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QSAR- MODELING OF ANTIVIRAL ACTIVITY A SERIES OF CARBOXAMIDE DERIVATIVES OF 5'-AMINO-2',5'-DIDEOXY-5-ETHYLURIDINE AND N^2-PHENYLGUANINES

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A quantitative analysis of relationships between structures of a series of carboxamide derivatives of 5'-amino-2',5'-dideoxy-5-ethyluridine and N^2-phenylguanines and efficiency of inhibition of the catalytic activity of murine herpes simplex virus thymidine kinase (HSV-TK types I and II) 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 40 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 5'-amino-2',5'-dideoxy-5-ethyluridine and N^2-phenylguanines against murine HSV-TK (types I and II) 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 59 and 15 structures of murine HSV-TK (types I) 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 murine HSV-TK (types I). Similarly, we simulated the antiviral activity of the same compounds for murine HSV-TK type 2. All QSAR-models can be used for quantitative prediction of potential antiviral drugs against murine HSV-TK (types I and II). Atoms and structural fragments of the studied structures influencing on increase and decrease of HSV-TK (types I and II) inhibition were identified. These results can be considered in the molecular design of active substances of known antiviral drugs in order to enhance their antiviral activity.

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 -5.146 – 0.721.

Training set	Models	N	R^2_{OB}	R^2_{TB}	F	S.D.	Q^2	V
QSAR model based on QNA-descriptors								
TSet1	M1	59	0.910		88.007	0.561	0.889	6
TSet2	M2	44	0.941	0.835	100.927	0.453	0.925	8
QSAR model based on MNA-descriptors								
TSet1	M3	59	0.920	-	94.881	0.527	0.905	6
TSet2	M4	44	0.940	0.832	96.837	0.457	0.923	6
QSAR model based on MNA- and QNA-descriptors								
TSet1	M5	59	0.925	-	87.303	0.513	0.907	7
TSet2	M6	44	0.936	0.847	80.444	0.473	0.916	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; S.D. – 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.
2. Khayrullina V.R. et al. *Biochemistry (Moscow)*, 2015, **80** (1): 74–86.
3. ChEMBL: https://www.ebi.ac.uk/chembl/.