QSAR OF ANTIPROLIFERATIVE EFFECTS OF HALOGEN-, AND AMIDINO-SUBSTITUTED BENZOTHIAZOLES AND BENZIMIDAZOLES

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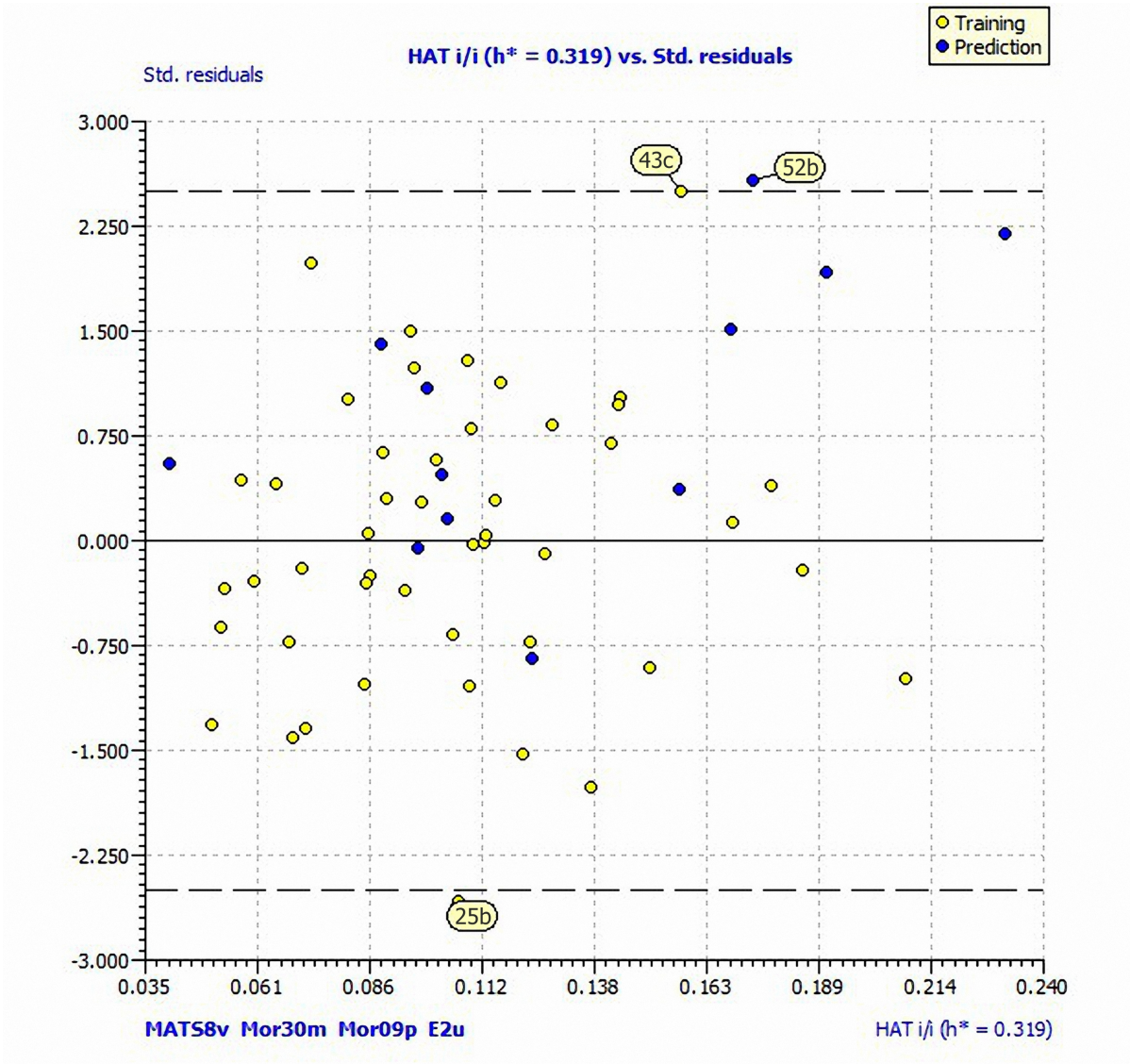
Novel derivates of benzothiazoles and benzimidazoles have been evaluated on T-cell lymphoma (HuT78), as well as on normal Madin-Darby canine kidney cells (MDCK-1). Cytotoxic effects of 77 benzothiazoles and benzimidazoles against non-tumour MDCK-1 cells were ranked by activities, and 17 compounds were chosen for the test set. The best QSAR model expressed by multiple linear regression equation was generated by five molecular descriptors calculated by DRAGON program: *SIC1*, *GATS4p*, *BEHv6*, *BELp1*, and *R7m*. Williams plot of the applicability domain, detected one molecule as a border outlier and no molecule out of the warning leverage. After removing outlier, the new model has the model achieved better statistical performance of internal and external validation: $R^2_{train} = 0.74$; $F = 30.76$; $\Delta K = 0.08$; $CCC_{tr} = 0.85$; $Q^2_{loo} = 0.68$; $CCC_{cv} = 0.81$; $R^2_{Yscr} = 0.09$; $Q^2_{Yscr} = -0.13$; $R^2_{ext} = 0.83$; $CCC_{ext} = 0.85$; $\Delta r^2_m = 0.25$. Molecules without atoms with higher atomic mass as substituents (Cl, F) and more equal neighbor atoms have higher activity. QSAR study for antiproliferative activity on T-cell lymphoma (HuT78) cell was performed on a total of 59 molecules (47 training, 12 test set). The best-obtained model includes three descriptors: *MATS8v*, *Mor09p*, *Mor30m*, and *E2u*. After exclusion of three outliers from data set, relived by Williams plot (Figure 1) resulted on the predictive model: $R^2_{train} = 0.87$; $F = 66.48$; $\Delta K = 0.12$; $CCC_{tr} = 0.93$; $Q^2_{loo} = 0.83$; $CCC_{cv} = 0.91$; $R^2_{Yscr} = 0.09$; $Q^2_{Yscr} = -0.15$; $R^2_{ext} = 0.87$; $CCC_{ext} = 0.85$; $\Delta r^2_m = 0.13$. An increasing number of atomic van der Waals volumes, such as in sulphur atom in benzothiazoles, as molecules without atoms, have higher atomic mass as substituents (Cl, F) enhancing antiproliferative activity on MDCK-1 cells.


Training
Prediction
HAT i/i (h* = 0.319) vs. Std. residuals
Std. residuals
3.000
2.250
1.500
0.750
0.000
-0.750
-1.500
-2.250
-3.000
43c
52b
25b
0.035
0.061
0.086
0.112
0.138
0.163
0.189
0.214
0.240
MATS8v Mor30m Mor09p E2u
HAT i/i (h* = 0.319)