[P20] Quantitative structure–activity relationship analysis for the antitumor activity of 3,4-ethylenedioxythiophene derivatives against six carcinoma cell lines

Vesna Rastija[1], Miroslav Bajić[2], Ivana Stolić[2], Luka Krstulović[2], Marijana Jukić[3], Ljubica Glavaš-Obrovac[3]

[1]*Department of Chemistry, Faculty of Agriculture, J. J. Strossmayer University of Osijek, Osijek, 31 000, Croatia*
[2]*Department of Chemistry and Biochemistry, Faculty of Veterinary Medicine, University of Zagreb, Croatia*
[3]*Faculty of Medicine, J. J. Strossmayer University of Osijek, Osijek, 31 000, Croatia*

Varying the substitutive group or substituent position in derivatives of 3,4-ethylenedioxythiophene (EDOT) such as, bisbenzimidazole amidines, diamidines and pentamidines can modify the potency of their antitumor activity. The aim of this study was to derive a quantitative structure–activity relationship (QSAR) analysis for the antitumor activity of 27 3,4-ethylenedioxythiophene derivatives against six carcinoma cell lines: AGS (gastric adenocarcinoma); MIAPaCa2 (pancreatic carcinoma); (CaCo2) colon adenocarcinoma, HEp2 (larynx carcinoma); HeLa (cervix adenocarcinoma); NCI H358 (bronchioalveolar carcinoma). The goals of the QSAR analysis was to find out which physicochemical and quantum-chemical molecular properties have influence on enhanced antitumor activity

The dataset used for building QSAR models consists of 27 molecules whose antitumor activity was measured and described in present and our previously published papers [1-3]. The 2D and 3D molecular descriptors used in this study were calculated by applying the Dragon program (http://146.107.217.178/lab/pclient/). The selection of descriptors based on the best-subset method and the multiple regression analysis (MLR) was performed with the use of STATISTICA 12 (StatSoft, Inc. Tulsa, USA). Splitting data into training test (n = 22) and a test set (n = 5) and calculating the QSAR models and their validation was performed by QSARINS v 2.2 [4].

The best obtained QSAR models include following group of descriptors: BCUT descriptors (BELp6, BELp3); WHIM descriptors (G1u, G1p); information indices (BIC5); 2D autocorrelations descriptors (MATS7e); 3D-MoRSE descriptors (Mor19e, Mor15v); GETAWAY descriptors ($R4u^+$); 2D frequency fingerprint (F09[N-O], F10[C-N].

Results of QSAR analysis suggest that derivates of 3,4- EDOT with following structural feature may exhibit great antitumor activity: larger molecules with symmetrical arrangement of substituents that allows as much as possible C and N atoms at the located at the topological distance 10, as well as, N and O atoms at the topological distance 9. We constructed a two predictive QSAR models of antitumor activity against gastric adenocarcinoma and pancreatic carcinoma based and estimated the activity of future molecule that may exhibits great activity.

Bibliography:

[1] Stolić I.; Mišković K.; Magdaleno A.; Silber A.M.; Piantanida I.; Bajić M.; Glavaš-Obrovac Lj. Bioorg. Med. Chem. 17 (2009) 2544–2554.
[2] Stolić I.; Mišković K.; Piantanida I.; Baus Lončar M.; Glavaš-Obrovac Lj.; Bajić M. Eur. J. Med. Chem. 46 (2011) 743–755.
[3] Stolić I.; Avdičević M.; Bregović N.; Piantanida I.; Glavaš-Obrovac Lj.; Bajić M. Croat. Chem. Acta 85 (2012) 457–467.
[4] Gramatica P.; Chirico N.; Papa N.; Cassani S.; Kovarich S. J. Comput. Chem. 34 (2013) 2121-2132.