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QSAR- MODELING OF ANTITUMOR ACTIVITY OF L-[(2-HYDROXYETHOXY)METHYL-5-BENZYLURACILS USING GUSAR

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A quantitative analysis of relationships between structures of l-[(2-hydroxyethoxy)methyl]-5-benzyluracils and efficiency of inhibition of the catalytic activity of murine liver uridine phosphorylase (UrdPase) was made by the program GUSAR 2013 (General Unrestricted Structure Activity Relationships) [1-2]. Biological data from ChEMBL [3] were used for creation of QSAR models. In general 50 statistically significant QSAR-models ($R_{train\ set}^2 > 0.6$, $R_{test\ set}^2 > 0.5$, $Q^2 > 0.6$) for prediction of IC_{50} values for various l-[(2-hydroxyethoxy)methyl]-5-benzyluracils against murine liver UrdPase were created based on MNA- and QNA-descriptors, as well as consensus of their combinations. The statistical characteristics of some of the models we constructed are presented in the Table1. Training set TrS2 and test set TS included 48 and 16 structures of UrdPase inhibitors, respectively. They were obtained by dividing the pre- sorted in ascending order of IC_{50} values in ratio 3:1, i.e. excluded from TrS1 every fourth compound to UrdPase. These models can be used for quantitative prediction of potential anti-tumor drugs against UrdPase. Atoms and structural fragments of the studied structures influencing on increase and decrease of UrdPase inhibition were identified by GUSAR 2013 visualization of quantitative "structure-activity" relationships in the created models. The results of structural analysis of the contribution of the different functional groups in the activity of UrdPase inhibition can be considered in the molecular design of active substances of known anticancer drugs in order to enhance the efficiency of their inhibitory action UrdPase.

Table 1. Characteristics and prediction accuracy of IC_{50} values for consensus models M1 - M6. pIC_{50} activity in TrS1 and TrS2 lies in the range -5.111 – -1.431.

Training set	Models	N	R^2_{OB}	R^2_{TB}	F	S.D.	Q^2	V
QSAR model based on MNA-descriptors								
TSet1	M1	48	0.899	-	29.462	0.349	0.871	8
TSet2	M2	36	0.924	0.763	25.155	0.319	0.893	8
QSAR model based on QNA-descriptors								
TSet1	M3	48	0.868	-	17.193	0.413	0.820	9
TSet2	M4	36	0.917	0.611	18.466	0.351	0.870	9
QSAR model based on MNA- and QNA-descriptors								
TSet1	M5	48	0.884	-	26.892	0.374	0.852	8
TSet2	M6	36	0.919	0.778	21.647	0.338	0.880	8

N – number of structures in the training set; R^2_{TrS} - a multiple coefficient of determination calculated for compounds from the training set; R^2_{TS} - a multiple coefficient of determination calculated for compounds from the test set; Q^2 – a cross-validated R^2 calculated during leave-one-out cross-validation procedure on data of the training set; F – Fisher's coefficient; SD – standard deviation; V- the number of variables in the final regression equation.

1. Filimonov D.A. et al. *SAR and QSAR in Environmental Research,* 2009. **20 (**7–8): 679–709.
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3. ChEMBL: https://www.ebi.ac.uk/chembl/.