Ju.Z. Akbasheva [1]
S.R.Rakhmatullina [1]
V.R. Khayrullina [1]
A.Ja. Gerchikov [1]

QSAR-MODELING OF BIS-AZAAROMATIC QUATERNARY AMMONIUM ORGANIC SALTS WITH NOOTROPIC ACTIVITY

[1]Department of Chemistry, Bashkir State University, Z. Validi Str., 32, Ufa, Russia

r.sveta@inbox.ru

This research is devoted to QSAR-modelling of bis-nicotinium, bis-pyridinium, bis-picolinium, bis-quinolinium, bis-isoquinolinium compounds. These compounds are antagonists for $\alpha_4\beta_2$ subtype of the nicotinic acetylcholine receptor of rat brain membranes (nAChR). The results of biological tests of these organic compounds in the form of K_i values are presented in the scientific publication [1]. This K_i values were used for creation of QSAR models. QSAR-models were made by the program GUSAR 2013 (General Unrestricted Structure Activity Relationships) [2-3]. In general 6 statistically significant QSAR-models ($R_{train\ set}^2 > 0.7$, $R_{test\ set}^2 > 0.6$, $Q^2 > 0.5$) for prediction of K_i values for selective $\alpha_4\beta_2$ nAChR subtype antagonists were created based on MNA- and QNA-descriptors, as well as consensus of their combinations. The characteristics of created models are shown in Table 1. Training set TrS2 and test set TS included 26 and 5 structures of $\alpha_4\beta_2$ nAChR subtype antagonists, respectively. They were obtained by dividing the pre- sorted in ascending order of K_i values in ratio 5:1, i.e. excluded from TrS1 each fifth compound to TS. These models can be used for quantitative prediction of potential nootropic drugs against $\alpha_4\beta_2$ nAChR subtype. Additionally the structure analysis of model compounds was made. It was determined that variation of N-n-alkyl chain length together with structural modification of the azaaromatic quaternary ammonium moiety afforded selective antagonists for $\alpha_4\beta_2$ nAChR subtype. The results of the structural analysis of bis-azaaromatic quaternary ammonium organic salts can be used in the molecular design of the active components of known nootropic drugs in order to increase their antagonistic activity for $\alpha_4\beta_2$ nAChR subtype.

Table 1. Characteristics and prediction accuracy of K_i values for consensus models M1 - M6. K_i activity in TrS1 and TrS2 lies in the range 5-9.

Training set	Models	N	$R^2_{ОВ}$	Q^2	$R^2_{ТВ}$	F	SD	V
QSAR model based on MNA-descriptors								
TSet1	M1	31	0.748	0.503	-	12.009	0.524	4
TSet2	M2	25	0.730	0.502	0.625	7.004	0.599	4
QSAR model based on QNA-descriptors								
TSet1	M3	31	0.798	0.608	-	13.307	0.473	5
TSet2	M4	25	0.750	0.506	0.688	8.009	0.571	4
QSAR model based on MNA- and QNA-descriptors								
TSet1	M5	31	0.801	0.645	-	14.195	0.471	5
TSet2	M6	25	0.755	0.522	0.699	8.634	0.566	4

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. Ayers J.T. et al. *Bioorganic & Medicinal Chemistry Letters*, 2002, **12**: 3067–3071.
2. Filimonov D.A. et al. *SAR and QSAR in Environmental Research,* 2009. **20 (**7–8): 679–709.
3. Masanda V.H. et al. *Der Pharma Chemica*, 2011, **3** (4): 517–525.