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

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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 ($R_{\text{train set}}^2 > 0.7$, $R_{\text{test set}}^2 > 0.6$, $Q^2 > 0.5$) 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_{OB} | Q^2 | R^2_{TB} | F | SD | V |
|---|--------|----|-------------------|-------|-------------------|--------|-------|---|
| <i>QSAR model based on MNA-descriptors</i> | | | | | | | | |
| 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 |
| <i>QSAR model based on QNA-descriptors</i> | | | | | | | | |
| 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 |
| <i>QSAR model based on MNA- and QNA-descriptors</i> | | | | | | | | |
| 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_{TS} - 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.