SNU-638) malignancy cells. Further, an assortment of antitumor specialists as of now utilized in chemotherapy or assessed in clinical preliminaries are known to hinder DNA topoisomerase I (topo I) or II (topo II). DNA topoisomerases are chemicals that catalyze the entry of individual DNA strands (type I) or twofold helices (type II) through each other, which is showed in the interconversion between topological isomers of DNA.7) These proteins have significant jobs in replication, recombination, record, chromosome buildup, and the support of genome stability,8) and consequently are acceptable focuses for antineoplastic drugs.9) The antitumor medications camptothecin, doxorubicin, and etoposide are agent topo I or topo II inhibitors. In this manner, in this examination, to research one potential component of activity of the cytotoxic action of benz[f]indole4,9-dione analogs, we assessed their capacity to restrain topo I or topo II exercises with DNA unwinding and a DNA decatenation test, individually. We report here that benz[f]-indole-4,9-dione analogs show likely cytotoxicity against malignant growth cell lines with topo I or II inhibitory movement.