Pharmaceutical Regulatory Affairs 2012: 2D-QSAR study of natural coumarin against human bladder carcinoma cell line EJ - Manipal University, India

N.V. Anil Kumar

Manipal University, India, E-mail: nv.anil@manipal.edu

Abstract

The seven natural coumarins are active against human bladder carcinoma cell line EJ. The IC50 values of these coumarins were collected from the literature and 2D-Quantitative Structure Activity Relationship studies were executed using Easy QSAR 1.0 tool. Multiple linear regression (MLR) analysis was carried out using the descriptors from PaDEL 2.13 software to determine the relationship between the structural properties and the anticancer activity. The result of the investigation showed the contribution of descriptors to the activity. The present study may be helpful for the design of potent inhibitors against human bladder carcinoma cell line EJ using natural coumarins. Chalcones are a group of molecules with a broad spectrum of biological activities, being especially appealing for their antiproliferative effects on several cancer cell lines. For this reason, we synthesized 23 chalcones with good to excellent yields and assessed their effect on the viability of the SH-SY5Y neuroblastoma cell line and on primary human fibroblasts. The results indicated that 18 of these compounds were more active than 5-fluorouracil in the cancer cell line and one of them was more selective than this reference drug. To identify structural features related to the antiproliferative activity of these compounds, as well as, the selectivity on the cancer cell line, a 2D-QSAR analysis was performed. The QSAR model ($q2 = 0.803$; $r2 = 0.836$) showed that lipophilicity (CLogP) is the most important factor to increase their cytotoxicity on the cancer cell line. On the other hand, the selectivity QSAR model ($q2 = 0.917$; $r2 = 0.916$) showed that changes in the Mulliken's charge of the carbonyl group and at the C4' position in the chalcone core can increase the selectivity for SH-SY5Y cell line compared to normal fibroblasts. Flavonoids have shown anticarcinogenic activity in cancer cell lines, animal models, and some human studies. Quantitative structure-activity relationship (QSAR) models have become useful tools for identification of promising lead compounds in anticancer drug development. However, epidemiological and clinical studies are still scarce. Compounds with flavonoid scaffold have been the subject of many mechanistic studies in cells, but information on human chemopreventive properties is still missing. The knowledge of the mechanisms of action, anti-multidrug resistance, and QSAR studies on flavonoids and related compounds may help to enhance research on these compounds and their bioactivity. Therefore, once the issue is introduced, the mechanisms involved, and QSAR studies developed to predict the activity and toxicity of these chemicals to biological systems are discussed. QSAR studies on flavonoids as inhibitors of breast cancer resistance protein (BCRP/ABCG2), 17β-hydroxysteroid dehydrogenase (17β-HSD), PIM-1 kinase and cyclin-dependent kinases (CDKs) are analyzed. Combined treatment of flavonoids with TRAIL and current chemotherapy agents is also discussed as a promising cancer chemoprevention and/or therapy.